

Breast cancer (early and locally advanced): diagnosis and treatment

Evidence Review

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This guideline was partially updated in July 2018. The sections that are no longer current are marked as 'Updated 2018' and grey shaded. Please see <https://www.nice.org.uk/guidance/ng101> for the updated evidence reviews.

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Chapter 2 – Initial assessment, investigation and staging

2.1 What is the role of breast magnetic resonance imaging (MRI) in the pre-operative staging of patients with biopsy proven ductal carcinoma in situ (DCIS) or invasive breast cancer?

Short Summary

MRI for detecting DCIS

Outcome data was identified from two case control studies and four case series, with a relatively high degree of consistency in results. However, data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.

There is good evidence from retrospective case control studies that MRI can complement mammography in guiding surgical treatment of DCIS by providing better assessment to the extent of the lesion. 26/30 (86.7% sensitivity) lesions were detected by MRI as well as 8 lesions without mammographically detected microcalcification. In 7/30 cases MRI showed tumour extent accurately compared with mammography, and the combined diagnosis improved the accuracy of evaluating tumour extent. (Shiraishi, 2003).

The sensitivity of MRI for detecting DCIS is lower than that achieved for invasive breast cancer. However, contrast enhanced MRI can show foci of DCIS that are mammographically occult. The MRI technique is of complementary value for a better description of tumour size and detection of additional malignant lesions (Francescutti, 2002).

There is some evidence from case series that MRI is significantly more sensitive than mammography in DCIS detection. In women with known or suspected DCIS, MRI may have an important role in assessing the extent of disease in the breast (Menell, 2005).

MRI for detecting invasive breast cancer

The outcome data was identified from one systematic review, nine case control studies and 11 case series, with a relatively high degree of consistency in results.

Data need to be interpreted with caution because of the limitations of the studies, low evidence levels and small sample sizes.

Studies consistently demonstrate moderate to high sensitivity (75-100%) and specificity (82-100%) for breast MRI in detecting multicentric tumour foci in fibroglandular or dense breasts (Blue Cross/Blue Shield-TEC Review, 2004 and Del *et al.* 2007). MRI will detect additional mammogram-occult foci greater than 2 cm from the index cancer in approximately 10% of women. These additional foci are similar to those detected by mammography and are therefore likely to be associated with an increased risk of local recurrence for breast conserving surgery (Schnall *et al.* 2005). In patients eligible for breast conserving surgery, MRI is more accurate than conventional imaging in the assessment of tumour extent in one out of four patients (23%) and had a significantly higher yield than mammography of confirmed invasive lobular cancers (Deurloo *et al.* 2006).

Patients who are likely to benefit from MRI are those with dense breasts on mammography, lobular carcinoma and occult primary tumour. In non-fatty breasts ultrasound and MRI were more sensitive than mammography for invasive cancer, but both MRI and ultrasound involved a risk of overestimation of tumour extent. Contrast enhanced MRI has the lowest false-negative rate in detecting invasive lobular carcinoma and has the highest accuracy in measuring the size of the invasive lobular carcinoma (Boetes *et al.* 2004). MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. However, intraductal component of breast cancer is more accurately detected by ultrasound than MRI. MRI provided superior correlation between tumour size and pathology. Combined mammography, clinical examination and MRI was more sensitive than any other individual test or routine triad (Chung *et al.* 2005).

Axillary lymph nodes can be evaluated as part of an MRI-mammography study without substantial increase in examination time, and provide information about the localisation of possible metastatic lymph nodes. Using dynamic contrast enhanced imaging an 83% sensitivity and a 90% specificity for the presence of lymph node metastases was found with the chosen threshold of abnormal signal intensity increase. There was a poor correlation with metastases (sensitivity 63% and specificity 80%) when the size and shape of the axillary lymph nodes in MRI were used as criteria. These results are comparable to computerised tomography (CT) examinations of the axilla but are poorer than the results from ultrasound examination. Axillary lymph nodes showed contrast enhancement in both axillary lymph node dissection (ALND)-positive and ALND-negative patients, but enhancement was stronger and more rapid in patients with metastases (Kvistad *et al.* 2004).

The evidence about when the decision to change treatment (which was based on MRI/rates of mastectomy/procedures initiated by MRI investigation) reported that between 2% and 15% of patients otherwise eligible for breast conserving surgery who have had an MRI as part of their staging workup, would have a multicentric tumour not found by conventional preoperative staging workups. These percentages may be higher for patients with DCIS or invasive lobular cancer. Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients. In anticipation of breast conserving surgery or no surgery after mammography and clinical examination in 96 breasts, additional tumour was found by MRI in 30 cases (Blue Cross/Blue Shield-TEC Review, 2004; Bremner *et al.* 2007; Del *et al.* 2007).

Breast MRI is accurate in staging extent of disease in the breasts of patients with histological grade 3 tumours. In 10 patients with histological grade 1 tumours, the MRI findings overestimated their disease. In 11/115 patients, the primary tumour or a second tumour was only seen by MRI. In 170 patients MRI detected 96% multifocal disease and 95% of multicentric disease, whereas mammography detected 37% and 18% respectively and ultrasound detected 41% and 9% respectively. All bilateral breast cancers were seen on MRI. Both mammography and ultrasound detected 56%. Additional malignant foci detected on MRI identified unsuspected multifocal, multicentric or bilateral breast cancer resulting in necessary changes in treatment (Schelfout *et al.* 2004).

The evidence about tumour recurrence showed that preoperative MRI of the breast is effective in patients with histopathologically verified breast cancer, for local staging. The ipsilateral breast tumour recurrence is significantly higher in women with breast conserving

surgery and no staging with MRI. Metachronous contralateral carcinoma has occurred significantly more in patients without preoperative MRI staging (Fischer *et al.* 2004).

PICO

Population	Intervention	Comparison	Outcome
Patients with early, invasive breast cancer who have not yet received definitive surgery	MRI Breast MRI Axilla	Mammography USS PET Scinti-mammography	<ul style="list-style-type: none"> • Sensitivity • Specificity • Incidence of decisions to change treatment based on MRI • Rates of mastectomy provoked by MRI
Patients with DCIS who have received definitive surgery.	MRI breast	Mammography USS	<ul style="list-style-type: none"> • Sensitivity • Specificity • Incidence of decisions to change treatment based on MRI information • Rates of Mastectomy (provoked by MRI) • Procedures provoked by MRI

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Invasive Breast Cancer:

The body of evidence for this topics consists of one systematic review, 9 case control studies and 11 observational studies - case series, with a relatively high degree of consistency in results.

All studies had comparable patient groups, good quality evidence was found comparing listed interventions.

Data needs to be interpreted with caution due to the limitations of the studies, low evidence levels and small sample sizes.

Studies consistently demonstrate moderate to high sensitivity (75-100%) and specificity (82-100%) for breast MRI in detecting multicentric tumour foci in fibroglandular or dense breasts.

Axillary lymph nodes can be evaluated as a part of an MR-mammography study without substantial increase in examination time, and provide information about the localisation of possible metastatic lymph nodes.

Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients.

Sensitivity and Specificity (improved detection)

There is strong evidence from systematic review that MRI of the breast has a better sensitivity for identifying multicentric breast tumours compared to the current presurgical evaluation. Approximately 2% to 15% of women who appear eligible for BCT would have multicentric disease detected on MRI and might be considered for mastectomy instead of BCT. These percentages of multicentric disease appear somewhat higher among subgroups of patients with either ductal carcinoma in situ (20-28%) or infiltrating lobular carcinoma (17-40%). Studies consistently demonstrate moderate to high sensitivity (75-100%) and specificity (82-100%) for breast MRI in detecting multicentric tumour foci. Positive predictive values (PPV) range from 50% to 100%, although the 3 most representative studies found a PPV for MRI of 67% to 100%. (Blue Cross/Blue Shield-TEC Review, 2004).

There is consistently good evidence from prospective cohort studies that preoperative MRI in patients eligible for BCT is more accurate than conventional imaging in the assessment of tumour extent in one out of four patients (23%). Patients <58 years old with irregular lesion margins at mammography and discrepancy in tumour extent by more than 10 mm between ultrasonography and mammography had a 3.2 X higher chance of accurate assessment at MRI (positive predictive value 50%, negative predictive value 84%, $p=0.0002$). (Deurloo *et al.* 2006).

Consideration needs to be given to integration of breast MRI into the pre-treatment evaluation of women seeking BCT. MRI had a significantly higher yield of confirmed cancer ILs than mammography (0.18 (95%CI: 0.142-0.214) for MRI versus 0.072 (95%CI: 0.050-0.100) for mammography). The cancer ILs detected by MRI alone appeared to be similar to those detected by mammography with respect to size and histology. The percentage of biopsies of ILs that resulted in a cancer diagnosis was similar between the modalities (MRI 0.72 (95%CI: 0.6-0.81); Mammography 0.85 (95%CI: 0.62-0.96)). The results demonstrate that MRI will detect additional mammogram occult foci greater than 2 cm from the index cancer in approx. 10% of women. These additional foci are similar to those detected by mammography and are therefore likely to be associated with an increased risk of local recurrence for BCT. (Schnall *et al.*, 2005).

There is further evidence that in non-fatty breasts US and MR imaging were more sensitive than mammography for invasive cancer, but both MR imaging and US involved risk of overestimation of tumour extent. Combined mammography, clinical examination and MR imaging were more sensitive than any of other individual test or combination of tests. Mammographic sensitivity decreased from 100% in fatty breasts to 45% in extremely dense breasts. Mammographic sensitivity was highest for invasive ductal carcinoma (IDC) in 81% of cases versus 34% of cases of invasive lobular carcinoma (ILC) ($p<0.001$) and 55% in ductal carcinoma in situ (DCIS) ($p<0.01$) .

US showed higher sensitivity than mammography in IDC depicting 94% of cases, and for ILC 86% of cases ($p<0.01$) and DCIS respectively, 47% ($p<0.01$). MR showed higher sensitivity than mammography for all tumour types ($p<0.01$) and higher sensitivity than US for DCIS – 89% of cases ($p<0.01$) and depicting 95% cases of IDC and 96% of ILC cases. Additional tumour was detected in 18% of breasts by US and 30 at MR. Extent was overestimated in 12% at US and 29% at MR. Combined mammography, clinical examination, US, and MR detected additional tumour in 12% breasts and led to an overestimation of extent in 6%. US showed no detection benefit after MR imaging. (Berg *et al.*, 2004).

Specificity and sensitivity for incidentally detected lesions in the ipsilateral or contralateral breast as reported in a large retrospective cohort study found that lesions in a different quadrant from the main lesion, are smaller than 10 mm in diameter, and show persistent enhancement on MR imaging suggest benign lesions. Therefore, patients with such lesions could avoid unnecessary surgical procedures unless lesions are proved to be malignant by cytology or biopsy. Lesions of over 10 mm tended to be malignant (11/16 ; 69%), whereas those equal or less than 5 mm tended to be benign (17.5; 71%; $p < 0.05$). Lesions in the same quadrant as the main lesion tended to be malignant (20/27.5; 73%), whereas those in a different quadrant tended to be benign (17.5/20.5; 85%; $p < 0.001$). Lesions with early peak of enhancement tended to be malignant (20/25; 80%), whereas those with persistent enhancement tended to be benign (20/23; 87%; $p < 0.001$). (Hidetake *et al.*, 2006).

The intraductal component of breast cancer is more accurately detected by US than MRI according to evidence from a retrospective cohort study. However, when US and MRI were used to diagnose the Intraductal component the results correlated well with histopathological findings. Sensitivity, Specificity and Accuracy were 57.1%, 84.2% and 78.7% respectively for US and 50%, 89.5% and 65.9% for MRI. When both US and MRI were used Sensitivity, Specificity and Accuracy were 75%, 84.2% and 78.7% respectively. (Sundararajan *et al.*, 2006).

Good evidence regarding the sensitivity and specificity of MRI in the detection of multiple malignant foci in fibroglandular or dense breasts comes from a prospective case control study. According to this study, breast MRI is more sensitive than mammography (MX) for the detection of multiple malignant foci in fibroglandular or dense breast. Mammography missed larger and more invasive cancer foci than MRI. A relative low PPV is a problem for both techniques. Of 99 breasts , pathologic findings revealed 52 unifocal, 29 multifocal and 18 multicentric cancers for a total of 188 malignant foci (158 invasive and 30 in situ). Overall sensitivity was 66% (124/188) for mammography and 81% (152/188) for MRI ($p < 0.001$) in favour of MRI. Sensitivity for invasive foci was 72% for mammography and 89 % for MRI ($p < 0.001$) in favour of MRI. Sensitivity for in situ foci was 37% for mammography and 40 % for MRI ($p > 0.05$) no significant difference. Malignant foci missed by mammography: 64; MRI 36, with median diameters of 8 mm for MX and 5 mm for MRI ($p = 0.033$) in favour of MRI. Overall Positive Predictive Value (PPV) was 76% for MMG and 68% for MRI, not significant. In breasts with fatty patterns sensitivity was 75% for MMG and 80% for MRI, not significant; PPV 75% and 65% respectively, not significant. In breasts with fibroglandular or dense patterns sensitivity was 60% for MX and 81% for MRI, ($p < 0.001$) in favour of MRI and PPV was 78% and 71% respectively, not significant. (Sardanelli *et al.*, 2004).

There is good evidence that MRI provided superior correlation between tumour size and pathology (Spearman correlation coefficient between tumour size on ultrasound and MRI with pathology was .19 ($p = .5$) and .88 ($p < 0.001$) respectively. (Kepple *et al.*, 2005).

Lower quality evidence shows that, in patients with ILC, MRI has a higher sensitivity than other imaging modalities and is able to accurately delineate multifocal disease not evident on conventional imaging, and is therefore a useful tool for accurate staging prior to surgery. MRI identified all the patients with subsequently histologically proven multifocal disease, with PPV

of 100% and NPV of 55.6%. Management was changed in 24% of the cases following MRI. (Kneeshaw *et al.*, 2003).

This evidence is corroborated by further retrospective case series which shows that in comparison with US and MX contrast enhanced MR has the lowest false-negative rate in detecting ILC and has the highest accuracy in measuring the size of the ILC. MR could play a key role in the pre-operative work-up for accurate tumour size determination. (Boetes *et al.*, 2004).

Also, mammography alone is not enough in detecting, and especially in the staging of ILC. Differences between Radiologists, proved to be responsible for the non-detections of ILCs on mammography or treatment delay. The understaging of ILC by mammography can have a serious influence on the clinical management of patients with ILC. 35% to 37% were understaged, the largest differences between radiologists were found in the breast imaging reporting and data system (BIRADS) classification and staging performance. Compared to the pathological findings, Radiologist 1 staged 60% correct, overstaged 3% and understaged 37% in Session A and similar percentages in Session B. Radiologist 2 staged 60% correct, overstaged 5% and understaged 35% in Session A and respectively 52%, 0%, 48% in Session B. Radiologist 1 differed in 17% patients between two sessions, Radiologist 2 in 21%. Intra-observer variation for staging was $k=0.66$ and $k=0.70$, respectively for both Radiologists. The k value for interobserver agreement was 0.46 and 0.65 comparing Sessions A and B. In the BIRADS classification, Radiologist 1 differed in 26% of patients between the two sessions and Radiologist 2 in 21% of patients. Comparing the results of both Radiologists from Session A and B resulted in 29% and 31% differences respectively. The k value for intra-observer variation was 0.42 and 0.68 respectively. Interobserver agreement was $k=0.45$ and 0.50 comparing the BIRADS classification for Sessions A and B respectively. (Veltman *et al.*, 2006).

Further lower quality evidence from case series suggests that MRI is more accurate than US and clinical examination, both of which underestimated tumour size. MRI and mammography are more accurate in estimating tumour size. MRI detected 21 of the 22 ILCs while mammography and US detected 16 and 20 respectively. Clinical examination detected 19 tumours. There was a significant difference in clinical and histological size ($p=0.0038$) with clinical examination underestimating tumour size in 63% of patients. There was no significant difference between mammographic and histological size ($p=0.3894$). There was a significant difference between US and histological size ($p=0.0003$), with US underestimating size in 90% of patients. There was no significant difference between MRI and histological size ($p=0.6288$). (Francis *et al.*, 2001).

MRI may play an important role in the evaluation of patients with ILC, which is often difficult to diagnose on clinical examination and conventional imaging and more likely occur in multiple sites and in both breasts. However, false-negative MR findings do occur in a small percentage of ILC. MR findings of unifocal, multifocal, single quadrant and multi quadrant disease were correlated with other imaging techniques and compared with histological findings. Most ILC presented on MRI as a single speculated/irregular, inhomogeneous mass (pattern 1, $n=12$) or as a dominant lesion surrounded by multiple small enhancing foci (pattern 2, $n=8$). Multiple small enhancing foci with interconnecting enhancing strands (pattern 3) and an architectural distortion (pattern 4) were both described in three cases. There was one case

of a focal area of inhomogeneous enhancement (pattern 5) and one normal MR examination (pattern 6). Unifocal and multifocal lesions were identified on MRI in four patients with normal conventional imaging. In nine women, multiple additional lesions or more extensive multiquadrant disease were correctly identified only on MRI. (Schelfout, 2004).

Axillary Node Staging

There is good evidence that axillary lymph nodes can be evaluated as a part of an MR-mammography study without substantial increase in examination time, and provide the surgeon with knowledge about the localisation of possible metastatic lymph nodes. Using dynamic contrast enhanced imaging, a 83% sensitivity and a 90% specificity for the presence of lymph node metastases was found with the chosen threshold of abnormal signal intensity increase. When using a signal intensity increase in the lymph nodes of >100% during the first postcontrast image as a threshold for malignancy, 57/65 patients were correctly classified (sensitivity 83%, specificity 90%, accuracy 88%). These results were not improved when lymph node size and morphology were used as additional criteria. When combining enhancement patterns (signal intensity increase) and morphological criteria of the tumour to improve specificity of the method, the sensitivity decreased to 65%, without significant increase in specificity. Using the size and shape of the axillary lymph nodes in MR images as a criteria correlated poorly to the presence of metastases, with a sensitivity of 63% and a specificity of 80%. These results are comparable to CT examinations of the axilla but are poorer than the results from ultrasound examination. Clinical evaluation had a very low sensitivity of 25%, and was found to be an inaccurate method for detection of axillary lymph nodes metastases. Axillary lymph nodes showed contrast enhancement in both ALND-positive and ALND-negative patients, but enhancement was stronger and more rapid in patients with metastases, and on average reached a peak value during the first 57s after contrast injection. Axillary lymph nodes can be evaluated as a part of an MR-mammography study without substantial increase in examination time, and provide the surgeon with knowledge about the localisation of possible metastatic lymph nodes. (Kvistad *et al.*, 2004).

There is also fairly good evidence to suggest the feasibility of semi automated, non-invasive nodal cancer staging using a nonparticle enhanced lymphotropic magnetic resonance (LMRI) technique. Nanoparticles traced by MRI displayed an abnormal pattern when there was metastases in the nodes and a computer software recognises this abnormality. Unique magnetic tissue parameters were found, which accurately distinguished metastatic from normal nodes with an overall sensitivity of 98% and specificity of 92%. The parameters can be applied to data sets in a semi automated fashion and used for 3D reconstruction of complete nodal anatomy for different primary cancers. (Harishinghani *et al.*, 2004).

Incidence of Decision to Change Treatment Based on MRI / Rates of Mastectomy / Procedures Provoked by MRI

There is strong evidence that the moderate specificity and relatively low PPV of MRI findings underscore the importance of performing image-guided biopsy of such lesions to confirm malignancy before committing the patient to mastectomy. If presurgical biopsy of multicentric foci is not performed, there is the distinct possibility of performing mastectomy when, in fact, no multicentric disease exists and there would be no possible long-term benefit to the patient. Between 2% and 15% of patients otherwise eligible for BCT who have had an MRI as part of their staging workup, would have multicentric tumour not found by conventional preoperative staging workups. These percentages may be higher for patients with DCIS or Infiltrating

Lobular Carcinoma. Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients. Of the total 13 patients who underwent mastectomy because of MRI findings, it appears that at least 2 of these were the result of false-positive MRI findings that were presumably not confirmed by preoperative MRI-guided biopsy. Potential benefits of breast conservation surgery are lower using MRI information to guide surgical treatment. Some studies point out that there is a harm of performing mastectomy for false-positive MRI findings when preoperative biopsy is not used for confirmation. There is strong evidence from systematic reviews comparing outcomes of mastectomy versus BCT for early stage breast cancer, that there is no significant difference in overall or disease-free survival during intermediate or long-term follow-up. (Blue Cross/Blue Shield-TEC Review, 2004).

There is good evidence from prospective cohort studies that, in anticipation of BCT or no surgery after mammography and clinical examination in 96 breasts, additional tumour was found by MRI in 30 cases, which altered surgical approach. (Berg *et al.*, 2004).

There is good evidence from a retrospective cohort study that Breast MRI does change surgical management by detecting additional malignancies. Breast MRI is accurate in staging extent of disease in the breast in patients with High-grade (HG) tumours. The size of the tumour on MRI correlated with the pathologic size for HG tumours (HG $R=0.76$ vs. LG $R=0.45$, $p=0.033$). Mastectomy was performed in 53 patients. In 10 patients with LG tumours, the MRI findings overestimated their disease. In 11 out of 115 patients, the primary tumour or a second tumour was only seen by MRI. (Blair *et al.*, 2006).

This concurs with evidence from a large prospective case control study that pre-operative MRI is an important adjunct to conventional imaging in loco-regional staging of breast cancer and a useful tool in treatment planning. In 170 patients MRI detected 96% of multifocal disease and 95% of multicentric disease, whereas MX detected 37% and 18% respectively and US detected 41% and 9% respectively. All bilateral breast cancers were seen on MRI. Both MX and US detected 56%. Findings of more extensive disease and unsuspected multiple foci were identified on MRI only. Additional malignant foci detected on MRI identified unsuspected multifocal, multicentric or bilateral breast cancer resulting in necessary changes in therapeutic strategy (60 of the 204 patients). Nine unnecessary wider excisions and 3 unnecessary FNA/core biopsies were performed because of MRI overestimation of number or size of malignant lesions. Correlation between histopathology and MRI was far better than MX and US, in diameter of malignant lesions. The PPV was best for MRI ($R^2: 0.56$). The predictions of MX and US were similar (0.37 and 0.35 respectively). (Schelfout *et al.*, 2004).

MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. Mammography and ultrasonography does not accurately assess the extent of DCIS which results in a high re-operation rate. Breast MRI can improve surgical planning in women with DCIS, improving the adequacy of initial treatment while reducing re-operation. In the study of 54 patients with predominantly DCIS, MRI altered surgical management in 26% of patients; unilateral changed to bilateral mastectomy (5); lumpectomy or re-excision to mastectomy (3); unilateral lumpectomy or mastectomy had additional biopsies for lesions in the ipsilateral or contralateral breast (6). There were 8 true-positives and 7 false-positives; sensitivity 86%, PPV 84%; MRI changed the surgical management to more appropriate therapy in 15% of patients, avoiding additional surgery while 11% underwent negative surgical interventions. (Chung *et al.*, 2005).

Further evidence from a retrospective case series shows that patients who desire Breast Conserving Therapy (BCT) should undergo MRI mammography before biopsy of a category 4/5 mammogram or immediately after a positive FNA biopsy result of a palpable mass. Prebiopsy or preoperative MRI mammography changed surgical management in 13/27 (48%) patients with breast cancer by discovering multicentric cancers or more extensive cancer. 9/27 patients with positive FNA biopsy results of palpable masses underwent preoperative MRI; 6/9 patients ipsilateral multicentric cancers or more extensive cancer was discovered that necessitated mastectomy rather than breast conservation. 18/27 patients had a category 4/5 mammograms. 10 of these patients had stereotactic biopsies followed by MRI; 4/10 had changes on the MRIs that required mastectomy rather than breast conservation. 8/27 patients had MRI before stereotactic biopsy; 3/8 patients had MRI abnormalities that required mastectomy. One patient had contralateral, multicentric cancers not seen on conventional mammography, necessitating bilateral mastectomies. (Bagley *et al.* , 2004).

Lower quality evidence shows that breast MRI is useful in diagnosis, staging and surgical management of ILC. Enhancement at MRI was seen for all 35 cancers. It was focal for 24 patients, regional for 10 and diffuse for 1. Malignancy was shown in 33 patients. For 11 patients, the MRI staging was positive finding 8 new cancers. MRI had an impact on the management of 11 patients (33%). MRI was beneficial in 8 of 11 patients (confirmed original BCT management in 3 cases, conversion to mastectomy in 3 cases, contralateral lumpectomy in 2 cases).MRI caused benign lesions to undergo biopsy in 3 patients (overestimated). (Fabre Demard *et al.*, 2005).

Other Reported Outcomes - Tumour Recurrence

There is good evidence from a large retrospective cohort study that preoperative MR of the breast is recommended in patients with histopathologically verified breast cancer, for local staging. The in-breast tumour recurrence is significantly higher ($p < 0.001$) in women with BCT and no staging with MRI. All cases had a conformity of histology and tumour localisation between primary index and tumour recurrence. Metachronous contralateral carcinoma has occurred significantly more in patients without pre-operative MRI staging. Tumour recurrence was detected between 6 and 45 months after surgical treatment. Contralateral cancer was detected 14 to 52 months after surgical treatment. (Fischer *et al.*, 2004).

DCIS:

Evidence Summary

The outcomes of interest reported are Sensitivity and Specificity and incidence of decision to change treatment based on MRI, rates of mastectomy provoked by MRI and procedures provoked by MRI.

All studies had comparable patient groups, good quality evidence was found comparing listed interventions. The studies were designed to address comparatively Mammography (MX), Ultrasonography (US), Clinical Examination (CE), Magnetic Resonance Imaging (MRI) vs. Histopathological findings in women with newly diagnosed Ductal Carcinoma In Situ (DCIS)

The outcomes of interest reported are Sensitivity and Specificity and incidence of decision to change treatment based on MRI, rates of mastectomy provoked by MRI and procedures

provoked by MRI. No study was found that addressed cost effectiveness or health economics. Some studies mentioned cost effectiveness but not in an assessable evidence level.

There is a high degree of consistency, with all studies reporting similar findings.

The sensitivity of MRI for DCIS detection is lower than that achieved for invasive breast cancer.

There is some evidence from case series that MRI is significantly more sensitive than mammography in DCIS detection. In women with known or suspected DCIS, MRI may have an important role in assessing the extent of disease in the breast.

Tumour size measured at MRI did correlate with histopathologic size, but in contrast to mammography MRI tended to overestimate the tumour extent.

Sensitivity and Specificity (improved detection)

There is good evidence from retrospective case control studies that MRI can complement mammography in guiding surgical treatment of DCIS by providing better assessment to the extent of the lesion. 26/30 (86.7% sensitivity) were detected through the MRI as well as 8 lesions without mammographically detected microcalcification. In 7/30 cases MRI showed tumour extent accurately compared with mammography, and the combined diagnosis improved the accuracy of evaluating tumour extent. (Shiraishi *et al.*, 2003).

Intensity-modulated parametric mapping technique for breast MRI resulted in the highest detection rate for the DCIS cases. Furthermore, the parametric mapping technique identified all intermediate and high-grade DCIS lesions, suggesting that a negative MRI using the parametric mapping technique may exclude intermediate and high-grade DCIS. With the use of a kinetic curve shape analysis, MRI classified 7/14 lesions (50%) as suspicious, including four with initial-rapid/late-washout and three initial-rapid / late-plateau. Using morphologic criteria, MRI classified 10/14 (71%) as suspicious., with the most prominent morphologic feature being a regional enhancement pattern. Using the intensity modulated parametric mapping technique, MRI classified 12/14 cases (86%) as suspicious. Parametric mapping identified all intermediate and high-grade DCIS lesions. (Mariano *et al.*, 2005).

There is also fairly good evidence that there are features that help differentiate high-grade DCIS from invasive carcinoma on MRI. High-grade DCIS is significantly more likely to show focal branching pattern ($p=0.003$) or to have an irregular contour ($p=0.003$) compared with invasive disease. All though of marginal statistical significance, DCIS lesions are more likely to have a lower morphological score than invasive carcinoma ($p=0.006$), whilst the latter is more likely to show ring enhancement ($p=0.007$). (Groves *et al.*, 2005).

The sensitivity of MRI for DCIS detection is lower than that achieved for invasive breast cancer. However, contrast enhanced MRI can depict foci of DCIS that are mammographically occult. The MRI technique is of complementary value for a better description of tumour size and detection of additional malignant lesions. On MRI, 21/22 (95%) DCIS lesions showed contrast enhancement. 14/15 (93%) pure DCIS lesions demonstrated respectively a low (3), undeterminate (5), and strong (6) enhancement. Morphologically, the enhancing lesion was focal in 7, segmental in 4 and with linear branching in 3 cases. Wash out was found in 4

cases, plateau curve in 8 and Type I curve in 2 cases. Multifocality was present in 5 cases. All DCIS with associated microinvasion demonstrated contrast enhancement: 1/7 cases showed a low enhancement, 2/7 showed an indeterminate enhancement and 4/7 showed a strong enhancement. Morphologically, the enhancing lesion was focal in 3/9, segmental in 5 and with linear branching in 1 case. The wash out was demonstrated in 3/7 cases, plateau curve in 3 and Type 1 curve in 1 case. Multifocality was present in 3 cases. (Francescutti *et al.*, 2002).

There is some evidence from case series that MRI is significantly more sensitive than mammography in DCIS detection. In women with known or suspected DCIS, MRI may have an important role in assessing the extent of disease in the breast. Of 33 breasts involved, DCIS was discovered by MRI alone in 21 (64%), by both MRI and mammography in 8 (24%) and by mammography alone in 1 (3%), DCIS found at mastectomy without findings of mammography or MRI in 3 breasts (9%). MRI had significantly higher sensitivity than mammography for DCIS detection (29/33 = 88% vs. 9/33 = 27%; $p < 0.00001$). Multiple sites of disease were present in 5 breasts, better demonstrated with MRI in 3, mammography in 1, and equally by both in 1. The predominant enhancement pattern of DCIS on MRI was linear / ductal in 18/29 breasts (62%); mammography found calcifications associated with DCIS in 8/9 (89%). The nuclear grade of DCIS found with MRI and mammography was similar; size of lesion was larger on MRI; breast density did not impact results. (Menel *et al.*, 2005).

Both DCIS and DCIS with small invasive carcinoma can be adequately visualised on MRI. Tumour size measured at MRI did correlate with histopathologic size, but in contrast to mammography MRI tended to overestimate the tumour extent. Mammographic rate of detection for DCIS was 84/52 (90%) and for DCIS with small invasive carcinoma 10/12 (83%). MRI revealed 1 false negative case and the rate of detection for DCIS was 16/17 (94%). Correlation of mammographic size with histopathologic size was $r = .44$ ($p < .01$) and $r = .49$ ($p < .03$) for MRI. Mammography underestimated the lesion size by 5 mm or more in 47%, whereas with MRI size was adequately assessed in 43% and overestimated in 38%. (van der Velden *et al.*, 2006).

Incidence of Decision to Change Treatment Based on MRI / Rates of Mastectomy / Procedures Provoked by MRI

No study was found that addressed incidence of decision to change treatment, provoke additional procedures or determine a change in the rates of mastectomy based on MRI for DCIS.

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Evidence Tables – Invasive Breast Cancer

<p>Magnetic Resonance Imaging of the Breast for Preoperative Evaluation in Patients with Localized Breast Cancer: Blue Cross and Blue Shield Association 2004: Technology Evaluation Center (Tec) Assessment Programme Volume 18, No.8, 2004.</p>
<p>Design: Systematic Review Evidence Level 1++</p>
<p>Country: International</p>
<p>Inclusion criteria: Diagnostic performance of MRI: articles pertaining to use of Contrast Enhanced MRI in humans for staging breast cancer, evaluating the effectiveness of preoperative MRI for early stage breast cancer (I or II), Trials on modified radical mastectomy vs. breast conservation therapy with respect to local recurrence, distant recurrence, or survival. Clinical outcomes relating to treatment decisions: study population followed prospectively, randomized and controlled, study effect on survival, local recurrence or distant recurrence, standard preoperative staging evaluation</p>
<p>Exclusion criteria Single case reports</p>
<p>Population: Patients with clinically localised early invasive breast cancer who have not yet received definitive surgery, considered eligible for breast conservation therapy (BCT) and who would prefer BCT instead of mastectomy.</p>
<p>Interventions: Breast MRI as an adjunct to conventional preoperative staging evaluation (eg. Mammography, physical exam, and possibly ultrasound) to determine the extent of tumour in the breast when conventional staging has deemed the patient eligible for BCT. The reference standard for determining the diagnostic performance of preoperative evaluation for identification of multicentric disease is histopathologic assessment.</p>
<p>Outcomes: The health outcomes considered in this assessment are survival, breast cancer recurrence, breast conservation, disease-free survival (incorporating the overall risk of recurrence) and locoregional recurrence (within the ipsilateral breast, chest wall, local lymph nodes or skin at the surgical site)</p>
<p>Results <u>Sensitivity (improved detection)</u> There is strong evidence that MRI of the breast has a better sensitivity for identifying multicentric breast tumours compared to the current presurgical evaluation. Approximately 2% to 15% of women who appear eligible for BCT would have multicentric disease detected on MRI and might be considered for mastectomy instead of BCT. These percentages of multicentric disease appear somewhat higher among subgroups of patients with either ductal carcinoma in situ (20-28%) or infiltrating lobular carcinoma (17-40%). Studies consistently demonstrate moderate to high sensitivity (75-100%) and specificity (82-100%) for breast MRI in detecting multicentric tumour foci. Positive predictive values (PPV) range from 50% to 100%, although the 3 most representative studies found a PPV for MRI of 67% to 100%.</p> <p><u>Incidence of Decision to Change Treatment Based on MRI</u> Between 2% and 15% of patients otherwise eligible for BCT who have had an MRI as part of their staging workup, would have multicentric tumour not found by conventional preoperative staging workups. These percentages may be higher for patients with DCIS or Infiltrating Lobular Carcinoma. Patients' treatment was changed to mastectomy based on MRI findings in 7% of the patients. Of the total 13 patients who underwent mastectomy because of MRI findings, it appears that at least 2 of these were the result of false-positive MRI findings that were presumably not</p>

confirmed by preoperative MRI-guided biopsy. Potential benefits of breast conservation surgery are lower using MRI information to guide surgical treatment. Some studies point out that there is a harm of performing mastectomy for false-positive MRI findings when preoperative biopsy is not used for confirmation.

There is strong evidence from systematic reviews comparing outcomes of mastectomy versus BCT for early stage breast cancer, that there is no significant difference in overall or disease-free survival during intermediate or long-term follow-up.

Procedure Provoked by MRI

There is strong evidence that the moderate specificity and relatively low PPV of MRI findings underscore the importance of performing image-guided biopsy of such lesions to confirm malignancy before committing the patient to mastectomy. If presurgical biopsy of multicentric foci is not performed, there is the distinct possibility of performing mastectomy when, in fact, no multicentric disease exists and there would be no possible long-term benefit to the patient.

OUTCOME INTEREST	OF	No. Studies	COMPARISON	RESULT
<u>Sensitivity (improved detection)</u>		18 (n=1401)	MRI vs. current presurgical evaluation	MRI of the breast has a better sensitivity for identifying multicentric breast tumours
			Sensitivity	Moderate to high (75-100%)
			Specificity	82-100%
			Positive Predictive Values	50-100%
<u>Incidence of Decision to Change Treatment Based on MRI</u>				2% to 15% of BCT patients with multicentric breast tumours detected only on MRI

General comments

Deurloo, E.E., Klein Zeggelink, W.F.A., Jelle Teertstra, H., Peterse, J.L., Rutgers, E J Th., Muller, S.H., Bartelink, H., Gilhuijs, K.G.A., "Contrast-enhanced MRI in Breast Cancer Patients Eligible for Breast-Conserving Therapy: Complementary Value for Subgroups of Patients", Eur Radiol No. 16, pp692-701, 2006

Design: Prospective Cohort Study Evidence Level 2++

Country: Netherlands

Setting: Hospital

Inclusion criteria: Patients with early breast cancer, identified through fine needle aspiration or core biopsy, eligible for BCT based on clinical examination and conventional imaging. All patients underwent mammography and ultrasonography.

Exclusion criteria Not reported

Population: 165 patients with 166 malignant tumours (one patient with a bilateral tumour confirmed at MRI)
Mean age was 55 years (range 28-86yrs).

<u>Density at Mammography</u>	N	%	<u>Suspicious Abnormality</u>	N	%
Almost entirely fat	10	6%	at mammography	158	95%
Scattered fibroglandular tissue	65	39%	at ultrasonography	159	96%
Heterogeneously dense	79	48%			
Extremely dense	12	7%	<u>Histological Type</u>		
			Invasive Ductal Carcinoma	138	83%
<u>Non-measurable</u>			Invasive Lobular Carcinoma	25	15%
at least one of two	31	19%	Ductal Carcinoma In Situ	3	2%
both mammography & ultrasonography	3	2%	Tumour negative axillary lymph nodes	132	80%
only at mammography	18	11%	Tumour positive axillary lymph nodes	33	20%
only at ultrasonography	10	6%	Tumour negative axilla	92	55%
			Tumour positive axilla	74	45%
<u>Interventions</u>					
BCT	135	81%			
Mastectomy	31	19%			
Sentinel Node Procedure	132	80%			
Lymph Node Dissection	32	20%			

Interventions: Pre-operative Breast MRI.

Outcomes: Correlation between imaging (Breast MRI) and pathology.
Assessment of complimentary value of MRI where conventional imaging underestimated or overestimated tumour extent (by more than 10 mm compared with histology) and MRI assessed the extent accurately.

Results

There is good evidence that preoperative MRI in patients eligible for BCT is more accurate than conventional imaging in the assessment of tumour extent in one out of four patients (23%). Patients <58 years old with irregular lesion margins at mammography and discrepancy in tumour extent by more than 10 mm between ultrasonography and mammography had a 3.2 X higher chance of accurate assessment at MRI (positive predictive value 50%, negative

predictive value 84%, p=0.0002).

Complimentary value of MRI to determine tumour extent

Estimate	Conventional imaging		MRI	
Correct	117	(70%)	150	90%
Overestimate	7	(4%)	6	4%
Underestimate	42	(25%)	10	6%

Tumour extent measured at conventional imaging and at MRI

Conventional imaging	MRI			
	Correct	Underestimation	Overestimation	Total
Correct	111	2	4	117
Underestimation	33	8	1	42
Overestimation	6	0	1	7
Total	150	10	6	166

Tumour extent measured at conventional imaging and at MRI

(lesions eligible for BCT measurable at both mammography and ultrasonography)

Conventional imaging	MRI			
	Correct	Underestimation	Overestimation	Total
Correct	93	2	4	99
Underestimation	25	7	0	32
Overestimation	3	0	1	4
Total	121	9	5	135

General comments

Schnall, M.D., Blume, J., Bluemke, D.A., Deangelis, G.A., Debruhi, N., Harms, S., Heywang-Korbrunner, S.H., Hylton, N., Kuhl, C.K., Pisano, E.D., Causer, P., Schnitt, S.J., Smazal, S.F., Stelling, C.B., Lehman, C., Weatherall, P.T., Gatsonis, C. MRI Detection of Distinct Incidental Cancer in Women with Primary Breast Cancer Studied in IBMC 6883, Journal of surgical Oncology, no 92 pp. 32-38, 2005

Design: Prospective Cohort Study Evidence Level 2++

Country: International

Setting: Hospital

Inclusion criteria: women presenting with a suspicious or highly suspicious imaging finding on conventional imaging (BiRads 4 and 5) or suspicious clinical findings requiring biopsy, in whom the index lesion diagnosis was established to be cancer.

Exclusion criteria

Population: 426 women

Characteristics:		Histology	
Age:	52±11	Invasive ductal (NOS)	59.6%
Family history of breast CA	39.7%	DCIS	14.3%
Index lesion size (mean)	24.7±1.3 mm	Invasive lobular	7.3%
Index lesion (median)	18 mm	Mixed lobular/ductal	11.7%
Index lesion palpable	51.4%	Tubular carcinoma	2.1%
Index lesion visible on mammography	88.5%	Colloid carcinoma	1.4%
		Other	3.6%

Interventions: Pre-operative Breast MRI.

Outcomes: Findings of incidental lesions; comparison of suspicious ILs on MRI with those on biopsy; mammography density detected by mammography or MRI only; characteristics of most advanced lesions.

Results: There is good evidence that consideration needs to be given to integration of breast MRI into the pre-treatment evaluation of women seeking breast conservation therapy (BCT). MRI had a significantly higher yield of confirmed cancer ILs than mammography (0.18 (95%CI: 0.142-0.214) for MRI versus 0.072 (95%CI: 0.050-0.100) for mammography). The cancer ILs detected by MRI alone appeared to be similar to those detected by mammography with respect to size and histology. The percentage of biopsies of ILs that resulted in a cancer diagnosis was similar between the modalities (MRI 0.72 (95%CI: 0.6-0.81); Mammography 0.85 (95%CI: 0.62-0.96)). The results demonstrate that MRI will detect additional mammogram occult foci greater than 2 cm from the index cancer in approx. 10% of women. These additional foci are similar to those detected by mammography and are therefore likely to be associated with an increased risk of local recurrence for BCT.

Findings of Incidental Lesions

Findings by:	mammography	MRI	MRI only
Women with complete scans	417	423	423
Women with at least one IL	41 (9.8%)	129 (30.5%)	101 (23.9%)

Women with at least one suspicious IL	36(8.6%)	103 (24.3%)	83 (19.6%)
Women with at least one suspicious IL+ pathology data	20 (4.8%)	78 (18.4%)	61 (14.4%)
Percent verified by pathology	55.5% (20/36)	75.7% (78/103)	73.5% (61/83)
Women with verified cancer IL	17	56	41
Percent of cancer IL in biopsied women	85% (17/20)	72.8 (56/78)	67.2% (41/61)

Comparison of the population with suspicious IL on MRI with those who underwent biopsy

	Suspicious IL	Suspicious IL with biopsy	Suspicious IL with missing biopsy
Number of women	103	78	25
Age (mean, SD)	54.3 (11) years	54.5 (11) years	53.4 (10) years
Post menopausal (%of total; %missing of total)	48 (46.6%; 0%)	35 (44.9%; 0%)	13 (52%; 0%)
Family history of breast CA (%of total; %missing of total)	38 (36.9%; 0%)	28 (35.9%; 0%)	10 (40%; 0%)
Index lesion size (mean, SD)	25.3 (2.7)mm	26.4 (3) mm	22.4 (6) mm
Index DCIS (%of total; %missing of total)	9 (8.7%; 0%)	6 (7.8%; 0%)	3 (12%; 0%)
IL size (mean, SD)	17.4 (17) mm	18.8 (18) mm	13.0 (16) mm
Upper ½ breast density scale (%of total; %missing of total)	59 (57.3%; 4.9%)	43 (55.7%; 5.2%)	16 (64%; 0%)

Mammography density in women with confirmed cancer IL

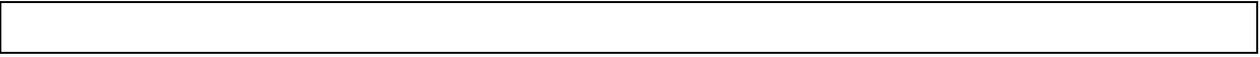
(detected by mammography and MRI only)

Breast density (n)	Mammography detected cancer IL (±MRI) (20)	MRI detected cancer IL (41)
Fatty (n)	35% (7)	2% (1)
Scattered fibroglandular density (n)	25% (5)	24% (10)
Heterogenously dense (n)	30% (6)	49% (20)
Extremely dense (n)	10% (2)	12% (5)
Not available (n)	0% (0)	12% (5)

Characteristics of most advanced lesion diagnosed as cancer IL

IL histology	Mammography detected	MRI detected
n	20	41
Invasive	16 (80%)	32 (78.1%)
Invasive lobular	2 (10%)	6 (15%)
Invasive lobular/ ductal	3 (15%)	3 (7.3%)
Tubular	1 (5%)	2 (4.9%)
DCIS	4 (20%)	9 (21.9%)
Median size	12 mm	11 mm
% grade 2 or 3	70%	84%

General comments



Berg, W.A., Gutierrez, L., NessAiver, M.S., Carter W.B., Bhargavan, M., Lewis, R.S., Ioffe, O.B. Diagnostic Accuracy of Mammography, Clinical Examination, US, and MR Imaging in Preoperative Assessment of Breast Cancer. Radiology, No. 233, pp. 830-849, 2004

Design: Prospective Cohort Study Evidence Level 2++

Country: USA

Setting: Hospital

Inclusion criteria: women older than 18 with newly diagnosed invasive breast cancer by means of core biopsy and-or high clinical or mammographic suspicion of invasive breast cancer.

Exclusion criteria: women unwilling or unable to consent or unable to undergo MR because of a pacemaker, aneurism clip or metallic foreign body; patients who have undergone open biopsy before mammography, US and MR.

Population: a cohort of 111 consecutive women,. Median size of foci 18 mm (range 2-107) Mean age 48.7, median age 48, range 26-81years). Lesions proved malignant in 110 patients (99.1%) with 177 malignant foci (73% palpable)

Interventions: assess the accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer.

Outcomes: sensitivity in tumour detection, correlated with histopathological findings

Results:

There is good evidence that in non-fatty breasts US and MR imaging were more sensitive than mammography for invasive cancer, but both MR imaging and US involved risk of overestimation of tumour extent. Combined mammography, clinical examination and MR imaging were more sensitive than any of other individual test or combination of tests. Mammographic sensitivity decreased from 100% in fatty breasts to 45% in extremely dense breasts.

Mammographic sensitivity was highest for invasive ductal carcinoma (IDC) in 81% of cases versus 34% of cases of invasive lobular carcinoma (ILC) ($p<0.001$) and 55% in ductal carcinoma in situ (DCIS) ($p<0.01$).

US showed higher sensitivity than mammography in IDC depicting 94% of cases, and for ILC 86% of cases ($p<0.01$) and DCIS respectively, 47% ($p<0.01$).

MR showed higher sensitivity than mammography for all tumour types ($p<0.01$) and higher sensitivity than US for DCIS – 89% of cases ($p<0.01$) and depicting 95% cases of IDC and 96% of ILC cases.

In anticipation of BCT or no surgery after mammography and clinical examination in 96 breasts, additional tumour was found in 30, which altered surgical approach.

Additional tumour was detected in 18% of breasts by US and 30 at MR. Extent was overestimated in 12% at US and 29% at MR.

Combined mammography, clinical examination, US, and MR detected additional tumour in 12% breasts and led to an overestimation of extent in 6%.

US showed no detection benefit after MR imaging.

Diagnostic performance in 258 proven lesions (177 malignancies and 81 benign lesions)

Modality	Sensitivity	Specificity	Positive predictive value	Accuracy
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Mammography	120/177 (67.8%)	61/81 (75%)	120/140 (85.7%)	181/258 (70.2%)
MMG and clinical examination	137/177 (77.4%)	58/81 (72%)	173/160 (85.6%)	195/258 (75.6%)
Clinical examination	89/177 (50.3%)	75/81 (92%)	89/95 (94%)	164/258 (63.6%)
US	147/177 (83.0%)	28/81 (34%)	147/200 (73.5%)	175/258 (67.8%)
MMG and US	162/177 (91.5%)	19/81 (23%)	162/244 (72.3%)	181/258 (70.2%)
MMG, clinical examination and US	165/177 (93.2%)	18/81 (22%)	165/228 (72.4%)	183/258 (70.9%)
MR imaging	167/177 (94.4%)	21/81 (26%)	167/227 (73.6%)	188/258 (72.9%)
MMG, clinical examination and MR	176/177 (99.4%)	6/81 (7%)	176/251 (70.1%)	182/258 (70.5%)

Summary of malignant Foci according to method of depiction and tumour type

Diagnosis and Modality	True positive	Negative at MMG	Negative at CE	Negative at US	Negative at MR
IDC (n=110)		21	37	6	5
Mammography	81%	n/a	68%	50%	80%
Clinical examination	66%	38%	n/a	17%	40%
US	94%	86%	86%	n/a	40%
MR imaging	95%	95%	92%	50%	n/a
ILC (n=29)		19	21	4	1
Mammography	34%	n/a	29%	n/a	n/a
Clinical examination	28%	21%	n/a	n/a	n/a
US	86%	79%	81%	n/a	n/a
MR imaging	97%	95%	95%	75%	n/a
DCIS (n=38)		17	30	20	4
Mammography	55%	n/a	57%	60%	100%
Clinical examination	21%	24%	n/a	10%	n/a
US	47%	53%	40%	n/a	25%
MR imaging	89%	100%	83%	85%	n/a

Evaluation of Disease Extent with Invasive Ductal Cancer for which BCT was planned

Modality	Accuracy	Negative	Foci missed	Size underest.	Foci overest.	Size overest.
Mammography	56%	12%	18%	6%	1%	3%
MMG and clinical examination	67%	8%	14%	3%	1%	3%
US	74%	6%	6%	3%	4%	n/a
MMG, clinical examination and US	76%	3%	4%	1%	6%	3%
MR imaging	85%	4%	n/a	n/a	8%	3%
MMG, clinical examination and MR	86%	n/a	n/a	n/a	8%	6%

All modalities combined	86%	n/a	n/a	n/a	8%	6%
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Evaluation of Disease with Invasive Lobular Carcinoma for which BCT was planned

Modality	Accuracy	Negative	Foci missed	Size underest.	Foci overest.	Size overest.
Mammography	42%	33%	25%	n/a	n/a	n/a
MMG and clinical examination	42%	17%	42%	n/a	n/a	n/a
US	67%	n/a	17%	n/a	17%	n/a
MMG, clinical examination and US	67%	n/a	17%	n/a	17%	n/a
MR imaging	58%	n/a	8%	n/a	33%	n/a
MMG, clinical examination and MR	58%	n/a	8%	n/a	33%	n/a
All modalities combined	58%	n/a	8%	n/a	33v	n/a

Evaluation of Disease with DCIS for which BCT was planned

Modality	Accuracy	Negative	Foci missed	Size underest.	Foci overest.	Size overest.
Mammography	50%	33%	8%	8%	n/a	n/a
MMG and clinical examination	83%	n/a	8%	8%	n/a	n/a
US	33%	33%	n/a	n/a	33%	n/a
MMG, clinical examination and US	75%	n/a	n/a	n/a	33%	n/a
MR imaging	42%	8%	n/a	n/a	42%	8%
MMG, clinical examination and MR	50%	n/a	n/a	n/a	42%	8%
All modalities combined	50%	n/a	n/a	n/a	42%	8%

General comments

Fischer, U., Zachariae, O, Baum, F., von Heyden, D., Funke, M., Liersch. The Influence of Preoperative MRI of the Breasts on Recurrence Rate in Patients with Breast Cancer. Eur. Radiol. 14: 1725-1731, 2004

Design: Retrospective Cohort Study Evidence Level 2++

Country: Germany

Setting: Hospital

Inclusion criteria: patients with histologically verified breast cancer; age >18, <78, interval between imaging and surgery <4 weeks; histopathology verified R0 resection with tumour free section ≥1 mm; standardised surgical approach; standardised adjuvant radiation therapy after BCT and adjuvant systemic therapy (hormonal/chemotherapy)

Exclusion criteria: haematogenous metastases of the breast carcinoma; other concomitant diseases; incomplete data

Population: 346 patients:

Arm A – n = 121 - patients (124 lesions) with preoperative contrast-enhanced MRI before surgery

Arm B – n = 225- patients (227 lesions) without preoperative MRI before surgery

Characteristics	Arm A	Arm B
Mean age	55.2 (27-74)	57.1(29-77)
Histology		
IDC	69.4%	75.3%
IL	9.7%	10.6%
DCIS	12.1%	3.5%
Other entities	8.8%	10.6%
Lymph nodes		
Negative	61.2%	54.2%
Positive	38.8%	45.8%
Tumour size		
pT1	63.3%	47.6%
pT2	28.9%	32.0%
pT3/4		20.4%
Grading		
G1	4.0%	2.6%
G2	79.0%	63.9%
G3	12.9%	27.8%
G4	4.0%	5.7%

Interventions: evaluate the benefit of preoperative MRI

Outcomes: in-breast tumour recurrence rate; contralateral carcinoma detected;

Results: There is good evidence that preoperative MR of the breast is recommended in patients with histopathologically verified breast cancer, for local staging. The in-breast tumour recurrence is significantly higher (p<0.001) in women with BCT and no staging with MRI. All cases had a conformity of histology and tumour localisation between primary index and tumour recurrence. Metachronous contralateral carcinoma has occurred significantly more in patients without pre-operative MRI staging. Tumour recurrence was detected

between 6 and 45 months after surgical treatment. Contralateral cancer was detected 14 to 52 months after surgical treatment.

Recurrence rate and treatment modality	Arm A	Arm B
Number of patients with BCT	71.1%	62.3%
In breast tumour relapse	1%	6.5%
Number of patients with ME	28.9%	38.7%
Contralateral breast cancer within follow-up	1.7%	4.0%

General comments

Hidetake Yabuuchi, Toshiro Kuroiwa, Chie Kusumoto, Tatsuro Fukuya, Shinji Ohno, Yoichi Hachitanda; Incidentally Detected Lesions on Contrast-Enhanced MR Imaging in Candidates for Breast-Conserving Therapy: Correlation Between MR Findings and Histological Diagnosis; Journal of Magnetic Resonance Imaging, 23:486-492 (2006)

Design: Retrospective Cohort Study Evidence Level 2++

Country: International

Setting: Hospital

Inclusion criteria: A cohort of MR images of 299 female breast cancer patients between June 2000 and September 2002 in which the maximum diameter was equal to or less than 4cm without a wide ductal spread and/or multicentric cancers on mammography and conventional US.

Exclusion criteria: Lesions smaller than 3mm in maximum diameter, because such small lesions were less likely to be detected, even on repeat US. Multiple lesions diffusely distributed in the entire breast, because these are frequently seen in patients with fibrocystic changes or hormonal changes.

Population: Incidentally detected lesions 59 (20%); Histological diagnosis obtained in 48/59 (81%). Ages ranged from 27 to 77 years (mean 59 years)

Histologic Type of the Main Lesion	N = 48
Invasive ductal carcinoma	41
Ductal carcinoma in situ (DCIS)	3
Mucinous carcinoma	2
Invasive lobular carcinoma	1
Malignant phyllodes tumour	1

Interventions: Investigate the correlation between MR findings and the histological diagnosis of incidentally detected lesions in candidates for Breast Conserving Therapy (BCT)

Outcomes: MRI Characteristics of Incidentally Detected Lesions; Sensitivity and specificity of combination of size, enhancement and quadrant.

Results: Incidentally detected lesions that are found in a different quadrant from the main lesion, are smaller than 10 mm in diameter, and show persistent enhancement on MR imaging suggest benign lesions. Therefore, patients with such lesions should avoid unnecessary surgical procedures unless lesions are proved to be malignant by cytology or biopsy.

Lesions of over 10 mm tended to be malignant (11/16 ; 69%), whereas those equal or less than 5 mm tended to be benign (17.5; 71%; $P < 0.05$). Lesions in the same quadrant as the main lesion tended to be malignant (20/27.5; 73%), whereas those in a different quadrant tended to be benign (17.5/20.5; 85%; $P < 0.001$). Lesions with early peak of enhancement tended to be malignant (20/25; 80%), whereas those with persistent enhancement tended to be benign (20/23; 87%; $P < 0.001$).

Combination of size, enhancement and quadrant	Ratio of benignancy	Ratio of malignancy
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Different quadrant and persistent enhancement	12.5/13.5 (93%)	1/13.5 (7%)*
Different quadrant and early peak enhancement	5/7 (71%)	2/7 (29%)
Same quadrant and early peak enhancement	0/18 (0%)	18/18 (100%)*
Same quadrant and persistent enhancement	7/9 (78%)	2/9 (22%)
Different quadrant and size 3-5 mm	8/8 (100%)	0/8 (0%)*
Different quadrant and size over 10 mm	4.5/7.5 (60%)	3/7.5 (40%)
Same quadrant and size 3-5 mm	4/10 (40%)	6/10 (60%)
Same quadrant and size over 10 mm	0/8 (0%)	8/8 (100%)*
Early peak enhancement and size 3-5 mm	2/6 (23%)	4/6 (67%)
Early peak enhancement and size over 10 mm	1/11.5 (9%)	10.5/11.5 (91%)*
Persistent enhancement and size 3-5 mm	10/11 (91%)	1/11 (9%)*
Persistent enhancement and size over 10 mm	3/4 (75%)	1/4 (25%)
Same quadrant only	7.5/27.5 (27%)	20/27.5 (73%)
Different quadrant only	17.5/20.5 (85%)	3/20.5 (15%)
Early peak enhancement only	5/25 (20%)	20/25 (80%)
Persistent enhancement only	20/23 (87%)	3/23 (13%)
Size of 3-5 mm only	12/17 (71%)	5/17 (29%)
Size of over 10 mm only	5/16 (31%)	11/16 (69%)

*Combinations showing good sensitivity or specificity which are over 90%

<u>MRI Characteristics of Incidentally Detected Lesions</u>		<u>Benign</u> <u>N = 25</u>	<u>Malignant</u> <u>N = 23</u>	<u>P Value</u>
<u>Number</u>	1	17	16	0.92
	2	7	6	
	3	1	1	
<u>Size (mm)</u>	3-5	12	5	< 0.05
	6-9	8	7	
	≥10	5	11	
<u>Morphology</u>	Focus/foci	10	3	0.0824
	Mass	15	20	
<u>Shape</u>	Round	14	18	0.863
	Oval	1	1	
	Lobular	0	0	
	Irregular	0	0	
<u>Margin</u>	Smooth	15	14	0.053
	Irregular	0	5	
<u>Mass Enhancement</u>	Homogeneous	14	18	0.853
	Heterogeneous	1	0	
	Rim enhancement	0	1	
	Dark internal septation	0	0	

	Central enhancement	0	0	
Non-mass like Enhancement		0	1	
Distribution Modifiers	Focal area	0	0	
	Linear	0	1	
	Ductal	0	0	
	Segmental	0	0	
	Regional	0	0	
	Multiple regions	0	0	
	Diffuse	0	0	
Quadrant	Same	7.5	20	< 0.001
	Different	17.5	3	
Kinetic Curve Assessment	Persistent	20	3	< 0.001
	Plateau/Washout	5	20	
General comments				

Blair, S., McElroy, M., Middleton, M.S., Comstock, C., Wolfson, T., Kamrava, M., Wallace, A., Mortimer, J., "The Efficacy of Breast MRI in Predicting Breast Conservation Therapy", Journal of Surgical Oncology, No.94, pp220-225, 2006

Design: Retrospective Cohort Study Evidence Level 2++

Country: USA

Setting: Hospital

Inclusion criteria: Patients with early breast cancer, identified through routine imaging mammogram or ultrasound or were palpable on physical exam and had pathological assessment of tumour specimens, who underwent bilateral breast MRI and subsequent definitive surgical treatment

Exclusion criteria:

Population

115 consecutive patients, high-grade tumours n=40, low-grade tumours n=75

Clinicopathologic Feature	Incidence	
Age	Mean 52 years	(Range 31-78 yrs)
Menopausal Status	64 (56%) pre-menopausal	51 (44%) post-menopausal
Grade	40 (35%) high	75 (65%) low
ER/PR	64 (56%) positive	51 (44%) negative
Her 2 neu	11 (10%) positive	104 (90%) negative
Histology	108 (94%) ductal	7 (6%) lobular

Reasons for MRI:	N = 85
Evaluation of lobular carcinoma	6
Part of a Protocol for Neoadjuvant therapy	26
Indeterminate findings on mammogram	53

Interventions: MRI breast

Outcomes: Correlation of breast MRI and pathology

Results: There is good evidence that Breast MRI does change surgical management by detecting additional malignancies. Breast MRI is accurate in staging extent of disease in the breast in patients with High-grade (HG) tumours. The size of the tumour on MRI correlated with the pathologic size for HG tumours (HG R=0.76 vs. LG R=0.45, P=0.033). Mastectomy was performed in 53 patients. In 10 patients with LG tumours, the MRI findings overestimated their disease. In 11 out of 115 patients, the primary tumour or a second tumour was only seen by MRI.

Correlation of Breast MRI and Pathology		Spearman rho	P=Value
Measurement of tumour on MRI and Pathologic of total amount of tumour		0.51	>0.001
Size by MRI and total tumour size	Previous	0.50	0.005

	Chemotherapy		
	Previous Excision	0.53	0.003
Pre-operative MRI measurement and pathologic measurement	HG tumours	0.73	<0.0001

Reasons for Mastectomy: Positive predictive value of 47%

Patient Reasons	N = 19	Imaging Reasons	N = 34
Patient choice	8	Residual disease on MRI after excision	3
Family history	3	Multi-centric disease on MRI	8
Inflammatory breast cancer	2	Large area disease on mammogram and MRI	13
Cancer recurrence after BCT	4	Large area disease on MRI alone	10
Positive margins after multiple lumpectomy	2	MRI corrected estimated disease	11
		MRI overestimated disease	10

Correlation of Pre-operative MRI Measurement of Tumour and Pathologic Measurement in the Literature:

Author	N =	Reason for MRI	Correlation Coefficient	P-value
Hata et al. [14]	54	Ductal spread of early stage cancer	0.42	0.001
Partridge et al. [10]	52	Neoadjuvant chemotherapy	0.89	0.001
Thibault et al. [8]	30	Neoadjuvant chemotherapy	0.79	0.01
Blair et al. (present series)	40	High-grade tumours	0.73	0.001
Blair et al. (present series)	115	All tumours	0.51	0.05

General comments

Sundararajan, S., Tohno, E., Kamma, H., Ueno, E., Minami, M. Detection of Intraductal Component around Invasive Breast Cancer Using Ultrasound: Correlation with MRI and Histopathological Findings. Radiation Medicine, Vol. 24, No. 2, pp. 108-114, 2006

Design: Retrospective Cohort Study Evidence Level 2++
Country: Japan
Setting: Hospital

Inclusion criteria: Patients with invasive breast cancer, with Intraductal component identified through fine needle aspiration or core biopsy, mammography (and ultrasonography (US))

Exclusion criteria: DCIS and non-mass forming tumours

Population: 47 patients with invasive breast cancer who had undergone a complete US examination for Intraductal component and mass-forming tumours. Age range: 29 to 81 (median age 52 years), T1 (n=27) T2 (n=20)

Interventions: Pre-operative Breast MRI

Outcomes: Efficacy of US in the detection of Intraductal component in comparison with MRI and histopathological findings

Results: There is good evidence that US examination depicted the Intraductal component of breast cancer more accurately than MRI. However, when US and MRI were used to diagnose the Intraductal component the results correlated well with histopathological findings.

Sensitivity, Specificity and Accuracy were 57.1%, 84.2% and 78.7% respectively for US and 50%, 89.5% and 65.9% for MRI. When both US and MRI were used Sensitivity, Specificity and Accuracy were 75%, 84.2% and 78.7% respectively.

Histopathological classification (HP) of Intraductal component and correlation with US and MRI

		HP		
		Wide >15 mm	Moderate 6-15mm	Minimal 0-5 mm
US	Wide	16	0	3
	Moderate	8	2	7
	Minimal	4	0	7
		HP		
		Wide >15 mm	Moderate 6-15mm	Minimal 0-5 mm
MRI	Wide	14	0	2
	Moderate	6	1	1
	Minimal	8	1	14

Histopathological classification (HP) of Intraductal component and correlation with US + MRI

		HP		
		Wide >15 mm	Moderate 6-15mm	Minimal 0-5 mm
<u>US+</u> <u>MRI</u>	Wide	21	0	3
	Moderate	5	2	7
	Minimal	2	0	7
General comments				

Schelfout, K., Van Goethem, M., Kersschot, E., Colpaert, C., Schelfout, A.M., Leyman, P., Verslegers, I., Biltjes, I., Van Den Haute, J., Gillardin, J.P., Tjalma, W., Van der Auera, J.C., Buytaert, P., De Schepper, A. Contrast –enhanced MR Imaging of Breast Lesions and Effect on Treatment. The Journal of Cancer Surgery, EJSO, :30, 501-507, 2004

Design: Prospective Case Control Study Evidence Level 2++

Country: Belgium

Setting: Hospital

Inclusion criteria: women under 80 years old, with a suspect breast lesion found on clinical examination (CE) and/or Mammography (MX) and/or ultrasonography (US) and if biopsy was indicated.

Exclusion criteria:

Population 204 consecutive women, age range 21-79 (mean 56.6 years)

pathological examination	invasive cancers	215
	pure DCIS foci	41
	benign lesions	76
positive family history		61%
positive histopathological examination		170
lesions detected on CE and/or MX and/or US and/or MRI:		332
	positive on CE (invasive +DCIS)	139
	positive on MX	173
	positive on US	160
	positive on MRI	247
index lesions	invasive carcinoma	204
	low grade	72
	intermediate grade	41
	high grade	34
	pure DCIS	20
	low grade	4
	intermediate grade	3
	high grade	13
	benign lesion	37
malignant lesions	palpable	123
	detected on MX	149
	detected on US	133
	detected on MRI	161
	MRI only (additional foci)	55

Interventions: MRI breast

Outcomes: Sensitivity of MRI vs. MX; Correlation; Effect on staging; Changes in therapeutic strategy.

Results: There is good evidence that pre-operative MRI is an important adjunct to conventional imaging in loco-regional staging of breast cancer and a useful tool in treatment planning. In 170 patients MRI detected 96% of multifocal disease and 95% of multicentric disease, whereas MX detected 37% and 18% respectively and US detected 41% and 9% respectively. All bilateral breast cancers were seen on MRI. Both MX and US detected 56%. Findings of more extensive disease and unsuspected multiple foci were identified on MRI only. Additional malignant foci detected on MRI identified unsuspected multifocal, multicentric or bilateral breast cancer resulting in necessary changes in therapeutic strategy (60 of the 204 patients). Nine unnecessary wider excisions and 3 unnecessary FNA/core biopsies were performed because of MRI overestimation of number or size of malignant lesions. Correlation between histopathology and MRI was far better than MX and US, in diameter of malignant lesions. The PPV was best for MRI (R^2 : 0.56). The predictions of MX and US were similar (0.37 and 0.35 respectively).

Additional lesions and subgroup characterisation:

Multifocal (MF), multicentric (MC) and bilateral (Bil) breast cancer;
 Histopathologic diagnosis (HPD), mammography (MX), ultrasound (US), magnetic resonance imaging (MRI)

	HPD	MX	US	MRI
MF	27	10	11	26
MC	22	4	2	21
Bil	9	5	5	9

Women with additional lesions detected on MRI only:

	Subpopulation (n=33)	Total study population (n=204)
Age	32-78 (mean 54 years)	21-79 (mean 56.6 years)
Family history positive	13	61
Breast density on MX	1 D1, 8 D2, 13 D3, 11D4	9 D1, 77 D2, 77 D3, 41 D4
(Diameter) index lesion	31 mm	25 mm
Grade of index IDC	10 LG, 6 IG, 16 HG	72 LG, 41 IG, 34 HG
Grade of index DCIS	1HG	4 LG, 3 IG, 13 HG
Index IDC+DCIS, EIC+	26, 9	104, 33

Therapeutic changes after breast MRI:

	Necessary	Unnecessary
Wider Excision	24	9
Extra FNA/core biopsy, same quadrant	0	1
Extra open biopsy, same quadrant	2	0
Extra FNA/core biopsy, different quadrant	0	1
Extra open biopsy, different quadrant	4	0
Extra FNA/core biopsy, different breast	0	1
Extra open biopsy, different breast	4	0
Mastectomy	18	0
Total	52	12

General comments

Sardanelli, F., Giuseppetti, G.M., Panizza, P., Bazzocchi, M., Lattanzio, V., Del Maschio, A., Sensitivity of MRI versus Mammography for Detecting Foci of Multifocal, Multicentric Breast Cancer in the Fatty and Dense Breasts using the Whole-Breast Pathologic Examination as a Gold Standard. AJR:183, 2004

Design: Prospective Case Control Study Evidence Level 2++

Country: Italy

Setting: Hospital

Inclusion criteria: Patients over 18 years old, with proven breast cancer and a planned mastectomy.

Exclusion criteria: Absolute contraindications to MRI, pregnancy or breast feeding, severe renal failure, known hypersensitivity to gadolinium chelates, inclusion in other clinical trials, clinical status that would limit data reliability.

Population: 90 patients, mean age 58.6± 16.1, including nine bilateral synchronous breast cancers, with complete mammographic, MRI and pathologic correlation

Pathologic type

Pathologic findings			Diameter Dimension (mm) of Lesion											
Type	No	%	Median	Mean±SD	<5		5-10		10-20		>20		Not assessed	
					No	%	No	%	No	%	No	%	No	%
Invasive	158	84	18.0	21.8±17.8	9	6	22	14	47	30	70	44	10	6
IDC	91	48.4	17.5	22.8±20.6	6	7	13	14	28	31	41	45	3	3
ILC	28	14.9	12.0	15.7±10.5	2	7	5	18	9	32	8	29	4	14
IDC+DCIS	18	9.6	22.5	23.3±14.8	1	6	2	11	5	28	10	56	0	0
IDC+ILC	9	4.8	30.0	24.3±9.9	0	0	1	11	2	22	6	67	0	0
Other	12	6.4	17.5	21.1±15.4	0	0	1	8	3	25	5	42	3	25
In situ	30	16	5.0	8.8±9.2	5	17	7	23	3	10	2	7	13	43
DCIS	26	13.8	5.5	9.3±9.3	4	15	7	27	3	12	2	8	10	38
LCIS	3	1.6	-	-	1	33	0	0	0	0	0	0	2	67
DCIS+LCIS	1	0.5	-	-	0	0	0	0	0	0	0	0	1	100
Total	188	100	16.0	20.4±17.5	14	8	29	15	50	27	72	38	23	12

Interventions: MRI breast

Outcomes: Correlation of breast MRI and pathology; Sensitivity of MRI versus Mammography

Results: There is good evidence that Breast MRI is more sensitive than mammography (MMG) for the detection of multiple malignant foci in fibroglandular or dense breast. Mammography missed larger and more invasive cancer foci than MRI. A relative low PPV is a problem for both techniques. Of 99 breasts , pathologic findings revealed 52 unifocal, 29 multifocal and 18 multicentric cancers for a total of 188 malignant foci (158 invasive and 30 in situ).

Overall sensitivity was 66% (124/188) for mammography and 81% (152/188) for MRI (p< 0.001) in favour of MRI

Sensitivity for invasive foci was 72% for mammography and 89 % for MRI (p< 0.001) in favour of MRI

Sensitivity for in situ foci was 37% for mammography and 40 % for MRI (p>0.05) no significant difference

Malignant foci missed by mammography: 64; MRI 36, with median diameters of 8 mm for MMG and 5 mm for MRI (p=0.033) in favour of MRI

Overall Positive Predictive Value (PPV) was 76% for MMG and 68% for MRI, not significant.

In breasts with fatty patterns sensitivity was 75% for MMG and 80% for MRI, not significant; PPV 75% and 65% respectively, not significant.

In breasts with fibroglandular or dense patterns sensitivity was 60% for MMG and 81% for MRI, (p<0.001) in favour of MRI and PPV was 78% and 71% respectively, not significant.

Focus by focus analysis of diagnostic performance of Mammography and dynamic MRI in Pathology controlled study (n=99 breasts)

Features	Mamography	MRI	p
True-positive	124	152	-
False-negative	64	36	-
Overall sensitivity	66% (124/188)	81% (152/188)	<0.001
Sensitivity for invasive foci	72% (113/158)	89% (140/158)	<0.001
Sensitivity for in situ foci	37% (11/30)	40% (12/30)	NS
Invasive/non-invasive ratio of false negativity	2.4 (45/19)	1.0 (18/18)	0..43
Diameter of false negative (mm)			
Mean ± SD	10.9±18.2	5.6 ± 4.5	0.033
Median	8.0	5.0	-
Range	0.5-13.0	0.5-15.0	-
False positive	40	70	-
Positive predictive value	76% (124/164)	68% (152/222)	NS

Pathologic type of malignant foci missed in Mammography and dynamic MRI in Pathology controlled study (n=99 breasts)

Pathologic type	MMG	MRI
Invasive	45	18
IDC	20	8
ILC	17	7
IDC+ILC	5	1
Other	3	2
In situ	19	18
DCIS	17	16
LCIS	2	2
Total	64	36

Concordant and Discordant Results between Mammography and dynamic MRI in Detecting 188 malignant foci (n=99 breasts)

Cases	No.	%
True-positive on both MMG and MRI	121	64
True-positive on MMG and false-negative on MRI	3	2
False-negative on MMG and true-positive on MRI	31	16
False-negative on both MMG and MRI	33	18
Total	188	100

Sensitivity and Positive Predictive Value of MMG and MRI in Detecting 188 malignant foci (n=99 breasts) for different patterns on MMG

Statistics	Fatty Breasts			Scattered fibroglandular, Heterogeneously Dense and Extremely Dense Patterns			Total		
	MMG	MRI	p	MMG	MRI	p	MMG	MRI	p
Sensitivity	75% (56/75)	80% (60/75)	N S	60% (68/113)	81% (92/113)	<0.001	66% (124/188)	81% (152/188)	<0.001
PPV	73% (56/77)	65% (60/92)	N S	78% (68/87)	71% (92/130)	NS	76% (124/164)	68% (152/222)	NS

Sensitivity and Positive Predictive Value of MMG and MRI in Detecting 188 malignant foci (n=99 breasts) for different patterns on MMG

Type	Total	Mammography			MRI		
		Under	Correct	Over	Under	Correct	Over
Unifocal	52	1 (2%)	40 (77%)	11 (21%)	0 (0%)	35 (67%)	17 (33%)
Multifocal	29	14 (48%)	9 (31%)	6 (21%)	12 (41%)	9 (31%)	8 (28%)
Multicentric	18	15 (83%)	1 (6%)	2 (11%)	7 (39%)	6 (33%)	5 (28%)
Total	99	30 (30%)	50 (51%)	19 (19%)	19 (19%)	50 (51%)	30 (30%)

General comments

Kepple, J., Layeeque, R., Klimberg, S., Harms, S., Siegel, E., Korourian, S., Gusmano, F., Henry-Tillman, R.S. Correlation of magnetic resonance imaging and pathologic size of infiltrating lobular carcinoma of the breast. The American Journal of Surgery, 190: 623-627, 2005

Design: Retrospective Case Control Study Evidence Level 2++

Country: USA

Setting: Hospital

Inclusion criteria: patients evaluated for ILC prior to definitive treatment

Exclusion criteria:

Population: 29 patients, median age 62 years

Tumour size

Lymph node

	n=	%	Negative	21/28	75%
T1	15	52%	Positive	7/28	14%
T2	7	24%			
T3	5	17%			
T4	2	7%			

Interventions: determining the accuracy of gadolinium enhanced MRI in delineating the extent of ILC, verified by pathologic size

Outcomes: MRI accuracy

Results: There is good evidence that MRI provided superior correlation between tumour size and pathology (Spearman correlation coefficient between tumour size on ultrasound and MRI with pathology was .19 ($p=.5$) and .88 ($p<0.001$) respectively.

<u>Mammography</u>		<u>Ultrasound</u>		<u>MRI</u>		
Normal mammograms	41%	Lesion identified	64%	Multifocal Ipsilateral	10%	
Architectural distortions	28%	Mean tumour size	1.52±.79	Contralateral biopsy	14	
Masses	24%	Normal ultrasound	36%			
Microcalcifications	7%	(false negatives)				
<u>Intervention prompted by MRI</u>			<u>Correlation – tumour size</u>			
Mastectomies		52%	Ultrasound/pathology	.19	$p=.5$	
Lumpectomies		48%	MRI/pathology	.88	$p<0.001$	
Mastectomy for positive margins		7%				
Re-excision for positive margins		3%				
False negative		1				

MRI						
General comments						

Chung, A., Saouaf, R., Scharre, K., Phillips, E.; The Impact of MRI on the Treatment of DCIS; The American Surgeon; Vol 71, Issue 9; pp 705-710; 2005

Design: Retrospective Case Control Study Evidence Level 2+

Country: USA

Setting: Hospital

Inclusion criteria: Diagnosis of Breast Cancer with some component of DCIS patients who underwent breast MRI at various points during their clinical management

Exclusion criteria:

Population: 54 patients - Mean age 53 (range 38-73 years)

Patient Tumour Characteristics	N=		N=
Histopathology	100% DCIS	28	Tumour Size* Tis 28
	IDC + DCIS	22	<1 cm 10
	ILC + DCIS	4	1-3 cm 8
			>3 cm 10
LN Disease	Yes	9	T1 16
	No	17	T2 9
	n/a	28	T3 1
			T4 0

Interventions: Comparison of change in management in patients with pure DCIS and DCIS with invasive cancer

Outcomes: Change in management

Results: MRI has been shown to detect occult invasive breast cancers with the sensitivity of 97%-100%. Mammography and ultrasonography does not accurately assess the extent of DCIS which results in a high re-operation rate. Breast MRI can improve surgical planning in women with DCIS, improving the adequacy of initial treatment while reducing re-operation. In the study of 54 patients with predominantly DCIS, MRI altered surgical management in 26% of patients; unilateral changed to bilateral mastectomy (5); lumpectomy or re-excision to mastectomy (3); unilateral lumpectomy or mastectomy had additional biopsies for lesions in the ipsilateral or contralateral breast (6).

There were 8 true-positives and 7 false-positives; sensitivity 86%, PPV 84%; MRI changed the surgical management to more appropriate therapy in 15% of patients, avoiding additional surgery while 11% underwent negative surgical interventions.

Change in Management in Patients with Planned Local Excision (n=28)

	n	%	True +ve	False +ve
No change	16	57	-	?
Mastectomy	3	11	3	0
B. mastectomy	2	7	2	0

Ipsilateral Biopsy	2	7	2	0
Contralateral Biopsy	2	7	1	1

Change in Management in Patients with Planned Mastectomy (n=16)

	n	%	True +ve	False +ve
No change	11	69	-	?
B. mastectomy	3	19	0	3
Contralateral Biopsy	2	13	0	2

Comparison of Change in Management (%) in Patients with Pure DCIS and DCIS with Invasive Cancer

	Affected	Not Affected
Pure DCIS	25	75
Invasive + DCIS	27	73

General comments

Bagley, F.H., The Role of Magnetic Resonance Imaging Mammography in the Surgical Management of the Index Breast Cancer; Arch Surg, Vol 139, pp 380-383, (2004)

Design: Retrospective Case Series Evidence Level 3

Country: USA

Setting: Hospital

Inclusion criteria: Patients with breast cancer who underwent prebiopsy or preoperative MRI mammography

Exclusion criteria:

Population: 27 patients, age not reported

Interventions: Surgical management of breast cancer

Outcomes: Change in surgical management prompted by findings on MRI mammography

Results: There is good evidence that patients who desire Breast Conserving Therapy (BCT) should undergo MRI mammography before biopsy of a category 4/5 mammogram or immediately after a positive FNA biopsy result of a palpable mass.

Prebiopsy or preoperative MRI mammography changed surgical management in 13/27 (48%) patients with breast cancer by discovering multicentric cancers or more extensive cancer. 9/27 patients with positive FNA biopsy results of palpable masses underwent preoperative MRI; 6/9 patients ipsilateral multicentric cancers or more extensive cancer was discovered that necessitated mastectomy rather than breast conservation. 18/27 patients had a category 4/5 mammograms. 10 of these patients had stereotactic biopsies followed by MRI; 4/10 had changes on the MRIs that required mastectomy rather than breast conservation. 8/27 patients had MRI before stereotactic biopsy; 3/8 patients had MRI abnormalities that required mastectomy. One patient had contralateral, multicentric cancers not seen on conventional mammography, necessitating bilateral mastectomies.

Ability of MRI to Detect Multicentricity Compared with the Single Index Cancer, and to Predict Size, Compared with Mammography and/or Clinical Examination

Group	No. of Patients	No. of Patients		
		Multicentricity	Increased Size	Agreement
Positive FNA	9	3	3	3
Positive stereotactic biopsy	10	2	2	6
Category 4/5 mammogram	8	1	2	5
Total	27	6	7	14

Accuracy of MR Imaging Compared with Pathological Findings

	Multicentricity Cancers	No. of	Larger Cancer than Mammogram or Examination, No. of

Group	Cancers			
	MR Imaging Predicted	Pathologically Confirmed	MR Imaging Predicted	Pathologically Confirmed
Positive FNA	8	8	6	6
Positive stereotactic biopsy	4	4	8	8
Category 4/5 mammogram	2	2	7	4
Total	14	14	21	18

General comments: Confounders not accounted for as there is no report on Age, HRT, Menopause, etc.

Kneeshaw, P.J., Turnbull, L.W., Smith, A., Drew, P.J. Dynamic Contrast-Enhanced Magnetic Resonance Imaging Aids the Surgical Management of Invasive Lobular Breast Cancer. European Journal of Surgical Oncology, 29:32-37, 2003

Design: Retrospective Case Series Evidence Level 3
Country: UK
Setting: Hospital

Inclusion criteria: patients with ILC form the BASO database who had undergone triple assessment and had the size of tumour and multifocality recorded according to mammogram, ultrasound and clinical examination and has undergone MRI. Final histological diagnosis and tumour diameter was obtained form the histology report.

Exclusion criteria:

Population: 21 patients with ILC , mean age 57 years (range 43-72 years).
 12 patients had concurrent LCIS
 4 patients had concurrent DCIS
 No other characteristics reported

Interventions: evaluating the efficacy of current imaging modalities compared with MRI in the evaluation of ILC

Outcomes: correlation of tumour size and detection sensitivity between modalities, altered surgical management

Results: There is some evidence that MRI has a higher sensitivity than other imaging modalities and is able to accurately delineate multifocal disease not evident on conventional imaging, and is therefore a useful tool for accurate staging prior to surgery for ILC.

MRI identified all the patients with subsequently histologically proven multifocal disease, with PPV of 100% and NPV of 55.6%. Management was changed in 24% of the cases following MRI.

Sensitivity of each modality the detection of ILC

Sensitivity and specificity of each modality for detection of multifocal ILC

Modality	Sensitivity		Sensitivity	Specificity	PPV	NPV	Accuracy
Clinical assessment	76.2%	MX + US	27.3%	100.0%	100.0%	55.6%	61.9%
Mammography	90.5%	MRI	100.0%	90.0%	91.7%	100.0%	95.2%
Ultrasound	87.5%						
Cytology or core biopsy	85.7%	<u>Comparison of tumour diameter prediction by modalities</u>					
MRI	95.2%			Correlation	p=	R square	
Triple assessment	100.0%	Clinical assessment		0.47	0.103	0.22	
		MX/US		0.93	< 0.001	0.87	
		MRI		0.86	<0.001	0.74	

Fabre Demard, N., Boulet, P., Prat, X., Charra, L., Lesnik, A., Taourel, P.; Breast MRI in Invasive Lobular Carcinoma: Diagnosis and Staging; Editions Francaises de Radiologie; Vol 86; No 9; pp 1027-1034; 2005

Design: Retrospective Case Series Evidence Level 3

Country: France

Setting: Hospital

Inclusion criteria: Surgically treated patient with pure Invasive Lobular Carcinoma (ILC)

Exclusion criteria:

Population: 35 patients, mean age 55 years (range 38-76 years).

Mammographic abnormalities:	Opacity 45%
	Asymmetrical Density 55%

Interventions: Breast MRI

Outcomes: Regional staging

Results: Breast MRI is useful in diagnosis, staging and surgical management of ILC.

Enhancement at MRI was seen for all 35 cancers. It was focal for 24 patients, regional for 10 and diffuse for 1. Malignancy was shown in 33 patients. For 11 patients, the MRI staging was positive finding 8 new cancers.

MRI had an impact on the management of 11 patients (33%). MRI was beneficial in 8 of 11 patients (confirmed original BCT management in 3 cases, conversion to mastectomy in 3 cases, contralateral lumpectomy in 2 cases).MRI caused benign lesions to undergo biopsy in 3 patients (overestimated).

Regional Staging and Impact on Management

Additional Foci	31.5%	
	N=	
Enhancing Focus		
Ipsilateral, same lesion	3	
Ipsilateral, different quadrant	5	
Contralateral	3	
Multifocal Carcinoma	3	Biopsy proven
Multicentric Disease	5	

General comments

Boetes, C., Veltman, J., Van Die, L., Bult, P., Wobbes, T., Barentsz, J, O., The Role of MRI in Invasive Lobular Carcinoma. Breast Cancer Research and Treatment; 86; pp31-37; 2004

Design: Retrospective Case Series Evidence Level 3

Country: Holland

Setting: Hospital

Inclusion criteria: Surgically treated patient with pure Invasive Lobular Carcinoma (ILC), with available pre-operative imaging measurements (MX), US and MRI

Exclusion criteria:

Population: 34 patients, mean age 55 years (range 35-78 years).
Mean tumour size at pathological examination 4.9 cm (range 1 to 15 cm)
Intervention: 26 patients underwent mastectomy : 10 patients had BCT
Axillary lymph node involvement - 56% of patients

Interventions: Retrospectively re-evaluate imaging measurements for tumour detection and size; findings compared with pathology.

Outcomes:

MR detection and measurement of tumour size, compared to MX and US in patients with ILC.

Results: There is some evidence that of the three imaging modalities contrast enhanced MR has the lowest false-negative rate in detecting ILC and has the highest accuracy in measuring the size of the ILC. MR could play a key role in the pre-operative work-up for accurate tumour size determination

	<u>MX</u>	<u>US</u>	<u>MRI</u>
False-negative scores	14%	3%	0%
Underestimated	56%	53%	14%
Correctly estimated	33%	47%	75%
Overestimated	17%	0%	11%

The correlation coefficients for mammography were respectively $r = 0.34$ ($p < 0.05$) and $r = 0.27$ ($p < 0.05$) for both radiologists, for ultrasound $r = 0.24$ ($p < 0.05$) and for MRI $r = 0.81$ ($p < 0.01$).

General comments: Imaging measurements on MX, US and MR vs. pathology measurements are presented in scatter diagrams - any extraction of figures would be highly speculative.

Veltman, J., Boetes, C., Van Die, L., Bult, P., Blickman, J, G., Barentsz, J, O., Mammographic Detection and Staging of Invasive Lobular Carcinoma. Journal of Clinical Imaging; 30; pp94-98; 2006

Design: Retrospective Case Series Evidence Level 3

Country: Holland

Setting: Hospital

Inclusion criteria: Surgically treated patient with pure Invasive Lobular Carcinoma (ILC)

Exclusion criteria:

Population: 42 patients, mean age 64 years (range 44-85 years).
 Mean tumour size at pathological examination 33 mm (range 3-110 mm)
 Intervention: 27 patients underwent mastectomy : 15 patients had BCT
 Staging: T1 - 20 patients; T2 - 13 patients; T3 - 9 patients

Interventions: Evaluate mammography in detecting and staging of ILC.

Outcomes: Evaluate mammography in detecting and staging of ILC.

Results: There is some evidence that mammography alone is not enough in detecting, and especially in the staging of ILC. Differences between Radiologists, proved to be responsible for the non-detections of ILCs on mammography or treatment delay. The understaging of ILC by mammography can have a serious influence on the clinical management of patients with ILC. 35% to 37% were understaged, the largest differences between radiologists were found in the breast imaging reporting and data system (BIRADS) classification and staging performance.

Compared to the pathological findings, Radiologist 1 staged 60% correct, overstaged 3% and understaged 37% in Session A and similar percentages in Session B. Radiologist 2 staged 60% correct, overstaged 5% and understaged 35% in Session A and respectively 52%, 0%, 48% in Session B. Radiologist 1 differed in 17% patients between two sessions, Radiologist 2 in 21%. Intra-observer variation for staging was $k=0.66$ and $k=0.70$, respectively for both Radiologists. The k value for interobserver agreement was 0.46 and 0.65 comparing Sessions A and B. In the BIRADS classification, Radiologist 1 differed in 26% of patients between the two sessions and Radiologist 2 in 21% of patients. Comparing the results of both Radiologists from Session A and B resulted in 29% and 31% differences respectively. The k value for intra-observer variation was 0.42 and 0.68 respectively. Interobserver agreement was $k=0.45$ and 0.50 comparing the BIRADS classification for Sessions A and B respectively.

Staging Results

Tumour Stage		Radiologist 1		Radiologist 2	
	Pathology	Session A	Session B	Session A	Session B
T0	-	1	3	4	5

T1	20	27	29	24	28
T2	13	11	8	11	7
T3	9	1	2	3	2

BIRADS Classification Results

BIRADS Classification	Radiologist 1		Radiologist 2	
	Session A	Session B	Session A	Session B
1	1	3	4	5
3	1	-	4	4
4	31	38	21	17
5	9	11	13	16

General comments

Francis, A., England, D.W., Rowlands, D.C., Wadley, M., Walker, C., Bradley, S.A.. The diagnosis of invasive lobular breast carcinoma. Does MRI have a role? *The Breast*, 10:38-40, 2001

Design: Retrospective Case Series Evidence Level 3

Country: UK

Setting: Hospital

Inclusion criteria: invasive lobular carcinoma diagnosed by core biopsy

Exclusion criteria:

Population: 22 patients, characteristics not reported

Interventions: comparison between clinical, ultrasound scan, mammographic imaging and MRI

Outcomes

Results: There is some evidence that MRI is more accurate than US and clinical examination, both of which underestimated tumour size. MRI and mammography are more accurate in estimating tumour size.

MRI detected 21 of the 22 ILCs while mammography and US detected 16 and 20 respectively. Clinical examination detected 19 tumours.

There was a significant difference in clinical and histological size ($p=0.0038$) with clinical examination underestimating tumour size in 63% of patients.

There was no significant difference between mammographic and histological size ($p=0.3894$).

There was a significant difference between US and histological size ($p=0.0003$), with US underestimating size in 90% of patients.

There was no significant difference between MRI and histological size ($p=0.6288$)

Comparative size (mm) of ILC in 22 patients as estimated by clinical examination (CE), mammography (MX), ultrasonography (US), magnetic resonance imaging (MRI)

	CE	MX	US	MRI	Histology		CE	MX	US	MRI	Histology
1	0	0	0	24	40	12	20	20	12	23	19
2	0	0	24	65	60	13	20	35	21	30	34
3	30	50	32	30	60	14	10	0	10	30	20
4	15	20	10	24	27	15	20	15	11	0	16
5	20	20	17	30	60	16	40	40	40	70	36
6	30	50	50	30	58	17	30	30	25	28	25
7	30	0	24	30	30	18	20	30	25	35	33
8	15	18	10	21	15	19	10	6	12	7	13
9	15	20	15	20	20	20	10	0	6	8	9
10	10	15	10	28	26	21	80	0	0	120	150
11	0	8	4	8	3	22	35	40	8	60	61

General comments: study too small to have statistical power. Population characteristics

(age, tumour stage, etc) not reported.

Schelfout, K., Van Goethem, M., Kersschot, E., Verslegers, I., Biltjes, I., Leyman, P., Colpaert, C., Thienpont, L., Van den Haute, J., Gillardin, J, P., Tjalma, W., Buytaert, Ph., Schepper, A. De., Preoperative Breast MRI in Patients with Invasive Lobular Breast Cancer. Eur Radiol: 14: pp1209-1216, 2004

Design: Retrospective Case Report Evidence Level 3

Country: Belgium

Setting: Hospital

Inclusion criteria: Patients who had been diagnosed with Infiltrative Lobular Carcinoma (ILC) +/- LCIS (Lobular Carcinoma in situ) and who had undergone preoperative MR imaging of the breast and had all original pathology, imaging and clinical examination reports available for review.

Exclusion criteria: Associated ductal carcinoma

Population: 26 women, age range 41-74 (mean 56.9 years)

Interventions: MRI

Outcomes: Use of MRI in preoperative staging of ILC and detection of multifocal/multicentric disease

Results: MRI may play an important role in the evaluation of patients with ILC, which is often difficult to diagnose on clinical examination and conventional imaging and more likely occur in multiple sites and in both breasts. However, false-negative MR findings do occur in a small percentage of ILC. MR findings of unifocal, multifocal, single quadrant and multi quadrant disease were correlated with other imaging techniques and compared with histological findings. Most ILC presented on MRI as a single speculated/irregular, inhomogeneous mass (pattern 1, $n=12$) or as a dominant lesion surrounded by multiple small enhancing foci (pattern 2, $n=8$). Multiple small enhancing foci with interconnecting enhancing strands (pattern 3) and an architectural distortion (pattern 4) were both described in three cases. There was one case of a focal area of inhomogeneous enhancement (pattern 5) and one normal MR examination (pattern 6). Unifocal and multifocal lesions were identified on MRI in four patients with normal conventional imaging. In nine women, multiple additional lesions or more extensive multiquadrant disease were correctly identified only on MRI.

<u>Features of ILC on Clinical Examination, Mammography, US and MRI</u>		Clinical Examination	Mammography	Ultrasound	MRI
	Case 1	Palpable mass	-	-	P4
	Case 2	Skin retraction	-	-	P1
	Case 3	Thickness	-	-	P3
	Case 4	Skin retraction	-	-	P2
	Case 5	Palpable mass	Spiculated mass + m	-	P2
	Case 6	-	Arch dist + m	-	P3
	Case 7	Palpable mass	Spiculated mass	Irreg inh shad	P2
	Case 8	Palpable mass	Arch dist	Irreg inh shad	P2
	Case 9	Thickness	Spiculated mass	Sh without mass	P2
	Case 10	Thickness	Arch dist	-	P5

	Case 11	Palpable mass + col	Asym dens + m	Irreg shad	inh	P2
	Case 12	Palpable mass + sr	Spiculated mass	Irreg shad	inh	P2
Col - colouring of the skin; sr - skin reaction; p - pain; m - microcalcifications; Arch dist - architectural distortion; Asym dens - Asymmetric density; Irreg inh shad - irregular inhomogeneous with shadowing; Sh without mass - shadowing without a distinct mass; lobulated well circ - lobulated well-circumscribed.	Case 13, Lesion 1	Palpable mass + p	Spiculated mass + m	Irreg shad	inh	P3
	Case 13, Lesion 2	-	Microcalcifications	-		
	Case 14	Palpable mass	Spiculated mass	Irreg shad	inh	P2
	Case 15	Palpable mass + p	Arch dist	Irreg shad	inh	P1
	Case 16	-	Asym dens	Irreg shad	inh	P1
	Case 17	-	Arch dist	-		P4
	Case 18	Palpable mass + sr	Spiculated mass	Irreg shad	inh	P1
	Case 19	Palpable mass	Spiculated mass	Irreg shad	inh	P1
	Case 20	Palpable mass	Spiculated mass	Irreg shad	inh	P1
	Case 21	-	Spiculated mass	Irreg shad	inh	P1
	Case 22	Thickness	Arch dist	Sh without mass		P1
	Case 23, Lesion 1	Palpable mass	Arch Dist	Irreg shad	inh	P1
	Case 23, Lesion 2	Palpable mass	Spiculated mass	Irreg shad	inh	P1
	Case 24, Lesion 1	-	Arch Dist	Irreg shad	inh	P4
Case 24, Lesion 2	-	Arch Dist	-		P1	
Case 25	Palpable mass + sr	Arch Dist	Irreg shad	inh	P1	
Case 26	-	Asym dens + m	Lobulated well circ		P6	

<u>Women with unifocal, multifocal, single quadrant and multiquadrant disease</u>		Mammography	Ultrasound	MRI	HPD
	Case 1	-	-	UF/SQ	UF/SQ
	Case 2	-	-	UF/SQ	UF/SQ
	Case 3	-	-	MF/SQ	UF/SQ
	Case 4	-	-	MF/MQ	MF/MQ
	Case 5	UF/SQ	-	MF/SQ	MF/SQ
	Case 6	UF/SQ	-	MF/SQ	MF/SQ
	Case 7	UF/SQ	UF/SQ	MF/SQ	MF/SQ
	Case 8	UF/SQ	UF/SQ	MF/SQ	MF/SQ
	Case 9	UF/SQ	UF/SQ	MF/SQ	MF/SQ
	Case 10	UF/SQ	-	UF/MQ	UF/MQ
	Case 11	UF/SQ	UF/SQ	MF/MQ	MF/MQ

	Case 12	UF/SQ	UF/SQ	MF/MQ	MF/MQ
	Case 13, Lesion 1	MF/SQ	UF/SQ	MF/MQ	MF/MQ
	Case 13, Lesion 2				
	Case 14	UF/SQ	UF/SQ	MF/SQ	UF/SQ
	Case 15	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 16	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 17	UF/SQ	-	UF/SQ	UF/SQ
	Case 18	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 19	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 20	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 21	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 22	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 23, Lesion 1	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 23, Lesion 2	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 24, Lesion 1	MF/SQ	UF/SQ	MF/SQ	MF/SQ
	Case 24, Lesion 2				
	Case 25	UF/SQ	UF/SQ	UF/SQ	UF/SQ
	Case 26	UF/SQ	UF/SQ	-	UF/SQ
UF - Unifocal MF - Multifocal SQ - Single Quadrant MQ - Multicquadrant HPD Histopathological Diagnosis					
General comments					

Kvistad, K.A., Rydland, J., Smethurst, H.-B., Lundgren, S., Fjosne, H.E., Haraldseth, O. Axillary Lymph Node Metastases In Breast Cancer: Preoperative Detection with Dynamic Contrast-Enhanced MRI. *Eur. Radiol*, 10: 1464-1471, 2004

Design: Prospective Case Control Evidence Level 2++

Country: Norway

Setting: Hospital

Inclusion criteria: patients with invasive breast cancer to be treated with axillary node dissection

Exclusion criteria:

Population: 65 patients with level I and II axillary node dissection; mean age 59.4 (range 38-79)

<u>Characteristics</u>	<u>n=</u>	<u>Histology</u>	<u>n=</u>	<u>Tumour staging</u>	<u>n=</u>
Premenopausal	18	Invasive ductal carcinoma	54	T1a	0
Postmenopausal	47	Invasive lobular carcinoma	3	T1b	13
		Mucinous carcinoma	4	T1c	25
Intervention	n=	Tubular carcinoma	2	T2	20
Mastectomy	45	Undifferentiated adenocarcinoma	2	T3 and T4	7
Wide local incision	20				

Interventions: evaluating the value of MRI in axillary node staging

Outcomes: sensitivity, specificity, accuracy

Results: There is good evidence that axillary lymph nodes can be evaluated as a part of an MR-mammography study without substantial increase in examination time, and provide the surgeon with knowledge about the localisation of possible metastatic lymph nodes. Using dynamic contrast enhanced imaging, a 83% sensitivity and a 90% specificity for the presence of lymph node metastases was found with the chosen threshold of abnormal signal intensity increase.

When using a signal intensity increase in the lymph nodes of >100% during the first postcontrast image as a threshold for malignancy, 57/65 patients were correctly classified (sensitivity 83%, specificity 90%, accuracy 88%).

These results were not improved when lymph node size and morphology were used as additional criteria.

When combining enhancement patterns (signal intensity increase) and morphological criteria of the tumour to improve specificity of the method, the sensitivity decreased to 65%, without significant increase in specificity.

Using the size and shape of the axillary lymph nodes in MR images as a criteria correlated poorly to the presence of metastases, with a sensitivity of 63% and a specificity of 80%.

These results are comparable to CT examinations of the axilla but are poorer than the results from ultrasound examination.

Clinical evaluation had a very low sensitivity of 25%, and was found to be an inaccurate method for

detection of axillary lymph nodes metastases.

Axillary lymph nodes showed contrast enhancement in both ALND-positive and ALND- negative patients, but enhancement was stronger and more rapid in patients with metastases, and on average reached a peak value during the first 57s after contrast injection.

Axillary lymph nodes can be evaluated as a part of an MR-mammography study without substantial increase in examination time, and provide the surgeon with knowledge about the localisation of possible metastatic lymph nodes.

Comparison of Results of clinical assessment and MRI of axillary lymph nodes

Parameter	Clinical assessment	Abnormal SI increase	Abnormal SI increase and positive washout sign	Lymph node size >0.5 cm and abnormal morphology	Abnormal SI increase and size >0.5 cm and abnormal morphology
True positive	6	20	17	15	15
True negative	40	37	37	33	38
False positive	1	4	4	8	3
False negative	18	4	7	9	9
Sensitivity (%)	25	83	71	63	63
Specificity (%)	98	90	90	80	93

Results of patients with at least one axillary lymph node corresponding to the assigned short-axis diameters as measured on the MR images and related to the histopathological axillary lymph node (ALND)

	Lymph node size ≤0.5 cm	Lymph node size ≤0.5 cm and ≤1.0 cm	Lymph node size ≤0.5 cm and ≤1.0 cm and abnormal morphology	Lymph node size ≤1.0 cm and ≤2.0 cm	Lymph node size ≤1.0 cm and ≤2.0 cm and abnormal morphology	Lymph node size ≤2.0 cm	Lymph node size ≤2.0 cm and abnormal morphology
ALND-positive patients (n=24)	22	15	12	5	5	2	2
ALND-negative patients (n=41)	41	15	8	1	1	0	0

Harishinghani, M. G., Weissleder, R.; Sensitive, Noninvasive Detection of Lymph Node Metastases. Plos Medicine; Vol 1; Issue 3; pp 202-209; 2004

Design: Prospective Case Control Study Evidence Level 2-

Country: USA

Setting: Hospital

Inclusion criteria: Histologically validated lymph nodes from patients with primary cancers

Exclusion criteria:

Population: Test dataset/lymph nodes histologically validated (n=216) prospective cases, from 34 patients with primary cancers; Learning dataset / lymph nodes with known histopathology (n=97) retrospective cases

<u>Parameter</u>	<u>Learning dataset</u>	<u>Test dataset</u>
Patients (n)	37	34
Lymph nodes (n)	97	216
Malignant (n/%)	44 (45%)	46 (21%)
Benign (n/%)	53 (55%)	170 (79%)
Short axis (M±SD/range/mm)	10.5±6.2 (3-39)	10.0±5.9 (3-39)
Volume (mean, median, range cm ²)	2.0, 0.4, 0.24-45.4	1.8, 4.1, 0.14-45.4
Age (mean, range)	59.7 (28-85)	58.9 (30-82)
Sex (M/F)	24/12	25/9
Primary cancer sites		
	Prostate	21
	Bladder	9
	Testes	5
	Ureter	1
	Colon	1
	Breast	7
	Penile	4

Interventions: semi automated, non-invasive nodal cancer staging using a nonparticle enhanced lymphotropic magnetic resonance (LMRI) technique

Outcomes: accurate staging; magnetic tissue parameters of cancer metastases and normal unmatched lymph nodes

Results: There is fairly good evidence to suggest the feasibility of semi automated, non-invasive nodal cancer staging using a nonparticle enhanced lymphotropic magnetic resonance (LMRI) technique. Nanoparticles traced by MRI displayed an abnormal pattern when there was metastases in the nodes and a computer software recognises this abnormality. Unique magnetic tissue parameters were found, which accurately distinguished metastatic from normal nodes with an overall sensitivity of 98% and specificity of 92%. The parameters can be applied to data sets in a semi automated fashion and used for 3D reconstruction of complete nodal anatomy for different primary cancers.

Discriminatory power of Imaging Parameters in Learning dataset

Analysis	Parameter	Sensitivity	Specificity	PPV	NPV
Visual analysis	Short axis >10	59.0	81.1	72.2	70.4

	mm				
	Round > 8 mm	43.1	73.5	57.7	60.9
	Heterogeneous	52.2	96.2	92.0	70.8
	Focal defect	15.9	100.0	100.0	58.8
	Central hypersensitivity	2.2	81.1	9.0	50.0
Semiautomated Difference (pre/post)	δ SI <30%	38.6	98.1	94.4	65.8
	δ SNR <4.2	52.2	94.3	88.4	70.4
	δ LNM <0.031	79.1	83.0	79.1	83.0
	δ T2* <34.9ms	86.4	92.5	90.5	89.1
Semiautomated (post only)	SNR >2.1	95.5	84.9	84.0	95.7
	LNM ratio	97.7	73.6	75.4	97.5
	T2*	93.2	94.3	93.2	94.3
	Pixel variance	97.7	90.6	89.6	98.0
	T2* and variance	97.7	94.3	93.5	98.0

General comments: very small study, only 7 of the histologically proven malignancies (lymph nodes) came from breast cancer patients all in the test dataset.

Evidence Tables- DCIS

Shiraishi, A., Kurosaki, Y., Maehara, T., Suzuki, M., Kurosumi, M.; Extension of Ductal Carcinoma In Situ: Histopathological Association with MR Imaging and Mammography; Magnetic Resonance in Medical Sciences; Vol. 2; No. 4; pp159-163; 2003

Design: Retrospective Case Control Study Evidence Level 2++

Country: Japan

Setting: Hospital

Inclusion criteria: Women with DCIS and DCIS with microinvasion

Exclusion criteria:

Population: 30 women with 30 histologically verified lesions (12 pure DCIS; 18 DCIS with microinvasive foci);

Mean age: 49.8 years (range 34-70 years)

Treated with: 19 mastectomy; 11 BCT

Interventions: Evaluating capability of breast MRI and mammography in determining tumour extent and detectability of DCIS.

Outcomes: Correlation of MR, Mammography and Histopathological results; Sensitivity

Results: There is good evidence that MRI can complement mammography in guiding surgical treatment of DCIS by providing better assessment to the extent of the lesion. 26/30 (86.7% sensitivity) were detected through the MRI as well as 8 lesions without mammographically detected microcalcification. In 7/30 cases MRI showed tumour extent accurately compared with mammography, and the combined diagnosis improved the accuracy of evaluating tumour extent.

Difference in Tumour Extent Between Imaging and Specimen

	0	≤ 10mm	11-20mm	≥ 21mm	≤ 10mm	11-20mm	≥ 21mm
	underestimation				overestimation		
MRI	2 (9.1%)	8 (36.4%)	3 (13.6%)	6 (27.3%)	3 (13.6%)	0	0
Mammography	1 (4.5%)	7 (31.8%)	3 (13.6%)	7 (31.8%)	3 (13.6%)	0	1 (4.5%)
MRI + Mammography	2 (9.1%)	8 (36.4%)	4 (18.2%)	3 (13.6%)	4 (18.2%)	0	1 (4.5%)

MRI + mammography: combined evaluation with MRI and mammography

Difference in Size Divided by Actural Size of Specimen

	0-20%	21-40%	41-60%	61-80%	81-100%	100%<
MRI	12	3	4	1	2	0
Mammography	9	6	3	2	1	1

General comments:

Mariano, M.N., van den Bosch., M.A.A.J., Daniel, B.L., Nowels, K.W., Birdwell, R.L., Fong, K.J., Desmond, P.S., Plevritis, S., Stables, L.A., Zakhour, M., Herfkens, R.J., Ikeda, D.; Contrast-Enhanced MRI of Ductal Carcinoma In Situ: Characteristics of a New Intensity-Modulated Parametric mapping Technique Correlated with Histopathological Findings; Journal of Magnetic Resonance Imaging; Vol 22; pp520-526; 2005

Design: Retrospective Case Control Study Evidence Level 2++

Country: USA

Setting: Hospital

Inclusion criteria: Patients with pure DCIS on pathology who underwent conventional mammography and contrast-enhanced (CE) MRI using the intensity-modulated parametric mapping technique

Exclusion criteria: Concurrent microinvasion; LCIS; IDC; ILC or inflammatory carcinoma in the specimen

Population: 14 patients; Mean age 43 years (range 26-52 years)

Interventions: Intensity modulated parametric mapping MRI

Outcomes: Correlation with histopathological findings

Results: There is good evidence that intensity-modulated parametric mapping technique for breast MRI resulted in the highest detection rate for the DCIS cases. Furthermore, the parametric mapping technique identified all intermediate and high-grade DCIS lesions, suggesting that a negative MRI using the parametric mapping technique may exclude intermediate and high-grade DCIS.

With the use of a kinetic curve shape analysis, MRI classified 7/14 lesions (50%) as suspicious, including four with initial-rapid/late-washout and three initial-rapid / late-plateau. Using morphologic criteria, MRI classified 10/14 (71%) as suspicious., with the most prominent morphologic feature being a regional enhancement pattern. Using the intensity modulated parameteric mapping technique, MRI classified 12/14 cases (86%) as suspicious. Parametric mapping identified all intermediate and high-grade DCIS lesions.

Detection Rate of 14 Pure DCIS Lesions by Mammography and Contrast-Enhanced MRI Criteria

Modality	DCIS cases detected
Mammography	9/14 (64%)
MRI kinetic curve-only	7/14 (50%)
MRI morphology-only	10/14 (71%)
MRI parametric mapping technique	12/14 (86%)

Detection Rate of 14 Pure DCIS Lesions Stratified by Nuclear Grade by Mammography and Contrast-Enhanced MRI

	Low nuclear grade (n=4)	Intermediate nuclear grade (n=3)	High nuclear grade (n=7)

Mammogram suspicious	2 (50%)	2 (67%)	5 (71%)
MRI kinetic curves suspicious	2 (50%)	0 (0%)	5 (71%)
MRI morphology suspicious	1 (25%)	3 (100%)	6 (86%)
MRI parametric mapping suspicious*	2 (50%)	3 (100%)	7 (100%)

* MRI parametric mapping identified all intermediate and high grade DCIS lesions

Level of Periductal Lymphocytic Infiltration Stratified by Nuclear Grade in 14 Pure DCIS Lesions

	None infiltration (n=4)	Intermediate infiltration (n=5)	Moderate or intense infiltration (n=5)
Low grade DCIS	2 (50%)	2 (40%)	0 (0%)
Intermediate grade DCIS	2 (50%)	1 (20%)	0 (0%)
High grade DCIS	0 (0%)	2 (40%)	5 (100%)

General comments

Francescutti, G.E., Londero, V., Berra, I., Del Frate, C., Zuiani, C., Bazzocchi, M.; Breast MRI of Ductal Carcinoma in situ: Is there MRI role? Radiol Oncol; Vol 36(4); pp305-312; 2002

Design: Retrospective Case Control Study Evidence Level 2+

Country: Italy

Setting: Hospital

Inclusion criteria: Women diagnosed with DCIS lesions who underwent contrast enhanced MRI within 7 days after mammographic examination

Exclusion criteria:

Population: 22 women - Mean age 53 (range 42-75 years)
 Histological Diagnosis: Surgical Biopsy (n=6); Core Needle Biopsy (n=16)
 DCIS (n=15); DCIS plus Microinvasive Component or Microfoci of IDC (n=7)

Interventions: Contrast enhanced MRI

Outcomes: Sensitivity

Results: There is fairly good evidence that the sensitivity of MRI for DCIS detection is lower than that achieved for invasive breast cancer; however, contrast enhanced MRI can depict foci of DCIS that are mammographically occult. The MRI technique is of complementary value for a better description of tumour size and detection of additional malignant lesions. On MRI, 21/22 (95%) DCIS lesions showed contrast enhancement. 14/15 (93%) pure DCIS lesions demonstrated respectively a low (3), undeterminate (5), and strong (6) enhancement. Morphologically, the enhancing lesion was focal in 7, segmental in 4 and with linear branching in 3 cases. Wash out was found in 4 cases, plateau curve in 8 and Type I curve in 2 cases. Multifocality was present in 5 cases.

All DCIS with associated microinvasion demonstrated contrast enhancement: 1/7 cases showed a low enhancement, 2/7 showed an indeterminate enhancement and 4/7 showed a strong enhancement. Morphologically, the enhancing lesion was focal in 3/9, segmental in 5 and with linear branching in 1 case. The wash out was demonstrated in 3/7 cases, plateau curve in 3 and Type 1 curve in 1 case. Multifocality was present in 3 cases.

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Enhancement rates in 14 DCIS and 7 DCIS with associated minimum invasion

% of signal intensity increase	DCIS	DCIS+DCI	Total
<70%	3 (21%)	1 (14%)	19%
70%-140%	5 (36%)	2 (29%)	33%
>140%	6 (43%)	4 (57%)	48%
Configuration			
Focal mass like	7 (50%)	3 (43%)	48%
Segmental	4 (27%)	3 (43%)	33%
Linear-branching	3 (21%)	1 (14%)	19%
Signal intensity curve			
Type i	2 (14%)	1 (14%)	14%
Type ii	8 (57%)	3 (43%)	52%
Type iii	4 (29%)	3 (43%)	33%

Groves, A.M., Warren, R.M.L., Gogward, S., Rajan, P.S.,; Characterization of Pure High-grade DCIS on Magnetic Resonance Imaging Using the Evolving Breast MR Lexicon Terminology: Can it be differentiated from pure invasive disease? Magnetic Resonance Imaging; Vol. 23; pp733-738; 2005

Design: Retrospective Case Control Study Evidence Level 2+

Country:UK

Setting: Hospital

Inclusion criteria: Histologically proven pure high-grade DCIS

Exclusion criteria: Previous chemotherapy, inadequate MRI, all cases with mixed lesions (invasive and DCIS, including microinvasion) and one patient who was too breathless to undergo an adequate examination

Population: 26 patients (13 DCIS compared with 13 invasive carcinoma)

		DCIS	Invasive
Mean Age		56.2 years (range 34-74 years)	53 years (range 42-68 years)
Grade	1	0	3
	2	0	3
	3	13	7
Size	<9 mm	1	1
	10-20 mm	2	5
	>20 mm	10	7
Mean Size		37.3mm (range 6-89mm)	31mm (range 6-97mm)
Unifocal		13	11
Multifocal		0	2

Interventions: MRI

Outcomes: MRI characteristics of DCIS and invasive breast carcinoma

Results: There is fairly good evidence that there are features that help differentiate high-grade DCIS from invasive carcinoma on MRI. High-grade DCIS is significantly more likely to show focal branching pattern ($p=0.003$) or to have an irregular contour ($p=0.003$) compared with invasive disease. All though of marginal statistical significance, DCIS lesions are more likely to have a lower morphological score than invasive carcinoma ($p=0.006$), whilst the latter is more likely to show ring enhancement ($p=0.007$).

Summary of MRI DCIS and Invasive Breast Carcinoma MRI Characteristics

	Age (years)	Size (mm)	Percentage Enhancement	Morphological Score	Total Score
No. of DCIS (n=13)	56.2	37.3	180.9	5.38	20.4
No. of invasive carcinoma	53	31	220.2	4.62	23.1

(n=13)							
	Focal branching	Ring enhancement	Margin			Shape	
			Well	Poorly	Spiculated	Round	Irregular
No. of DCIS (n=13)	4	0	0	11	2	0	13
No. of invasive carcinoma (n=13)	0	3	4	6	3	4	9
	Contrast washout pattern			Category by score			
	Rising	Plateaux	Washout	Benign	Suspicious	Malignant	
No. of DCIS (n=13)	1	9	3	1	8	4	
No. of invasive carcinoma (n=13)	0	6	7	0	7	6	
General comments							

van der Velden, A.P.S., Boetes, C., Bult, P., Wobbes, T. The Value Of MRI In Diagnosis And Size Assessment Of In Situ And Small Invasive Breast Carcinoma. The American Journal of Surgery, No.192, pp.172-78, 2006

Design: Retrospective case series evidence level 3

Country: Netherlands

Setting: Hospital

Inclusion criteria: histopathologically confirmed diagnostic of DCIS, histologic core needle biopsy

Exclusion criteria

Population: 54 consecutive patients

Age at diagnosis	%	N	DCIS diagnosis	%	N
34-55	59	39	Clinical symptoms	30	20
55-75	41	27	Mammography	62	41
Location of DCIS			MRI	5	3
Inner quadrant	18	12	Unknown	3	2
Outer quadrant	58	38	Re-excision		
Central	24	16	Lumpectomy	22	8
Pre-op histologic biopsy			Mastectomy	57	24
DCIS	58	38	Axillary lymph node dissect.	11	4
Not conclusive	12	8	Grading of DCIS		
Not performed	30	20	Grade I, well differentiated	6	4
Final treatment			Grade II, moderately diff.	35	23
Lumpectomy	44	29	Grade III, poorly diff.	35	23
Mastectomy	56	37	Not specified	6	4
Histopathologic size of DCIS			DCIS with small invasive carcinoma		
<10 mm	15	9	Present	18	12
10-20 mm	18	11	Not present	82	54
>20mm	67	40			

Interventions: Pre-operative Breast MRI.

Outcomes: correlation coefficients to assesses differences in size between imaging and histopathologic examination

Results:

There is some evidence that DCIS and DCIS with small invasive carcinoma can be adequately visualised on MRI. Tumour size measured at MRI did correlate with histopathologic size, but in contrast to mammography MRI tended to overestimate the tumour extent.

Mammographic rate of detection for DCIS was 84/52 (90%) and for DCIS with small invasive carcinoma 10/12 (83%)

MRI revealed 1 false negative case and the rate of detection for DCIS was 16/17 (94%).

Correlation of mammographic size with histopathologic size was $r = .44$ ($p < .01$) and $r = .49$ ($p < .03$) for MRI. Mammography underestimated the lesion size by 5 mm or more in

47%, whereas with MRI size was adequately assessed in 43% and overestimated in 38%

Mammographic Findings (n=64) and MRI findings (n=22)

BiRads clasification	Mammography		MRI	
	%	N	%	N
Negative	11	7	5	1
Benign finding	1	1	0	0
Probably benign finding	16	10	9	2
Suspicious abnormality	50	32	81	18
Highly suggestive malignancy	16	10	5	1
Unknown	6	4	0	0

Size assessment of mammography (n=49) and MRI (n=21) compared to histopathologic size

Radiologic size assessment	Difference between histopathologic and radiologic	Mammography		MRI	
		%	N	%	N
Overestimation	>20 mm	10	5	14	3
	11-20 mm	6	3	5	1
	6-10 mm	10	5	19	4
Adequate	0-5 mm	27	13	38	8
Underestimation	6-10 mm	10	5	0	0
	11-20 mm	8	4	5	1
	>20 mm	29	14	19	4

General comments

Menell, J.H., Morris, E.A, Dershaw, D.D., Abramson, A.F., Brogi, E., Liberman, L.,; Determination of the Presence and Extent of Pure Ductal Carcinoma In Situ by Mammography and Magnetic Resonance Imaging; The Breast Journal; Vol. 11; No. 6; 2005

Design: Retrospective Case Series Evidence Level 3

Country: USA

Aim: Hospital

Inclusion criteria: Patients with pure DCIS on pathology who underwent conventional mammography and contrast-enhanced (CE) MRI using the intensity-modulated parametric mapping technique:

Exclusion criteria:

Population: 32 women (33 breasts), 39 sites of pure DCIS; Mean age 53 years (range 34-79 years); no invasive or microinvasive tumour was found

Interventions: Contrast-Enhanced MRI

Outcomes: Correlation of presence and extent of pure DCIS by mammography and MRI

Results: There is some evidence that MRI is significantly more sensitive than mammography in DCIS detection. In women with known or suspected DCIS, MRI may have an important role in assessing the extent of disease in the breast. Of 33 breasts involved, DCIS was discovered by MRI alone in 21 (64%), by both MRI and mammography in 8 (24%) and by mammography alone in 1 (3%), DCIS found at mastectomy without findings of mammography or MRI in 3 breasts (9%). MRI had significantly higher sensitivity than mammography for DCIS detection (29/33 = 88% vs. 9/33 = 27%; $p < 0.00001$). Multiple sites of disease were present in 5 breasts, better demonstrated with MRI in 3, mammography in 1, and equally by both in 1. The predominant enhancement pattern of DCIS on MRI was linear / ductal in 18/29 breasts (62%); mammography found calcifications associated with DCIS in 8/9 (89%). The nuclear grade of DCIS found with MRI and mammography was similar; size of lesion was larger on MRI; breast density did not impact results.

Detection of any DCIS in 33 Breasts by Imaging Modality, MRI vs. Mammography

	MRI	Mammography	Neither
Detection of DCIS	29 (88)	9 (27)	3 (9)
Detected only by	21 (64)	1 (3)	
Sensitivity	88%	27%	
False-negative	12%	73%	

DCIS Lesion Size (in mm) vs. Method of Detection in 39 Lesions

	Imaging size, median (range)	Pathology size, median (range)
All mammographically detected (n=10)	35 (5-90)	11 (2-25)
All MRI detected (n=34)	20 (6-110)	7 (1-25)
Only MRI detected (n=25)	17 (6-110)	7 (1-20)
Detected by both, MRI measured (n=9)	42 (9-79)	11 (2-25)

Detected by both mammographically measured (<i>n</i> =9)	35 (5-90)	11 (2-25)
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Lesion Nuclear Grade Versus Method of Detection

	All lesions	MRI detected	Mammographically detected	Neither
Low	10 (28)	8 (25)	2 (20)	1 (33) ^a
Intermediate	16 (44)	15 (47)	4 (40)	1 (33) ^b
High	10 (28)	9 (28)	4 (40)	1 (33) ^c
Total	36	32	10	3

Percentage of DCIS in this grade is in parentheses

^a 0.1cm

^b 0.2cm

^c Paget's disease; 0.1cm

General comments

Health Economic Summary

A single literature review was performed to assess the cost-effectiveness of breast MRI in the preoperative staging of invasive breast cancer patients and CDIS patients. From 100 references initially identified through the search, 25 were considered further, although only 9 papers were finally retrieved. In total, 8 papers were excluded: 3 were about screening (Baron et al 2005; Hailey et al 1997; Plevritis et al 2000), 3 did not include an economic analysis (Heiberg et al 1996; Hylton et al 1999; Pietan et al 1999), 1 assessed a study population different to that considered in the topic (Hrung et al 1999), 1 assessed thoracic X-ray as the main intervention, while MRI was used selectively across patients (Norum et al 2000). Only 1 study was finally included in the systematic review (Esserman et al 1999). The only included study (Esserman et al 1999)¹ was a partial economic evaluation (since only costs of MRI were reported). The study was conducted in USA and investigated the usefulness of conducting contrast-enhanced MRI compared to mammography to assess the extent of cancer in the breast before surgery. The study sample included patients with invasive breast cancer, DCIS, Paget's disease and others; therefore, there seemed to be considerably heterogeneity in terms of the type of patients considered at analysis. A small patient sample was considered (i.e. 57 patients in total). The usefulness of MRI was assessed prospectively in the diagnostic study, while the usefulness of mammographies were retrospectively reviewed. The mammography costs were not considered in the cost analysis. Overall, there were relevant limitations both in terms of the clinical and the cost analysis. Moreover, it is not clear whether the study sample, the clinical practice and the unit costs used in the study would be representative within a UK setting. Therefore, the usefulness of this study is very limited and uncertainty remains regarding whether MRI is a cost-effective strategy in the preoperative staging of EBC patients.

REFERENCES

Esserman L et al. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. *Journal of Clinical Oncology* 1999; 17(1):110-119.

Evidence Table

Economic evaluations

Esserman L et al. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. <i>Journal of Clinical Oncology</i> , 1999. 17(1): p. 110-119.
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Design:

Type of economic evaluation:

Partial economic evaluation (the costs of one of the interventions –mammography- were not included). The type of economic analysis was cost-effectiveness analysis (cost-consequences), with effectiveness derived from a single study and no modelling exercise conducted.

Clinical effectiveness:

It was derived from a diagnostic study, for which MRI was conducted prospectively and mammographies, when available, were reviewed retrospectively.

Cost estimation:

It considered the potential savings (in terms of surgical procedures –mastectomy, lumpectomy, reconstruction and implants- and radiation therapy) associated with better

¹ Note that a quality assessment was not undertaken for this paper for not being a full economic evaluation.

staging achieved with MRI. Some resource consumption derived from authors' assumptions based on their clinical experience, and unit costs from 1997 Medicare reimbursement fees. Resources used were not identified independently of costs. The price year was 1995.

Country: USA, **setting:** Hospital

Inclusion criteria

Patients with diagnosis of breast cancer (by fine needle aspiration for malignancy, core biopsy for DCIS or invasive breast cancer, or excisional biopsy with positive surgical margins) and planned surgical excision
 Enrolment: June 1995 – September 1996

Exclusion criteria

Not stated

Population

57 patients, accounting for 58 diagnoses: 33 patients (57%) with invasive cancer (29 ductal, 2 lobular, 2 multiple histology); 9 patients (16%) with intraductal carcinoma (i.e. invasive cancer plus extensive DCIS) 7 patients (12%) with DCIS; 1 patient (2%) with Paget's; 8 patients (14%) with no residual disease or with LCIS only.

50 of them showed residual tumour at final pathology, and in 5 cases mammography was not repeated after initial biopsy. Final sample size: 45 patients with MRI and mammograms

Interventions

- Contrast-enhanced MRI (three-dimensional imaging technique TARGET, with General Electric 1.5 tesla Signa whole body imager) for local staging
- Mammography

The reference standard used in the study was pathologic size (the authors reported that the use of pathologic size as reference standard was somewhat arbitrary, even if blindly conducted for the study)

Follow up – It seems that from the moment of conducting the mammogram after initial biopsy to the moment the MRI and pathological results were available

Results

MRI was more accurate identifying the extent of disease and would lead to savings by identifying more accurately the type of surgery to undergo.

OUTCOME OF INTEREST*	MRI	Mammography	OVERALL RESULT
Correctly identified presence or absence of disease (number of cases)	55/58	Non stated	-
Accurate in predicting extent of disease (number of cases)	54/58	Non stated	-
False positive results	2/58	Non stated	-
False negative results	2/58	Non stated	-
Concordance with tumour pathology to identify malignancy	44/45 (98%)	38/45 (84%)	P = 0.03
Concordance with tumour pathology on tumour extent	43/44 (98%)	21/38 (55%)	P = 0.001

(overall)			
Concordance with tumour pathology on tumour extent for unifocal disease (invasive)	19/19 (100%)	10/14 (71%)	-
Concordance with tumour pathology on tumour extent for multifocal/multicentric disease	10/10 (100%)	4/9 (44%)	-
Concordance with tumour pathology on tumour extent for intraductal carcinoma	7/8 (88%)	4/8 (50%)	-
Concordance with tumour pathology on tumour extent for DCIS	6/6 (100%)	37 (43%)	-
Concordance with tumour pathology on tumour extent for Paget's disease	1/1 (100%)	21/38 (55%)	-
Cases for which MRI, but not clinical examination and mammography, identified disease too extensive for lumpectomy (i.e. change to mastectomy)	10 (17.54%)	-	-
Cases in which MRI would have changed surgical decision making by predicting successful breast conservation; number (%)	14 (24.56%)	-	-
Unit cost of MRI (charge per hour, \$1995; in 1998, 30 minutes were required per patient)	\$1,500	-	-
Total savings for the study sample by using MRI (\$1995)	\$102,659	-	-
* The most relevant outcomes have been reported in bold			

Authors' conclusions –

MRI was better than mammograms for both identification of malignancy (98% versus 84%; $p = 0.03$), concordance on extent (98% versus 55%; $p < 0.001$) and extent of disease in extensive intraductal carcinoma (88% versus 50%), and it has potential to lead to cost savings.

General comments –

In terms of the analysis of clinical effectiveness, the study was a diagnostic study that used prospective data to assess MRI and retrospective data to assess mastectomy. The investigator recording MRI measurements was blinded to mammographic results and pathology was independently reviewed in a blinded way. However, the sample size of the study was small, and included patients with invasive breast cancer, DCIS patients, patients with Paget's disease, etc. As the authors stated, the study was designed to gather information to assess MRI, and not to direct surgical therapy, therefore the

outcome 'potential impact of MRI on surgical decision making' may be of limited usefulness. The authors additionally highlighted, as potential barrier for the introduction of MRI, the difficulties in image interpretation and reader variability, although they mention that the type of technology used in the study (TARGET) helps reducing both problems. The authors mentioned that the study sample was likely to be representative of the patients seen within the community and at academic centres who are likely to benefit from MRI, although they may have referred to a USA setting. In terms of generalisability of the results, the study was conducted in USA (therefore the clinical practice may be different, and so resource use may differ from the UK, as will costs/prices). For these reasons, the study may not be generalisable/ applicable to the UK setting. There was not a direct comparison of the costs of MRI with those of mammography; therefore, the authors' conclusions are questionable. Given that the costs of the alternative of using mammograms were not considered in the study, nothing can be clearly concluded regarding the cost-effectiveness of MRI compared to mammograms.

2.2 What is the role of pre-treatment ultrasound assessment in staging the axilla?

Short Summary

The evidence for this topic comes from case series studies and one meta-analysis which pooled estimates.

Eight studies reported the proportion of cases in whom it was possible to visualise axillary lymph nodes on ultrasound. This proportion had a mean of 76% and median 81% but varied widely, with a range 35% to 99%. The remaining proportion represents patients for whom ultrasound does not add any information. (Altinyollar *et al.* 2005, Brancato *et al.* 2004, Damera *et al.* 2003, Deurloo *et al.* 2003, Dixon *et al.* 1992, Esen *et al.* 2005, Nori *et al.* 2005 and Podkrajsek *et al.* 2005).

The systematic review by Alvarez *et al.* (2006) performed a meta-analysis of staging outcomes for 'grey scale' axillary ultrasound based upon 16 case series studies. The meta-analysis provided pooled estimates of staging outcomes. When patients with palpable and non-palpable axillary lymph nodes were combined, lymph nodes that were suspicious on ultrasound based on their size (> 5mm); sensitivity was 69.2% and specificity was 75.2%. If lymph nodes were suspicious on ultrasound based on their morphology the sensitivity was 71.0% and specificity was 86.2%. Considering only studies of patients with non-palpable lymph nodes, ultrasound had reduced sensitivity (using the morphologic criterion for nodal involvement) and there was little change in specificity. When a meta-analysis including only patients in whom it was possible to obtain biopsy material by ultrasound were considered, the pooled sensitivity was 75.0% and the pooled specificity was 98.3%. In a meta-analysis of patients in whom ultrasound-guided biopsy was planned, and defining failure to find a node on ultrasound or failure to collect biopsy material as a negative screen was conducted, the effect of these classifications was to reduce the sensitivity of ultrasound compared to earlier values, with little change in its specificity.

From case series studies the staging performance of 'grey scale' ultrasound alone showed a mean sensitivity of 62%, a mean specificity of 87%, a positive predictive value of 86% and a negative predictive value of 71%. (Altinyollar *et al.* 2005, Bartonkova *et al.* 2006, Brancato *et al.* 2004, Chandawarkar *et al.* 1997, Esen *et al.* 2005, Heusinger *et al.* 2005, Lee *et al.* 1996, Hergan *et al.* 1996, Sato *et al.* 2004 and Van Rijk *et al.* 2006).

The staging performance of 'grey scale' ultrasound plus colour doppler ultrasound showed a mean sensitivity of 65%; a mean specificity of 89% a positive predictive value of 78% and a negative predictive value of 81%. (Couto *et al.* 2004, Dixon *et al.* 1992, Esen *et al.* 2005, Lee *et al.* 1996, Nori *et al.* 2005, Perre *et al.* 1996, Podkrajsek *et al.* 2005 and Walsh *et al.* 1994).

The staging performance of ultrasound guided fine needle aspiration cytology (FNAC) showed a mean sensitivity of 43%, a mean specificity of 100%, a positive predictive value of 99% and a negative predictive value of 72%. (Brancato *et al.* 2004, Damera *et al.* 2003, De Kanter *et al.* 2006, Deurloo *et al.* 2003, Lemos *et al.* 2005, Podkrajsek *et al.* 2005, Stewart *et al.* 2006 and Van Rijk *et al.* 2006). Ciatto *et al.* (2007) reported an overall sensitivity of 72.6% and specificity of 95.6% with a negative predictive value of 67.2% and a positive predictive value 96.6% when excluding inadequate results from analysis; including inadequate results as a negative gave a sensitivity of 64.6%, specificity of 95.7%, negative predictive value of 61.3% and a positive predictive value of 96.6%. Sahoo *et al.*

(2007) reported an overall sensitivity of 96% and specificity of 93%. Somasunder et al. (2006) reported an increase in sensitivity from T1 (35%) to T3/4 (78%) and specificity from T1 (96%) to T3/4 (100%). The likelihood of node FNAC being positive was linked with tumour stage (Ciatto *et al.* 2007; Somasunder *et al.* 2006). Ciatto *et al.* (2007) also reported a significant association with histological grade and number of nodes involved. Sahoo *et al.* (2007) reported that 40 (70%) patients with positive ultrasound FNAC were spared the additional step of SLNB while Somasunder *et al.* (2006) reported that 79 (47%) patients with positive ultrasound FNAC were spared SLNB.

PICO

Population	Intervention	Comparison	Outcomes
Patients with early invasive breast cancer who require staging of the axilla and staging procedure planned is less than an axillary clearance.	Ultrasound assessment of the axilla	No USS assessment	Diagnostic accuracy of nodal involvement
	Report results by subgroups: i) with concurrent core biopsy/FNAB ii) without concurrent core biopsy/FNAB if possible between FNAB and core biopsy	USS assessment but no FNAC/core biopsy USS assessment including FNAC/core biopsy where appropriate.	Utility (operations prevented) Changes to treatment strategy – particularly use of neoadjuvant chemotherapy Unnecessary treatment Cost effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The majority of the studies are set in the context of selecting patients for either axillary dissection, or less extensive surgery (most often SLNB) on the basis of US imaging and in some studies, US guided axillary biopsy.

The majority of studies (16) are of series of patients treated in Europe. Two series of patients were treated in Turkey, one series in Taiwan, and one series in Japan. One case series study appears to represent a US-Indian team of authors and the systematic review was undertaken in Spain.

Studies vary in terms of their choice of gold standard: either axillary clearance, axillary sample or SLNB.

Criteria for suspicious (i.e. disease positive) nodes on US also vary, but are usually based on the size of lymph nodes or more commonly, morphologic criteria and in the case of colour doppler US, vascular criteria.

The staging performance outcomes vary considerably across the studies, as evidenced by the demonstrated heterogeneity in the systematic review by Alvarez et al. (2006). In particular, the rate of visualising axillary nodes on US varies widely across the studies, and in fact, many authors do not report this rate in their series.

Staging performance outcome measures

		Axillary nodal disease status attributed by Gold Standard		
		Present	Absent	
US imaging result	+	a	b	test positive a+b
	-	c	d	test negative c+d
		Axillary disease positive a+c	Axillary disease negative b+d	Total

Sensitivity = $a/[a+c]$

1-sensitivity = false negative rate

Specificity = $d/[b+d]$

1-specificity = false positive rate

Positive predictive value (PPV) = $a/[a+b]$

Negative predictive value (NPV) = $d/[c+d]$

Visualisation of axillary nodes by US

Only 8 studies reported the proportion of cases² in whom it was possible to visualise axillary lymph nodes on US. This proportion had mean 76% and median 81% but varied widely, with range 35% to 99%. The complement of this proportion represents patients for whom US does not add any information.

[Altinyollar *et al.* 2005, Brancato *et al.* 2004, Damera *et al.* 2003, Deurloo *et al.* 2003, Dixon *et al.* 1992, Esen *et al.* 2005, Nori *et al.* 2005 and Podkrajsek *et al.* 2005]

The remaining studies do not report a rate of identification of axillary nodes on US, but some (for example, Sato *et al.* 2004) report staging outcomes for their entire, consecutive series of patients. This implies that either axillary nodes were identified in 100% of patients, or that failure to identify any nodes was considered to be a negative result by US, or that only patients with successfully visualised axillary nodes on US were analysed.

Staging performance of axillary US

Systematic review evidence

Of the 22 included studies, there was one systematic review that performed meta-analysis of staging outcomes for grey scale axillary US based upon 16 case series studies (Alvarez *et al.* 2006). The meta-analysis provided pooled estimates of staging outcomes as shown

² Some studies counted the number of axillae rather than patients, such that a patient with bilateral breast cancer underwent two imaging procedures, counted as two axillae.

below. For the majority of meta-analyses performed, there was significant statistical heterogeneity amongst individual study results.

Meta-analysis of patients with palpable axillary nodes and patients with non-palpable axillary nodes combined (Alvarez et al. 2006):

Nodal size criterion³:

Sensitivity = 69.2% [95% CI 63.4-74.6]

Specificity = 75.2% [95% CI 70.4-79.6]

Morphologic criterion⁴:

Sensitivity = 71.0% [95% CI 65.2-76.3]

Specificity = 86.2% [95% CI 82.6-89.3]

Therefore US using either criterion was associated with similar sensitivity, whereas US using the morphologic criterion had higher specificity.

Meta-analysis of patients with non-palpable axillary nodes only (Alvarez et al. 2006):

Considering only studies of patients with non-palpable nodes, US had reduced sensitivity to the above, when using the morphologic criterion for nodal involvement and there was little change in specificity:

Nodal size criterion:

Pooled sensitivity = 60.9% [95% CI 54.5%-67.1%]

Pooled specificity = 77.3% [95% CI 72.5%-81.6%]

Morphologic criterion:

Pooled sensitivity = 43.9% [95% CI 37.1%-50.8%]

Pooled specificity = 92.4 [95% CI 88.7%-95.2%]

Meta-analysis of only patients in whom it was possible to obtain biopsy material by US (Alvarez et al. 2006):

Pooled sensitivity = 75.0% [95% CI 70.3%-79.3%]

Pooled specificity = 98.3% [95% CI 96.2%-99.4%]

Meta-analysis of patients in whom US guided biopsy was planned, but defining failure to find a node on US as a negative screen and failure to collect biopsy material as a negative screen (Alvarez et al. 2006):

The effect of these classifications was to reduce the sensitivity of US compared to the above, with little change in its specificity:

Pooled sensitivity = 45.4% [95% CI 40.0%-50.9%]

Pooled specificity = 99.6% [95% CI 98.6%-100%]

Other studies

21 case series studies provide data in a similar format. These are as follows.

Grey scale US alone

³ Where nodes are suspicious on US based on their size being >5mm.

⁴ Where nodes are suspicious on US based on their morphology.

11 studies provided data on the staging performance of grey scale US alone, with summary statistics as follows:

	Sensitivity	Specificity	PPV	NPV
mean	62%	87%	86%	71%
median	64%	87%	87%	75%
Highest	81%	100%	100%	88%
lowest	35%	71%	74%	46%

[Altinyollar 2005, Bartonkova 2006, Brancato 2004, Chandawarkar 1997, Damera 2003*, Esen 2005, Heusinger 2005, Lee 1996, Hergan 1996, Sato 2004 and Van Rijk 2006].

* *This study was included in the systematic review by Alvarez et al. (2006).*

US including colour doppler

8 studies provided data on the staging performance of grey scale US plus colour doppler US, with summary statistics as follows:

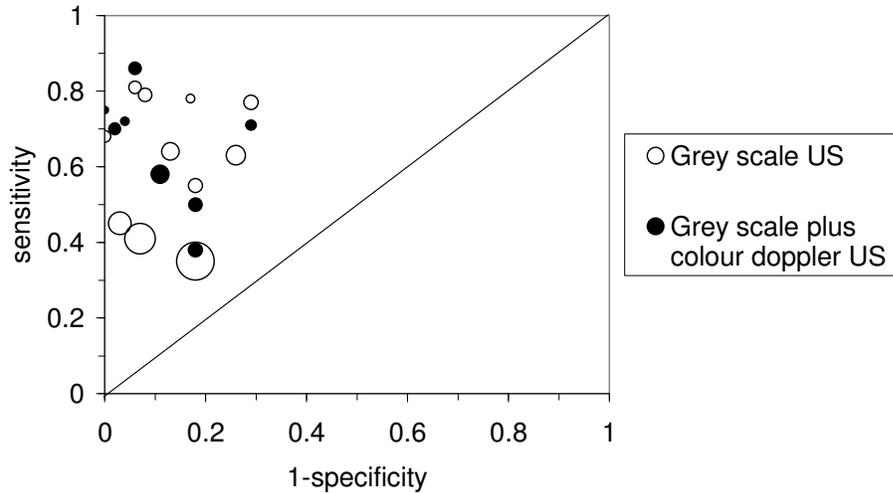
	Sensitivity	Specificity	PPV	NPV
mean	65%	89%	78%	81%
median	71%	92%	85%	81%
Highest	86%	100%	100%	90%
lowest	38%	71%	52%	73%

[Couto 2004, Dixon 1992, Esen 2005, Lee 1996, Nori 2005, Perre 1996, Podkrajsek 2005 and Walsh 1994].

Figure 1 illustrates the staging performance of grey scale US and combined grey scale US with colour doppler based on 17 series of patients.

Figure 1

ROC curve for pre-operative detection of positive axillary nodes by grey scale US and grey scale plus colour doppler US (17 studies)
 Circle area is proportional to the number of subjects in each study



Grey scale US series:

Altinyollar *et al.* 2005, Bartonkova *et al.* 2006, Brancato *et al.* 2004, Chandawarkar *et al.* 1997, Damera *et al.* 2003, Esen *et al.* 2005, Heusinger *et al.* 2005, Lee *et al.* 1996, Hergan *et al.* 1996, Sato *et al.* 2004, Van Rijk *et al.* 2006.

Grey scale plus colour doppler US series:

Couto *et al.* 2004, Dixon *et al.* 1992, Esen *et al.* 2005, Lee *et al.* 1996, Nori *et al.* 2005, Perre *et al.* 1996, Podkrajsek *et al.* 2005, Walsh *et al.* 1994

US plus FNAC

8 studies provided data on the staging performance of US guided FNAC, with summary statistics as follows:

	Sensitivity	Specificity	PPV	NPV
mean	43%	100%	99%	72%
median	46%	100%	100%	73%
Highest	59%	100%	100%	85%
lowest	21%	98%	97%	63%

[Brancato 2004, Damera 2003*, De Kanter 2006, Deurloo 2003*, Lemos 2005, Podkrajsek 2005, Stewart 2006 and Van Rijk 2006].

* These two studies were included in the systematic review by Alvarez *et al.* (2006).

Figure 2 illustrates the staging performance of combined US and FNAC based on 8 series of patients.

UPDATE EVIDENCE

Three observational studies reported on the sensitivity and specificity of US guided FNAC, two of these studies also reported on surgical management.

Ciatto *et al.* (2007) reported an overall sensitivity of 72.6% and specificity of 95.6% with NPV of 67.2% and PPV 96.6% when excluding inadequate results from analysis; including inadequate results as negative gave a sensitivity of 64.6%, specificity of 95.7%, NPC of 61.3% and PPV of 96.6%.

Sahoo *et al.* (2007) reported an overall sensitivity of 96% and specificity of 93%.

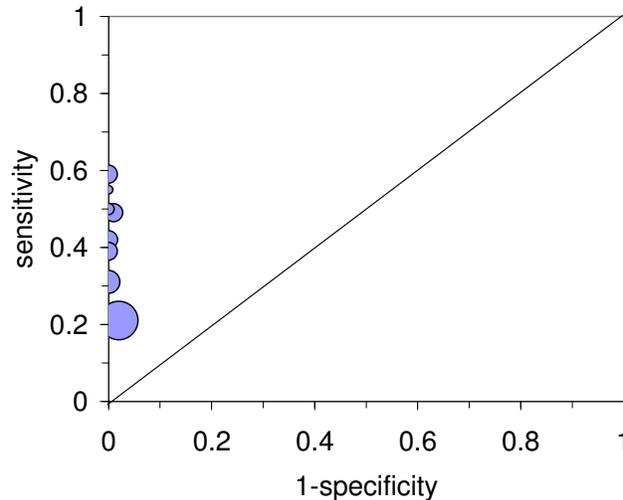
Evidence from two studies show that the likelihood of node FNAC being positive was linked with tumour stage (Ciatto *et al.* 2007; Somasunder *et al.* 2006). Ciatto *et al.* (2007) also reported a significant association with tumour grade ($p < 0.00001$) and number of nodes involved ($p < 0.001$). Somasunder *et al.* (2006) reported an increase in sensitivity from T1 (35%) to T3/4 (78%) and specificity from T1 (96%) to T3/4 (100%). No p values were given.

Sahoo *et al.* (2007) reported that 40 (70%) patients with positive US FNAC were spared the additional step of SLNB while Somasunder *et al.* (2006) reported that 79 (47%) patients with positive USFNAC were spared SLNB.

Figure 2

ROC curve for pre-operative detection of positive axillary nodes by combined US with FNAC (8 studies)

Circle area is proportional to the number of subjects in each study



Brancato 2004, Damera 2003, De Kanter 2006, Deurloo 2003, Lemos 2005*, Podkrajsek 2005*, Stewart 2006, Van Rijk 2006.

** Indicates two studies that used colour doppler US with biopsy. All other studies are of grey scale US.*

Avoidance of unwarranted surgical procedures

In the study by Brancato et al. (2004) a post hoc analysis demonstrated that in a series of 155 patients, the use of axillary US with performance of FNAC in all visualised axillary nodes avoided 6 inappropriate axillary clearances (in patients with negative definitive axillary histology) and 5 of 34 inappropriate SLNB procedures (in patients with positive definitive axillary histology) that would have arisen without the use of US guided FNAC.

The same study also demonstrated that had FNAC only been performed in patients with suspicious nodes on US, then 6 inappropriate axillary clearances and 3 of 34 inappropriate SLNB procedures would have been avoided that would have arisen without the use of US guided FNAC.

Health economics

Only one study provided any health economic information. The study by Brancato et al. (2004) calculated the cost of staging one patient by surgery alone, with no axillary US/FNAC, as EUR 104.

The use of US with FNAC performed in all cases with visualised nodes as per the study protocol resulted in a cost of EUR 103 to stage one patient.

The use of US with performance of FNAC only in cases with suspicious nodes on US resulted in a cost of EUR 90 to stage one patient.

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Evidence Tables

Systematic review of diagnostic studies

Alvarez, Anorbe, Alcorta, Lopez, Alonso & Cortes . Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. [Review] [29 refs]. AJR American Journal of Roentgenology. 186[5]. 2006.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: 2+

Country: Spain, setting: Secondary care

Inclusion criteria Studies had to report on:

Patients with breast cancer;

US axilla performed before SLNB or axillary clearance;

US at 7MHz or higher;

Sonographic criteria for positivity or based upon US guided biopsy;

Axillary dissection or SLNB as gold standard;

Results expressed as sensitivity and specificity.

Also, for meta analysis, studies had to provide data from which numbers of true positive, true negative, false positive and false negative results could be determined.

Exclusion criteria See above.

Interventions Aim: to evaluate the role of US, with or without US guided biopsy, in staging the axilla.

Outcomes Pooled estimates of sensitivity and specificity for:

Studies of patients with palpable and non-palpable axillary nodes;

Studies of patients with non-palpable axillary nodes only;

Studies of only patients who underwent US guided axillary node biopsy.

Outcomes are reported in two further sub-groups:

1. Where nodes are suspicious on US based on their size >5mm;
2. Where nodes are suspicious on US based on their morphology.

Follow up Not reported.

Results Meta-analysis of patients with palpable axillary nodes and patients with non-palpable axillary nodes combined:

1. Nodal size criterion on US

Pooled sensitivity = 69.2% [95% CI 63.4-74.6]

Pooled specificity = 75.2% [95% CI 70.4-79.6]

2. Morphologic criterion on US

Pooled sensitivity = 71.0% [95% CI 65.2-76.3]

Pooled specificity = 86.2% [95% CI 82.6-89.3]

For these results, statistical heterogeneity was demonstrated for all but sensitivity in the setting (1.).

Meta-analysis of patients with non-palpable axillary nodes only:

1. Nodal size criterion on US

Pooled sensitivity = 60.9% [95% CI 54.5%-67.1%]

Pooled specificity = 77.3% [95% CI 72.5%-81.6%]

2. Morphologic criterion on US

Pooled sensitivity = 43.9% [95% CI 37.1%-50.8%]

Pooled specificity = 92.4 [95% CI 88.7%-95.2%]

Statistical heterogeneity was demonstrated for all of these results.

Meta-analysis of only patients in whom it was possible to obtain biopsy material by US:

Pooled sensitivity = 75.0% [95% CI 70.3%-79.3%]

Pooled specificity = 98.3% [95% CI 96.2%-99.4%]

Statistical heterogeneity was demonstrated for both of these results.

Meta-analysis of patients in whom US guided biopsy was planned, but defining failure to find a node on US as a negative screen and failure to collect biopsy material as a negative screen:

Pooled sensitivity = 45.4% [95% CI 40.0%-50.9%]

Pooled specificity = 99.6% [95% CI 98.6%-100%]

Statistical heterogeneity was demonstrated for both of these results.

General comments Literature search was performed on MEDLINE only, but studies written in four European languages were eligible for inclusion.

Of 367 possible studies, 31 articles were selected and 16 were finally included.

Quality assessment of studies was rigorous and included:

Prospective/retrospective design;

Whether patients were in consecutive series;

Choice of gold standard, and its criteria for node positivity;

US test criteria for node positivity;

Whether assessment of test or gold standard were blind.

All sensitivity and specificity values reported use a combination of axillary clearance or SLNB as gold standard.

Prospective case series

Altinyollar, Dingil & Berberoglu . Detection of infraclavicular lymph node metastases using ultrasonography in breast cancer. J Surg Oncol 92[4]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Turkey, setting: Secondary care

Inclusion criteria 100 consecutive patients with invasive breast cancer of clinical stage I-II (n=79) and stage III (n=21).

Exclusion criteria None stated.

Population number of patients = 100, age range 23 to 76 years, median age = 47 years.

Interventions Aim: to evaluate the role of preoperative US in identifying axillary and infraclavicular lymph node metastases.

All patients underwent preoperative axillary/infraclavicular US and axillary clearance of levels I, II and III.

Outcomes Staging performance of US.

Follow up Not reported.

Results The mean no. of nodes retrieved by axillary clearance was 24.7 (range 11-39).

Staging performance of axillary ultrasound (all axillary nodes):
Rate of detection of axillary nodes by US = $77/100=77\%$.

Sensitivity = $49/62 = 79\%$ [95% CI 67%-87%]

Specificity = $35/38 = 92\%$ [95% CI 79%-97%]

PPV = $49/52 = 94\%$ [95% CI 84%-98%]

NPV = $35/48 = 73\%$ [95% CI 59%-83%]

Staging performance of US for status of infraclavicular nodes only:

Sensitivity = $19/40 = 48\%$ [95% CI 33%-63%]

Specificity = $59/60 = 98\%$ [95% CI 91%-99.7%]

PPV = $19/20 = 95\%$ [95% CI 76%-99%]

NPV = $59/80 = 74\%$ [95% CI 63%-82%]

Upstaging:

79 patients had clinical stage I-II prior to US, and 21 patients stage III. Following US, respective values were 61 and 39 patients and on definitive histology, respective values were 51 and 49 patients.

General comments In 21 patients with clinical stage III disease, US was performed after neoadjuvant chemotherapy.

Criteria for suspicious nodes on US were one or more of the following

features:

disappearance of fatty hilus;
ratio of short:long axis between 0.5-1.0;
decreased echogenicity;
eccentric cortical hypertrophy.

Gold standard for staging performance is axillary clearance. Calculation defines cases of nodes not identified by US as 'screened negative'.

Histology technique for axillary nodes: haematoxylin and eosin.

No reporting of blinding with regard to either test (US) or gold standard (axillary clearance) results.

Bartonkova, Schneiderova, Standara, Fait & Fabian . Sensitivity of ultrasound examination of axillary nodes in breast cancer. Ceska.Radiologie. 60[2]. 2006.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Czech Republic (sometimes also rendered as Czechia, setting: Secondary care

Inclusion criteria 196 consecutively treated patients with breast cancer.

Exclusion criteria Not known.

Population number of patients = 196.

Interventions Aim: to evaluate the role of US in assessing the status of axillary nodes.

Patients underwent axillary US plus definitive surgical staging.

Outcomes Staging performance of axillary US.

Follow up Not reported.

Results A mean of 8 axillary nodes were examined to provide definitive histology.

Staging performance of US in detecting axillary metastases:

Sensitivity = $87/138 = 63\%$ [95% CI 55%-71%]

Specificity = $43/58 = 74\%$ [95% CI 62%-84%]

PPV = $87/102 = 85\%$ [95% CI 77%-91%]

NPV = $43/94 = 46\%$ [95% CI 36%-56%]

General comments Article written in Czeck: data extracted from tabulated data in the paper plus English language abstract.

Results should be interpreted with caution since entire paper not read.

Staging data are based on the entire series of patients (n=196), who were a consecutive series.

Brancato, Zappa, Bricolo, Catarzi, Risso, Bonardi, Cariaggi, Bianchin, Bricolo, Rosselli Del, Cataliotti, Bianchi & Ciatto . Role of ultrasound-guided fine needle cytology of axillary lymph nodes in breast carcinoma staging. Radiol.Med (Torino) 108[4]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria 159 consecutively treated patients with breast cancer. There were 4 cases of bilateral cancer making a total of 163 axillae but axillary surgery was omitted in four cases, leaving 159 axillae evaluable (155 patients).

Exclusion criteria None reported.

Population number of patients = 159, age range 23 to 89 years, mean age = 59 years.

Interventions Aim: to evaluate the efficacy US guided FNAC in the staging of breast cancer and in the reduction of inappropriate surgery i.e. SLNB where the axilla is positive, or axillary clearance where the axilla is negative.

All patients underwent grey scale US and FNAC was performed in all cases with nodes visualised on US.

Outcomes Staging performance of US alone and US guided FNAC;

Inappropriate surgery avoided through use of US guided FNAC.

Cost.

Follow up Not reported.

Results The rate of visualisation of axillary nodes on US was 133/159 = 83.6%.

Staging performance of US:

Sensitivity = 45/70 = 64% [95% CI 53%-75%]

Specificity = 77/89 = 87% [95% CI 78%-92%]

PPV = 45/57 = 79% [95% CI 67%-88%]

NPV = 77/102 = 75% [95% CI 66%-83%]

Staging performance of combined US and FNAC:

Sensitivity = 41/70 = 59% [95% CI 47%-69%]

Specificity = 89/89 = 100% [95% CI 96%-100%]

PPV = 41/41 = 100% [95% CI 91%-100%]

NPV = 89/118 = 75% [95% CI 67%-82%]

Avoidance of inappropriate operations in 155 evaluable patients:

1. At the time of the study, accepted practice at the centre was to not perform axillary US/FNAC and to perform axillary clearance in all cases of clinically palpable lymph nodes, and SLNB in non palpable cases. In the light of the study, accepted practice would have resulted in 6 inappropriate axillary

clearances and 34 inappropriate SLNBs.

2. The use of US and FNAC of all visualised nodes as per the study protocol avoided all 6 inappropriate axillary clearances and 5 of 34 inappropriate SLNBs.

3. In a post hoc analysis, if US were performed in all cases but FNAC only in cases with suspicious nodes on US, then all 6 inappropriate axillary clearances and 3 of 34 inappropriate SLNBs.

Cost:

1. The cost of staging one patient by accepted practice (no axillary US/FNAC) was EUR 104.

2. The use of US and FNAC of all visualised nodes as per the study protocol resulted in a cost of EUR 103 to stage one patient.

3. In a post hoc analysis, if US were performed in all cases but FNAC only in cases with suspicious nodes on US, then the cost of staging one patient was calculated as EUR 90.

The use of US and FNAC in cases (2) and (3) above was associated with no additional average cost per patient to avoid inappropriate surgery.

General comments On US, criteria for suspicious nodes were:
enlargement/assymetry;
increased echogenicity;
irregular structure of the medulla;
absence of hypechoic hilum;
greater longitudinal diameter than transverse diameter.

Gold standard was either SLNB or axillary clearance (histological technique not reported).

Cytology smears from FNAC were reported 'in accordance with European Community recommendations'.

Blinding not reported.

Inappropriate procedures were defined as an axillary clearance in the case of negative histology or a SLNB in the case of positive histology.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Chandawarkar & Shinde . Preoperative diagnosis of carcinoma of the breast: Is a 'cost-cutter' algorithm tenable? J Surg Oncol 64[2]. 1997.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: US/India, setting: Secondary care

Inclusion criteria 109 patients prospectively recruited, with breast cancer of stage pT1-pT4, who were scheduled for radical mastectomy.

Exclusion criteria Not reported.

Population number of patients = 109, age range 23 to 69 years.

Interventions Aim: to assess the staging performance of palpation, US and mammography in patients with breast cancer.

All patients underwent preoperative clinical examination including palpation of the axilla, followed by US axilla and then mammography of the breast and axilla.

Outcomes Staging performance of palpation, US and mammography.

Follow up Not reported.

Results Staging performance of axillary mammography:

Sensitivity = 69%

Specificity = 67%

PPV = 86%

NPV = 43%

Staging performance of axillary US:

Sensitivity = 77%

Specificity = 71%

PPV = 88%

NPV = 52%

Staging performance of axillary palpation:

Sensitivity = 88%

Specificity = 85%

PPV = 94%

NPV = 72%

Staging performance of combined axillary mammography plus palpation:

Sensitivity = 90%

Specificity = 86%

PPV = 95%

NPV = 76%

Staging performance of combined axillary US plus palpation:

Sensitivity = 94%

Specificity = 90%

PPV = 98%

NPV = 82%

General comments No criteria reported for positive test result for palpation, US or mammography.

Gold standard was radical mastectomy; pathological technique not described; blinding not described.

Data provided in paper is insufficient to see details e.g. the numbers of patients with successful imaging, or to calculate confidence intervals.

Couto, Dias, Goncalo, Pinto & de Oliveira . Diagnostic value of ultrasound and color Doppler in identifying axillary lymph node metastases in patients with breast cancer. Eur J Gynaecol.Oncol 25[5]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Portugal, setting: Secondary care

Inclusion criteria 55 patients with biopsy-proven breast cancer of stage T1-2, N0 with no indications for neoadjuvant treatment.
One patient had bilateral breast cancer.

Exclusion criteria None reported.

Population number of patients = 55.

Interventions Aim: to evaluate the diagnostic ability of US and colour doppler to identify metastases in axillary lymph nodes.

All patients underwent US/doppler of the axilla and axillary dissection.

Outcomes Staging performance of US/doppler.

Follow up Not reported.

Results Staging performance of US/doppler:

Sensitivity = $15/21 = 71\%$ [95% CI 50%-86%]

Specificity = $25/35 = 71\%$ [95% CI 55%-84%]

PPV = $15/25 = 60\%$ [95% CI 41%-77%]

NPV = $25/31 = 81\%$ [95% CI 64%-91%]

General comments Criteria for suspicion of metastasis on US/doppler were:
globular shape;
irregular cortical thickening;
loss of germinal echogenicity;
intranodal hypoechogenic mass;
increased vascularisation in the cortex;
increased blood flow rates.

Authors describe 'prospective study' but do not state that the patients were a consecutive series. Definitive histology technique not described. No evidence presented of blinding of researchers.

Staging results are reported for 56 axillae in 55 patients.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:
http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Damera, Evans, Cornford, Wilson, Burrell, James, Pinder, Ellis, Lee & Macmillan . Diagnosis of axillary nodal metastases by ultrasound-guided core biopsy in primary operable breast cancer. Br J Cancer 89[7]. 2003.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria 166 patients with operable, invasive breast cancer.

Exclusion criteria Patients with definite locally advanced disease.

Study also excludes patients with suspicious nodes clinically or by imaging that were found to be non-malignant by biopsy or definitive surgery and also patients who did not proceed to definitive surgery.

Population number of patients = 166, age range 33 to 81 years.

Interventions Aim: to evaluate US guided core biopsy of abnormal axillary nodes in order to decide between axillary clearance or axillary sample/sentinel node biopsy.

Patients underwent US axilla. Patients with abnormal nodes on US underwent US guided core biopsy or FNA.

Patients with metastases detected by US plus core biopsy/FNA underwent axillary clearance to level III.

Patients with no metastases detected by US plus core biopsy/FNA underwent axillary sampling or SLNB.

Outcomes Diagnostic performance of US alone and US with core biopsy/FNA.

Follow up Not reported.

Results Rate of detection of nodes by US = $103/166 = 62\%$.

Nodes were suspicious on US in $54/103 = 52.4\%$ of patients with nodes seen on US, and these 54 patients underwent US guided biopsy.

Staging performance of US:

Sensitivity = 55%

Specificity = 82%

PPV = 74%

NPV = 65%

Staging performance of US guided biopsy:

Sensitivity = 42%

Specificity = 100%

PPV = 100%

NPV = 74%

The sensitivity of 42% represents 27 patients out of all those with axillary

metastases eventually revealed by surgery (64), who could proceed straight to axillary clearance on the basis of US guided biopsy.

General comments Nodes defined as suspicious on US were those with a longitudinal axis: transverse axis of greater than 2 or a nodal cortex thicker than 2mm.

Staging results classify nodes that were not visualised as failures e.g. false negatives.

De Kanter, Menke-Pluijmers, Henzen-Logmans, van Geel, van Eijck, Wiggers & Eggermont . Reasons for failure to identify positive sentinel nodes in breast cancer patients with significant nodal involvement. Eur J Surg Oncol 32[5]. 2006.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria 161 clinically node-negative patients with breast cancer, due to undergo definitive surgery.

Exclusion criteria None reported, patients appear to be a consecutive series.

Population number of patients = 161, mean age = 56 years.

Interventions Aim: to investigate the incidence of cases where a falsely negative SLNB result occurs, and to explore explanatory factors.

All patients underwent US axilla with FNAC, followed by SLNB plus axillary clearance.

Outcomes Provides data to derive staging outcomes for US plus FNAC.

Follow up Not reported.

Results Staging performance of US with FNAC:

Sensitivity = $31/79 = 39\%$ [95% CI 29%-50%]

Specificity = $82/82 = 100\%$ [95% CI 96%-100%]

PPV = $31/31 = 100\%$ [95% CI 89%-100%]

NPV = $82/130 = 63\%$ [95% CI 55%-71%]

General comments Study primarily explores a hypothesis to explain cases of falsely negative SLNB, but provides sufficient data (in table 4) to derive staging performance of US with FNAC.

Gold standard: axillary clearance. All axillary nodes were examined using haematoxylin and eosin histology (and sentinel nodes with IHC).

Data present US/FNAC result as 'malignant'/'not malignant'. This indicates that any cases in which no nodes were seen on US would be classed as 'not malignant', pending the gold standard result.

No reporting of blinding.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe, Cardiff University:
http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Deurloo, Tanis, Gilhuijs, Muller, Kroger, Peterse, Rutgers, Valdes & Schultze Kool . Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer.[see comment]. Eur J Cancer 39[8]. 2003.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria 265 patients with breast cancer and clinically uninvolved axillary nodes, including 3 patients with bilateral breast cancer, hence data represent 268 axillary procedures.

Exclusion criteria Stated by inclusion criteria.

Population , age range 27 to 91 years, mean age = 56 years.

Interventions Aim: to evaluate the role of preoperative US plus FNAC in preventing unnecessary SLNB in patients with breast cancer.

Patients underwent US axilla. Patients with suspicious lymph nodes underwent FNAC. Patients with tumour cells detected by FNAC underwent axillary clearance.

Patients with no cancer cells detected by FNAC or in whom US revealed no lymph nodes underwent SLNB.

Outcomes Rate of prevention of SLNB by detecting axillary disease preoperatively.

Quantitative features on US to predict nodal involvement (data not shown)

Data permit calculation of staging performance of combined US and FNAC.

Follow up Not reported.

Results The success rate of US to detect axillary nodes was 93/268 = 34.7%.

Staging performance of combined US and FNAC:

Sensitivity = 37/121 = 30.6% [95% CI 23.1%-39.3%]

Specificity = 147/147 = 100% [95% CI 97.5%-100%]

PPV = 100% [95% CI 90.6%-100%]

NPV = 63.6% [95% CI 57.3%-70.0%]

Of all 268 cases, 37 (13.8%) were spared SLNB procedures.

General comments On US, nodes were considered suspicious if the cortex appeared atypical or if the smallest diameter was ≥ 5 mm.

Staging performance outcomes for combined US plus FNAC calculated by constructing the 2:2 table from the data provided; failure to find nodes by US, failure to perform FNAC or no cells found by FNAC all classed as negative [95% CIs provided by Cardiff University: R Newcombe, http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls].

Dixon, Walsh, Paterson & Chetty . Colour Doppler ultrasonography studies of benign and malignant breast lesions. Br J Surg 79[3]. 1992.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria Study included two groups:
32 randomly selected patients with cytologically proven breast cancer;
21 patients with cytologically proven benign breast mass (no data shown).

Exclusion criteria Not reported.

Population number of patients = 53, age range 15 to 71 years.

Interventions Aim: to evaluate the role of US with colour doppler imaging in illustrating primary breast cancer tumours and axillary nodal metastases.

32 patients with cytologically proven breast cancer underwent preoperative US with colour doppler of the breast (no data shown) and the axilla, followed by surgical axillary staging.

Outcomes Staging performance of US with colour doppler.

Follow up Not reported.

Results Axillary nodes were identified in 31 patients. Definitive histological assessment of the axilla was available for 29 patients.

Staging performance of US plus colour doppler:

Rate of detection of axillary nodes by US = $31/32 = 97\%$.

Sensitivity = $9/12 = 75\%$ [95% CI 47%-91%]

Specificity = $17/17 = 100\%$ [95% CI 82%-100%]

PPV = $9/9 = 100\%$ [95% CI 70%-100%]

NPV = $17/20 = 85\%$ [95% CI 64%-95%]

General comments Two groups in the study appear to be convenience samples, although data provided here for one series only.

Criteria for suspicious nodes on US and colour doppler:

For nodes seen on US, any clear-cut, persistent doppler signal in or immediately around the node.

Gold standard was either axillary clearance or axillary node sample. No details provided of histological methods. No evidence of blind assessment of results.

Staging results are reported for 29 patients with definitive histological data available (gold standard). Numbers involved are small. 2:2 table constructed from data provided in paper.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls

Esen, Gurses, Yilmaz, Ilvan, Ulus, Celik, Farahmand & Calay . Gray scale and power Doppler US in the preoperative evaluation of axillary metastases in breast cancer patients with no palpable lymph nodes. Eur Radiol. 15[6]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Turkey, setting: Secondary care

Inclusion criteria 85 consecutive patients with breast cancer and clinically non-palpable axillary nodes.

Exclusion criteria 2 patients were found to have benign disease by definitive surgery and were excluded from the analysis.

Population number of patients = 85, age range 30 to 78 years, mean age = 56 years.

Interventions Aim: to evaluate the staging performance of US with colour doppler imaging in patients with breast cancer and clinically negative axillary nodes.

All patients underwent US plus colour doppler of the axilla followed by axillary clearance to levels I and II.

Outcomes Staging performance of grey scale US and doppler imaging.

Follow up Not reported.

Results Rate of detection of axillary nodes by US = 82/83 = 98.8%.

Staging performance of grey scale US:

Sensitivity = 81%

Specificity = 94%

PPV = 93%

NPV = 85%

Staging performance of doppler US:

Sensitivity = 51%

Specificity = 97%

PPV = 94%

NPV = 69%

Staging performance of combined grey scale/doppler:

Sensitivity = 86%

Specificity = 94%

PPV = 91%

NPV = 90%

General comments Criteria for suspicious nodes on US/doppler:

Absence of echogenic hylum;

Diffuse/asymmetric thickening of the hypoechoic cortex;

Peripheral vascularisation.

No details provided for histological technique. No evidence of blinding.

Heusinger, Lohberg, Lux, Papadopoulos, Imhoff, Schulz-Wendtland, Beckmann & Fasching . Assessment of breast cancer tumor size depends on method, histopathology and tumor size itself*. Breast Cancer Research & Treatment 94[1]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Germany, setting: Secondary care

Inclusion criteria 486 patients with invasive breast cancer. Results reported are for those who underwent axillary US plus definitive histology, identified from a prospective, consecutive series of 503 patients.

Exclusion criteria Not reported.

Population number of patients = 486, mean age = 56 years.

Interventions Aim: to ascertain the value of axillary US in patients with invasive breast cancer.

All patients underwent US axilla and definitive axillary surgery.

Outcomes Staging performance of axillary US.

Follow up Not reported.

Results Staging performance of axillary US:

Sensitivity = $64/156 = 41\%$ [95% CI 34%-49%]

Specificity = $307/330 = 93\%$ [95% CI 90%-95%]

PPV = $64/87 = 74\%$ [95% CI 63%-82%]

NPV = $307/399 = 77\%$ [95% CI 73%-81%]

General comments Criteria for suspicious axillary nodes on US not reported. Definitive histology (gold standard) data is tabulated but no details are provided on surgical procedure nor histological technique.

No reporting of blinding.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Lee, Lee, Su, Liu & Lee . Color Doppler ultrasound evaluation of axillary lymph node in patients with breast tumor. Journal of Medical Ultrasound 4[3]. 1996.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Taiwan (ROC), setting: Secondary care

Inclusion criteria 39 female patients with 41 breast cancer tumours.

Exclusion criteria Not reported.

Population number of patients = 39, age range 36 to 80 years, mean age = 52 years.

Interventions Aim: to evaluate the capability of colour doppler US to detect axillary nodal metastases in patients with breast cancer.

All patients underwent preoperative colour doppler US followed by axillary clearance of level I-III.

Outcomes Staging performance of colour doppler US.

Follow up Not reported.

Results Staging performance of grey scale US alone:

Sensitivity = $14/18 = 78\%$ [95% CI 55%-91%]

Specificity = $19/23 = 83\%$ [95% CI 63%-93%]

PPV = $14/18 = 78\%$ [95% CI 55%-91%]

NPV = $19/23 = 83\%$ [95% CI 63%-93%]

Staging performance of combined grey scale and colour doppler US:

Sensitivity = $13/18 = 72\%$ [95% CI 49%-88%]

Specificity = $22/23 = 96\%$ [95% CI 79%-99%]

PPV = $13/14 = 93\%$ [95% CI 69%-99%]

NPV = $22/27 = 81\%$ [95% CI 63%-92%]

General comments Study is limited by small series size.

40 primary tumours were malignant on definitive surgery, in 39 patients.

Diagnostic criteria on colour doppler US:

Any definable mass in the axilla was taken to be an axillary node. Any persistent colour doppler signal was recorded as a suspicious node.

Gold standard was axillary clearance; no details provided of histological technique. Blinding not reported.

2x2 contingency tables for grey scale US versus gold standard and combined grey scale with colour doppler versus gold standard provided. Staging outcomes are calculated with a total of 41 tumours, one of which was benign, with the effect of lowering the prevalence of axillary disease.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe, Cardiff University:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls

Lemos, Dias, Goncalo, Pinto, Fernandes & Oliveira . Detection of axillary metastases in breast cancer patients using ultrasound and colour Doppler combined with fine needle aspiration cytology. Eur J Gynaecol.Oncol 26[2]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Portugal, setting: Secondary care

Inclusion criteria 40 patients with biopsy-proven operable, invasive breast cancer of stage T1-2, N0.

Exclusion criteria Patients due to receive neoadjuvant chemotherapy.

Population , age range 38 to 85 years, mean age = 59 years.

Interventions Aim: to evaluate the staging performance of colour doppler US with FNAC in patients with invasive breast cancer.

All patients underwent US colour doppler of the axilla with FNAC performed on suspicious nodes.

Outcomes Staging performance of colour doppler US with FNAC.

Follow up Not reported.

Results Staging performance of combined greyscale, colour doppler US and FNAC:

Sensitivity = 55%

Specificity = 100%

PPV = 100%

NPV = 85%

General comments Criteria for suspicious nodes:

Grey scale US:

Globular shape;

Increased cortical thickness;

Hypoechoic germinal centre;

Presence of 'nodes within the lymph node'.

Doppler:

Increased flow globally or peripherally;

High velocity flow.

Gold standard was histological findings of axillary clearance. Histological technique not reported.

Study is limited by small series size.

Nori, Bazzocchi, Boeri, Vanzi, Nori, Mangialavori, Distante, Masi, Simoncini & Londero . Role of axillary lymph node ultrasound and large core biopsy in the preoperative assessment of patients selected for sentinel node biopsy. Radiol.Med (Torino) 109[4]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria 117 women scheduled for breast conserving surgery and SLNB.

Exclusion criteria Clinically involved axillary nodes;
Multifocal breast cancer;
Pregnancy;
Previous breast surgery/excisional biopsy.

Of 117 eligible patients in the series, 15 were excluded, 6 due to benign pathology and 9 due to failure to visualise a minimum of 4 axillary nodes on US. Therefore staging outcomes are based on 102 patients.

Population number of patients = 102, age range 29 to 88 years, mean age = 54 years.

Interventions Aim: to evaluate the staging performance of axillary US with US guided core biopsy in patients with breast cancer scheduled for SLNB.

All patients underwent US axilla (including colour doppler in an undisclosed number of patients). US guided core biopsy was planned in patients with suspicious nodes on US.

Outcomes Staging performance of US guided core biopsy.

Follow up Not reported.

Results The rate of visualisation of axillary nodes on US (based on 4 exclusions noted above) was 113/117 = 96.6%.

Staging performance of US alone:

Sensitivity = 13/34 = 38% [95% CI 24%-55%]

Specificity = 56/68 = 82% [95% CI 72%-90%]

PPV = 13/25 = 52% [95% CI 34%-70%]

NPV = 56/77 = 73% [95% CI 62%-81%]

Core biopsy:

Core biopsy was indicated in 25 patients with suspicious nodes on US. 11 patients underwent core biopsy and core biopsy was omitted in 14 patients due to deep nodes or nodes close to blood vessels. Compared to definitive histology, core biopsy results were truly positive in 8 patients, truly negative in 2 patients and falsely negative in 1 patient.

General comments In some cases colour doppler US was used to avoid puncture of large blood vessels when performing core biopsy. In other cases core biopsy was not performed due to risk of bleeding. Colour doppler was also used in some cases for diagnostic purposes, but was not investigated per

se. Use of doppler may enhance the performance of grey scale US in this study.

Criteria for suspicious nodes on grey scale US:

globular morphology;

disappearance of hilar fat hyperechogenicity;

eccentric focal thickening/denting of cortex.

Criteria for suspicious nodes on colour doppler US (used selectively):

peripheral vascularisation;

focal absence of vascularisation;

displacement of intranodal vessels.

Definitive histology results are reported, but not the technique used. Paper implies that gold standard was either SLNB or axillary dissection as indicated by US or core biopsy, but not stated absolutely. No reporting of blinding.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Perre, Koot, De, Weits & Leguit . Colour Doppler ultrasonography in the diagnosis of axillary lymph node metastases in breast cancer. Breast 5[1]. 1996.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria 98 consecutive patients with breast cancer.

Exclusion criteria None stated.

Population number of patients = 98.

Interventions Aim: to determine the value of colour doppler US in the preoperative detection of axillary metastases in patients with breast cancer.

All patients underwent colour doppler US.

Outcomes Staging performance of colour doppler US.

Follow up Not reported.

Results Staging performance of colour doppler US for the whole series (n=100):

Sensitivity = $16/32 = 50\%$ [95% CI 34%-66%]

Specificity = $56/68 = 82\%$ [95% CI 72%-90%]

PPV = $16/28 = 57\%$ [95% CI 39%-73%]

NPV = $56/72 = 78\%$ [95% CI 67%-86%]

Staging performance of colour doppler US for patients who underwent prior breast surgery (n=26):

Sensitivity = $1/3 = 33\%$ [95% CI 6%-79%]

Specificity = $20/23 = 87\%$ [95% CI 68%-95%]

PPV = $1/4 = 25\%$ [95% CI 5%-70%]

NPV = $20/22 = 91\%$ [95% CI 72%-97%]

Staging performance of colour doppler US for patients who did not undergo prior breast surgery (n=74):

Sensitivity = $15/29 = 52\%$ [95% CI 34%-69%]

Specificity = $36/45 = 80\%$ [95% CI 66%-89%]

PPV = $15/24 = 63\%$ [95% CI 43%-79%]

NPV = $36/50 = 72\%$ [95% CI 58%-83%]

General comments Data are presented for 100 axillae in 98 patients.

Criteria for suspicious lymph nodes:

Nodes visualised on grey scale US were studied with colour doppler US, and peripheral flow was regarded as malignant (central flow benign).

Gold standard: axillary clearance. Histological technique not reported. Blinding not reported.

26 patients underwent breast surgery (but not axillary clearance) prior to axillary US. Results are also provided for these patients separately. Sub

group analysis results in small numbers (and wide confidence intervals).

For calculation of outcomes, authors classified equivocal colour doppler US findings (n=5) as negative (whether proven false negative or true negative by definitive histology).

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe,
Cardiff University:
http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Podkrajsek, Music, Kadivec, Zgajnar, Besic, Pogacnik & Hocevar . Role of ultrasound in the preoperative staging of patients with breast cancer. Eur Radiol. 15[5]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Slovenia, setting: Secondary care

Inclusion criteria 165 patients with biopsy-proven breast cancer and clinically uninvolved axillary nodes, who were scheduled for SLNB.

Exclusion criteria None stated.

Population number of patients = 165, age range 26 to 80 years, mean age = 56 years.

Interventions Aim: to evaluate the utility of grey scale and colour doppler US with US guided FNAC in the diagnosis of axillary metastases.

All patients underwent preoperative US axilla. Nodes seen on grey scale US underwent colour doppler evaluation. Nodes that were suspicious for malignancy underwent US guided FNAC.

Patients with any axillary malignancy detected by FNAC underwent axillary clearance to level I and II. Patients with no axillary malignancy detected by FNAC underwent SLNB.

Outcomes Staging performance of US alone (including colour doppler) and of US guided FNAC.

Follow up Not reported.

Results Rate of detection of lymph nodes by US = $90/165 = 55\%$ [95% CI 47%-62%].

Staging performance of combined grey scale/colour doppler US and FNAC:

1. As reported in paper:

Sensitivity = $32/38 = 84\%$ [95% CI 70%-93%]

Specificity = $10/11 = 91\%$ [95% CI 62%-98%]

PPV = $32/33 = 97\%$ [95% CI 85%-99%]

NPV = $10/16 = 63\%$ [95% CI 39%-82%]

Note: these values are based only on 49 patients who underwent FNAC. The values considering all 165 patients in the series are as follows:

2. For all patients:

Sensitivity = $32/65 = 49\%$ [95% CI 37%-61%]

Specificity = $99/100 = 99\%$ [95% CI 95%-100%]

PPV = $32/33 = 97\%$ [95% CI 85%-99%]

NPV = $99/132 = 75\%$ [95% CI 67%-82%]

Staging performance of grey scale/colour doppler US alone:

Sensitivity = $38/65 = 58\%$ [95% CI 46%-70%]

Specificity = $89/100 = 89\%$ [95% CI 81%-94%]

PPV = $38/49 = 78\%$ [95% CI 64%-87%]

NPV = 89/116 = 77% [95% CI 68%-83%]

In patients with no detectable lymph nodes on US, the prevalence of axillary metastases by SLNB was 18/75 = 24% [95% CI 16%-35%].

In the whole series 32/165 = 19% [95% CI 14%-26%] of patients were spared a second surgical procedure.

General comments Colour doppler US was performed on all nodes seen on grey scale US. Study does not report outcomes for grey scale US and colour doppler US separately, but combined.

Criteria for suspicious nodes on US:

Longitudinal:transverse axes ratio <1.5;

Hilus not visible;

Cortex thickness >3mm;

non-hilar-peripheral or mixed vascularity (on colour doppler).

Gold standard for staging outcomes is either SLNB or axillary clearance. Histological technique for FNAB and for SLNB was immunohistochemistry. Technique for axillary clearance was reported as 'standard method'. No reporting of blinding.

Staging outcomes for the whole series of patients denote patients with no nodes seen on US or in whom FNAC was not performed as 'negative on US' and patients with equivocal results on FNAC as 'negative on FNAC'.

95% CIs calculated using spreadsheet: acknowledgement to R Newcombe, Cardiff University:
http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

Stewart, Meacock, Ljutikov, Evans, Wasan, Milnes, Akbar, Dutt, Li & Michell .
Ultrasound and fine needle aspiration assessment of the axilla in patients with
operable invasive breast cancer. Breast Cancer Research 8[Suppl 1]. 2006.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria 71 patients with invasive breast cancer.

Exclusion criteria Not reported.

Population number of patients = 71.

Interventions Aim: to evaluate US with FNAC in staging the axilla in patients
with invasive breast cancer.

All patients underwent US axilla with FNAC, and axillary staging surgery.

Outcomes Staging performance of US with FNAC.

Follow up Not reported.

Results Staging performance of US with FNAC:

Sensitivity = 50%

Specificity = 100%

PPV = 100%

NPV = 71%.

General comments Study available in abstract only.

US criteria to indicate FNAC were:

Cortex >2mm;

Eccentrically thickened cortex;

Loss of normal morphology.

Gold standard was axillary surgery; no details of histology technique provided,
nor of blinding.

Walsh, Dixon, Chetty & Paterson . Colour Doppler studies of axillary node metastases in breast carcinoma. Clin Radiol. 49[3]. 1994.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria 80 patients with breast cancer were randomly selected over a period of 8 months. One patient had bilateral cancer. T stage was T1 (n=15), T2 (n=53), T3 (n=8), or T4a (n=5, where n refers to number of tumours).

Exclusion criteria Not reported.

Population number of patients = 75, age range 22 to 71 years, mean age = 54 years.

Interventions Aim: to determine whether colour doppler US can reliably demonstrate axillary node metastases in patients with breast cancer.

All patients underwent grey scale US and any nodes visualised underwent colour doppler US.

Outcomes Staging performance of colour doppler US.

Follow up Not reported.

Results Staging performance of colour doppler US:

Sensitivity = $23/33 = 70\%$ [95% CI 53%-83%]

Specificity = $41/42 = 98\%$ [95% CI 88%-100%]

PPV = $23/24 = 96\%$ [95% CI 80%-99%]

NPV = $41/51 = 80\%$ [95% CI 68%-89%]

General comments Criterion for suspicious nodes on colour doppler US: signals within 5mm of the periphery of the lymph node or within the lymph node.

75 patients underwent 'gold standard' definitive staging procedure: sampling of a minimum of 6 nodes. Pathological technique not described, but the single pathologist was blind to the colour doppler findings.

Retrospective case series

Hergan, Haid, Zimmermann & Oser . [Preoperative axillary ultrasound in breast carcinoma: value of the method in routine clinical practice]. [German]. *Ultraschall Med* 17[1]. 1996.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Austria, setting: Secondary care

Inclusion criteria 74 patients with breast cancer who underwent US, identified from a larger series of 191 patients.

Exclusion criteria Not known.

Population number of patients = 74, age range 34 to 82 years, mean age = 61 years.

Interventions Aim: to compare the staging performance of axillary ultrasound with clinical palpation and definitive histology.

Patients underwent clinical palpation of the axilla, preoperative US of the axilla and axillary clearance to levels I and II.

Outcomes Staging performance of axillary ultrasound with clinical palpation.

Follow up Not known.

Results Staging performance of axillary US (all T stages):

Sensitivity = 68%

Specificity = 100%

PPV = 100%

NPV = 88%

Staging performance of axillary US (T1 tumours only):

Sensitivity = 50%

Specificity = 100%

PPV = 100%

NPV = 95%

Staging performance of clinical palpation (all T stages):

Sensitivity = 41%

Specificity = 96%

PPV = 82%

NPV = 79%

Staging performance of clinical palpation (T1 tumours only):

Sensitivity = 25%

Specificity = 100%

PPV = 100%

NPV = 92%

General comments Article in German: information extracted from abstract plus tables/minimal text.

Patients appear to be a consecutive series.

Criteria for suspicious nodes on US:

Round to oval shape;

Long:short ratio <2 ;

Assymmetric hypoechogenic component.

For staging performance results, rate of failure to identify any axillary nodes is not known; data is tabulated for all 74 patients who underwent US. Gold standard was axillary clearance; histological methods not known. Extent of blinding not known.

Sato, Tamaki, Tsuda, Kosuda, Kusano, Hiraide & Mochizuki . Utility of axillary ultrasound examination to select breast cancer patients suited for optimal sentinel node biopsy. Am J Surg 187[6]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria 262 consecutively treated patients patients with biopsy-proven breast cancer of stage T1-3.

Exclusion criteria Pregnancy, multiple primary breast tumours, history of neoadjuvant chemotherapy.

Population number of patients = 262, age range 21 to 83 years, mean age = 55 years.

Interventions Aim: to examine the usefulness of axillary US in selecting patients for SLNB.

All patients underwent US axilla followed by SLNB and axillary clearance.

SLNB technique: radiocolloid.

Histology technique: standard (haematoxylin and eosin)

Outcomes Staging performance of SLNB overall, and considering only patients with no evidence of axillary metastases on US.

Provides data on staging performance of US.

Follow up Not reported.

Results Staging performance of US:

Sensitivity = $50/112 = 45\%$ [95% CI 36%-54%]

Specificity = $146/150 = 97\%$ [95% CI 93%-99%]

PPV = $50/54 = 93\%$ [95% CI 82%-97%]

NPV = $146/208 = 70\%$ [95% CI 64%-76%]

Of the whole series, US detected axillary metastases in $50/262 = 19\%$ of patients [95% CI 15%-24%].

The SN localisation rate was $205/208 = 98.6\%$ in patients with negative result on US, compared to $26/54 = 48.1\%$ in patients with positive result on US: difference 50.4%, [95% CI for difference 37%-63%], $p < 0.005$, (Chi square).

The FNR of SLNB was $9/83 = 10.8\%$ [95% CI 5.8%-19.3%] in all patients, and $1/60 = 1.7\%$ [95% CI 0.3%-8.9%]

in patients with negative US axilla result. These values for accuracy of SLNB were $222/231 = 96\%$ [95% CI 93%-98%] and $204/205 = 99.5\%$ [95% CI 97.3%-99.9%] respectively.

General comments Criteria for suspicious nodes on US: homogeneously hypoechoic node without an echo rich centre.

Gold standard: axillary clearance. Histology technique: standard methods. No

different histology technique was reported for sentinel nodes.

Study does not report a rate of detecting nodes on US, but all 262 patients are classified as either positive or negative on US. This implies a detection rate of 100% but may reflect classification of cases of failure to detect any nodes as 'negative'. Study does not report blinding.

Staging performance of US derived from constructing a 2x2 contingency table, based on data provided in the paper. 95% CIs calculated using spreadsheet: acknowledgement to R Newcombe, Cardiff University: http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls.

van Rijk, Deurloo, Nieweg, Gilhuijs, Peterse, Rutgers, Kroger & Kroon . Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. Ann Surg Oncol 13[1]. 2006.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria 726 patients with clinically T1-T3 (or T4 due to involvement of skin) unifocal breast cancer, who were scheduled for SLNB.

Exclusion criteria Implied by inclusion criteria.

Population number of patients = 726, age range 18 to 94 years, mean age = 58 years.

Interventions Aim: to evaluate the sensitivity of preoperative US with FNAC to detect axillary metastases and hence avoid a SLNB procedure.

All patients underwent axillary US. Patients with suspicious nodes on US underwent FNAC.

If US was not suspicious or if FNAC revealed no metastases, patients underwent SLNB. Patients with axillary metastases by US guided FNAC underwent axillary clearance or axillary RT.

Outcomes Staging performance of US plus FNAC.

Proportion of patients in whom SLNB could be omitted due to detection of axillary metastasis by US and FNAC.

Follow up Not reported.

Results 176/732 axillae were suspicious by US, prompting FNAC.

Of these:

59/176 = 34% were positive for axillary metastasis by FNAC;

117/176 = 66% were negative for axillary metastasis by FNAC.

Of the whole series of patients, 59/726 = 8% were spared SLNB and proceeded to axillary RT or clearance [authors report that these patients may be candidates for neoadjuvant chemotherapy].

271/732 = 37% of all axillae were tumour positive by definitive histology.

Staging performance:

US alone had sensitivity 35% [95% CI 29%-41%] and specificity 82% [95% CI 78%-86%].

FNAC had sensitivity 62% [95% CI 51%-72%] and specificity 99% [95% CI 93%-100%].

Combined technique (US + FNAC) had sensitivity 21% [95% CI 17%-27%] and specificity 99.8% [95% CI 99%-100%], PPV 98% [95% CI 91%-99.7%] and NPV 68% [95% CI 65%-72%].

General comments 726 patients were included; representing 732 treated axillae (i.e. 6 cases of bilateral cancer).

Criteria for suspicious nodes on US were cortex thickness of >2mm, irregular cortex, round or ovoid shape, hypoechoic core, smaller diameter >5mm; later changed to solely a cortex thickness >2.3mm.

NB By US, nodes are reported as 'suspicious' or 'not suspicious' for all patients, implying a 100% node detection rate. It may be the case that nodes that could not be detected on US were classed as 'non suspicious', indicating SLNB.

24 patients received neoadjuvant chemotherapy after US and in cases of negative US result, after SLNB.

FNAC staging performance reported is for all patients with suspicious US results.

Combined technique staging performance is for 732 axillae, and PPV and NPV values are calculated from constructing the 2:2 table from the data [95% CI provided by Cardiff University: R Newcombe, http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls].

UPDATE EVIDENCE

Ciatto, Brancato, Risso, Ambrogetti, Bulgaresi, Maddau, Turco, Houssami. Accuracy of fine needle aspiration cytology (FNAC) of axillary lymph nodes as a triage test in breast cancer staging (2007) *Breast cancer Research & Treatment* 103:85-91

Design: Retrospective Data Analysis **Evidence Level:** 3

Country:

Aim: To examine the accuracy of US-guided FNAC of clinically or sonographically indeterminate or suspicious axillary nodes

Inclusion criteria

All consecutive cases with axillary node FNAC from 1990-March 2005.

Exclusion criteria

Population

N=476; mean age 52 years, average pT size = 21.1mm.

Interventions

Clinical examinations, ultrasound and fine needle aspiration cytology. Ultrasound was performed with knowledge of clinical findings and FNAC was on sonographically abnormal nodes.

Outcomes

Sensitivity and specificity for axillary FNAC

Results

	Excluding C1 (inadequate) results	Including C1 results
FNAC Sensitivity	72.6%	64.6%
FNAC Specificity	95.6%	95.7%
Negative Predictive Value	67.2%	61.3%
Positive Predictive Value	96.6%	96.6%

The likelihood of node FNAC being positive was strongly linked to both tumour grade and stage and was significantly associated with the number of nodes involved with metastases on histology.

	Patients with positive axillary node FNAC
Tumour Grade (p<0.00001) (Excludes 22 positive FNAC in 30 cases where grade not reported/missing)	
Grade 1	21.5%
Grade 2	35.0%
Grade 3	53.4%
Pathological State (p<0.00001)	
T1a	46.6%
T1b	20.0%
T1c	34.2%
T1	66.6%
T2	57.6%
Number of Metastatic Nodes (p<0.001) (Excludes 1 positive FNAC in 3 cases where number of metastatic nodes is not reported/missing)	
1-3	55.1%
4-10	70.6%
>10	81.6%

FNAC sensitivity was highest in women with clinically suspicious nodes; 92.5% (88.2-96.7) as compared with

50.0% (41.3-58.7) in women with sonographically abnormal and clinically negative nodes. Specificity for both groups was high; 81.2% (54.5-96.0) and 97.2% (94.6-99.9) respectively.

The False- Negative rate was 15.3% and the False-Positive rate for the study was 1.4%.

General comments

Abnormal nodes were defined as having enlarged size, absence of hyperechoic hilum, eccentric thickening or asymmetry of the cortex or a greater vertical than horizontal diameter.

Sahoo, Sanders, Roland, Pile, Chagpar. A strategic approach to the evaluation of axillary lymph nodes in breast cancer patients: analysis of 168 patients at a single institution (2007). *The American Journal of Surgery* 194;524-526

Design: Retrospective Data Review **Evidence Level:** 3

Country: USA

Aim: To examine and determine the number of operative procedures that could be excluded using both fine needle aspiration biopsy (FNAB) and/or intra-operative evaluation of the sentinel lymph nodes.

Inclusion criteria

All patients with breast cancer that had their axillae sonographically evaluated.

Exclusion criteria

Population

N=168

Interventions

Outcomes

Sensitivity and specificity of USFNAB

Number of patients who underwent SLNB and immediate ALND based on intra-operative evaluation of SLNs

Results

The overall sensitivity and specificity of USFNAB was 96% and 93% respectively (overall sensitivity and specificity was calculated from those patients who had follow-up).

For the intra-operative diagnosis for SLNB the sensitivity was 98% and specificity was 100%

40 patients with positive USFNAB were spared the additional step of SLNB.

General comments

Somasunder, Gass, Steinhoff, Koeliker, Dizon, Cady, Taneja. Role of ultrasound-guided axillary fine-needle aspiration in the management of invasive breast cancer (2006) *American Journal of Surgery* 192;458-461

Design: Retrospective Data Review **Evidence Level:** 3

Country: USA

Aim: To report on further experience with USFNAB in staging the axilla and its subsequent affect on management decisions.

Inclusion criteria

Women with breast cancer who were undergoing USFNAB for the diagnosis and staging.

Exclusion criteria

Patients with multicentric tumours, inflammatory breast cancer or without surgical axillary evaluation.

Population
N=168

Interventions

Outcomes
Sensitivity and specificity of USFNAB for patients who underwent primary surgery

Results
47% (N=79) patients had positive USFNAB and were spared SLNB having either ALND or NACT followed by ALND.

T Stage	Primary Surgery (N=107)	
	Sensitivity	Specificity
T1	35%	96%
T2	67%	100%
T3/4	78%	100%

Health Economics Summary (for full summary please see Appendix 3 of the full guideline)

A systematic review of the evidence regarding the cost-effectiveness of using pre-treatment ultrasound combined with needle biopsy (US+NB, either fine needle aspiration (FNA) or core biopsy (CB)) to stage the axilla of EBC patients identified three relevant studies: one full economic evaluation (Brancato et al 2004) and two partial economic evaluations (Genta et al 2007; Davies et al 2006). Two of these studies were conducted in Italy (Brancato et al 2004; Genta et al 2007) and the third one in USA (Davies et al 2006). All these studies were cost-consequences analysis, since they reported several health benefit outcomes measured as natural units, mainly the accuracy of the staging procedures and the number of patients avoiding secondary staging with US+NB (among other outcomes). None of the studies estimated the number of QALYs gained with each of the staging strategies. The costs associated with the different staging procedures were estimated and reported, either from the perspective of the hospital (Davies et al 2006), of the health care provider (Brancato et al 2004), or both (Genta et al 2007). However, no price year was reported in any of the studies. In all the studies some sort of extrapolation and/or assumptions were used to obtain the clinical effectiveness of one or more of the staging procedures compared. As the study by Brancato et al (2007) highlighted, considerable variations exist regarding the costs of the different staging procedures across countries; therefore, it is difficult to generalise the results from country to country. This was confirmed by the differences in the unit costs observed across studies: in the study by Davies et al (2006) the cost of SLNB was much higher than that of ANC, i.e. \$6,300 (£3,895) and \$3,700 (£2,287), respectively; on the other hand, the study by Brancato et al (2007) reported a unit cost of €216 (£156) for SLNB and €1,550 (£1,119) for ANC. All studies concluded that US+NB seemed to be a cost-effective staging strategy when compared to SLNB, although none of them stated on what basis they considered cost-effectiveness. All three studies identified the potential of US+NB to lead to cost-savings under specific scenarios.

Summary of individual studies

The study by Brancato et al (2004) was based in a diagnostic study that assessed the accuracy of palpation, US and FNA. The study design seemed appropriate since the three staging procedures were undertaken and compared across all included patients. The results of the diagnostic study were used to simulate five staging strategies by extrapolating the results. The cost analysis was conducted from the Italian NHS perspective and the cost costs included were those of the procedures. The price year was not reported, which would hinder reflation exercises to other settings. The authors reported that considerable variations exist regarding the unit costs of the staging procedures across countries; consequently, results do not seem to be generalisable to settings different to the Italian context. No ICER was provided to identify the additional cost per patient avoiding an inappropriate procedure (although enough information was reported in the paper as to make the corresponding estimation). No sensitivity analyses were conducted to assess the uncertainty surrounding the study results. The authors concluded that the most cost-effective staging procedure appeared to be US for all patients followed by FNA if lymph nodes suspicious at US and immediate ANC in those patients with suspicious nodes at FNA only. This strategy would avoid SLNB in 13 patients over 159 patients examined, at a cost of €133 per patient staged (compared to €104 per patient staged following current practice in the Italian setting). Palpation and US, either alone or in combination, were reported to be inadequate procedures to stage the axilla of BC patients.

The partial economic evaluation by Davies et al (2007) was based on a diagnostic study that assessed the accuracy of US+FNA/CB to stage the axilla in EBC patients. The authors reported the number of patients avoiding SLNB by undergoing US+FNA/CB. In total, 15 patients (out of 37) would avoid SLNB with US+FNA/CB. Since the study included patients at high risk of axillary metastasis, the prevalence of metastasis among the included group of patients was 59% (much higher than that observed from the clinical review of topic 6). No relevant effectiveness outcomes were reported for SLNB. The cost of the SLNB group was estimated by implicitly assuming that all patients with axillary metastasis would be appropriately identified with SLNB (i.e. there would not be false negative patients, which does not correspond with the review of the clinical evidence for this topic). Therefore, the costs related to SLNB may have been overestimated (by assuming that all patients with nodal metastasis would undergo complete clearance, rather than only those actually identified by SLNB). The authors concluded that the use of US+FNA/CB in EBC patients at high risk of axillary metastasis is cost-effective since it can reduce the number of patients undergoing SLNB and decrease the associated costs by approximately 20% (according to their data).

The partial economic by Genta et al (2006) used a somewhat confusing study design, since the effectiveness of three of the staging strategies evaluated seemed to have been obtained through extrapolation of the results of a cohort study assessing the accuracy of US+FNA. On the other hand, the cost analysis compared three alternative staging strategies comprising a combination of staging procedures. There seems to be a contradiction in the study: the authors reported that US+FNA was conducted in patients with clinically positive nodes, while SLNB was conducted in patients with clinically negative nodes (which

would limit any potential comparison between the two staging strategies); however, when results were reported, it seemed that all the patients included in the study had undergone US. The cost analysis did not include only the costs of the staging procedures but also the costs of breast surgery. Additionally, the costs were not compared across the different staging strategies, but the study was limited to compare, for each staging strategy, the costs that the Italian NHS would pay with the costs that the hospital would bill. The price year was not reported. The authors concluded that US+FNA can identify reliably the presence of axillary metastasis and can be used to refer these patients directly to ANC without further SLNB. In total, 33% of patients would avoid SLNB with US+FNA. According to the authors, the cost saving from the lower number of SLNBs conducted seemed to be compensated by the costs of US+FNA.

References

Brancato, B., M. Zappa, et al. (2004). "Role of ultrasound-guided fine needle cytology of axillary lymph nodes in breast carcinoma staging." *Radiologia Medica* 108(4): 345-355.

Davis, J.T., et al., Ultrasound-guided fine-needle aspiration of clinically negative lymph nodes versus sentinel node mapping in patients at high risk for axillary metastasis. *Annals of Surgical Oncology*, 2006. 13(12): p. 1545-1552.

Genta F, Zanon E, Camanni M, Deltetto F, Drogo M, Gallo R, Gilardi C. Cost/accuracy ratio analysis in breast cancer patients undergoing ultrasound-guided fine-needle aspiration cytology, sentinel node biopsy, and frozen section node. *World J Surg* 2007; 31:1155-1163

Evidence Tables
Economic Evaluations

Brancato, B., et al., Role of ultrasound-guided fine needle cytology of axillary lymph nodes in breast carcinoma staging. *Radiologia Medica*, 2004. 108(4): p. 345-355.

Design:

Type of economic evaluation:

Full economic evaluation.

Clinical effectiveness:

A diagnostic study was conducted to assess the accuracy of several staging procedures for axillary metastasis in EBC. Three staging procedures were undertaken for all patients and the reference standard used was reported.

Cost estimation:

The authors estimated the additional costs of alternative staging strategies when compared to clinical practice from the Italian NHS perspective. The costs included were those of the staging procedures undertaken. The Italian's National Health Service price-list was used as the source of unit costs (ultrasonography = €36.15; cytologic examination = €33.78; SLNB (as outpatient procedure) = € 216.29; ANC (i.e. price of mastectomy + ANC – mastectomy) = €1,550). The price year not identified.

Country: Italy, **setting:** Hospital

Inclusion criteria Not stated

Exclusion criteria Not stated

Population

Patients with breast carcinoma (159 patients, 163 axillae examined), with 155 patients (159 axillae) with known lymph node histology available after the study.

Interventions

The accuracy of three staging procedures was assessed in the clinical study: palpation, US and FNAB. Histological findings at SLNB or at ANC were used as the reference standard used to assess accuracy. In study, all patients with visible nodes underwent FNA.

For the economic evaluation, the authors simulated five alternative staging strategies (including Italian current practice) based on the previous staging procedures:

- a. US in all cases, followed by cytology for visible nodes and immediate ANC for positive nodes and SLNB for negative nodes
- b. US in all cases, followed by cytology for suspicious nodes and ANC for those resulting positive, SLNB for the remaining cases.
- c. US for clinically negative axilla, followed by cytology on all visible nodes, and ANC for those with suspicious findings at palpation or cytology, and SLNB in the remaining cases.
- d. US only for those with clinically negative axilla, followed by cytology if suspicious visualised nodes, ANC on suspicious findings at palpation or after cytology, and SL in remaining cases.
- e. Current practice: Palpation with suspicious cases followed by ANC and all other by SLNB (followed by ANC only if positive node involvement is found)

Results –

OUTCOME OF INTEREST	Palpation	US
Sensitivity for palpable lymph nodes	62.9	91.4
Sensitivity for suspicious lymph nodes	51.9	64.3
Specificity for palpable lymph nodes	74.2	22.5
Specificity for suspicious lymph nodes	93.0	86.5
Positive predictive value for palpable lymph nodes	65.7	48.1
Positive predictive value for suspicious lymph nodes	85.7	78.9
Negative predictive value for palpable lymph nodes	71.7	76.9
Negative predictive value for suspicious lymph nodes	70.9	75.5
Visualisation of axillary lymph nodes (%)	-	83

OUTCOME OF INTEREST	US+FNA		
	Excluding inadequate cases	Inadequate cases assumed negative	Inadequate cases assumed positive
Sensitivity	68.3	64.1	58.6
Specificity	100	100	100
Positive predictive value	100	100	100
Negative predictive value	76.5	75.0	75.4

OUTCOME OF INTEREST	A	B	C	D	Current practice
Number of inappropriate ANCs	0	0	6	6	6
Δ Number of inappropriate ANCs compared to current practice	6	6	0	0	-
Number of inappropriate SLNBs	29	31	21	23	34
Δ Number of inappropriate SLNBs compared to current practice	5	3	13	11	-
Total cost (€)	16,511	14,377	21,178	19,213	16,654
Δ average cost to avoid inappropriate surgical procedures (compared to current practice)	-143	-2,277	348	232	-
Cost per staged case (€)	103	90	133	120	104

Other outcomes reported were: true positive and negative patients, false positive and negative patients.

Authors' conclusions –

The authors concluded that the most cost-effective staging procedure appeared to be US for all patients followed by FNA if lymph nodes suspicious at US and immediate ANC in those patients with suspicious nodes at FNA only. Palpation and US, either alone or in combination, are inadequate procedures to stage the axilla of BC patients.

General comments –

The economic evaluation was based in a diagnostic study, which seem appropriate since three staging procedures were undertaken in all possible patients. The results of the diagnostic study were used to simulate five staging strategies by extrapolating the results. The cost analysis appeared to be appropriate given the study question and included the costs of the procedures. The price year was not reported, which would hinder reflation exercises to other settings. The authors reported that considerable variations exist regarding the unit costs of the staging procedures across countries; consequently, results do not seem to be generalisable to settings different to the Italian context. No ICER was provided to identify the additional cost per patient avoiding an inappropriate procedure (although enough information was reported in the paper as to make the corresponding estimation). No sensitivity analyses were conducted to assess the uncertainty surrounding the study results.

Partial Economic Evaluations

Davies JT, Brill YM, Simmons S, et al. Ultrasound-guided fine-needle aspiration of clinically negative lymph nodes versus sentinel node mapping in patients at high risk for axillary metastasis. *Annals of Surgical Oncology* 2006; 13(12):1545-1552.

Design:

Type of economic evaluation:

Partial economic evaluation (effectiveness for SLNB was not reported, only costs). The study was a cost-consequences analysis.

Clinical effectiveness:

Cohort study

Cost estimation:

Costs included were those of the hospital, according to the number of procedures undertaken, and included: ultrasonography (unit cost: \$200), FNA/CB (unit cost: \$1250), SLNB (unit cost: \$6300) and complete axillary node dissection (unit cost: \$3700). The source of the costs was the hospital administration. The cost estimation does not include physician charges and does not represent actual insurance reimbursement. No price year reported.

Country: USA, **setting:** Hospital

Inclusion criteria Patients with clinically negative axilla at high risk of axillary nodal metastasis (i.e. grade III, size > 1cm or grade II, size > 1.5cm at the time of initial diagnosis, with or without lymphovascular invasion).

Exclusion criteria Not stated

Population number of patients = 37 (selected from a total of 144 patients)

Interventions

Ultrasound-guided fine-needle aspiration biopsy (US+FNA/CB) followed by complete axillary node dissection in patients with detected positive nodes, and by SLNB in patients with negative nodes (whom, at the same time, would follow complete axillary node dissection if positive nodes detected).

Follow up After sonographic evaluation of the axilla

Results

OUTCOME OF INTEREST	US+FNA/CB	SLNB
Patients with axillary metastasis at the time of definitive surgery: number (%)	22 (59%)	-
Patients with accurate prediction of axillary status with FNA: number (%)	16 of 21 (71%)	-
Patients with accurate prediction of axillary status with CB: number (%)	13 of 16 (81%)	-
False negative patients with FNA/CB: number	3	-
False negative patients for US only: number	4 of 15	-
Patients avoiding SLNB by US+FNA/CB	15	-
Total cost per group of 37 patients (\$)	254,900	314,500
Cost per patient (\$)	6,890	8,500

Other outcomes reported were: the number of patients with normal versus abnormal US; the number of patients with positive/negative US/FNA after abnormal US; the number of patients with SLNB positive/negative after normal US; the number of patients with SLNB positive/negative after negative US/FNA results.

Authors' conclusions –

The authors concluded that the use of US+FNA/CB in EBC patients at high risk of axillary metastasis is cost-effective since it can reduce the number of patients undergoing SLNB and decrease the associated costs by approximately 20% (according to their data).

General comments –

It seems that the gold standard used to assess accuracy of US+FNA/CB was SLNB or ANC, depending on the last procedure the patients undertook; while ANC is an accepted gold standard to identify nodal status, SLNB is not 100% sensitive, which introduces potential biases into the accuracy results. Note that this seems to be a potential bias present in most of the studies of the same type, since patients identified as node negative also by SLNB do not usually undergo any further staging procedure. In terms of the relevance of this study for the PICO question posed, the most relevant outcome to consider here would be the number of patients avoiding SLNB by undergoing US+FNA/CB. In total, 15 patients (out of 37) would avoid SLNB with US+FNA/CB. Since the study included patients at high risk of axillary metastasis, the prevalence of metastasis among the included group of patients was 59% (much higher than that observed from the clinical review of topic 6).

No relevant effectiveness outcomes were reported for SLNB. The cost of the SLNB group was estimated by implicitly assuming that all patients with axillary metastasis would be

appropriately identified with SLNB (i.e. there would not be false negative patients, which does not correspond with the review of the clinical evidence for this topic). Therefore, the costs related to SLNB may have been overestimated (by assuming that all patients with nodal metastasis would undergo complete clearance, rather than only those actually identified by SLNB).

No quality assessment checklist was completed for this study since it was a partial economic evaluation.

Genta F, Zanon E, Camanni M, et al. Cost/accuracy ratio analysis in breast cancer patients undergoing ultrasound-guided fine-needle aspiration cytology, sentinel node biopsy, and frozen section of node. *World J Surg* 2007; 31:1155-1163.

Design:

Type of economic evaluation:

Partial economic evaluation since effectiveness for three of the four staging strategies considered at analysis was hypothetical. The study was a cost-consequences analysis.

Clinical effectiveness:

Cohort study

Cost estimation:

Two alternative perspectives were considered when estimating the costs: that of the Italian NHS and that of the hospital (i.e. amount billed by the hospital for the procedures). The costs included not only the staging procedures undertaken but the costs of breast surgery as well. For the hypothetical interventions, costs were extrapolated using data from interventions assessed in the cohort study. The cost analysis took into account a combination of the staging strategies considered at analysis: 1) Palpation + postoperative SLNB if suspicious nodes; 2) US+FNA, followed by postoperative SLNB if negative nodes; 3) US+FNA followed by SLNB (both intra and postoperatively) if patients identified with negative nodes. The price year was not reported.

Country: Italy, **setting:** Hospital

Inclusion criteria Consecutive patients eligible for SLNB and with: <3cm, unifocal, invasive or microinvasive, previously untreated cancer; or high grade or > 4cm DCIS. Only patients with clinically positive axilla underwent US.

Exclusion criteria Not stated

Population 417 patients: 381 with invasive or microinvasive BC, 36 with DCIS

Interventions

- US, followed by FNA if suspicious nodes were found with US. If FNA positive, ANC was conducted; if FNA negative, intraoperative SLNB (i.e. frozen section) was conducted.

The authors extrapolated the results of the observational study to obtain three hypothetical scenarios, representing three additional interventions assessed in the partial economic evaluation:

- Palpation followed by ANC if patients had clinically suspected nodes
- Postoperative SLNB for all the patients, followed by ANC if nodes positive.
- Intraoperative SLNB followed by ANC if nodes positive and postoperative SLNB if nodes negative. If postoperative SLNB positive, then delayed ANC would be conducted.

Results

EFFECTIVENESS RESULTS: OUTCOME OF INTEREST	US+FNA	Preoperati ve SLNB	Postoperat ive SLNB	Palpation
Patients for whom SLN could not be identified (%)	-	22 (5.28%)	-	-
Sensitivity	For US alone: 0.51 For			0.29

	US+FNA: 0.33			
Specificity	For US alone: 0.87 For US+FNA: 1.00			0.93
Patients with positive nodes (%)	131 (32.43%)			
Positive node rate among patients with invasive BC	26.3%			
Patients with positive nodes correctly identified	43 (33.33%)	40 (31.01%)	46 (35.66%)	38 (29.46%)
Patients avoiding SLNB	43 (33.33%)	0	0	0
Patients undergoing unnecessary ANC	-	-	-	15
COST RESULTS (€)	US+FNA + SLNB (preop and postop)	US+FNA + SLNB (postop)	Palpation + SLNB (postop)	
Total cost per group (Italian NHS perspective)	1,218,256	1,226,881	1,125,841	
Total cost per group (hospital billing)	1,063,689	1,079,308	1,034,668	
Δ cost per group (Italian NHS - Hospital billing)	154,567	147,573	91,173	

Authors' conclusions –

The authors concluded that US+FNA can identify reliably the presence of axillary metastasis and can be used to refer these patients directly to ANC without further SLNB. The cost saving from the lower number of SLNBs conducted seemed to be balanced by the costs of US+FNA.

General comments –

The study design was somewhat confusing since the effectiveness of three of the staging strategies evaluated seemed to have been obtained through extrapolation of the results of the cohort study for US+FNA. On the other hand, the cost analysis was done for a combination of strategies. There seems to be a contradiction in the study: the authors reported that US+FNA was conducted in patients with clinically positive nodes, while SLNB was conducted in patients with clinically negative nodes (which would limit any potential comparison between the two staging strategies); however, when results were reported, it seemed that all the patients included in the study had undergone US. The cost analysis did not include only the costs of the staging procedures but also the costs of breast surgery. Additionally, the costs were not compared across the different staging strategies, but the study was limited to compare, for each staging strategy, the costs that the Italian NHS would pay with the costs that the hospital would bill. The price year was not reported.

No quality assessment checklist was completed for this study since it was a partial economic evaluation.

2.3 What are the effective strategies to manage psychological distress in patients with early stage breast cancer?

Short summary

The evidence base for this topic comprises 24 papers: 3 systematic review (Tatrow & Montgomery, 2006, Bantum *et al.*, 2007 and Zimmermann *et al.* 2007) 20 RCTs (Allard, 2007, Allen *et al.* 2002, Andersen *et al.* 2004, Antoni *et al.* 2006, Badger *et al.* 2007, Burton *et al.* 1995, Cohen & Fried, 2007, Dey *et al.* 2002, Gotay *et al.* 2007, McArdle *et al.* 1996, Mutrie *et al.* 2007, Ritz *et al.* 2000, Samarel *et al.* 2002, Sandgren and McCaul, 2003, Sandgren and McCaul, 2007, Stanton *et al.* 2005, Manne *et al.*, 2007, Classen *et al.*, 2008, Vos *et al.*, 2007 and Meneses *et al.*, 2007) and two prospective comparative studies (Mock *et al.* 1997 and Ambler *et al.* 1999). The quality of papers was generally good and most study designs compared the effects of one or more interventions with one or more controls measured at two or more time points, the maximum follow-up being one year.

Cognitive behavioural therapy (CBT)

A high quality systematic review of RCTs found that CBT interventions had a low effect size compared with controls. There was RCT evidence of no significant difference between CBT and guided imagery in reducing psychological stress or the perception of stress, although both interventions were significantly better than non-interventional controls.

Good quality evidence from two RCTs suggested that group therapy with non-CBT counselling or a group therapy intervention comprising CBT and several other psychosocial elements significantly reduced subjective levels of emotional distress whilst objective assessments of anxiety were not significantly different from controls.

Group therapy

A moderate quality systematic review found that group interventions provided significant improvements in emotional well-being when compared with individual interventions. The provision of multiple treatment elements was more useful than targeted clinical services. Only self help and information/education as single interventions had significant effects on emotional well-being.

RCT data showed that those who derived benefit from a couple-focused group intervention were women who naturally selected an emotional coping strategy to having breast cancer and women with unsupportive partners who attempted to understand and express their emotional reactions.

A multi-centre RCT showed that, compared with education, there was no evidence that psychological distress was alleviated by brief supportive-expressive group therapy. Neither was therapist training and experience associated with any treatment effect. It was thought that perhaps women with early breast cancer may be more likely to have pragmatic, rather than existentialist, concerns.

A small RCT compared group psychotherapy with group social support, neither of which was effective in improving psychosocial adjustment to breast cancer. Generally, body image improved significantly over time, particularly in women who had received breast-conserving surgery, and the limitations of breast cancer on recreation were also reduced.

Other interventions

Several, generally good quality, RCTs demonstrated that a variety of interventions including preoperative interview, attention focus and symptom management, telephone interpersonal counselling and structured exercise programs alleviated anxiety for variable lengths of time whilst not significantly improving depression, negative affect or general quality of life.

Intervention providers

A systematic review and meta-analysis found that psychologists were better qualified to deliver CBT to a woman with breast cancer either after the diagnosis, surgery or much later but not during other medical treatment. Nursing staff were better in delivering education to women with early stage disease, either individuals or in groups, preferably after diagnosis or surgery.

Moderate quality evidence suggested that adding the services of an advanced practice care nurse to standard care significantly reduced uncertainty, complexity, inconsistency and unpredictability without influencing quality of life or mood. Other studies found that support from a breast care nurse specialist following cancer surgery alleviated depression over time but made no significant difference to anxiety. However, receiving support from the breast care nurse specialist before and after receiving a pre-surgical diagnosis significantly lowered clinical relevant anxiety when measured two weeks after surgery, regardless of eventual diagnosis.

RCT evidence also showed that a psychoeducational intervention, delivered by a specialist nurse, demonstrated effectiveness amongst women with breast cancer after primary treatment thus providing a ‘safe passage’ from treatment to survivorship.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with early stage breast cancer (with clinically manifest psychological distress)	Any strategy to treat psychological distress: <ul style="list-style-type: none"> • Educational/provision of information • Counselling/cognitive behavioural therapy (CBT) • Psychotherapeutic • Group support • Drugs (e.g. antidepressants) • Exercise • ‘Buddy’ system/use of volunteers • Practical support e.g. financial, child care 1] The engagement / involvement of family and/or friends	Versus each other or versus no intervention	Alleviation of psychological distress Note who provides the intervention (i.e. type of professional)

POPULATION	INTERVENTION	COMPARISON	OUTCOME
	2] Alternative therapies - relaxation therapies e.g. yoga – reflexology. 3] Linking to specialist nurses e.g. Macmillan to advise and assist		

The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Full evidence summary

The evidence base for this topic comprises eighteen papers (n=5,630 study participants): 1 systematic review, 15 RCTs and 2 prospective comparative studies from the USA (n=10), UK (n=5), Israel (n=1) and Canada (n=1). The quality of papers is generally good and most study designs compare the effects of one or more interventions with one or more controls measured at two or more time points, the maximum follow-up being one year.

The statistical methodology employed is usually single and repeated-measures analyses of variance (ANOVA). A few reviewers also compared study arms at specific time points using unpaired t-tests, the validity of which is open to question. When an intervention is assessed with multiple instruments, and hence reported in different ways, (as dichotomous or continuous data, for example) the overall effect size was sometimes reported as Cohen's d statistic. It is generally held that a value for Cohen's d of 0.2 is indicative of a small effect, 0.5 a medium and 0.8 a large effect size.

The studies examined issues broadly addressing quality of life, depression and psychological distress but at different times in the patient pathway: at diagnosis (n=2), before surgery (n=2), after surgery and/or before or during adjuvant therapy (n=10), after all treatment (n=1) or on first recurrence (n=1). The systematic review did not make these distinctions but included all women with breast cancer and all treatment points, as did one RCT (Ritz *et al.*, 2000).

The majority of studies did not specifically enrol women with 'clinically manifest psychological distress' but, given the circumstances attendant at any particular point in the patient pathway, made general assumptions on the likely emotional state of the women that they were recruiting and since, in many studies, outcomes such as anxiety declined over the course of time this may have been appropriate.

The interventions examined in these studies included: cognitive behavioural therapy (CBT), psychoeducation, group support, individual counselling, specific nursing roles, exercise, relaxation and problem-solving. The diversity of interventions and treatment stages means that there is only limited evidence for any one circumstance. The strongest evidence base, including as it does a systematic review and two RCTs is for CBT.

One possible problem with consistency across studies is the large variety of measures and assessment instruments used throughout since the transferability between these is not

known and hence studies cannot easily be combined and must be seen only as individual pieces of work. The study populations, however, are broadly consistent and, despite all efforts from some quarters to enrol women from ethnic minorities, participants are generally white, middle income, educated and married.

The evidence has been summarised by treatment phase since this parameter is easier to categorise clearly than the numerous therapies. Abbreviations used are explained at the end of the text:

[i] All stages of breast cancer

A high quality systematic review (Tatrow and Montgomery, 2006) included 19 RCTs of CBT techniques (including activity pacing, assertiveness & communication training, autogenic training, behavioural activation, biofeedback, cognitive and attentional distraction, cognitive restructuring, contingency management, goal setting, imagery, hypnosis, meditation, modelling, pleasant activity scheduling, problem-solving, relaxation training, role playing, systematic desensitisation or visualisation) used to treat women with breast cancer for the relief of distress. Of 19 included studies, 63% were of women with early breast cancer (total n=1,649).

The adjusted overall effect size (Cohen's d) of the CBT technique for the treatment of distress, taking into account the variability of sample sizes in each RCT, was 0.13 (95%CI: -0.2-0.29; nsd). This result is between zero and the 'low' threshold in terms of effect size and could be interpreted as: 55% of participants in the intervention arms had a better outcome when compared with the average control participant.

The authors concluded that CBT appeared to have some benefits for breast cancer patients and the results suggested that individual therapies might be better than group therapies ($P < 0.05$), if only for the outcome of addressing distress. The stage of cancer did not appear to make a significant difference to this outcome.

Ritz *et al.* (2000) conducted an RCT of moderate size (n=211) assessing the impact made by adding the services of an advanced practice care nurse to standard medical care for women with breast cancer of all stages (96% of which were 0-III) and at all points in the patient pathway i.e. before and after surgery, during adjuvant therapy and after all treatment. Follow-up extended over two years but was only presented up to 1 year because of high attrition thereafter. The outcome 'uncertainty' was significantly lower in the intervention group at 1 month ($P=0.001$) 3 months ($P=0.026$) and 6 months ($P=0.011$) compared with baseline assessment and control values. The intervention group also had significantly lower scores compared with the control group on the 'complexity' ($P=0.005$), 'inconsistency' ($P=0.005$) and 'unpredictability' ($P=0.038$) subscales (instrument=MUIS). Mood or sub-scale elements were not significantly affected by the intervention (instrument=POMS) unless a sub-group analysis controlling for marital status, treatment history and family history were included. Similarly, QOL was not significantly improved when assessed by the FACT-B instrument unless marital status was controlled for in the analysis.

[ii] At the time of breast cancer diagnosis

Ambler *et al.* (1999) presented a good quality prospective comparative study of UK women (n=110) with either a benign or malignant breast condition (n=67) who were awaiting surgery and about to receive a diagnosis of their condition. This RCT compared standard

practice, in which the breast care nurse (BCN) met patients only after the diagnosis with a change of protocol such that the BCN took the role of patient advocate before the diagnosis, helped the woman to prepare for the interview, accompanied her to see the surgeon and played a shortened counselling and support role afterwards. The total nursing time was not changed, just the way in which that time was used. The intervention group showed a significantly lower incidence of clinically relevant anxiety ($P < 0.05$) at 2 weeks post-surgery compared with pre-surgery, regardless of diagnosis, but this was not true for the women with breast cancer sub-group when separately analysed (instrument=HADS). However, women with breast cancer reported a significant reduction in distress at 2 weeks post-surgery compared with pre-surgery ($P < 0.05$) (instrument=RSCL).

Dey *et al.* (2002) compared attendance at a one-stop NHS clinic ($n=267$) for the diagnosis of suspected breast cancer with attendance at a dedicated breast clinic ($n=211$). At the one-stop clinic, attendees received a mammogram, cytology and ultrasonography, if indicated. When imaging reports were available, a consultant assessed patients and discussed future management. Women in the control group received similar care but the women generally had to wait a week for their results. The purposes of the RCT were to examine cost-effectiveness and reduce the added psychological distress of waiting for test results. Anxiety was found to be significantly lower at 24 hours for women who had attended the one-stop clinic ($P < 0.0001$) but after 3 weeks was not significantly different from control group participants (instrument=STAI). Similar outcomes were non-significant when measured by a different instrument (HADS). The cost of providing rapid laboratory results outweighed the transient advantage to patients.

[iii] Participants recruited before surgery

Two papers recruited women with breast cancer scheduled to receive surgery. McArdle *et al.* (1996) designed a four-arm RCT to evaluate the effects of receiving support from a BCN, a voluntary support organisation, a combination of both or routine support on the prevalence of psychological morbidity after surgery for breast cancer. Participants were recruited before surgery ($n=272$). The BCN was highly qualified and experienced with this patient group and her role included information, support, counselling, reassurance and provision of future contact. The Glasgow-based support group, Tak Tent, offered three types of support: information, counselling, and regular group meetings with fellow cancer sufferers. Assessments were made at 1, 3, 6 and 12 months post surgery. General health ($P=0.015$), anxiety & insomnia ($P=0.027$) and social dysfunction ($P=0.031$) were all significantly improved in those patients receiving care from the BCN alone (instrument-GHQ). Depression was also significantly lower in her patients over time than in any other group ($P=0.003$) but anxiety was no different between study arms (instrument=HADS).

Burton *et al.* (1995) designed a four-arm RCT for UK women about to undergo mastectomy for breast cancer ($n=244$) and which compared a preoperative interview (conducted with a clinical psychologist) with or without an unstructured chat or psychotherapeutic intervention (both with by a Rogerian trained consultant surgeon) to standard care. The preoperative interview dealt with the patient's history, emotions, responses, information requirement, regrets, concerns and worries. Expression of feelings by the patient was encouraged. The post-interview intervention placed the crisis of illness within the patient's life situation whereas the chat was purposely not related to illness or surgery. Anxiety and depression both decreased over time (4 days, 3 months and 1 year post-surgery) for all participants but only anxiety was significantly reduced in the intervention groups compared with controls ($P=0.043$) (instrument=HADS). Coping ability also improved with time for all women, especially intervention participants, but, of all sub-

scales, only 'fighting spirit' was significantly higher for the intervention groups compared with controls ($P=0.031$). The interview, with or without intervention/chat, had a highly significant positive effect on body image distress ($P=0.009$). However, only women who had experienced a highly stressful life gained a particular advantage to the intervention, compared with the chat, following interview ($P=0.04$).

[iv] Participants recruited after surgery and/or before or during adjuvant therapy

Allard (2007) described a Canadian RCT ($n=117$) comparing usual care with an Attention Focus and Symptom Management Intervention (AFSMI) delivered by telephone to women who had undergone breast cancer surgery 9-10 days previously. A follow-up call was made a week later on days 17-18 after surgery. During these calls patients were encouraged to discuss symptoms and self-care strategies with the researcher, who also collected outcome data. Emotions expressed by the woman were acknowledged. Control participants received a telephone call from the ward nurse in which their well-being was briefly discussed. On the whole, the intervention made no significant impact on functional status, with the exception of the 'home management' sub-scale score, which was significantly affected by the intervention ($P=0.03$) (instrument=SIP). Emotional distress was also significantly reduced by the intervention between baseline (2-3 days post-surgery) and the first post-operative follow-up call ($P=0.03$), but distress and confusion were not significantly affected (instrument=POMS).

Allen *et al.* (2002) conducted a study amongst young women in the US ($n=164$) who were about to start their first course of adjuvant chemotherapy for stage 0-III breast cancer. The study assessed the efficacy of a program of 6 training sessions on problem-solving skills including problem orientation, problem definition, generation of alternatives, decision making and solution implementation and verification when compared with a single session for controls. None of the outcomes (mental health or psychological reaction, measured using MHI and IES instruments) showed significant differences between arms, a result which the authors felt was possibly due to the 'soft' nature of the intervention, the purpose of which had been to see if it could be adapted to help women cope with problems and emotional difficulties as result of receiving this diagnosis in mid-life.

Antoni *et al.* (2006) presented a study of women with early breast cancer who had received surgery in the previous 8 weeks. The authors compared a 1-day educational seminar given to a group but with no group interactions, with a program of ten weekly group interventions practising elements of CBT, stress management, relaxation exercises, home assignments (e.g. relaxation practice), role modelling, skills in anxiety reduction, conflict resolution, encouragement of emotional expression and confidence building. Baseline outcomes assessments were followed up at 6 and 12 months. Thought intrusion was significantly different between intervention and control groups ($P<0.005$) but thought avoidance was not significantly different (instrument=IES). A significant effect of the intervention was also seen for the outcome of emotional distress where Cohen's $d=0.43$, a medium effect, (instrument=ABS) but there was no significant difference between arms for interviewer-rated anxiety (instrument =HRSA).

Mock *et al.* (1997) presented a small US RCT ($n=50$) comparing a 6-week program of unsupervised walking exercise with usual care. The participants were women with early breast cancer who had undergone breast conserving surgery and were starting radiotherapy. The exercise was self-paced and progressive in intensity. Researchers kept in communication with participants by telephone throughout to assess progress and offer encouragement. Significant differences were found between study arms in pre- and post-

test measures of exercise level ($P < 0.001$), anxiety ($P = 0.029$), sleeping difficulty ($P = 0.027$) but not depression (instrument=SAS).

Andersen *et al.* (2004) described a moderate RCT ($n = 227$) which, having recruited US women with stage II or III breast cancer awaiting adjuvant therapy, compared a group therapy intervention designed to improve mood disturbance with a non-interventional control group. The therapy group met weekly for 18 weeks and were led by clinical psychologists who taught methods for reducing stress and emotional distress including progressive muscle relaxation, positive coping, problem solving, relaxation training and understanding stress responses. Baseline assessments of total mood disturbance were repeated after 4 months in both groups and, when levels of initial cancer stress were included as a variable, showed a significant reduction of mood disturbance overall between study arms ($P < 0.05$). For the anxiety sub-scales, there was a significant reduction in anxiety in the intervention group compared with controls ($P < 0.05$) (instrument=POMS) regardless of initial levels of stress.

Badger *et al.* (2007) presented the results of a three-arm US RCT ($n = 96$) of telephone interpersonal counselling (TIPC) compared with a self-managed exercise program and a control group. The TIPC group received weekly calls for 6 weeks which were given by a psychiatric nurse counsellor and dealt with cancer education, social support, awareness and management of the symptoms of anxiety & depression and role transition. The exercise group focused on regular, low impact exercise with weekly telephone calls to check progress and give encouragement. The control group received just one brief, non-interventional call a week. All follow-up assessments were made by telephone. Depression was not significantly reduced by the interventions compared with the control or for all participants over time. Anxiety decreased for all participants over time ($P < 0.001$) and this decline was significantly stronger for the intervention groups ($P = 0.01$). Post hoc tests suggested that this improvement in anxiety was sustained, but not increased, up to 10 weeks after the final telephone call (instrument=various, including CES-D, SF-12, ICS, PNAS and others).

Cohen and Fried (2007) presented the results from an Israeli RCT of cognitive behavioural therapy (CBT) versus relaxation & guided imagery (RGI) compared with each other and with a control. These interventions were tested in women with early breast cancer ($n = 144$) undergoing adjuvant therapy to determine the effects on psychological distress. The CBT techniques included eliciting negative thinking patterns, monitoring automatic thoughts, restructuring automatic thoughts into more adaptive patterns, mental distraction, reframing, problem solving, decision making, activity scheduling, grading of task assignments, distraction and behavioural experiment techniques. RGI included deep relaxation, deep breathing and autogenic relaxation. Participants were also taught techniques to reduce pain, anxiety and nausea and to improve sleep. The control group received standard care. There was no significant difference between CBT and RGI interventions in the reduction of psychological or perceived stress at any time point or overall but both groups showed a significant reduction in psychological stress over time compared with the control arm with an effect size, $\eta_p^2 = 0.07$ (where medium=0.6). Similarly, the reduction in perceived stress was significant for both interventions compared with control and $\eta_p^2 = 0.08$ (instruments=BSI, PSS).

Mutrie *et al.* (2007) presented the findings from a high quality UK RCT ($n = 201$) comparing a 12-week exercise program, including attendance at two classes and one home regime every week, with a standard care control group. All the participants were receiving

adjuvant therapy. The exercise schedule comprised a warm-up period, structured exercise such as walking or cycling and a cool-down period and then participants met for a group discussion which dealt with themes concerning behavioural changes in relation to exercise. Although there was no significant difference in the general quality of life (instrument=FACT-G) between study arms, breast cancer-specific outcomes (instrument=FACT-B) showed an overall significant improvement both from baseline to 3 months ($P=0.0007$) and from 3 months to 6 months ($P=0.039$). Positive affect was also significantly higher in the intervention group at both time periods ($P=0.0005$ and $P=0.0008$ respectively) (instrument=PANAS) although negative affect was not changed.

Samarel *et al.* (2002) presented a high quality paper reporting the results of a three arm US RCT which compared two telephone interventions given by oncology nurses or social workers, compared with a non-intervention control group. The study had three timed phases during which each group had a different exposure: the intervention group had weekly telephone support/ weekly in-person support + resource kit/twice monthly telephone support, the 1st control group had weekly telephone support/ weekly telephone support + resource kit/twice monthly telephone support and the 2nd control group had just the resource kit. The kit contained a variety of formats all centred on reflections of self-concept and interdependence, special exercises to enhance learning and other reading. The purpose of the study was to address the frequency and intensity of cancer-related worry (instrument=VAS-W) and mood disturbance (instrument=POMS) and to improve well-being (instrument=EWBS) of women with early breast cancer following surgery and before or during adjuvant therapy. There were no significant differences between the groups for any outcome except for mood disturbance which was significantly lower in the intervention group and 1st control compared with 2nd control at all assessment phases ($P<0.01$ to $P=0.03$) but not between intervention and 1st control at any point.

Sandgren and McCaul (2003) described a high quality US RCT ($n=222$) which assessed the value of two nurse-led interventions both using the telephone compared with standard care. Participants had either stage I or II breast cancer and were undergoing adjuvant therapy. One telephone intervention centred on health education (understanding breast cancer, managing post-surgical changes, understanding treatment, managing side effects & fatigue and maintaining a healthy life style) and the other on emotional expression in which women were encouraged to express their feelings and were provided with support and encouragement. Both interventions were ineffective with respect to knowledge, self-efficacy (instrument=CBI), QOL (instrument=FACT-B), mood (instrument=POMS) and perceived control (with the exception of the sub-scale of health education ($P<0.01$)) (instrument=PSS), although some parameters declined over time for all women. An update paper (Sandgren and McCaul, 2007) showed no significant changes after long-term follow-up.

[v] After active therapy

Stanton *et al.* (2005) presented results on an US RCT of women ($n=558$) who were finishing active treatment for breast cancer and were allocated to one of three groups in the 'Moving Beyond Cancer' study. A psychoeducational counselling intervention comprised an individual in-person session and one telephone session which centred on the patient's concerns about physical health, emotional well-being, interpersonal relationships and life perspectives. As well as reviewing goals and making an action plan for the future, women were also given information in the form of a booklet 'Facing Forward' and a manual 'Moving Beyond Cancer' which deal with issues relating to cancer survival.

Participants of the videotape intervention received the same manual and a videotape version of the 'Facing Forward' booklet. Women in the control group were sent a letter and a copy of the booklet 'Facing Forward'. Data were analysed at three time points – baseline, after 6 months and after 1 year. Of the many outcomes assessed, including vitality, cancer-specific stress, depression and post-traumatic growth, only that of vitality was significantly different between the videotape intervention and control arms at the 6 month assessment point (instrument=SF-36). All other comparisons at all time points were of no statistical significance. The authors hypothesised that these disappointing results may have been due to baseline inequalities or the 'soft' nature of the interventions.

[vi] At first disease recurrence

Gotay presented a good quality US RCT (n=305) comparing a telephone intervention with standard care for women who had been treated with stage I-III breast cancer and who were experiencing a first disease recurrence which was defined as any distant metastatic site, chest wall or nodal site. A telephone intervention was given by trained counsellors who were also breast cancer survivors and at least one year post recurrence. Participants received 4-8 counselling/information sessions by weekly telephone calls, one to two calls per week. The content reflected the most common domains in multi-dimensional models of QOL and patient need. A standardised packet of information (NCI pamphlets) was also sent to each woman. The control group received standard care. Assessments were made at baseline, 3 months and 6 months. Examining only those women whose scores showed them as being at risk for either psychosocial stress (instrument=CARES-SF) or depression (instrument=CES-D) were reported. There were no significant differences in either outcome between intervention and control arms at any time point or across the follow-up period as a whole.

Updated evidence - Summary

Updated evidence on the management of psychological distress comprised two moderate quality systematic reviews on psychosocial interventions (Bantum *et al.*, 2007 and Zimmermann *et al.* (2007) a RCT on a couple-focused group intervention (Manne *et al.*, 2007) a RCT on supportive-expressive group therapy (Classen *et al.*, 2008) a poor quality RCT comparing a group psycho-therapy intervention with group social support (Vos *et al.*, 2007) and a RCT comparing a psychoeducational intervention with a wait control (Meneses *et al.*, 2007).

One systematic review found that with respect to significant improvement of emotional well-being, group interventions provided some advantage over individual interventions. The provision of multiple treatment elements was seen as being more useful than targeted clinical services. Only self help and information/education as single interventions had significant effects on emotional well-being. A second review included a meta-analysis the results of which suggested that psychologists were the most appropriate persons to deliver CBT in an individual context to women at any disease stage, preferably after diagnosis/surgery or much later but not during treatment. Medical staff appeared to be better suited for delivering education to individuals or groups, preferably after diagnosis or surgery, but only for women with early stage disease.

RCT data suggested that women with early stage breast cancer who naturally selected an emotional coping strategy may benefit from a couple-focused group intervention. In particular, women who had unsupportive partners and who attempted to understand and

express their emotional reactions to having cancer may derive the most benefit from such an intervention.

A multi-centre RCT showed that, compared with education, there was no evidence that distress was alleviated by brief supportive-expressive group therapy. Neither was therapist training and experience associated with any treatment effect. It was thought that perhaps women with early breast cancer may be more likely to have pragmatic, rather than existentialist, concerns.

A small RCT compared a group psychotherapy intervention with group social support, neither of which was effective in improving the participants' psychosocial adjustment to breast cancer. The authors observed few significant changes in psychosocial parameters over the period of follow-up which may have been because women's' baseline levels were comparable to the general population and therefore little improvement may have been expected. Body image improved significantly over time, particularly in women who had received breast-conserving surgery and the limitations of breast cancer on recreation were also improved.

RCT evidence also showed that a psychoeducational intervention, delivered by a specialist nurse, demonstrated effectiveness amongst women with breast cancer after primary treatment thus providing a 'safe passage' from treatment to survivorship.

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Tatrow & Montgomery (2006)
Design: Systematic review of RCTs (therapy), evidence level: 1+ Country: United States
Inclusion criteria: Included studies: RCTs of CBT techniques Studies were published in English Use of a 'no treatment' or 'standard care' control group Sufficient data to allow for calculation of effect size Randomisation Prospective design Measures of distress (and pain) Included patients: Women with breast cancer
Exclusion criteria: Excluded studies: Studies not using any CBT technique
Population: Number of patients = 1,649
Interventions: Studies using any CBT technique (including activity pacing, assertiveness & communication training, autogenic training, behavioural activation, biofeedback, cognitive and attentional distraction, cognitive restructuring, contingency management, goal setting, imagery, hypnosis, meditation, modelling, pleasant activity scheduling, problem-solving, relaxation training, role playing, systematic desensitisation or visualisation)
Outcomes: [1] Estimates of overall effect size of CBT techniques on distress [2] Comparison of effect sizes of CBT on individual versus group treatment formats for distress [3] Comparison of effect sizes by cancer stage Across all studies, outcomes were measured using one or more of the following tools: BDI (Beck Depression Inventory) CES-D (Centre for Epidemiological Studies-Depression Scale) DES-IV (Differential Emotions Scale-IV) EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) HADS (Hospital Anxiety and Depression Scale) IES (Impact of Event Scale) MOS (Medical Outcomes Scale) POMS (Profile of Moods Scale) STAI (State Trait Anxiety Inventory) VAS (Visual Analogue Scale)

Affects scales
Faces mood scale
Mood rating scale

Follow up:
NA

Results:

[1] Estimates of overall effect size of CBT techniques on distress

The overall effect size (Cohen's d) of the CBT technique for the treatment of distress was 0.31 (95%CI: 0.07-0.55; $P < 0.05$ when compared with 0). This result is between 'low' and 'medium' in terms of effect size and could be interpreted as: 62% of participants in the intervention arms had a better outcome when compared with the average control participant (note that the absolute minimum percentage in this respect would be 50% and so this result is not impressive by comparison).

These data were adjusted to take into account the variation in sample sizes between individual studies. The adjusted (d) value (D) was 0.13 (95%CI: -0.2-0.29; nsd) reducing the 62% to 55% and rendering the effect size as not significantly different from 0.

[2] Comparison of effect sizes of CBT on individual versus group treatment formats for distress

When examining the data from 16 individual therapy studies versus 7 group therapy studies, the authors calculated a (d) value for individual therapies of 0.48 (95%CI: 0.17-0.78) and for group therapies of -0.06 (95%CI: -0.22-0.09). The difference between these two being significant ($P < 0.05$) in favour of individual therapy.

[3] Comparison of effect sizes by cancer stage

When examining the data from 13 studies from women with, versus without, metastases, the authors calculated a (d) value for patients with non-metastatic cancer of 0.43 and for women with metastatic cancer of 0.18. The confidence intervals and P values were not given but the data were stated to be not significantly different between the comparators.

General comments:

This paper presented a systematic review and meta-analysis of cognitive behavioural therapy given to breast cancer patients. The outcomes of interest were relief of depression (and pain).

Twenty RCTs were included in the analysis but one of these dealt with pain only and hence 19 studies included measures of depression.

Of 19 studies, 3 were of breast cancer patients with metastases, 5 were of patients with mixed breast cancer stages but the majority, 12 studies, were of women with early breast cancer only.

The following databases were searched for relevant literature: PsychInfo,

Medline, CancerLit and CINAHL. Searches were conducted from 1974 to June 2004. The search terms were given. The authors did not state by how many reviewers papers were screened for inclusion/exclusion or how conflicts were resolved.

The statistical methodology used to calculate individual effect sizes (where not stated by authors) and the overall effect size appears to be sound and generated a value for Cohen's d. This statistic gives the overall effect size across multiple tests in which the outcomes may have been reported in different ways (as dichotomous or continuous data, for example). It is generally held that a value for Cohen's d of 0.2 is indicative of a small effect, 0.5 a medium and 0.8 a large effect size.

Only the outcome [1] reflects the aims of the included studies i.e. determining the effect of CBT when compared with a standard treatment or no therapy. The comparisons of group versus individual therapy and by cancer stage are observations made on the data which could have been made *post hoc*, although the authors stated otherwise. None of the included studies made these comparisons and hence they have not been formally tested and the results and authors' conclusion should be viewed with caution.

The authors concluded that CBT appeared to have some significant benefits for breast cancer patients and that the results suggested that individual therapies might be better than group therapies, if only for the outcome of addressing distress. The stage of cancer did not appear to make a significant difference to this outcome.

Allen <i>et al.</i> 2002
Design: Randomized controlled trial (therapy), evidence level: 1- Country: United States
Inclusion criteria: Women <50 years of age No history of breast cancer Histologically/cytologically confirmed breast cancer stage 0-III Starting first course of chemotherapy Written informed consent
Exclusion criteria: None stated
Population: Number of patients = 164, mean age = 42 years.
Interventions: Intervention (n=87): A program of 6 training sessions on problem-solving skills and a instructional manual, 'Home Care Guide for Women with Breast Cancer'. Problem-solving skills training included: problem orientation, problem definition, generation of alternatives, decision making and solution implementation and

verification.

The book was adapted from an earlier manual 'Home Care Guide for Cancer' and based on prior research from focus groups populated by the target population, identifying their needs, both physical and psychosocial.

The training sessions were led by an oncology research nurse. Following identification of specific problems, study participants were coached in the use of problem-solving techniques and given feedback on their progress in the application of the intervention.

Control (n=77):

Women in the control arm met the research nurse for a single problem-solving skills training session which focused on breast cancer survivorship issues.

Outcomes:

[1] Mental health (emotional distress) - measured by the Mental Health Inventory (MHI) which is a 5 item subscale of the Medical outcomes Study 36-Item Short-Form General health Survey (SF-36) that scores from 0-100. Higher scores indicate better mental health.

[2] Psychological reaction to distressing events e.g. cancer diagnosis - measured on the Impact of Events Scale (IES) which has two sub-scales, intrusion (7 items, scored from 0-35) and avoidance (8 items, scored from 0-40)

[3] Assessing the level of rehabilitation needs, describing the unmet need for assistance and social problem-solving ability (data not presented here). These measures were undertaken to determine whether or not certain groups of women would be more likely to benefit than others at baseline from the intervention.

Follow up:

Progress was monitored by telephone. Four calls were made, each two weeks apart. Participants were asked to complete worksheets and were also encouraged to contact the interventionist at any time to discuss pertinent issues.

Follow-up assessments were made 4 and 8 months post baseline, a time when the majority of participants would have finished their oncology therapy. Most participants completed the first (baseline) questionnaire just over three weeks from their first chemotherapy session.

By the final assessment, 76/87 (87%) women in the intervention arm and 73/77 (95%) in the control arm provided outcome data.

Results:

The sample of women who completed the study were predominantly: with a PSP (78%), married (66%), with children (75%), educated to bachelor's degree or above (40%) and with good incomes (40%). The women who failed to complete the study were significantly less likely to have been white, non-Hispanic, employed or have good incomes. However, participants who dropped out were also more likely to have had higher baseline levels of physical and

psychosocial problems.

Results

[1] Mental health (control vs intervention) mean +/- SD:

Baseline 64.6 (16.0) vs 65.2 (17.0)

4 months 68.7 (15.6) vs 73.1 (15.4)

8 months 69.7 (16.8) vs 72.1 (16.6)

[2] Psychological reaction (control vs intervention) mean +/- SD:

Intrusion

Baseline 14.6 (9.5) vs 14.3 (8.4)

4 months 10.6 (8.8) vs 10.6 (8.8)

8 months 11.0 (7.5) vs 11.6 (9.1)

Avoidance

Baseline 12.0 (9.0) vs 12.2 (8.7)

4 months 12.6 (8.4) vs 10.8 (7.4)

8 months 9.5 (7.9) vs 9.8 (9.4)

None of the results from this comparison between arms and across time showed statistical significance (MHI or IES scales)

Regression analyses were undertaken to identify possible factors that might impact on outcomes. These showed that women in the intervention arm were significantly less likely to report unmet need for practical assistance at 4 months ($P < 0.05$) and also had an improved mood state ($P < 0.05$) but neither was statistically significant at 8 months.

General comments:

This paper describes a study of problem solving therapy (based on CBT principles) given to young women with non-metastatic breast cancer who were recruited between April 1996 and November 1999 from 31 oncology practices throughout the USA. The purpose of this study was to see if this intervention could be adapted to help women cope with problems and emotional difficulties as result of receiving this diagnosis in mid-life.

Participants were first approached by letter from the principal investigator, followed by a telephone call and assessment of eligibility. Candidates completed the baseline interview and returned a mailed questionnaire before being randomised into control and intervention arms. Data were randomised on treatment centre and involvement, or otherwise, of a primary support person (PSP) nominated by the subject e.g. partner, significant other.

Data were analysed by single ANOVA to assess the difference in mean outcome scores over time (within-group) and between groups. The effects of controlling factors, such as the influence of a PSP, on outcomes were tested using regression analyses.

The authors observed that whilst this intervention was effective for helping the majority of participants to deal with a range of problems relating to cancer and its treatment, those with lower baseline problem-solving skills would be less

likely to derive such a benefit. They expressed the opinion that such women may even have found the intervention an additional burden, perhaps because of its 'light' nature. There was some, inconclusive evidence that women with excellent baseline problem-solving skills may similarly have been adversely affected by the intervention and that therefore appropriate targeting of the intervention was important.

Cohen & Fried (2007)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Israel

Inclusion criteria:

Women with breast cancer of stage I or II
Surgery between 2-12 months previously
Receiving chemotherapy or radiotherapy
Fluent spoken Hebrew
No known psychiatric illness

Exclusion criteria:

none stated

Population:

Number of patients = 144.

Interventions:

Interventions were conducted by the first author and other qualified personnel. Groups of 6-8 participants met weekly for 90-minute sessions over the course of 9 weeks. A new group started every 12 weeks.

Intervention 1 (n=39):

Cognitive behavioural therapy (CBT) included learning and practising: eliciting negative thinking patterns, monitoring automatic thoughts, restructuring automatic thoughts into more adaptive patterns, mental distraction, reframing, problem solving, decision making, activity scheduling, grading of task assignments, distraction and behavioural experiment techniques. Participants were given written material and exercises to perform at home. The experience of the intervention was discussed.

Intervention 2 (n=42):

Relaxation & guided imagery (RGI) included learning and practising: deep relaxation, deep breathing and autogenic relaxation. Participants were also taught techniques to reduce pain, anxiety and nausea and to improve sleep. Participants were given audio cassettes or CDs to continue therapy at home. The results and experiences of these exercises were discussed and help was given if problems were identified.

Control (n=43):

Standard care in the oncology unit, including support from the social work and nursing teams (no further details)

Outcomes:

[1] Overall psychological distress – Brief Symptom Inventory (BSI) was used to measure 9 symptoms (somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) each scored on a 5-point scale from 0 (not at all) to 4 (extremely). A Global Severity Index (GSI) was calculated from the mean of these scores. The GSI comprised 8 symptom dimensions. One dimension, somatisation, had been excluded since results could have been ascribed to the concurrent use of chemotherapy or radiotherapy

[2] Subjective feelings of stress – measured by the Perceived Stress Scale (PSS), a single item scale from 1 (no stress) to 6 (extreme feelings of stress)

[3] Adherence to practice at home – measured on a scale of 1 (not at all) to 5 (five times a week or more)

Follow up:

Assessments of outcomes were made at baseline (pre-intervention), post-intervention and 4 months after conclusion of the therapy cycles.

Out of the 170 patients invited to participate in the study, 144 were enrolled. Data were not analysed for 30 participants (CBT = 16 and RGI = 14) because they had missed more than 2 of the 9 scheduled meetings for reasons not given.

10 women did not provide all three assessment measurements (CBT = 1, RGI = 3, control = 6) for reasons not given.

Results:

Data were analysed for 79% of the enrolled participants (CBT = 38, RGI = 39 and control = 37). Approximately 60% of participants were undergoing chemotherapy during the study and the remainder were having radiotherapy.

There was no significant difference between CBT and RGI in the reduction of psychological or perceived stress at any time point or overall.

[1] Overall psychological distress and [2] Perceived stress

Within-group levels of stress (from GSI and perceived stress measures) dropped significantly in both intervention groups between pre-treatment and post-treatment assessments ($P < 0.001$ for both). The control groups scores, whilst declining, did not change significantly over the same time period.

Within-group levels of stress (from GSI and perceived stress measures) also dropped significantly in both intervention groups between pre-treatment and follow-up assessments ($P < 0.01$ for both). The control group scores, whilst declining, did not change significantly over the same time period.

MANOVA showed that the intervention arms both had a significant reduction in GSI over time compared with the control arm with an effect size, $\eta_p^2 = 0.07$. Similarly the reduction in perceived stress was significant for both interventions compared with control and $\eta_p^2 = 0.08$

Regression analysis showed that participants who received chemotherapy achieved less reduction in perceived stress.

[3] Adherence to practice at home

Participants in the RGI intervention group reported significantly higher adherence to home practice than those in the CBT group (Cohen's $d = 0.53$; $P < 0.05$ a medium effect).

Regression analysis showed that adherence to home practice was significantly associated with enhanced decreases of GSI scores over time.

General comments:

This paper describes a RCT of cognitive behavioural therapy (CBT) versus relaxation & guided imagery (RGI) compared with each other and with a control. These interventions were tested in women with early breast cancer to determine the effects on psychological distress (also fatigue and perceptions of health locus of control which are not reported here). Participants were recruited from the out-patient department of a single oncology centre by social workers and nurses.

The data were analysed using multivariate repeated measured analysis of variance (MANOVA) to determine the change in outcome over the three time points for each group and univariate analysis with *post hoc* analysis measured the differences between pairs of groups (e.g. intervention 1 *cf* intervention 2, intervention 1 *cf* control etc.) for each outcome. An effect size was expressed as η_p^2 , a measure that can be translated as values of 0.1 being a small effect, 0.6 a medium and 0.14 a large effect size. The *t* test was used to analyse compliance with home practice and an effect size was computed and expressed as Cohen's *d* statistic. The independent variables (time since diagnosis, type of treatment, intervention group and adherence to practice at home) were tested for their significance in affecting outcomes in multiple regression analysis.

The authors stated that the findings support their hypothesis, and that of other studies, that show a significant improvement in overall psychological distress as a result of participation in an intervention group for cancer patients with a primary disease. They concluded that it was evident that both CBT and RGI were equally efficient in reduction psychological distress I primary breast cancer patients.

Although a good study, the reason for the high attrition rate was not examined thoroughly. It is plausible that bias may have been introduced since the remaining study population may have differed e.g. degree of motivation, level of psychological distress, from those who failed to complete the study or provide follow-up data. A longer follow-up period may have been of value. The statistical data analysis was not intention-to-treat, which can reduce type I error and, using MANOVA as opposed to, for example, latent growth curve modelling, meant that a lot of data were lost that might have been used. However, for the purpose of not rejecting the null hypothesis for the outcomes of interest, these arguments may not be of great importance.

Antoni <i>et al.</i> (2006)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: United States
Inclusion criteria: Women with breast cancer stage 0-III Surgery in the previous 8 weeks
Exclusion criteria: Prior cancer Prior psychiatric treatment for a serious disorder (detailed) Lack of fluency in English
Population: Number of patients = 199, mean age = 50 years.
Interventions: Both intervention and control conditions comprised groups of 8 people meeting in rooms equipped with couches and a comfortable seating area. Sessions were led by trained personnel who rotated between study arms but who did not carry out the patient assessments. Intervention (n=107): A 10 week intervention was started between 10-12 weeks after surgery for breast cancer. Participants met together every week for a 2 hour session within which were practised elements of CBT stress management, relaxation exercises, home assignments (e.g. relaxation practice), role modelling, skills in anxiety reduction, conflict resolution and emotional expression, encouragement of emotional expression and confidence building. Control (n=92): Women were invited to attend a 1 day seminar which lasted 5-6 hours. Participants received a condensed educational version of the same information as received by the intervention group. However, there was no opportunity for the same group interactions, role playing, support, learning physical exercises, relaxation techniques or coping strategies.
Outcomes: [1] Thought intrusion and avoidance - measured by the Impact of Events Scale (IES) measured on two subscales, with responses coded 0,1, 3 and 5. The thought in question was 'the diagnosis and treatment of breast cancer' [2] Interviewer-rated anxiety - measured by the Hamilton Rating Scale for Anxiety (HRSA) and assessed by personnel specifically trained by clinical psychologists [3] Emotional distress - measured by the Affects Balance Scale (ABS) assessing negative affect, depression, hostility, guilt and anxiety experienced in the past week and scoring on a range from 0 (never) to 5 (always).
Follow up:

Baseline assessment was made at three time points: upon recruitment (4-8 weeks post surgery) and then repeated 6 and 12 months later.

Results:

Number of participants per stage:

Intervention (n=107):

0 = 17

I = 44

II = 39

III = 7

Control (n=92):

0 = 10

I = 32

II = 43

III = 7

[1] Thought intrusion and avoidance

The predictive nature of the latent growth-curve model for thought intrusion showed that the third time point at 1 year did not fit the data. To give the best linear relationship this point was freely modelled and was found to be 7.02 months, only a slight progression from time point 2 at 6 months. Hence the improvement in scores over time would not have continued to increase at the same rate beyond this point.

The group effect of the intervention on thought intrusion scores overall was (Cohen's d) = 1.22 with $P < 0.001$ (a large effect). The differences between intervention and control scores were significant at 6 months ($P < 0.03$) and at 12 months ($P < 0.005$)

This means that the within-group scores changed significantly over time for the intervention and the between-group scores were significantly different between the intervention and the control.

The effect of the intervention on thought avoidance was not significant compared with the control but scores decreased significantly in both arms over time. This means that this parameter naturally improved with time but that the intervention did not speed the process significantly.

[2] Interviewer-rated anxiety

The data modelled well to the three time points. Although there was a significant decrease in anxiety over time for the intervention arm, the initial scores between experimental and control arms were very different which led to a crossover effect. There were, for this reason, no significant between-groups differences at any time point.

This means that although the intervention arm experienced a significant within-group improvement in this parameter over time, there was no valid comparator to inform the researchers whether or not the therapy was responsible for this improvement.

[3] Emotional distress

The data modelled well to the three time points. The group effect changed the slope of the three data points where $(d) = 0.33$, a medium effect. At the third time point (1 year) the groups were also significantly different and the effect size of the intervention was expressed by $(d) = 0.43$

This means that the within-group scores changed significantly over time for the intervention and the between-group scores were significantly different between the intervention and the control.

General comments:

The study design did not control for the attention time i.e. 6 hours for controls versus 20 hours for intervention but did alleviate the likelihood of attrition from a non-treatment control.

Data were analysed at three time points using latent growth-curve modelling. This method measures the trajectory of change over time and can, more successfully than repeated measures ANOVA, cope with missing data instead of deleting all data from participants who don't provide a complete data set. In addition, this model can adequately address non-linear change in the outcome e.g. if the benefits of an intervention plateau at a particular time point rather than continue to increase. Effect size was reported as Cohen's (d) .

This was a good paper with a well conducted study and report. The methodology of the statistics was complex but thorough but there was less detail about randomisation, allocation and blinding which means that bias cannot be excluded with certainty.

Ritz *et al.* (2000)

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United States

Inclusion criteria:

Women ≥ 21 years
Diagnosed with breast cancer between 1995 and 1997
Able to read and write English
Able to give informed consent

Exclusion criteria:

History of cancer
Comorbidities that limited functional ability
Severe psychiatric illness

Population:

Number of patients = 211.

Interventions:

Intervention group (n=106):

Standard medical care plus the care of an advanced practice nurse (APN). The interventions with the nurse were presented in a lengthy and fully detailed

summary but briefly included:

- a] Pre-operative: assessment, education and care co-ordination,
- b] Post-operative: assessment, education and care co-ordination
- c] Therapy: assessment, education, symptom management, care co-ordination, consultation and referral
- d] Post-treatment follow-up: assessment, education and care co-ordination

Initial APN contact was within 2 weeks of diagnosis and included written and verbal information about breast cancer, what to expect in a consultation, answering questions and giving support. Subsequent contacts were made at scheduled clinic visits, by telephone and at home, sometimes at the initiation of the patient.

Control group (n=105):

Standard medical care (not detailed)

Outcomes:

Quality of life (QOL) - measured on three scales:

[1] Mishel Uncertainty in Illness Scale (MUIS) which assesses the inability to determine the meaning of illness-related events (a higher score means greater uncertainty)

[2] Profile of Moods State (POMS) which includes 6 measures of mood and has been previously validated in studies of adjustment to breast cancer (a higher score means greater mood disturbance)

[3] Functional Assessment of Cancer Therapy (breast) (FACT-B) which measures QOL on 6 dimensions (a higher score relates to greater well-being).

Follow up:

Participants completed baseline questionnaires at enrolment and by mail 1, 3, 6, 12, 18 and 24 months thereafter. Participants received several reminders when questionnaires were due to be returned.

One patient in the control group was re-staged after enrolment and removed from this study.

Results:

Cancer grades of participants (%):

Intervention group (n=106) vs Control group (n=104):

I = 14 vs 15

II = 52 vs 39

III = 27 vs 43

IV = 7 vs 2

These data are significantly different (P=0.04) at baseline. In addition a higher percentage (59%) of women in the intervention were receiving endocrine therapy than controls (43%) which was significant (P=0.03) at baseline.

Results:

QOL - [1] MUIS:

Uncertainty was significantly lower in the intervention group compared with the control group at 1 month (P=0.001), 3 months (P=0.026) and 6 months (P=0.011) but not at 12 months (P=0.589).

The intervention group had significantly lower scores compared with the control group on the complexity (P=0.005), inconsistency (P=0.005) and unpredictability (P=0.038) subscales.

QOL - [2] POMS:

The intervention and control groups did not differ significantly in scores across six subscales and across all time periods when all women were included in the analysis.

There was a significant difference in mood between study arms when the participant data were analysed according to marital status: unmarried women in the intervention group had a significantly greater decrease in mood disturbance than control at 1 month (P=0.01) and 3 months (P=0.043) and women with no family history of breast cancer also had a greater decrease in mood disturbance at 1 month (P=0.002), 3 months (P=0.01) and 6 months (P=0.004) when compared with controls.

QOL – [3] FACT-B:

Intervention and control groups did not differ significantly at any time point either as a global score or in individual sub-scales. Unmarried women in the intervention group had a greater well being than control at 1 month (P=0.036) only.

General comments:

This paper describes a RCT which aimed to assess the value of the advanced practice nurse, in terms of QOL (and health economics). The intervention covered most aspects of this nursing role with regard to breast cancer patients when compared with standard medical care.

Univariate and multi-variate tests were used to analyse QOL data, with regression analyses for repeated measures. There were two significant baseline differences between the intervention and control arms: women in the intervention group were significantly more likely to have lower histology (P=0.04) and to receive adjuvant hormone therapy (P=0.03), factors which may have influenced outcomes.

QOL analyses were conducted for up to 12 months because the response rate was considerably reduced by 24 months (76% for intervention and 52% for controls) and the need for support was also reduced and QOL scores were not, by then, significantly different between arms.

That authors concluded that women with newly diagnosed breast cancer and who are given APN interventions show decreased uncertainty for up to 6 months. Unmarried women and those with no family history of breast cancer also gain significant improvements in QOL with respect to mood or well being.

Overall this was a reasonable paper but it would have been helpful to know the exact number of participants who provided data at each time point in order to

appreciate the power of the statistical significance. This information was only given for baseline and 1 year.

Ambler *et al.* (1999)

Design: Prospective comparative study (therapy), evidence level: 2++
Country: United Kingdom

Inclusion criteria:

Women attending at a breast care clinic
Benign or malignant breast condition
Scheduled to undergo surgery

Exclusion criteria:

None stated

Population:

Number of patients = 110, age range 22 to 80 years, mean age = 50 years.

Interventions:

Both intervention and control participants were seen by the same specialist breast care nurse before and/or after the consultation in which the patient would be informed of her test results i.e. formal diagnosis.

Control (n=66):

Standard care nursing: The breast care nurse met with each patient following the diagnostic consultation. This meeting would last approximately 25 minutes.

Intervention (n=37):

Advocacy nursing: The breast care nurse, after training by a clinical psychologist, met with the patient immediately before the diagnostic consultation, identified the patient's main concerns and helped her to prepare for the consultation by developing a list of questions that could be asked. This meeting lasted approximately 9 minutes. The nurse (unaware of the patient's diagnosis) attended the consultation with the patient and helped her by ensuring all questions were dealt with by the surgeon and intervening, if necessary, on the patient's behalf. After the consultation the nurse continued counselling the patient for a short while (mean 16 min) and contacts thereafter were conducted on an 'as needed' basis.

Outcomes:

[1] Anxiety, depression and psychological distress - measured on the Hospital Anxiety and Depression Scale (HADS) which has 14 items. A higher score suggests increased anxiety or depression. Scores of >11 are deemed to be clinically relevant.

[2] Extent to which patients were bothered by symptoms - measured by the Rotterdam Symptom Checklist (RSCL) which includes a sub-scale relating to psychological well being.

Follow up:

1 person died before study completion prior to her last assessment; 6 pts failed to attend this last assessment and, therefore, n=103 (data incomplete so

ppts withdrawn). Three were lost from controls and 4 from the intervention group.

Data collection was started before surgery and follow-up assessments were made by an independent researcher 2 weeks and 6 months thereafter.

Results:

Of all the women who provided data for this study (n=103), 67 had a diagnosis of breast cancer and the remainder had a benign breast lump. 21/67 (31%) women with breast cancer were in the intervention arm.

Post-surgical treatment of women with BC by allocation (% intervention vs control):

Adjuvant therapy:

Chemotherapy: 4 vs 14

Radiotherapy (RT): 52 vs 33

Chemotherapy & RT: 13 vs 5

No treatment: 30 vs 48

Outcome results:

[1] Anxiety, depression and psychological distress – HADS:

Women with breast cancer had significantly higher levels of pre-surgical anxiety than women with benign breast lumps (P=0.03). There was no significant differences in levels of depression between the intervention and control groups. Participants in the intervention arm had significantly lower levels of anxiety at 2 weeks post-surgery (P=0.034). However, when subsequent diagnosis was taken into consideration, there was no significant difference in anxiety between intervention and control groups for women with breast cancer at any assessment time point. However, the incidence of clinically relevant anxiety was higher for women in the control group, regardless of diagnostic outcome:

Incidence of clinically relevant anxiety (intervention vs control) n (%) :

Pre-surgery: 9 (43) vs 25 (54)

2 weeks post-surgery: 1 (4.8) vs 6 (13)***

6 months post-surgery: 2 (9.5) vs 6 (13)

*** P<0.05

[2] Psychological well being - RSCL:

There were no statistically significant differences in scores or in the levels of clinical relevance between the intervention and control arms. However, women with breast cancer who were in the intervention arm reported a bigger drop in distress between pre-surgery and the 2-week assessment point when compared with women with breast cancer in the control group:

Psychological distress (intervention vs control) mean (SD) :

Pre-surgery: 10.80 (5.48) vs 9.35 (5.63)

2 weeks post-surgery: 5.00 (4.18) vs 6.85 (4.36)***

6 months post-surgery: 5.00 (3.70) vs 5.69 (4.84)

*** P<0.05

General comments:

This paper describes a study on the optimal role of specialist nurse counsellor

to determine the effects of advocacy nursing compared with a more conventional style (in which the nurse meets the patient for the first time after the patient's initial consultation and following her diagnosis). Participants of this comparative study (not a RCT) were recruited after receiving the intervention or control treatment in order to ask for follow-up assessments to be made at two later dates.

The study ran consecutively i.e. firstly, all participants in what would become the control group were treated, using the standard protocol, by the nurse after which all participants in what would become the intervention arm were treated, using the revised protocol. This design was felt to remove possible confounders of having two nurses taking part in the study whilst avoiding the impracticality of the same nurse using alternating methodology. Whilst not a RCT, this comparative study seems practical and is observing the effects of a change in practice.

Whilst there may be some useful data in this study, the emphasis for the researchers was to test a new mode of therapy on all breast patients, regardless of diagnosis. The results highlighted the obvious distress and anxiety felt by all women awaiting a potentially life-changing diagnosis and tried to address this problem by changing what was the current protocol into a regime calculated to alleviate this distress. Because women with breast cancer were not specifically targeted the numbers of such patients within the larger study arms are low which makes the results statistically underpowered and the conclusions open to question.

Dey <i>et al.</i> (2002)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: United Kingdom
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: Number of patients = 478, age range 35 to 95 years, mean age = 50 years.
Interventions: Intervention: Attendance at an one-stop clinic (n=267): Attendees received a mammogram, cytology and ultrasonography, if indicated. When imaging reports were available, a consultant assessed patients and discussed future management. Control: Attendance at a dedicated breast clinic (n=211): Attendees were assessed by a surgeon and, if further investigations were made, women were asked to return a week later to discuss the results and further management.
Outcomes: Psychological distress - measured by:

[1] State Trait Anxiety Inventory (STAI) and
[2] the anxiety element of the Hospital Anxiety and Depression Scale (HADS)

Follow up:

Data was obtained at baseline for both questionnaires and then after 24hrs (STAI), 3 weeks and 3 months (HADS)

Results:

Mean anxiety scores in both groups were lower at all assessment times compared with baseline. The reduction in mean anxiety was greater for one-stop clinic patients at 24 hours but not thereafter.

STAI:

One stop (n=220) vs dedicated (n=172) clinic, mean (SD):
Baseline: 48.1 (14.9) vs 47.2 (14.9)
24 hours: 34.5 (14.6) vs 39.8 (15.8) P<0.0001

HADS:

One stop (n=208) vs dedicated (n=153) clinic, mean (SD):
Baseline: 8.9 (4.4) vs 8.8 (5.0)
3 weeks: 7.3 (4.7) vs 7.4 (4.3) (P=0.55)

HADS:

One stop (n=220) vs dedicated (n=158) clinic, mean (SD):
Baseline: 8.9 (4.4) vs 9.0 (5.0)
3 months: 7.0 (4.6) vs 7.5 (4.7) (P=0.22)

General comments:

This paper describes the findings from a NHS study of a one-stop clinic for the assessment of women with suspected breast cancer. Patients were recruited at one hospital between April 1995 and November 1996.

Participants were allocated by clerks and randomised by a balanced block design which had been generated by an independent statistician. Women were randomised prior to giving their consent to take part in the trial.

Unexpected sources of attrition caused the study to be extended but, even then, insufficient women were recruited to achieve more than a 79% power to exclude a 15% difference between arms.

This paper was predominantly examining the use of a one-stop clinic compared to a dedicated breast clinic, both on the grounds of health economics and for the alleviation of patient anxiety and depression, as a result of not having to wait so long for test results. Unfortunately, the relief was only very transient (24 hours) and did not offset the increased cost of same-day reporting of the diagnostic tests.

McArdle *et al.* (1996)

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: United Kingdom

Inclusion criteria:

Women <70 years
Undergoing breast cancer surgery

Exclusion criteria:

None stated

Population:

Number of patients = 272.

Interventions:

Before surgery, patients were randomised by telephone to one of four groups:

- (a) Routine support from ward staff and an information booklet (Understanding Cancer of the Breast - BACUP) (n=67)
- (b) Routine ward care and support from a specialist breast care nurse (n=66)
- (c) Routine ward care and support from a voluntary organisation (n=69)
- (d) Routine ward care and support from both the breast care nurse and the voluntary organisation (n=70).

The breast care nurse in this trial was appropriately qualified and highly experienced with this group of patients. Her role included informing patients of pre- and post-operative routines, possible after effects of surgery, provision of prosthesis if required, advising on appropriate exercise to regain physical function, explanation of post-surgical adjuvant therapies, counselling, listening, reassurance and provision of future contact. Her initial consultation lasted for about 30 minutes and subsequent appointments were tailored to need and time constraints.

The voluntary organisation was called Tak Tent (Glasgow based) and offered three types of support: information, counselling, and regular group meetings with fellow cancer sufferers. Patients allocated to receive support from them were given an introductory leaflet and subsequently contacted by one of the counsellors after discharge from hospital. It was up to individual counsellors to decide the level of support required and there were no restrictions on the methods the organisation might use which might include maintaining contact by telephone or post, arranging one to one meetings for counselling and encouraging attendance at group meetings.

Outcomes:

To evaluate the effect of support from a nurse specialising in breast care and a voluntary support organisation on prevalence of psychological morbidity after surgery for breast cancer.

Psychological morbidity was measured with self rating scales:

[1] A 28 item general health questionnaire - scores ranged from 0 to 28 and measured non-specific psychological morbidity. The questionnaire also contained subscales: somatic symptoms, anxiety & insomnia, social dysfunction and severe depression. Lower scores indicate better outcomes.

[2] Hospital Anxiety and Depression Scale (HADS) - scores range from 0 to 21 for both anxiety and depression. Lower scores indicate better outcomes.

Follow up:

Assessments were made at the first post-operative clinic visit and at 3, 6 and 12 months after surgery.

Within the first year after surgery 14 patients developed local recurrence, 12 developed disseminated disease and 9 died.

48/272 women missed 1 or more of their 4 planned assessments: 10 patients were terminally ill or had died, 6 developed other serious illnesses, 8 were chronic non-attenders 8 refused to fill in questionnaires and data were not available for 16 patients.

Results:

122 patients underwent a mastectomy, 144 underwent a lumpectomy, 124 patients received no adjuvant treatment or tamoxifen alone, 103 received radiotherapy and 41 patients received chemotherapy.

Most assessment scores tended to fall over the 12 month period. For each scale, scores were consistently lower in the group of patients offered support from the breast care nurse alone compared with the other groups, which were similar to each other.

[1] 28 item General Health questionnaire.

General Health. Mean (SD) at 1, 3, 6 and 12 months:

Routine: 5.2 (5.7); 5.2 (5.7); 4.2 (6.0); 3.7 (6.2)

Breast care nurse: 3.4 (4.6); 2.7 (3.7); 2.7 (3.6); 1.9 (3.5)

Tak Tent: 5.4 (5.4); 5.3 (5.5); 3.8 (4.5); 5.0 (6.5)

Nurse and Tak Tent: 5.1 (5.6); 4.6 (5.0); 4.4 (5.7); 3.9 (4.9)

General health. P=0.015 overall

Subscale results:

Anxiety and insomnia. Mean (SD) at 1, 3, 6 and 12 months:

Routine: 5.8 (4.2); 5.4 (4.2); 4.4 (4.7); 4.7 (4.6)

Breast care nurse: 4.9 (4.1); 4.3 (3.5); 4.0 (4.1); 3.5 (3.4)

Tak Tent: 6.7 (4.3); 6.4 (4.7); 5.2 (4.1); 5.7 (5.1)

Nurse and Tak Tent: 6.3 (4.5); 6.0 (4.3); 5.8 (4.8); 5.5 (4.4)

Anxiety & insomnia P=0.027

Severe depression. Mean (SD) at 1, 3, 6 and 12 months:

Routine: 1.3 (3.0); 1.5 (3.0); 1.6 (3.8); 1.4 (3.9)

Breast care nurse: 1.0 (1.9); 0.7 (1.6); 0.7 (1.3); 0.7 (1.4)

Tak Tent: 1.7 (2.4); 1.8 (2.5); 1.2 (1.9); 1.3 (2.4)

Nurse and Tak Tent; 1.5 (3.3); 1.4 (2.9); 1.7 (3.1); 1.3 (2.5)

Severe depression P=0.072 (nsd)

Social dysfunction. Mean (SD) at 1, 3, 6 and 12 months:

Routine: 8.6 (2.6); 8.7 (2.8); 8.0 (2.6); 7.8 (2.3)
Breast care nurse: 8.0 (3.0); 7.3 (2.0); 7.3 (1.9); 7.1 (1.9)
Tak Tent: 8.6 (2.7); 8.5 (2.4); 7.9 (2.3); 8.2 (2.9)
Nurse and Tak Tent: 8.6 (3.0); 8.3 (2.7); 7.8 (2.1); 7.4 (2.6)
Social dysfunction P=0.031

Somatic symptoms. Mean (SD) at 1, 3, 6 and 12 months:
Routine: 4.9 (3.6); 5.0 (3.6); 4.8 (4.1); 4.1 (3.4)
Breast care nurse: 4.0 (3.1); 3.9 (3.2); 4.2 (3.3); 3.8 (3.4)
Tak Tent: 5.2 (3.6); 5.9 (4.0); 5.2 (3.3); 5.4 (4.0)
Nurse and Tak Tent: 5.0 (3.8); 5.4 (3.7); 5.1 (3.6); 4.9 (3.8)
Somatic symptoms P=0.053 (borderline)

[2] HADS

Anxiety. Mean (SD) at 1, 3, 6 and 12 months:
Routine: 5.9 (4.2); 5.2 (3.9); 4.9 (4.5); 4.8 (4.7)
Breast care nurse: 5.3 (3.8); 4.4 (3.1); 4.7 (3.6); 4.4 (3.6)
Tak Tent: 7.1 (4.4); 6.4 (4.4); 6.0 (4.3); 6.3 (5.0)
Nurse and Tak Tent: 6.4 (4.2); 6.2 (4.2); 6.1 (4.2); 5.8 (4.7)
Anxiety P=0.093 (nsd)

Depression. Mean (SD) at 1, 3, 6 and 12 months:
Routine: 3.3 (3.3); 3.6 (4.3); 3.0 (3.5); 3.0 (4.0)
Breast care nurse: 2.3 (2.7); 1.6 (1.7); 1.7 (1.7); 1.4 (1.8)
Tak Tent: 3.4 (3.5); 3.2 (3.2); 3.0 (2.6); 3.2 (3.2)
Nurse and Tak Tent: 3.0 (3.5); 2.7 (2.8); 3.0 (2.9); 3.0 (3.4)
Depression P=0.003

General comments:

This paper describes a RCT in which participants were randomly allocated to receive routine care from ward staff, routine care plus support from breast care nurse, routine care plus support from a voluntary organisation, or routine care plus support from the breast care nurse and from the organisation. The aim was to assess the impact of the breast care nurse and a support organisation on the prevalence of psychological morbidity in patients undergoing surgery for breast cancer.

Within the first year after surgery, members of the Tak Tent organisation contacted patients by telephone on 456 occasions and by letter on 72 occasions. Counsellors received 14 telephone calls from patients and visited patients on 64 occasions. Patients attended 25 group meetings. 26 counsellors participated in the study.

During the course of the study the breast care nurse received 101 telephone calls either directly from patients or their immediate relatives. Queries included patients seeking information, concerns about recurrence, prostheses, side effects of treatment to requiring reassurance and calming of anxiety states or suicidal thoughts.

The timing of interventions differed in that the nurse saw the patients in the perioperative period whereas the voluntary organisation saw them after

discharge. These differences reflect the reality of how breast care nurses and many self help organisations operate.

Authors concluded that support from breast care nurse could significantly reduce psychological morbidity, as measured by self rating scales, in women undergoing breast cancer surgery.

This is a good paper of apparently sound design. However, there were few details of inclusion, exclusion criteria, allocation or randomisation methodology which means that the possibility of bias in selection cannot be excluded.

Mock *et al.* (1997)

Design: Prospective comparative study (therapy), evidence level: 2
Country: United States

Inclusion criteria:

Women undergoing treatment for stage I or II breast cancer
Aged 35-65 years
Had breast-conserving surgery
Scheduled to receive radiotherapy
Written informed consent

Exclusion criteria:

Concurrent major health problems including cardiovascular disease, acute or chronic respiratory disease or cognitive dysfunction
Being <35 years or >65 years
Already participating in a structured exercise program

Population:

Number of patients = 50, age range 35 to 64 years, mean age = 49 years.

Interventions:

Intervention group:

Self-paced and progressive program of brisk, incremental walking for 20-30 minutes followed by 5 minutes of slow walking. Subjects walked in their local neighbourhood or in a gym and self-prescribed the frequency (4 or 5 times per week) and exercise intensity.

Participants kept a diary with dates, exercise regimes and subjective data. Adherence was measured after the study but women were encouraged to stick to the schedule and were recommended to walk with a partner for support. Researchers made regular contact by telephone or during clinic visits in order to assess progress and provide encouragement.

Control group:

Usual care (not defined). These women were also contacted by researchers in order to minimise differential treatment effects.

Outcomes:

Symptom experience - measured by the Symptom Assessment Scales (SAS). Difficulty sleeping, depression and anxiety are three of the elements included in this assessment tool.

The main outcomes of this study (not reported here) were fatigue and physical function.

Follow up:

Baseline measurements of physical status were made using the 12-minute walk test and assessed using the Symptom Assessment Scales (SAS) and Piper Fatigue Scale (PFS). These tests were repeated at mid-therapy (about 3 weeks) and at the end of RT (about 6 weeks).

Four participants left the study: 1 because of treatment complications, 2 withdrew from RT and 1 woman left because of time constraints.

Results:

72% of women had stage I breast cancer (17 in the intervention group and 16 in the control group). Subjects in both study groups received RT for 5 days per week and there were no significant differences overall in dose and intensity.

SAS (analysis of covariance - mean scores):

Exercise level for intervention group: 4.51

Exercise level for control group: 0.92

P<0.001

Depression for intervention group: 9.51

Depression for control group: 21.05

P=0.104 (nsd)

Anxiety for intervention group: 10.44

Anxiety for control group: 26.93

P=0.029

Difficulty sleeping for intervention group: 12.38

Difficulty sleeping for control group: 32.58

P=0.027

General comments:

This paper describes a prospective comparative study conducted by two teaching hospitals which hypothesised an association between exercise and improvement of physical or psychosocial well-being in women with early breast cancer scheduled to receive RT after surgery.

Outcomes over the three time periods were tested by using multi-variate ANOVA controlling for possible confounders such as age, marital status, employment status, ethnicity etc.

Significant differences were found between study arms in pre- and post-test measures of exercise level, anxiety, sleeping difficulty but not depression. Fatigue was also significantly lower in the intervention group.

Measures of dissatisfaction with body correlated positively with fatigue, anxiety, depression and difficulty sleeping and negatively with walking (P=0.004).

The authors commented that subjects of the intervention increased their level of exercise as radiotherapy progressed whilst control subjects tended to do more less physical activity. They observe that patients in the intervention group appeared to be less fatigued, sleep better and experience lower levels of anxiety but not, for some reason, depression.

One weakness of the study was that participants in the intervention arm performed their exercises in their chosen environment and therefore the adherence was self-reported. Secondly, this was not a RCT and therefore the results may conceal a selection bias which may have affected internal validity i.e. was the observed effect due to the intervention alone?

Mutrie *et al.* (2007)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United Kingdom

Inclusion criteria:

Women with stage 0-III breast cancer
Receiving chemotherapy or radiotherapy
Written informed consent

Exclusion criteria:

Concurrent unstable cardiac, hypertensive or respiratory disease, cognitive dysfunction
Already taking regular exercise

Population:

Number of patients = 201, age range 29 to 76 years, mean age = 52 years.

Interventions:

Intervention group (n=99):

Standard care from the healthcare team plus participation in a 12-week exercise program. This involved attendance at 2 classes and one home exercise regime per week. The 45-minute exercise program involved a 10 minutes warm-up, 20 minutes of activity (such as walking, cycling low level aerobics, muscle strengthening) followed by a cool-down and relaxation period. Participants were monitored to ensure that they did not exceed 50-75% of age-adjusted maximum heart rate.

Exercise was followed each week for 6 weeks, by a group discussion which dealt with a new theme each time. Conversations centred on relevant topics in order to promote behaviour change in relation to exercise and encourage women to continue with individually constructed exercise programs at the end of the study. Women were also invited to join a local general practice referral scheme after the 3 months assessment.

Control group (n=102):

Standard care and receipt of a leaflet about safe exercise regimes. After 6 months women were given an individually constructed exercise programs and invited to join a local general practice referral scheme.

Outcomes:

[1] Quality of life (QOL) - measured by the Functional Assessment of Cancer Therapy, general (FACT-G) which includes a core domain of emotional function (FACT-GE) and can be complemented by the addition of the breast cancer-specific scale (FACT-B)

[2] Depression - measured using the Beck Depression Inventory (BDI)

[3] Positive and negative affect scale (PANAS)

[4] Physical activity outcomes (not described here)

Follow up:

Baseline assessments were repeated at 3 and 6 months.

15 women (12 from the intervention group) were lost to follow-up at 3 months because they: were not contactable (n=4), were excluded from the analysis (wrong treatment) (n=2), did not return questionnaires (n=7) or had died (n=2). Some of these women were assessed after 6 months.

At 6 months, 11 women (7 from the intervention group) were lost to follow-up because they: did not return their questionnaire (n=6), withdrew (n=1), were not contactable (n=2), were too ill (n=1) or had died (n=1).

Results:

Intervention group (n=82)

Control group (n=95)

Effect size estimates (95%CI):

FACT-GE from baseline to 3 months = 0.7 (-0.3-1.7) P=0.19

FACT-GE from 3 months to 6 months = 0.6 (-0.4-1.7) P=0.23

FACT-B from baseline to 3 months = 2.5 (1.0-3.9) P=0.0007*

FACT-B from 3 months to 6 months = 1.5 (0.1-2.9) P=0.039*

BDI from baseline to 3 months = -1.7 (-0.3-7-0.2) P=0.083

BDI from 3 months to 6 months = -1.8 (-3.8-0.1) P=0.064

PANAS+ from baseline to 3 months = 4.0 (1.8-6.3) P=0.0005*

PANAS+ from 3 months to 6 months = 3.9 (1.6-6.1) P=0.0008*

PANAS- from baseline to 3 months = -0.7 (-2.5-1.0) P=0.41

PANAS- from 3 months to 6 months = -0.7 (-2.5-1.0) P=0.39

* of statistical significance.

General comments:

This good quality paper describes a pragmatic randomised controlled open trial assessing a 12-week exercise program intended to improve quality of life for early breast cancer patients who were receiving chemotherapy or radiotherapy at (three) oncology clinics in Scotland.

Participants were recruited between January 2004 and January 2005 and randomised into two groups, stratified on the basis of treatment schedule and centre, by means of a permuted block design. Allocation was done by telephone using an interactive voice system. Blinding was not possible but assessments responses were concealed from researchers and measured independently.

The number of participants was sufficient to give a 90% power to detect a change of 7.5 in the FACT-G scores between study arms. Data were analysed on an intention-to treat basis.

There was no significant intervention effect on FACT-G (general scale) at 3 months and this was still non-significant ($P=0.053$) at 6 months. Breast cancer-specific QOL and mood were significantly positively affected by the intervention both at the 3 and 6 months follow-ups.

The authors admit that it would not be easy to determine which part of the intervention may have been responsible for the successful psychological outcomes e.g. whether exercise or the group setting itself but since some of the physical outcomes were significantly improved e.g. shoulder mobility, these at least can be directly attributed to exercise.

The authors concluded that supervised group exercise in addition to usual care could provide functional and psychological benefits at the end of a 12 week program and at least up to the 6 months follow-up.

Stanton *et al.* (2005)

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United States

Inclusion criteria:

Women with stage I or II breast cancer
Any surgery for primary breast cancer must have been within previous 6 weeks
Invasive epithelial cancer of any nodal status

Exclusion criteria:

Prior history of breast cancer
Non-invasive breast cancer or inflammatory breast cancer
Planned use of neoadjuvant chemotherapy or high dose chemotherapy with stem cell rescue
Protracted reconstructive surgery
Surgical complications
Severe physical, cognitive or psychiatric illness
Inability to read and write in English

Participation in another RCT with a QOL intervention

Population:

Number of patients = 558, age range 26 to 86 years, mean age = 58 years.

Interventions:

After randomisation, participants were allocated to one of three groups:

[a] Psychoeducational counselling (EDU) (n=184) - participation in one individual counselling session (of duration 80 minutes) and one telephone session with trained educators. Participants were invited to voice their concerns in each of the domains of physical health, emotional well-being, interpersonal relationships and life perspectives. By identifying a particular concern the woman could review their goals and develop an action plan. participants were also given a copy of the NCI booklet 'Facing Forward' and a 60-page manual entitled 'Moving beyond Cancer: Your Guide to a Successful Recovery'. The follow-up telephone call dealt with reactions to the material and revisions of strategies and action plans.

[b] Videotape intervention (VID) (n=187) - a personalised letter thanking the recipient for completing the baseline questionnaire and enclosing a copy of the NCI booklet 'Facing Forward'. Also enclosed was a NCI videotape entitled 'Moving beyond Cancer' which lasts for 24 minutes and addresses challenges for re-entry including physical health, emotional well-being, interpersonal relationships and life perspectives. This film was designed to promote adaptive modelling by portraying four breast cancer survivors outlining the problems and advice on coping skills.

[c] Standard print control group (CTL) (n=187) - a personalised letter thanking the recipient for completing the baseline questionnaire and enclosing a copy of the NCI booklet 'Facing Forward' which contains information for cancer survivors.

Outcomes:

[1] Vitality - a subscale from the Short Form-36 (SF-36)

[2] Cancer-specific distress - measured with the Revised Impact of Events Scale (IES) which graded how distressing 22 experiences had been on a 5-point scale from 0 (not at all) to 5 (extremely). Such experiences included, for example, intrusive thoughts, avoidance, hyperarousal etc.

[3] Depressive symptoms - measured using the Center of Epidemiologic Studies-Depression Scale (CES-D) which has 20 items to rate depressive symptoms in the previous week on a 4-point scale where total scores range from 0-60.

[4] Positive changes after stressful experience - measured on the Post-Traumatic Growth Inventory (PTGI). Women rated items with regard to cancer as the life stressor from 0 (change not experienced) to 5 (experiencing the change to a very great degree)

Other outcomes included intervention fidelity, medical outcomes and perceived preparedness for re-entry (data not presented here).

Follow up:

Follow-up was conducted for 12 months.

Overall, 67% of participants completed three assessments, the first at baseline and then at 6 and 12 months. 66 patients completed baseline one follow-up point and 117 completed only at the baseline. Participants who did not complete the 6 month assessment tended to be older ($P<0.001$), employed ($P=0.009$), to be taking tamoxifen ($P=0.009$) and less likely to report cancer-specific distress ($P=0.002$) or depressive symptoms ($P=0.005$) at baseline. The findings were similar at 12 months.

7/151 women in the EDU arm failed to participate in the intervention because they: were unable to be contacted ($n=2$), had a schedule conflict ($n=3$) or for other reasons ($n=2$)

Results:

At 6 months data were available for CTL ($n=136$), VID ($n=139$) an EDU ($n=143$) and at 12 months for CTL ($n=134$), VID ($n=135$) and EDU ($n=130$).

There were significant baseline differences in the scales of depressive symptoms, vitality and other variables (the control groups scored highly for vitality and low for depressive symptoms compared with either intervention group) and so the analysis used these baseline scores as a covariate.

Results - 6 months and 12 months:

SF-36 vitality - 6 months/12 months. Mean (SD):

SPC: 3.84 (1.58) / 6.06 (1.53)

VID: 9.06 (1.54) / 9.38 (1.51)

EDU: 5.00 (1.54) / 7.36 (1.56)

VID vs CTL at 6 months ($P=0.018$)

Log (IES) - 6 months/12 months. Mean (SD):

SPC: -0.09 (0.02) / -0.13 (0.02)

VID: -0.08 (0.02) / -0.10 (0.02)

EDU: -0.06 (0.02) / -0.11 (0.02)

No significant differences at either time point

CES-D - 6 months/12 months. Mean (SD):

SPC: -0.94 (0.62) / -1.79 (0.57)

VID: -1.25 (0.61) / -1.32 (0.56)

EDU: 0.02 (0.61) / -0.68 (0.58)

No significant differences at either time point

PTGI - 6 months/12 months. Mean (SD):

SPC: 0.75 (1.46) / 2.43 (1.58)

VID: 2.65 (1.43) / 3.00 (1.56)

EDU: 3.32 (1.41) / 5.44 (1.60)

No significant differences at either time point

General comments:

This paper describes a RCT which compared a peer-modelling videotape with

two educational sessions or a control. Participants were initially recruited from the offices of collaborating oncologists. Volunteers were then contacted at the end of active treatment, completed baseline questionnaires and randomly assigned via a random number generated list. Assignment was stratified by treatment, clinic and marital status. Participants were recruited between July 1999 and June 2002.

Recruitment was close to providing a 90% power sufficient to detect a standardised effect size of 0.46. Data were analysed on an intention-to-treat basis using appropriate statistical methods (ANOVA).

The results were not as anticipated by the reviewers. No significant differences were found for the majority of outcomes, possibly because of the inequality at baseline forcing adjustment to the statistical analyses. Additionally, the interventions were relatively 'light' and hence non-compliance and failing to submit questionnaires might be understandable.

Burton <i>et al.</i> (1995)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: UK
Inclusion criteria: Women with breast cancer awaiting total or partial mastectomy Written informed consent (intervention groups only)
Exclusion criteria: None stated
Population: Number of patients = 244, mean age = ~61 years.
Interventions: The preoperative interview covered subjects such as: discovery of breast lump, patient's thoughts about possible cause of illness, response to the need for surgery, desire for information, worries about body image, past and future regrets, concerns etc. Expression of feelings by the patient was encouraged. The psychotherapeutic intervention placed the crisis of illness and surgery within the patient's life situation. Patient's feelings were explored. [a] Pre-operative interview between the patient and a clinical psychologist followed by a 30 minutes brief psychotherapeutic intervention which was given by the consultant surgeon who was trained in Rogerian counselling techniques. [b] Pre-operative interview as above, plus a 30 minute chat with the consultant surgeon described as 'a friendly discussion of matters unrelated to illness and surgery'. [c] Pre-operative interview, as above. [d] Standard care from surgical and nursing staff.

Outcomes:

[1] Hospital Anxiety and Depression Scales (HADS). This was administered at the four time points for interview groups and at 3 months and 1 year for controls.

[2] Coping – a manual was devised to measure this outcome and classified: denial, fighting spirit, stoic acceptance, helpless/hopelessness and anxious preoccupation.

[3] Body image distress.

Follow up:

After preoperative interviews, patients (other than controls) completed baseline outcomes measures. These patients were followed up in hospital at 4 days after surgery and (all patients) at 3 months and 1 year.

Results:**Reduction in anxiety and depression over time in the three interview groups (no control):**

Mean HADS score – Anxiety (n=86):

Pre-operatively: 7.2

4 days post-surgery: 4.3

3 months post-surgery: 4.5

1 year post-surgery: 4.4

P<0.00001

Mean HADS score – Depression (n=86):

Pre-operatively: 3.2

4 days post-surgery: 2.4

3 months post-surgery: 3.1

1 year post-surgery: 3.3

P=0.01

NB. This is a within-group analysis i.e. changes across time for all intervention groups, not a comparison

Comparison of HADS scores at 3 months and 1 year (all interview groups vs controls):

Mean HADS score – anxiety at 3 months:

Interview + intervention: 4.3

Interview + chat: 4.2

Interview only: 5.1

Control: 6.1

P=0.043

Mean HADS score – depression at 3 months:

Interview + intervention: 2.8

Interview + chat: 3.0

Interview only: 3.4

Control: 3.7

nsd

Mean HADS score – anxiety at 1 year:

Interview + intervention: 4.6

Interview + chat: 3.4

Interview only: 5.3

Control: 5.6

nsd

Mean HADS score – depression at 1 year:

Interview + intervention: 3.7

Interview + chat: 2.3

Interview only: 3.9

Control: 3.7

nsd

NB. This is a between-groups analysis i.e. comparison between interventions and controls.

Significant changes in coping ability over time in the three interview groups (no control):

% Coping Scores (n=130):

Denial preoperatively: 29

Denial 1 year post-surgery: 13

P<0.00001

Fighting spirit preoperatively: 31

Fighting spirit 1 year post-surgery: 43

P<0.00001

Stoic acceptance preoperatively: 19

Stoic acceptance 1 year post-surgery: 17

Helpless/hopelessness preoperatively: 9

Helpless/hopelessness 1 year post-surgery: 10

Anxious preoccupation preoperatively: 12

Anxious preoccupation 1 year post-surgery: 17

P=0.0002

NB This is a within-group analysis i.e. changes across time for all intervention groups, not a comparison

Comparison of coping ability at 1 year (all interview groups vs controls) % total coping:

Denial:

Interview + intervention: 13

Interview + chat: 16

Interview only: 11

Control: 15

nsd

Fighting spirit:

Interview + intervention: 45

Interview + chat: 40
Interview only: 44
Control: 36
P=0.031

Stoic acceptance:
Interview + intervention: 15
Interview + chat: 21
Interview only: 14
Control: 18
nsd

Helpless/hopelessness:
Interview + intervention: 8
Interview + chat: 11
Interview only: 12
Control: 11
nsd

Anxious preoccupation:
Interview + intervention: 19
Interview + chat: 13
Interview only: 19
Control: 21
nsd

Comparison of body image distress between preoperative interview and controls:

The interview, with or without intervention/chat had a significant effect on body image distress. All experimental groups vs controls:
Mean body image distress at 3 months = 1.34 vs 3.22
Mean body image distress at 1 year = 1.03 vs 2.96
When these data were analysed with non-parametric methods, because of skewed distributions, the results were lower than original findings but still highly significant (P=0.009)

Comparison between the psychological intervention and the chat:

An analysis of this comparison showed that only patients who had experienced severe stressful life events found the intervention superior to the chat with respect to distress (P=0.04).

General comments:

This paper presents the results of a UK four-arm RCT which examined the impact of a preoperative interview with or without a chat and/or psychotherapeutic intervention compared with routine care. The anticipated benefits for the patient were measured by several psychological variables a few days after mastectomy and in the months following.

Patients were randomised to their study arms by the use of random number tables. Unusually, women randomised to the control arm were not formally told that they were participating in a RCT until the one year follow-up because the 3 month interview was conducted by a member of the Mastectomy Association

rather than by a reviewer. The reasons given for this methodology was that if informed and given baseline questionnaires this group would cease to be considered as receiving 'standard care' by definition. This has methodological merit, but means that, as there were no baseline data for controls, the interview can be compared against one another but individual interventions cannot be compared with a non-intervention (control) group.

The authors noted the high drop-out pre-randomisation (80 patients) and their reasons for refusal to join a CT which, commonly, were either a denial of having feelings about the surgery or a desire not to express their feelings on this subject. Coping strategies changed over time with significant changes in denial, fighting spirit and anxious preoccupation shown by interview groups but a comparison with control at 1 year showed that only fighting spirit was significantly different (lower) in controls.

The authors concluded that the comparisons between outcomes in interview groups suggested that the pre-surgical interview was more likely to have contributed to the most positive outcomes than either the intervention or the chat. This would have been a useful comparison to have made with a control group. It might also be feasible for such an intervention to have been given by a clinical nurse specialist as opposed to a clinical psychologist.

Andersen <i>et al.</i> (2004)
Design: Randomized controlled trial (therapy), evidence level: 1- Country: USA
Inclusion criteria: Women with stage II or III breast cancer and awaiting adjuvant therapy
Exclusion criteria: Stage I disease (mentioned in the results section) Prior cancer diagnosis Refusal of cancer treatment Age <20 >85 Living more than 90 miles from the research centre Mental retardation, severe or untreated psychopathology, neurological disorders, dementia Any immunologic disease or condition
Population: Number of patients = 227, mean age = 51 years.
Interventions: Control group (n=113): Baseline assessment of psychological, behavioural, medical and treatment data was made. Blood samples were taken for immunological outcomes that are not reported here. Intervention group (n=114): Identical baseline assessments were made as for controls. Participants were grouped in 13 cohorts (n=8-12 participants). Each group met weekly for one and a half hours over 18 weeks. Sessions were conducted by two clinical

psychologists and were described as including strategies to 'reduce stress, improve mood, alter health behaviours and maintain adherence to cancer treatment':

Stress: Understanding stress responses, progressive muscle relaxation training
Emotional distress: Relaxation training, positive coping, problem solving

Statistical analysis showed that there was no difference in the way that successive intervention sessions were conducted or in the way in which individual components were rated for helpfulness or the intervention for its importance as a whole. If a patient was absent from a session a therapist would call, give support if required and discuss the current topic in the group intervention.

Outcomes:

[1] Stress – measured by the Impact of Events Scale (IES) which examines stress-related intrusive thoughts, denial of thoughts and avoidance behaviours relating to cancer and treatment.

[2] Emotional distress – measured by Profile of Moods States (POMS) which measures negative mood and consists of five scales: anxiety, depression, anger, fatigue and confusion. Total Mood Disturbance is the sum of these scales minus the score for vigour.

There were many other outcomes including health behaviours, adherence to treatment and immunological response which are not detailed here.

Follow up:

Baseline assessment of psychological, behavioural, medical and treatment data was made. Blood samples were taken for immunological outcomes. Tests were repeated after 4 months.

Before the 4 month assessment, 29 patients (intervention = 22) dropped out (from the intervention but remained in the trial), missed their assessments, experienced disease recurrence (n=2) or had died (n=1). Only 12/224 patients missed their final assessment. Absences were often due to work commitments or treatment toxicities.

Results:

Participants had stage II or III breast cancer. Between 89-90% of these women in total were of stage II.

[1] Stress. Baseline scores were not significantly different between intervention and control groups: 26.26 (\pm 14.42) vs 26.28 (\pm 14.46) respectively. This outcome may only have been used to assess baseline stress since no 4 month data were given.

[2] Emotional distress. Baseline values were significantly different between intervention and control groups and a single ANOVA showed nsd between groups. The data were then re-analysed with initial levels of cancer-related stress as a co-factor:

Total Mood Disturbance - POMS (intervention vs control):

31.38 (± 32.11) vs 41.42 (± 35.67) P<0.05

Subscales (intervention vs control):

Anxiety: 12.02 (± 6.91) vs 14.17 (± 7.72) P<0.05

Depression: 10.83 (± 9.32) vs 12.68 (± 11.28)

Anger: 7.49 (± 6.7) vs 8.22 (± 6.19)

Confusion: 8.19 (± 5.37) vs 9.75 (± 5.53)

Fatigue: 8.65 (± 5.97) vs 10.49 (± 6.49)

Vigour: 16.0 (± 6.43) vs 13.89 (± 6.13)

No 4 month data were given in the text but analyses were performed as indicated. Straightforward two-way analysis of data for Total Mood Disturbance showed no significant difference between intervention and control groups. A three-way analysis, introducing the variable of subjects with high initial cancer stress, however, rendered the data of significance in favour of the intervention (P=0.04). When the authors focused on the anxiety sub-scale they found that there was a significant two-way interaction such that there was a greater reduction of anxiety in the intervention arm than in the control arm (P=0.04) but which was not affected statistically by initial cancer stress.

General comments:

This paper describes a RCT which compared a psychological intervention with a non-intervention control group in assessing the effects of this therapy on various outcomes, either relating to treatment, physical health and biochemical status but also to distress. The study appears to have been well conducted but there were no details about recruitment, allocation or randomisation. Since bias is a strong possibility, findings from this trial must be viewed with some caution.

Data were analysed with appropriate statistics (repeated measures and multivariate ANOVA) and intention-to treat, including 15% of the intervention group who did not participate but remained in the trial.

The authors focus on the positive outcome for the anxiety sub-scale of the POMS which conferred an advantage to the intervention but showed no data for the remaining sub-scales which were not significant (except for fatigue which was significant if initial cancer stress was factored in). More positive results were forthcoming for other outcomes such as dietary habits, smoking cessation and biochemical and immunological measures.

Samarel *et al.* (2002)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: USA

Inclusion criteria:

Women with non-metastatic (0-III) breast cancer

Previous surgery within 4 weeks

No previous cancer diagnosis (except non-melanoma skin cancer)

No major medical problems e.g. chronic renal or cardiac disease

Written informed consent

Exclusion criteria:

None stated

Population:

Number of patients = 183, age range 30 to 83 years, mean age = 54 years.

Interventions:

For all three groups, treatment was phased: (i) 8-10 weeks beginning 4 weeks after surgery (ii) 8 weeks and (iii) 8 months:

[a] Intervention group:

- (i) Weekly telephone social support and education
- (ii) Weekly in-person social support and education (including resource kit handed out in 1st meeting)
- (iii) Twice monthly telephone social support and education for 3 months followed by monthly telephone social support and education for 5 months

[b] Control 1 group:

- (i) Weekly telephone social support and education
- (ii) Weekly telephone social support and education (including resource kit handed out in 1st meeting)
- (iii) Twice monthly telephone social support and education for 3 months followed by monthly telephone social support and education for 5 months

[c] Control 2 group:

- (i) No intervention
- (ii) Mailed resource kit (women could telephone oncology nurse or social worker re. contents)
- (iii) No intervention

The content of the telephone and group components comprised elements of managing symptoms and stress, dealing with fear of recurrence and issues of self-image and sexuality. The resource kit consisted of an information manual, audiotapes, videos and pamphlets which together encompassed reflections of self-concept and interdependence, special exercises to enhance learning and other reading. Telephone interventions were provided by oncology nurses or social workers.

Outcomes:

[1] Frequency and measure of cancer-related worry – measured on the Visual Analogue Scale – Worry (VAS-W) which has possible scores ranging from 0-200 from low to high frequency and intensity.

[2] Well-being, satisfaction with life was measured on the Existential Well-Being Scale (EWBS) which is a sub-scale of the Spiritual Well-Being Questionnaire and asks questions the response to which range from 0-6 on a Likert scale.

[3] Mood disturbance – measured on the Profile of Mood States (POMS) which has six polarised sub-scales: tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia and confusion-bewilderment each rated on a 5-point Likert Scale.

Follow up:

58 patients were dropped from the data analyses: lack of continued interest

(n=35), missing more than 2 group sessions (n=2), data not returned or beyond deadline (n=18), death (n=2) and not receiving education materials (n=1). Of these 58 women, 21 were in the intervention group, 20 in the control 1 group and the remaining 17 in the control 2 group with no significant differences in attrition rate.

Baseline data were collected and follow-up assessments were made at the completion of each treatment phase.

Results:

Post-surgical treatment: chemotherapy (n=55) or radiotherapy (n=33). Data at the baseline were not significantly different between the three arms and hence these data were not used as a covariate in statistical analysis. Experimental group (n=34), control group 1 (n=48) and control group 2 (n=43).

[1] Frequency and measure of cancer-related worry. Range: 0-200. Mean (SD):

[a] Intervention:

Baseline: 78.24 (46.63)

Phase i: 54.12 (42.77)

Phase ii: 58.18 (46.13)

Phase iii: 54.97 (45.13)

[b] Control 1:

Baseline: 80.44 (57.82)

Phase i: 61.69 (47.20)

Phase ii: 71.60 (55.49)

Phase iii: 55.77 (53.79)

[c] Control 2:

Baseline: 89.74 (58.28)

Phase i: 81.95 (56.53)

Phase ii: 82.74 (52.28)

Phase iii: 70.49 (50.10)

[2] Well-being, satisfaction with life. Range: 0-60. Mean (SD):

[a] Intervention:

Baseline: 23.21 (9.20)

Phase i: 21.29 (6.82)

Phase ii: 20.65 (7.77)

Phase iii: 19.15 (8.29)

[b] Control 1:

Baseline: 23.79 (9.59)

Phase i: 22.85 (10.25)

Phase ii: 24.60 (11.06)

Phase iii: 23.04 (9.59)

[c] Control 2:

Baseline: 24.12 (9.27)

Phase i: 24.47 (10.21)

Phase ii: 25.77 (10.70)

Phase iii: 23.37 (10.18)

[1] Mood disturbance. Range: -32-+232. Mean (SD):

[a] Intervention:

Baseline: 25.68 (37.53)

Phase i: 14.06 (27.69)

Phase ii: 14.06 (35.92)

Phase iii: -2.40 (23.19)

[b] Control 1:

Baseline: 21.21 (33.52)

Phase i: 13.00 (29.71)

Phase ii: 11.17 (24.97)

Phase iii: -5.00 (15.71)

[c] Control 2:

Baseline: 23.14 (34.62)

Phase i: 35.16 (38.77)**P=0.02 (cf Experimental group) or P<0.01 (cf Control 1)

Phase ii: 39.65 (37.84)**P<0.01 (cf Experimental group or cf Control 1)

Phase iii: 27.68 (27.99)**P<0.01 (cf Experimental group) or P=0.03 (cf Control 1)

There were no significant differences between groups for any other outcome, apart from mood disturbance and no significant difference between the intervention and control 1 groups for any outcome, including mood disturbance.

General comments:

This good quality paper describes a three-arm RCT which tests interventions with a view to improving the self concept and interdependence modes of the Roy (1999) model of nursing. Participants were recruited in response to mailed invitations sent to areas in New Jersey, USA.

Patients were randomised using a permuted block design. When successive cohorts of 4-8 women had been recruited each cohort was randomly assigned to a treatment arm using a sealed envelope technique. Enough women were recruited to achieve 80% power to detect for effect size of 0.25. Appropriate statistics (MANOVA or non-parametric tests) were used to analyse the data but it was not stated whether or not these analyses were performed independently.

The authors observed that the results were surprising and had not supported hypotheses about the efficacy of this model of support and education. It was also unexpected that, whilst mood was changed significantly between the education-only group and the other two groups, none of the protocols had a significant effect on either well-being or cancer-related worry. The authors concluded that perhaps social support and education may not be as influential in overcoming such emotions at a time when a woman is receiving treatment for a potentially life-threatening illness.

Allard (2007)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: Canada

Inclusion criteria:

Women with newly diagnosed breast cancer or a suspected lesion
Scheduled to undergo first breast surgery on an out-patient basis
Able to speak and write French
Age >18 years
No hearing impairment
Possession of a home telephone
Written informed consent

Exclusion criteria:

Previous cancer or major psychiatric diagnosis

Population:

Number of patients = 117, age range 26 to 86 years, mean age = 54 years.

Interventions:

Intervention group:

Attention Focus and Symptom Management Intervention (AFSMI). The researcher collected baseline data from participants 2-3 days after surgery. The first interventional telephone call was made 9-10 days after surgery during which the researcher assessed outcome responses by inviting a detailed, objective description of symptoms giving encouragement and suggesting new or additional self-care strategies in response to such requests from the woman. Emotions expressed by women were acknowledged by the researcher who also completed outcome questionnaires with each participant. Duration of the call was not limited. This intervention was repeated one week later and outcome data collected.

Control group:

Usual care comprised peri-operative teaching given by nurses both before surgery and after leaving hospital. Participants also received a telephone call from the staff nurse of the surgical ward enquiring after their well-being. The researcher also called and collected outcome data at the same time intervals as intervention participants.

Outcomes:

[1] Functional status – measured by the Symptom Impact Profile (SIP) which examines the extent to which surgery impacts on daily life. The higher the score the higher the level of disruption.

[2] Emotional distress – measured with the short form of the Profile of Moods States (POMS) which has 37 items each rated on a 5 point Likert scale. Sub-scales include anger, depression, confusion and anxiety and a higher score indicates a higher level of anxiety.

Follow up:

Assessments were made at baseline (T1: 2-3 days after surgery), one week after the 1st intervention session (T2: 9-10 days after surgery) and one week following the 2nd intervention session (T3: 17-18 days after surgery).

Results:

The majority of women with a final diagnosis of breast cancer were at stage I (40%) or stage II (25%). Nine women had benign disease. The authors only presented statistically significant outcomes.

[1] Functional status:

Only the home management element (score range: 0-100) of this outcomes measure was significantly affected by the intervention:

Scores across time. Mean (SD):

Intervention group (n=?):

T1: 45.26 (25.30)

T2: 18.91 (18.49)

T3: 12.12 (15.00)

Control group (n=?):

T1: 45.54 (30.50)

T2: 25.87 (25.62)

T3: 17.10 (17.51)

Both groups showed declines in mean score over time which reached significance between T2 and T3, meaning that this element was naturally less disruptive as time passed. The intervention and control groups were statistically significantly different from one another across time ($P=0.03$) but not at any specific time point, meaning that being in the intervention group was associated with a better rate of decline in disruption to home management.

[2] Emotional distress (sub-scale of POMS where range: 27-135):

Scores across time. Mean (SD):

Intervention group (n=?):

T1: 47.23 (15.51)

T2: 41.20 (14.69)*

T3: 41.03 (15.87)

Control group (n=?):

T1: 49.96 (19.76)

T2: 47.91 (18.12)*

T3: 45.61 (16.41)

Neither group showed significant changes in mean score over time nor was there an overall group effect but intervention and control groups were significantly different from one another at time T2 ($P=0.03$). This means that at the second time point, being in the intervention group was associated with a lower level of emotional distress but that, on the whole, group assignment made no significant difference to outcome.

Confusion (sub-scale of POMS where range: 5-25):

Scores across time. Mean (SD):

Intervention group (n=?):

T1: 9.79 (3.73)

T2: 7.98 (3.58)*

T3: 8.03 (3.54)

Control group (n=?):

T1: 9.57 (4.13)

T2: 9.49 (3.98)*

T3: 8.82 (3.74)

Both groups showed significant declines in mean score over time ($P=0.01$) and

the rate of decline was significantly different between groups across time ($P=0.02$) and between groups at time T2 ($P=0.05$). This means that the element of confusion naturally improved over time but that being in the intervention group was associated both with a better rate of decline and a lower mean score for confusion at time T2.

The scores in the Depression sub-scale also naturally declined over time ($P=0.05$) but there was no group differences either over time or between specific time points.

General comments:

This paper describes a Canadian RCT which examined the effects of a psycho-educational nursing intervention which was given in the immediate post-operative period following day surgery for breast cancer. The purpose of the intervention was to help women to focus on symptom experiences and the decisions made to manage those symptoms. Since recruitment and use of the intervention occurred prior to a final diagnosis, some of the participants did not have breast cancer. However, for the purposes of assessment, these women were included since it may be that their levels of emotional distress were equal to women who were later diagnosed positively.

Women were recruited over a 2 years period from rural and urban areas. The study numbers were sufficient to detect a moderate effect size (no number given) with 80% power. Randomisation was achieved by means of a table of random number and women were allocated by a research assistant. Data were stratified by whether or not they had axillary node biopsy as part of their surgery.

Significant differences in baseline data between groups necessitated the use of the pre-test scores to be used as covariates in the statistical ANOVA. Importantly, it was not clear how many of the 117 recruited participants actually completed all the assessments or how many were in each study arm. This information would have useful in confirming the validity of the published results and so conclusions should, perhaps, be viewed with some degree of caution since less than 117 women would render the trial underpowered.

Authors concluded that AFSMI significantly affected the home management element of functioning and had an overall positive effect on emotional distress, particularly in the early post-surgical period, and improved the symptoms of confusion both across time and in the early post-surgical period. Other outcomes were not significant. The authors felt that a nursing intervention applied immediately after surgery could reduced emotional distress and enhance coping.

Sandgren & McCaul (2003)

Design: Randomized controlled trial (therapy), evidence level: 1+

Country: United States

Inclusion criteria:

Diagnosis of stage I-III breast cancer

Ability to speak English
Ability to talk by phone
Undergoing adjuvant treatment

Exclusion criteria:

Serious comorbid conditions

Population:

Number of patients = 222, age range 30 to 84 years, mean age = 55 years.

Interventions:

Intervention group:

Nurse phone intervention which comprised five weekly telephone calls, each lasting for 30 minutes. A follow-up call was made after a further 6 months, usually when chemotherapy had finished. The intervention centred on 2 approaches:

(a) Health education (n=78): participants received a curriculum detailing study subjects which included understanding breast cancer, managing post-surgical changes, understanding treatment, managing side effects & fatigue and maintaining a healthy life style.

(b) Emotional expression (n=89): participants received the same number of calls as the other intervention arm. Women were encouraged to express their deepest feelings about the cancer and any attendant issues. The nurse listened and provided support and encouragement.

Nurses were trained, and initially supervised, to give these interventions. 7 nurses completed the entire project and were all involved with both sub-groups.

Control group (n=55): Standard care which included access to the usual nursing care line, if required.

Standard care

Outcomes:

[1] Knowledge - measured by means of testing knowledge on a specific topic (lymphoedema) and asking an open ended question: 'list the way to prevent lymphoedema'.

[2] Perceived control - measured from 4 items on the Perceived Stress Scale (PSS) and scored from 0-4.

[3] Self-efficacy - measured using 2 sub-scales from the Cancer Behaviour Inventory (CBI) comprising 8 items to assess the degree to which the user sought and understood medical information and 7 items to assess affect regulation.

[4] QOL - measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B). which assesses physical, functional, social and emotional well-being and is also directed to issues relating specifically to breast cancer.

[5] Mood - measured by the Profile of Mood States (POMS) sub-scales for depression-dejection, tension-anxiety, fatigue-inertia, vigour-activity, anger-

hostility and confusion-bewilderment.

Follow up:

Baseline measures were made before the start of the intervention (T1), usually post-surgery and during adjuvant therapy. The follow-up assessment was after 5 months (T2).

All randomised participants completed the study.

Results:

Of 222 patients that completed the study, 49% had stage I and 13% had stage II breast cancer.

[1] Knowledge

No baseline measures were tested and so this outcome is presented as the result at time T2. Results scale = 0-10. Mean (SD):

(a) Health education arm: 2.86 (2.30)

(b) Emotional expression arm: 1.92 (1.70)

(c) Standard care arm: 1.74 (1.30)

$P < 0.01$ when (a) compared with (b)

[2] Perceived control. Results scale = 0-16. Mean (SD):

(a) Health education arm:

T1: 5.12 (2.90)

T2: 3.53 (2.80)

(b) Emotional expression arm:

T1: 4.75 (3.00)

T2: 3.81 (2.60)

(c) Standard care arm:

T1: 5.27 (3.60)

T2: 4.56 (3.10)

$P = 0.03$ when (a) compared with (b)

Across all groups, women reported greater control ($P < 0.01$) with time but also more social constraint ($P = 0.03$). Other comparisons of mediators related to therapy (including CBI outcomes) did not produce results of significance over time or between study arms.

[4] QOL:

As a whole group, women reported significant improvements over time for physical, functional and emotional well-being and for QOL as a whole ($P < 0.01$) but not for social outcomes including the relationship with the physician.

[5] Mood:

As a whole group, women reported significant improvements over time for overall mood and individual mood states ($P < 0.01$), except for fatigue. None of the outcomes were significantly different between control and intervention groups.

General comments:

This paper presents results from a three arm RCT which compared two telephone interventions given by trained nursing staff. One intervention focused on elements of patient education and the other on emotional expression. Both were compared with a control condition of standard care.

Participants were recruited by a psychologist and two oncology nurses during clinic appointments and were randomly assigned to study group by means of block and stratified by stage. The statistics (ANOVA) were appropriate.

Only the health education participants showed positive outcomes when compared with control subjects, having greater knowledge and perceived control. Control was a parameter which improved as a whole for all subjects across time.

The sample size had 83% power to detect a moderate (Cohen's $d = 0.4$) difference between arms, had there been one. The authors offered hypotheses as to why the interventions were largely ineffective which summarised to (1) verbal emotional expression being possibly weaker than written emotional expression, (2) the telephone being a less effective medium than in-person therapy, (3) possible inadequacy in nurse qualification, (4) participant background, (5) incorrect follow-up time and (6) the lack of need for any intervention as women tended to improve in these outcomes over time anyway with good standard care alone.

These findings and conclusions were not changed by additional data presented in a follow-up paper (Sandgren *et al.*, 2007).

Badger *et al.* (2007)

Design: Randomized controlled trial (therapy), evidence level: 1-

Country: United States

Inclusion criteria:

Women with stage I-III breast cancer

Currently receiving adjuvant therapy for breast cancer

Ability to speak English

Ability to speak on the telephone

No physical or psychological disabilities (sufficient to prevent participation in any interventional activities)

Available partner (who were also involved in the trial but this element is not reported here).

Exclusion criteria:

None stated

Population:

Number of patients = 96.

Interventions:

All arms were conducted over the telephone and by counsellors suitable trained in the particular intervention.

Intervention 1 (n=38)

Telephone Interpersonal Counselling Intervention (TIP-C)

For 6 weeks, the participant received weekly telephone calls (mean duration of 34 minutes) from a psychiatric nurse counsellor who had oncology expertise. The conversation centred on cancer education, social support, awareness and management of depressive & anxiety symptoms and role transition.

Intervention 2 (n=23)

A 6-week self managed exercise protocol which focused on regular, low impact exercise with weekly telephone calls (mean duration of 11 minutes) to check progress and give encouragement. Scale of involvement was measured during the course of these calls - participants were asked rate the nature of the exercise, duration and intensity (on a scale of 0-10).

Control (n=37)

Participants received printed information about breast cancer and weekly (brief) telephone calls over the 6 week period. No counselling, advice or tips for exercise were offered and if any problems were highlighted during these calls the patient was referred to her doctor.

Outcomes:

[1] Depression - measured by a 20-item Centre for Epidemiological Studies - Depression Scale (CES-D) where scores >16 are considered positive for clinical depression.

[2] Anxiety - measured on several scales and combined into a 8-point composite index of anxiety:

(i) Positive and Negative Affect Scale - four sub-units: nervous, jittery, scared, afraid.

(ii) SF-12 - one sub-unit: calm & peaceful

(iii) Index of Clinical Stress - 3 items: feel so anxious want to cry, hard to relax, feel very panicked.

Follow up:

Baseline assessments (T1) were made before the trial started using various instruments including those reported in the paper. Follow-up assessments were made in the week after the sixth call (T2) and a month later, 10 weeks after the final call (T3). All assessments were conducted by telephone.

Three women dropped out before T2 and five before T3. Reasons included lack of interest or a failure to collect data. These women did not start the study with significantly higher levels of anxiety or depression than those women who remained in the study.

Results:

Of 96 participants, 53% had stage II breast cancer and 14% stage III, the rest

were stage I. 75% of women were undergoing chemotherapy, 36% were on endocrine therapy and 54% radiation therapy.

There were no baseline differences between groups, either in assessment for pre-study depression or anxiety, demographics, current treatment, type of breast cancer surgery or psychiatric history.

[1] Depression. Mean (SD):

TIP-C arm:

T1: 16.44 (1.74)

T2: 14.08 (1.52)

T3: 14.25 (1.76)

Exercise arm:

T1: 13.26 (2.39)

T2: 11.32 (2.10)

T3: 10.53 (2.42)

Control:

T1: 9.88 (1.79)

T2: 9.35 (1.57)

T3: 8.82 (1.81)

Over the duration of the study, levels of depression did not change significantly for the study population as a whole nor was there a significant difference between groups over time. This means that the interventions did not alter already non-significant changes in levels of depression. Unfortunately, there was a significant difference in overall levels of depression between the intervention arms and the control group with both intervention arms having a much higher level of depression from baseline and at all time points. However, the authors pointed out that one mean depression score which was >16 (in the TIP-C arm) did fall below this level by time T2.

[2] Anxiety. Mean (SD):

TIP-C arm:

T1: 4.39 (0.33)

T2: 3.21 (0.27)

T3: 3.19 (0.28)

Exercise arm:

T1: 4.14 (0.46)

T2: 2.64 (0.38)

T3: 2.85 (0.38)

Control:

T1: 3.05 (0.34)

T2: 2.85 (0.28)

T3: 2.81 (0.29)

Over the duration of the study, levels of anxiety did change significantly ($P < 0.001$) for the study population as a whole and there was a significant

difference between groups over time ($P=0.01$). There were no main group effects, unlike the analyses for depression, meaning that as a whole, the within group variance was not different between study arms, including at baseline.

Post-hoc t-tests were performed to attempt identification of time interval at which the effect of the interventions were significant. This occurred for the TIP-C ($P<0.001$) and exercise ($P=0.002$) groups between baseline and time 1 but changes between T1 and T2 were not significant. This means that improvements seen after six weeks were sustained but not enhanced a month later.

General comments:

This paper describes a small RCT of women and their partners who were recruited at a single oncology centre to participate in a trial which made comparisons between two interventions, one psychological, one physical and a control. All study arms involved an element of telephone use between researcher and participant. Partners of participants were also recruited and received the same interventions, albeit at a different rate and time but these outcomes are not included here.

Data were analysed with appropriate statistics (RM-ANOVA) but the significant difference in baseline scores between intervention and control arms for depression, but not anxiety, is unexplained. Such baseline variance may occur as a result of inadequate randomisation or biased allocation. Another important factor is that randomisation (the methodology for which no details were given other than it was undertaken by the project leader) occurred before baseline assessments were made. Perhaps knowledge of allocation may have affected levels of depression, if not anxiety. In any event, results should be treated with great caution as the possibility of bias is strong.

Gotay *et al.* (2007)

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: United States

Inclusion criteria:

Women with first recurrence after surgery for stage I, II or III breast cancer
Informed of recurrence within previous 56 days
No current psychiatric condition affecting participation
Ability to read and understand English
Completion of baseline assessment
Written informed consent
First recurrence was defined as any distant metastatic site and/or chest wall or nodal site

Exclusion criteria:

Women with ipsilateral breast tumour recurrence after lumpectomy or isolated contralateral, primary breast cancers.

Population:

Number of patients = 305, age range 25 to 93 years, median age = 54 years.

Interventions:

Telephone intervention (TG) (n=152):

The majority of trained counsellors were breast cancer survivors and were at least 1 year post-recurrence. Participants received 4-8 counselling/information sessions by weekly telephone calls, one to two calls per week. The content reflected the most common domains in multi-dimensional models of QOL and patient need. A standardised packet of information (NCI pamphlets) was also sent to each woman.

Intervention content included:

Physical concerns, social support, stress management and existential concerns.

Control group (CG) (n=153):

Usual supportive care.

Participants were mailed the same information received by the intervention group members at the 6 month point.

Outcomes:

[1] Psychosocial stress (emotional well-being) - measured by the Cancer Rehabilitation Evaluation System - Short Form (CARES-SF) Psychosocial scale which has 5 sub-scales. A score of 0.615 or more reflects a risk status for emotional problems.

[2] Depressive symptoms - measured with the Centre for Epidemiological Studies-Depression (CES-D). A score of 16 or more indicates a risk for depression.

Follow up:

After baseline assessment, follow-up data were collected by post at 3 months and 6 months. Participants were also asked to rate the intervention in terms of their satisfaction from 1 or (low) to 3 or 4 (high).

42% of control group patients and 26% of TG patients experienced disease progression whilst on study. At 3 months, 1% of TG patients and 5% CG patients had died and at 6 months this had increased to 7% and 10% respectively.

30/152 women on the TG did not complete the intervention because: patient refused (n=15), patient could not be reached (n=8), progression (n=5) or death (n=2).

Results:

Median total no. of telephone calls = 6 (range: 1-24)

Median no. of sessions = 5 (range: 0-9)

Median no. of mins delivering intervention = 120 (range: 0-390)

Topics discussed over study:

Physical concerns = 82%

Social support = 77%

Stress management = 76%

Existential concerns = 74%

Results:

Psychosocial stress. % of participants with a CARERS-SF score above 0.615:

TG (n=124):

Baseline: 77

3 months: 66

CG (n=122):

Baseline: 78

3 months: 70

There was no evidence to suggest that the intervention significantly impacted on the outcome (P=0.50).

Depression. % of participants with a CES-D score above 16:

TG (n=124):

Baseline: 48

3 months: 47

CG (n=128):

Baseline: 48

3 months: 40

There was no evidence to suggest that the intervention significantly impacted on the outcome (P=0.24).

No subsequent analyses, stratifying the data on psychosocial status, depressive symptoms or other factors, affected the statistical significance of these outcomes.

Despite the lack of significance of impact, the great majority of patients who had received the intervention expressed satisfaction with it.

General comments:

This paper describes a good quality RCT of women with newly recurrent breast cancer who received a telephone counselling and information intervention over a period of about 4 weeks.

Participants were recruited, between July 1998 and November 2002, by oncology nurses, research associates or physicians. After initial assessment, women were randomised via a central networked allocation system and data were stratified by age, recurrence site and time since diagnosis.

Despite the fact that three data sets were obtained for this study, only the results of the comparison between baseline and three months is presented in this paper. The participant number at this time point was sufficient for a 90% power to detect up to 21% difference between study arms in psychosocial stress or depression symptoms. The results were expressed only for patients in each study arm whose baseline assessment scores had exceeded cut-off points indicative for risk of stress and/or depression rather than the groups as a whole.

At baseline, more women in the TG arm had received chemotherapy for recurrence (P=0.01) whilst more women in the CG group had received endocrine therapy (P=0.03) and had experienced disease progression (P=0.004). These differences could have impacted on outcomes but the authors tested for this feature and found this not to be the case.

The authors tried, by several post-hoc analyses, to determine the factors which may have influenced the lack of impact of this intervention. They concluded that there being no relationship between intensity of intervention, no particular patient sub-group and no overall temporal decline in outcomes were responsible. Rather they intuited that at this moment in the patients' pathway such an intervention would not be effective.

Bantum (2007)
Design: Systematic review of randomised trials (therapy). Evidence level: 1 Country: United States of America
Inclusion criteria: Included studies: Randomised controlled trials
Included study participants: Women with breast cancer
Exclusion criteria: Studies which addressed specific health behaviours e.g. smoking.
Population: Number of patients = 4931 (mean number per study = 89). Mean age = ~52 years.
Interventions: Psychological, social or psychoeducational interventions (for example, the use of social support, targeted education, cognitive behavioural strategies or emotional expression).
Outcomes: Studies evaluated outcomes which included emotional well-being (87%), physical well-being or symptoms (53%) but were less likely to report social well-being (41%), global QOL (33%) functional well-being (25%) survival (8%) or coping strategies (33%). Across studies 34% reported significant improvements as a result of the intervention under consideration.
Follow up: -
Results: Type of intervention (n=61) / %: Individual treatment = 48.3 Group therapy = 41.4 Couple or family = 1.7 Other or not reported = 6.9 Intervention (n=61) / %: Emotional expression / venting of feelings = 52.5

Relaxation training = 52.5
Social support = 47.5
Information / education = 47.5
Rehearsal of new skills = 29.5
Problem-solving training = 27.9

Intervention provider (n=61) / %:

Nurse = 45.9
Psychologist = 37.7
Social worker = 29.5
Clinical trainee = 9.8
Psychiatrist = 9.8
Research assistant = 4.9
Cancer survivor = 1.6
No provider = 3.3

Studies with significant findings (n=61) / % of n (number of studies):

Coping = 45 of 20
Emotional well-being = 43.4 of 53
Functional well-being = 13.3 of 15
Physical well-being = 34.4 of 32
Social well-being = 32 of 25
Quality of life = 25 of 20
Growth/ benefit finding = 100 of 1
Survival = 20 of 5
Other = 52.9 of 34

Interventions that improved emotional well-being:

23 studies found significant improvements in this outcome and these studies had a mean of 5.35 treatment elements per intervention. 30 studies did not find a significant improvement in emotional well-being and had a mean number of 3.6 treatment elements per study ($P < 0.05$).

Professional providing the intervention (significant findings vs non-significant findings) / %:

Nurse = 39.1 vs 60.9
Psychologist = 43.5 vs 26.7
Social worker = 34.8 vs 26.7
Clinical trainee = 13 vs 10
Psychiatrist = 26.1 vs 0 ($P < 0.01$)
Research assistant = 4.3 vs 6.7
Cancer survivor = 4.3 vs 0
No provider = 0 vs 6.7

Type of intervention (significant findings vs non-significant findings) / %:

Individual treatment = 30.4 vs 66.7 ($P < 0.05$)
Group therapy = 60.9 vs 30 ($P < 0.05$)
Couple of family = 1.6 vs 0
Other or not reported = 4.3 vs 3.3

Mean quality of study score (significant findings vs non-significant findings) / %:

3.7 vs 3.5 (out of a maximum of 5 points).

General comments:

This paper presents the findings of a systematic review of 61 RCTs on psychological therapies for women with breast cancer where the outcomes were all or some measurable constituents of quality of life. These psychosocial interventions were to be aimed at helping patients manage the symptoms of their disease or develop adequate coping strategies in order to address their cancer experience. 65.6% of included studies were conducted with women having early stage breast cancer.

Papers were identified by searching PsychInfo, PubMed, Social Abstracts and ERIC databases up to 2004 (search terms were listed). An unknown number of reviewers rated each study for content, methodology and quality. Such factors included whether or not studies were likely to have had sampling bias, equivalence of study groups, follow-up and attrition. Of all the studies, 28% received the maximum of 5 marks for all possible parameters and 16% received only 1 mark.

Because emotional well-being was the most commonly used outcome across studies, this was reported in detail. The results of this analysis showed that studies reporting significant outcomes were those in which the interventions had used multiple treatment elements ($P = 0.012$) were more likely to have been provided by a psychiatrist ($P = 0.004$) utilised a group-based format ($P = 0.016$) and were less likely to treat participants individually ($P = 0.035$). Only two single interventions were rated with significant findings for emotional well-being: self help ($P = 0.05$) and information and/or education ($P = 0.022$). Fewer than half of the studies that reported this outcome demonstrated an improvement and of 245 separate measures, only 22% showed statistically significant improvements over time.

The authors concluded that group interventions would provide some advantage over individual interventions, for example the understanding and support which could be given by women facing similar experiences. The provision of multiple treatment elements was seen as being more useful than targeted clinical services.

This review offered no tests of heterogeneity between studies which would be expected to be considerable given the broad range of interventions and outcomes. The authors pointed out that many of the included studies had failed to give sufficient details of the sample population, intervention or outcome. This would make evaluation of efficacy difficult. There is also a possibility of publication bias (only positive outcomes reported) and also perhaps selection bias (very little ethnic mix). The findings of this review must therefore be interpreted with caution.

Zimmerman *et al.* (2007)

Design: Systematic review of RCTs (therapy). Evidence level: 1-
Country: Germany

Inclusion criteria:
Included studies:
Randomised controlled trials

Included study participants:
Women with breast cancer (a separate study was conducted with heterogeneous cancer types but the results are not reproduced here).

Exclusion criteria:
Studies in which details of the intervention provider were not given

Population:

Number of patients = 6419. Age range: 40 to 65 years. Mean age = 52.4 ± 4.7 years

Interventions:

Psychological, social or psychoeducational interventions (for example, the use of social support, targeted education, cognitive behavioural strategies or emotional expression). Interventions were categorised as psychoeducational (EDU) cognitive-behavioural (CBT) supportive (SUP) and relaxation (REL). Multi-modal treatments including a behavioural component were included in the CBT group.

Treatment providers were classified as either being or not being a psychologist.

The effect size of each factor was expressed as Cohen's d where values of 0.2, 0.5 and 0.8 corresponded with 'small', 'moderate' and 'large' respectively.

Outcomes:

To determine the modifying factors which determines the success of psychosocial interventions to treat emotional distress and focusing on the cancer type, intervention type and intervention giver primarily.

Follow up:

-

Results:

Effect size:

The average effect size across studies = -0.47 to 2.66 with a mean of 0.26 (SE 0.07) being different from zero ($P < 0.001$). The assumption of homogeneity between studies was rejected and moderators (including type of intervention and intervention giver) were tested.

Effect size of intervention type, format, timing and disease stage

Type of interventions were EDU (n=8) CBT (n=24) SUP (n=15) REL (n=2) 'mindfulness' (n=2) and a cosmetic class (n=1).

Effect size (d) of intervention vs control:

EDU = 0.53 ($P < 0.01$)

CBT = 0.19 (NSD)

SUP = 0.13 ($P < 0.01$)

REL = 0.30 ($P < 0.01$)

Mindfulness = 0.29 (NSD)

When a comparison was made between EDU and CBT, taking into account the nature of the control groups, the effect size of CBT vs standard care was further reduced to $d = -0.05$

96% of studies reported on the intervention format of which 28 studies were individual, 22 were group activities, 2 were couple and others were self-help (n=1) patient plus family (n=1). A comparison between group and individual interventions show a higher effect size for individual format than group ($d = 0.30$ vs $d = 0.19$) ($P < 0.001$).

82% of studies reported the timing of interventions of which 33% were conducted after diagnosis or surgery, 33% during or after medical treatment (i.e. chemotherapy or radiation therapy) and the remainder months or years after initial diagnosis. Those interventions conducted directly after diagnosis or surgery achieved a higher effect size ($d = 0.33$) than during treatment ($d = 0.18$) ($P < 0.01$) or years/months after diagnosis ($d = 0.16$) ($P < 0.001$).

54% of studies reported disease stage of the study participants of which 43% were stage I to III or

stage IV and 14% were of mixed stage. Patients with early stage disease had a higher effect size ($d = 0.32$) than those with advanced disease ($d = 0.13$) ($P < 0.01$).

Effect size of intervention practitioner

73% of studies reported the practitioner of the intervention of which 21 studies were led by a psychologist and 11 by a nurse. Psychologist-led interventions achieved a significantly higher effect size than those led by a nurse ($d = 0.30$) ($P < 0.001$)

For EDU interventions, delivery by medical staff had a higher effect size ($d = 0.73$) than those given by a psychologist ($d = 0.27$) whereas for CBT based interventions the effect size was greater if delivered by a psychologist ($d = 0.40$) and of no effect if delivered by given by nurses or social workers. With SUP interventions the practitioner was not influential and this could not be ascertained for REL interventions due to lack of comparative data.

Psychologists had greater effect size when working in individual treatment settings ($d = 0.52$) compared with group format interventions ($d = 0.16$) ($P < 0.05$) and were also more effective directly after diagnosis ($d = 0.12$) than during treatment ($d = 0.01$). Non-psychologist-led interventions were not influenced by either by format or timing.

Influence of control groups on effect size

89% of studies reported on the type of control group of which 30 studies employed standard care, 8 were waiting list groups, 8 groups received educational material and 1 had stress management, relaxation and support. Standard care and waiting list were deemed to be 'passive' whereas the remainder were 'active'. The effect size of intervention compared with passive controls was greater than those compared with an active control ($d = 0.34$ vs $d = 0.11$) ($P < 0.001$).

General comments:

This paper presents the findings of a meta-analysis of data from 34 RCTs on psychosocial therapies to relieve emotional distress in women with breast cancer. The reviewers wished to determine the factors which affected outcomes such as cancer type, intervention type and interventionist. Between this review and that of Bantum (2007) there are 24 included RCTs in common. Papers were identified by searching PsychInfo, Psynindex and Medline databases up to October 2004 (search terms were briefly listed). For the majority of studies, two reviewers coded papers with regard to type of cancer, intervention and intervention provider. No reference was made to the scoring of studies for quality etc. Where data were incomplete, study authors were contacted by reviewers.

Tests for homogeneity were performed and a random effects model applied to the meta-analysis. As with Bantum (2007) the authors pointed out a likely publication bias (only positive outcomes reported) and calculated an estimation of its impact.

The authors reported (data not shown here) that the effect size of psychosocial interventions was lower for breast cancer patients than for cancer patients as a whole and that this difference also applied according to the therapy with the exception of SUP (supportive) interventions. They hypothesised that this may be due to one or more of several factors including gender, natural recovery rates for breast cancer compared with other cancers or that the implications of having breast cancer are not addresses by these interventions i.e. having no focus on sexuality, personal relationships, body image etc.

The conclusions reached by the reviewers were that psychologists were the most appropriate persons to deliver CBT in an individual context to women at any disease stage, preferably after diagnosis/surgery or much later but not during treatment. Medical staff appeared to be well suited

for delivering educational interventions either to individuals or groups preferably after diagnosis or surgery and only for early stage disease.

Manne <i>et al.</i> (2007)
Design: Randomised controlled trial (therapy). Evidence level: 2 Country: United States of America
Inclusion criteria: Women with early stage breast cancer Breast cancer surgery within previous 6 months ECOG status of 0-1 Married or cohabiting with a significant other Were 18 years or older English speaking
Exclusion criteria: None stated
Population: Number of patients = 238. Age range: 27 to 75 years. Mean age = 49.5 ± 10.4 years.
Interventions: Intervention group (n=120): Couple-focused group (CG) comprising 6 weekly 90 minutes sessions focusing in understanding the psychological impact of cancer on the couple and their relationship plus enhancing the relationship, communication and support. Control group (n=118): Usual care. Assessment time points occurred pre-intervention (time 1) 1 week post-intervention (time 2) and 6 months after the intervention (time 3). Patients were paid to complete these questionnaires.
Outcomes: The primary outcomes were psychological distress and well-being over time. Instruments used to measure these outcomes included the Mental Health Inventory-18 and the Impact of Event Scale. The potential moderators of response were assessed by the Emotional Approach Coping Scale, Emotional Processing Scale, Acceptance (from COPE), Unsupportive Behaviours Scale and Protective Buffering Scale. The main objective of this exercise was to see if a couple-focused intervention would be more or less effective when taking into account the coping strategy already adopted by subjects before study entry.
Follow up: -
Results: There were no group differences for any of the outcomes at the first, baseline time (1). Patient age and physical functioning were significant predictors of all

outcomes. Participants in the intervention arm reported significantly lower depressive symptoms than controls. Partner unsupported behaviour moderated the treatment effects on depressive symptoms in the intervention but not control group.

Moderator analyses (ITT)

Emotional expression

Participants one standard deviation above the mean for this parameter had significantly lower mean depression than those women in the control arm ($P = 0.0033$). Participants that were one standard deviation below the mean for this parameter showed no treatment condition effect.

Emotional processing

Participants one standard deviation above the mean for this parameter had significantly lower mean depression than those women in the control arm ($P = 0.0088$). Participants that were one standard deviation below the mean for this parameter showed no treatment condition effect.

Acceptance

Participants one standard deviation above the mean for this parameter had significantly lower mean depression than those women in the control arm ($P = 0.0062$). Participants that were one standard deviation below the mean for this parameter showed no treatment condition effect.

Protective buffering

This parameter was not a moderator of treatment group for the outcome of depression.

These results indicate that women who started the intervention therapy with higher emotional processing and emotional expression had fewer depressive symptoms compared to participants who did not use these coping mechanisms. There were similar, although marginal, results for acceptance. Those women previously employing a partner buffering coping strategy received no advantage to treatment compared with controls.

General comments:

This paper describes a RCT comparing a couple-focused group with standard care for women with breast cancer. The primary outcomes were measures of psychological distress and well-being over time. The starting hypothesis was that the adoption of certain coping strategies by cancer patients before the study began might influence their response to the couple-based intervention which used the same strategies (emotional processing, emotional expression, protective buffering or acceptance).

Across the study, 36% of women had stage I breast cancer, 53% stage II, 3% stage IIIa and 9% had DCIS. Women were recruited from three cancer centres and four hospitals between April 2000 and October 2003.

The authors concluded from this complex analysis that women with early stage breast cancer who naturally selected an emotional coping strategy may benefit from a couple-focused group intervention. It was stressed, however, that the converse may not be true i.e. that women who were not naturally employing such

coping strategies would not benefit from this intervention. The authors also suggested that women who had unsupportive partners at baseline and who attempted to understand and express their emotional reactions to their cancer may derive the most benefit from this intervention.

Meneses *et al.* (2007)

Design: Randomised controlled trial (therapy). Evidence level: 2
Country: United States of America

Inclusion criteria:
Women of at least 21 years of age
Histological confirmation of stages 0-II breast cancer
No evidence of local recurrence or metastatic disease
Within 1 year of diagnosis
Surgery at least one month previously
Having had chemotherapy or radiotherapy
Able to communicate in English
Written informed consent

Exclusion criteria:
None stated

Population:
Number of patients = 261. Mean age = 54.5 ± 11.58 years

Interventions:
Intervention (n=129):
A psychoeducational support comprising individual face-to-face education and support sessions (months 1, 3 and 6), telephone and face-to-face follow-up education and support sessions (months 2, 4 and 5) with written and audiotape reinforcement. These educational supplements included a notebook of materials which corresponded with the education and support session and audiotapes also based on these sessions to reinforce learning.
Wait control (n=132): Women in this group received baseline assessment and then four attention control telephone calls (months 2, 4 and 5), three face-to-face education and support sessions (month 6) and one follow-up telephone education and support session (month 7).

Both intervention and control elements were delivered over a six-month period by a Breast Care Education Intervention (BCEI) nurse, part of a larger research team. The nurse had received training specifically for this trial and a procedure manual was produced and followed throughout.

Outcomes:
Overall quality life (QOL) including psychological well-being.

Instruments used included the Breast Care Treatment and Social Demographic Data Tool

Follow up:
All participants received baseline assessment of outcomes which were then repeated at 3 and 6 months. In the experimental group, four women dropped out before the 3 month assessment. In the control group one subject died from

unrelated causes before the 6 month assessment. All other participants were included in the final data analyses.

Results:

No significant difference in patient demographics or QOL outcomes was found between study arms at baseline. Data were compared between intervention and control groups by comparing each with their own baseline.

Difference in QOL between baseline and month 3 (time 0 to time 1) / significance:

Control group (n=132): P = 0.522 (NSD)

Intervention group (n=125): P < 0.001

Comparison between arms: P < 0.001

Difference in QOL between baseline and month 6 (time 0 to time 2) / significance:

Control group: P = 0.016

Intervention group: P < 0.001

Comparison between arms: P < 0.001

Difference in QOL between month 3 and month 6 (time 1 to time 2) / significance:

Control group: P = 0.004

Intervention group: P = 0.094 (NSD)

Comparison between arms: P = 0.274 (NSD)

Control group showed a reduction in QOL from baseline to time 1 but then a slight improvement by time 2. The intervention arms showed an improvement in time 2 and time 3. Therefore, the improvement in quality of life was significantly better for the intervention group than the control group and compared with its own baseline, an effect which was maintained with time.

A sub-group analysis of specific domains of the QOL instrument show significant improvements for the intervention compared with controls were shown for psychological and social well-being (P < 0.001) but not in the domains of physical or spiritual well-being.

General comments:

This paper describes the findings from a small trial comparing a psychoeducational intervention with a wait control for women who were classified as cancer survivors, being in the first year after their treatment for early stage disease.

Allocation and randomisation methods were not described but this procedure was carried out by a member of the research team (statistician) which does not eliminate the possibility of bias. The study is simply designed and appropriately analysed with modest participant numbers.

Quality of life assessments were made from baseline to 6 months and showed that the intervention arm experienced better outcomes in the domains of psychological and social well-being than the wait controls. Controls also showed an improvement in QOL between 3 and 6 months time points which may reflect

natural history but was still significantly below QOL achieved by the intervention group.

The authors concluded that this psychoeducational intervention, delivered by a specialist nurse, demonstrated effectiveness amongst women with breast cancer after primary treatment thus providing a 'safe passage' from treatment to survivorship.

Vos *et al.* (2007)

Design: Randomised controlled trial (therapy). Evidence level: 2
Country: The Netherlands

Inclusion criteria:

Women between 18 and 70 years of age
Having undergone surgery for primary breast cancer not earlier than 4 months prior to study
No distant metastases
Sufficient knowledge of Dutch language
No psychiatric illness
Written informed consent

Exclusion criteria:

None stated

Population:

Number of patients = 87. Age range: 29 to 68 years. Mean age = 49 ± 7.9 years

Interventions:

Intervention - Group psychotherapy (n= 33):

Based on experiential and existential theories. The intervention started with a relaxation or meditation exercise. Participants then related something of their feelings on cancer which allowed identification of topics of leading importance for the group and informed later discussions in which participants were encouraged as a group to address those feelings and thoughts. After a break participants were shown ideas and applications that they could make in daily life with reference to the earlier discussion. A second mediation or relaxation session ended the program.

Control - Social support group (n=34):

Based on letting cancer patients share their mutual experience about their disease and receiving information from experts on topics of interest. These groups also met for 2.5 hours with a 30 minutes break. Emotional and peer support was encouraged. Participants chose the discussion topics for the following week. The structure of the sessions was unchanging.

Both interventions were delivered over 12 weeks. Each session lasted 2.5 hours including a 30 minute break. After regular session there were follow-up sessions 1 and 2 months later. The groups were closed and each contained up to 10 women. All the facilitators were appropriately trained and, in each group, one was a woman. The leaders of group therapy were highly trained therapists who received one days extra training relevant to their intervention. The social support groups were led by social workers or oncology nurses who had received only

one days training for the intervention.

Outcomes:

- [1] Emotional adjustment: Profile of Mood States (POMS)
- [2] Psychosexual functioning: Sexual Functioning and Body Image modules of the QLQ-BR32 (part of European Organisation for Research and Treatment of Cancer QLQ-30)
- [3] Social adjustment: Social Interactions and Recreation modules of the Sickness Impact Profile instrument.

Follow up:

Baseline assessments (T0) which were made before randomisation, were followed up after completion of the study (time 1) and 12 months later (time 2).

20/87 women dropped out of the study due to: death (n=1) attendance at a group became too emotional (n=2) illness (n=3) did not meet expectations (n=1) or failed to give a reason (n=13).

Results:

There were no observed differences between study arms at baseline with regard to type of surgery, age, disease stage or psychological, psychosocial and social adjustment. At the end of the study, the mean number of group psychotherapy sessions attended was 9.6 with 10 women at all sessions and 3 women attending fewer than 2 sessions. The mean number of attendances in the social support group was 8.7 with 8 women at all sessions and 3 women attending fewer than 2 or fewer sessions.

There were no significant changes over the study time periods for the parameters Distress, Vitality, Sexual Functioning or Social Interaction. Body Image and Recreation changed positively with time (both $P < 0.001$). The type of surgery undergone was significantly related to Body Image outcomes with those having had breast conserving therapy reporting more positively.

The intervention resulted in no significant effects on psychosocial adjustment when compared with the control group.

General comments:

This paper describes the findings from a small RCT which compared group psychotherapy with group social support where the outcome was psychosocial adjustment. Women who participated in this trial were about 4 months post-surgery and had been recruited from several hospitals in the Netherlands during an unknown time period.

Despite the starting hypotheses of the authors no significant difference was seen between study arms and no significant changes occurred in many of the parameters over time. The authors pointed out that the women were psychologically well adjusted at baseline and comparable to women in the general population, according to assessments results, and hence there was perhaps little improvement to be made which might explain the lack of significant findings.

Classen *et al.* (2008)

<p>Design: Randomised controlled trial (therapy). Evidence level: 2 Country: United States of America</p>
<p>Inclusion criteria: Women with biopsy-proven breast cancer stages I-IIIa Diagnosis not more than 12 months prior to enrolment Completion of initial surgical treatment No detection of disease present Written informed consent</p>
<p>Exclusion criteria: Evidence of metastases beyond adjacent lymph nodes Recurrence if cancer prior to randomisation Diagnosis of other cancer (except BCC skin or CIS cervix) Other major medical problems likely to limit life expectancy to < 10 years History of major psychiatric illness for which patient was hospitalised or medicated (except for anxiety or depression treated for < 1 year) Attendance at a cancer support group for > 2 months</p>
<p>Population: Number of patients = 350</p>
<p>Interventions: Intervention (n=178): Education material comprising a brief videotape on self-examination and pamphlets from the American Cancer Society covering numerous topics of a practical nature but avoiding issues of emotional expression, coping or social support.</p> <p>Unstructured supportive-expressive group therapy. Groups, comprising up to 10 members, met weekly for 12 weeks. Each meeting lasted for 90 minutes and was led by two co-therapists. Women attended an average of 8/12 meetings.</p> <p>Therapists included 10 nurses, 11 social workers and 3 psychologists all of whom were specifically trained for this project on a 2-day workshop, studying a treatment manual and facilitating a pilot group. The training included examinations and supervision throughout the study by an expert in the intervention.</p> <p>Control (n=179): Educational material only (as above).</p>
<p>Outcomes: Relief of psychological distress across time. Outcomes were measured using the Profile of Mood States questionnaire (POMS) to which responses were recorded on 5-point Likert scales resulting in a score for mood disturbance.</p> <p>Secondary outcomes were measured on the Hospital Anxiety and Depression Scale (HADS), Mini-Mental Adjustment to Cancer Scale (MAC) Courtauld Emotional Control Scale, Impact of Event Scale (IES) Stanford Self-Efficacy Scale for Serious Illness, CARES Medical Interaction Subscale, Family Relations Index, Sleep Measure, Pain measure and Yale Support Index.</p> <p>Data were analysed on a modified intention to treat basis.</p>
<p>Follow up: Final assessments were completed in June 1998. Baseline assessments were</p>

repeated at 3, 6, 12, 18 and 24 months thereafter. A baseline score of 37 on the POMS scale was taken as an indication as a high initial level of distress

In the intervention group, 18 women provided no follow-up due to: refusal (n=3) refusing the group (n=4) being unable to attend the group (n=4) moving away (n=1) giving no response (n=5) or about whom no information was available (n=3).

In the control group, 9 women provided no follow-up due to: refusal of further participation (n=2) illness (n=1) finding the educational material unhelpful (n=1) death (n=2) disappointment at allocation (n=1) giving no response (n=1) or about whom no information was available (n=1).

159/178 of the intervention group and 167/179 of the control group provided baseline and at least one other follow-up for data analyses.

Results:

There were no significant differences between study arms for demographic or medical variables with the exception of disease stage since more women in the control arm had stage III disease (15 vs 6).

After removing an outlier with extreme distress (causing the subject to leave the trial) there was no significant difference in POMS scores between study arms using any data modelling and there were no differences either between arms for any secondary outcome measures.

General comments:

This paper describes the findings from a RCT comparing a short course of supportive-expressive therapy and provision of education material with education material only. Women were recruited at two academic sites and nine oncology centres across the USA between February 1994 and May 1996. Central randomisation was by a biased coin method and patients were stratified according to surgery type, nodal involvement, age and hormone receptor status.

Baseline levels of distress were not equal across the multiple sites which adversely affected the analysis of variance and these data were omitted subsequently. It was of note that the majority of women did not have high initial levels of psychological distress which may have reduced the ability of the intervention to have had much impact on this parameter. Using baseline distress as a stratification variable may, therefore, have been preferable to using prognostic variables more commonly associated with clinical trials.

The authors concluded that highly distressed women would be unlikely to benefit from the intervention. Therapist training and experience were not associated with any treatment effect and hence there was no evidence that distress was alleviated by brief supportive-expressive group therapy. They hypothesised that an intervention which was existentially oriented might not suit patients who, having potentially curable disease, may perhaps have had more pragmatic concerns.

Chapter 3 – Operable breast cancer

3.1 What is the optimal tumour-free tissue margin to achieve in patients who undergo wide local excision for (DCIS)?

Short Summary:

The best available evidence for this question was drawn from observational studies (Bijker *et al.* 2001; Boland *et al.* 2001, 2003; Boyages *et al.* 1999; Cabioglu *et al.* 2007; Chan *et al.* 2001; Cheng *et al.* 1997; Denoux *et al.* 2001; Dillon *et al.* 2007; Goldstein *et al.* 1999; Goldstein *et al.* 2000; Goldstein *et al.* 1998; Hetelekidis *et al.* 1999; Holland *et al.* 1998; Kell *et al.* 2005; Macdonald *et al.* 2005, 2006; Neuschatz *et al.* 2001,2002; Ratanawichitrasin *et al.* 1999; Rodrigues *et al.* 2002; Sahoo *et al.* 2005; Sigal-Zafrani *et al.* 2004; Silverstein *et al.* 1994, 1997, 1999, 2003; Solin *et al.* 2005; Tunon-de-Lara *et al.* 2001; Vargas *et al.* 2005; Vicini *et al.* 2001; Wong *et al.* 2006; Yau *et al.* 2006). There is no consistency regarding the optimal tumour-free tissue margin. Most existing studies agree that margins containing tumour cells are associated with local recurrence or bear the risk of residual cancer. There is consistency that the risk of local recurrence is reduced with very wide margins, e.g. more than 10mm of tumour-free tissue. Several studies reported a linear correlation between margin widths and recurrence. There is conflicting evidence regarding whether wide margins can and whether they should replace radiotherapy. There is also disagreement regarding which of the two should most be avoided. The included studies varied in more than the factor margin widths (i.e. co-treatment, lengths of follow-up) and results are therefore difficult to compare. Studies varied in their definition of 'wide'.

PICO

Population	Intervention	Comparison	Outcomes
Patients with DCIS	<ul style="list-style-type: none"> Wide Local Excision Breast Conserving Surgery 	Different margin widths: <2mm 2-5mm 5-10mm >10mm	<ul style="list-style-type: none"> Local Recurrence Rate Disease Free Survival Overall Survival Cosmetic result Psychological morbidity Health Economics

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There is a considerable body of observational studies looking at margin width, although one RCT is included, however the patients were not randomly assigned to margin widths but to excision alone versus adjuvant radiotherapy. The majority of the studies aimed to demonstrate a connection between margins and recurrence. None of the identified studies were designed to answer the question 'what is a minimum safe margin?' and only one study reported cosmetic outcomes.

There is no consistency regarding the optimal tumour-free tissue margin.

There is consistency that the risk of local recurrence is reduced with very wide margins, e.g. more than 10mm of tumour-free tissue. Several studies reported a linear correlation between margin widths and recurrence.

There is conflicting evidence regarding whether wide margins can and should replace radiotherapy.

The included studies varied in more than the factor margin widths (i.e. co-treatment, lengths of follow-up) and results are therefore difficult to compare. Studies varied in their definition of 'wide'.

The majority of studies investigated 'recurrences' without distinguishing true recurrence, marginal miss, treatment failure or similar so the evidence statement cannot differentiate these cases either.

Few studies reported survival data and not in all studies was it possible to attribute the outcome to the excision width as reexcisions could result in other treatment decisions such as mastectomies. There were too few clear descriptions of the margin width measurement method or pathology variables to allow the pursuit of this factor and its influence on the results.

General association margin width and clinical outcomes

The case series published by Macdonald et al. (2005), Chan et al. (2001), Neuschatz et al. (2001), Boland et al. (2003), Dillon et al. (2007), Silverstein and Buchanan (2003), Boland et al. (2001), Yau et al. (2006), Neuschatz et al. (2002), Holland et al. (1998), Sigal-Zafrani et al. (2004), Vargas et al., (2005), Tunon-de-Lara et al. (2001), Solin et al. (2005), and Silverstein et al. (1994) reported a linear correlation between margin widths and local recurrence or residual cancer or statistically significant differences between subgroups. This was also highlighted in a risk factor analysis of an RCT (Bijker et al., 2001) and in a meta-analysis by Boyages et al. (1999). It is noteworthy that the correlation was reported in both, studies that included positive and negative margins as well as studies comparing different negative margin widths, and the effect was found in uni- as well as multivariate analyses. These publications concluded in the majority that margin width is an important or the most important predictor for local recurrence or residual cancer.

Contrarily, Goldstein et al. (2000, 1998) concluded from two (in parts overlapping) case series that margin status (ranging from multifocal positive to >2cm negative margins) is not associated with local recurrence. Rodrigues et al. (2002) concluded from a case series with many missing data on margin status that positive or close margin status was not a significant predictor of local relapse. The difference in local recurrence rates in the case series by Hetelekidis et al. (1999) was not statistically significant. Denoux et al. (2001) found no statistically significant correlation between margin width and local recurrence but highlighted that none of the patients with margins ≥ 10 mm in the case series developed a local recurrence.

Macdonald et al. (2005) concluded that increasing margins decrease the risk for local recurrence, Silverstein et al. (1997) reported that the probability of local recurrence decreases as margin width increases, Boland et al. (2003) concluded that excision width is the most important predictor of local recurrence, Silverstein and Buchanan (2003) reported that as margin width increases the probability of local recurrence decreases, Boland et al. (2001) concluded that close resection margins are an even better predictor than the Van Nuys prognostic index for DCIS recurrence, Yau et al. (2006) concluded that wide

excisions plus radiotherapy appear to be a reasonable alternative in the treatment of DCIS, Ratanawichitrasin et al. (1999) did not find a statistically significant difference between >2mm and <2mm margins with regard to residual disease. The difference in local recurrence rates in the case series by Hetelekidis et al. (1999) was not statistically significant. Denoux et al. (2001) found no statistically significant correlation between margin width and local recurrence but highlighted that none of the patients with margins ≥ 10 mm in the case series developed a local recurrence. Chan et al. (2001) found a significant difference when comparing >1mm and ≤ 1 mm margins but subgroups beyond 1mm margins did not differ regarding recurrence free survival. Cheng et al. (1997) found no statistically significant difference between smaller or equal to 1mm negative margins compared to >1mm.

Positive margins

Macdonald et al. (2005), Sahoo et al. (2005), Tunon-de-Lara et al. (2001), Neuschatz et al. (2002), Goldstein et al. (1999; 1998), Silverstein et al. (1994), Ratanawichitrasin et al. (1999), Cheng et al. (1997), Vargas et al. (2005), Solin et al. (2005), showed in case series that positive margins are linked to local recurrence or residual cancer. A risk factor analysis of an RCT that included some data on margin status (Bijker et al., 2001) also demonstrate this link and a meta-analysis by Boyages et al. (1999) stated that most recurrences occur in the immediate vicinity of primary surgical site suggesting that recurrences arise from remaining tumour cells, i.e. incomplete surgical excision and that the presence of positive or close margins increases the risk of local recurrence even irrespective of radiation therapy. Sigal-Zafrani et al. (2004) showed that the presence of residual tumour correlated strongly with initial margin status and patients with greater involvement were more likely to end up with a mastectomy. Cabioglu et al. (2007) reported that patients with negative margins had a better 5yr ipsilateral recurrence free survival rate than patients with persistent positive / close margins after completion of all surgical treatment.

Goldstein et al. (1999) reported that multifocal positive margins were associated with the presence of residual DCIS in reexcision specimen but unifocal positive margins versus negative or close margins not and there was also no significant difference between negative versus close or positive margins. Vicini et al. (2001) showed that positive combined with close margins compared to >2mm margins differ significantly in ipsilateral breast failures and true recurrences / marginal miss, however, the authors concluded that margin status alone may be suboptimal in defining excision adequacy. Goldstein et al (2000) concluded from a case series that margin status (ranging from multifocal positive to >2cm negative margins) is not associated with local recurrence. Rodrigues et al. (2002) conclude in a case series with few analysable data that positive or close margin status was not a significant predictor of local relapse.

Specific negative margins and cancer related outcomes

Neuschatz et al. (2002) reported 41% of patients showed a tumour at re-excision. Boland et al. (2003) reported 38% recurrence. Boland et al. (2001) reported a 37% ipsilateral recurrence rate. Macdonald et al (2005) reported a local recurrence rate of 34%; with a 63% probability of remaining recurrence free at 5 years and 58% at 8yrs. Silverstein et al. (1999) reported a local recurrence rate of 30% with a probability of a recurrence within 8 years of 0.58 or 0.30 depending on the addition of radiation therapy. Silverstein et al. (1997) reported a 25% recurrence rate. Denoux et al. (2001) reported a 20% local recurrence rate, 93% of patients are without local recurrence at 5 years and 82% at 10 years.

Sigal-Zafrani et al. (2004) show that 44% of patients with ≤ 1 mm margins had a residual tumour at reexcision and 21% of the patients subsequently had a mastectomy. Chan et al. (2001) reported a recurrence rate of 38% for margins between 0.1 and 1mm. Holland et al. (1998) reported a 36% recurrence rate for ≤ 1 mm. Neuschatz et al. (2001) reported for ≤ 1 mm margins a 25% crude local failure rate and 30% 5yr local failure. Hetelekidis et al. (1999) reported a value of 25% actuarial 5 year local recurrence for ≤ 1 mm. Cheng et al. (1997) reported 19% with residual disease for margins of ≤ 1 mm. Dillon et al. (2007) reported a 60% residual disease rate although this is likely to include patients with positive margins as well. Silverstein & Buchanan (2003) stated that 1mm wide margins are inadequate when it comes to complete removal of DCIS, surgeons commonly leave residual disease.

Sahoo et al. (2005) reported 8% local recurrences for patients receiving adjunct radiation therapy.

MacDonald et al. (2005) reported a 34% rate of local recurrences with a probability of remaining without recurrence at 5 years between 63% and 73% depending on the cut-off category and 58% / 49% at 8 years. Ratanawichitrasin et al. (1999) reported 31% residual disease. Yau et al. (2005) achieved a 15% local failure rate with 77% 5 year actuarial local failure free rate for patients with adjuvant radiotherapy. Dillon et al. (2007) report 64% residual disease for margins 1 to 2mm and 60% for 0 to 1mm margins and concluded that patients with margin distances of ≤ 2 mm are at high risk of residual disease and propose a 5mm margin width. Neuschatz et al. (2002) reported that 31% of patients with margins between 1 and 2mm had a tumour at reexcision, 41% for 0 to 1mm. Goldstein et al. (1998) reported a 19% true recurrence rate and 6% recurrences elsewhere for patients receiving adjuvant radiation therapy and concluded that DCIS may be in inadequately excised if atypical ductal hyperplasia and DCIS or cancerisation of lobules and DCIS are near the margin. Rodrigues et al. (2002) reported a 14% recurrence rate for patients with ≤ 2 mm margins and adjuvant radiation therapy. Vargas et al. (2005) reported 13% ipsilateral recurrence or true recurrence or marginal miss at 5 years and 22% at 10 years but these data include patients with positive margins and margins equal to 2mm. Goldstein et al. (2000) reported an 8% true recurrence or marginal miss rate and a 4% rate of carcinoma elsewhere for patients receiving also radiation therapy and concluded that margin status is not associated with the analysed outcomes.

Goldstein et al. (1998) reported a 4% true recurrence and 3% recurrence elsewhere rate in a sample of consecutive patients treated with local excision plus radiation therapy. Vargas et al. (2005) report the same values for a larger sample (it is possible that there is overlap). Rodrigues et al. (2002) reported a 5% recurrence rate for patients receiving radiotherapy in addition. Goldstein et al. (2000) report a 5% recurrence rate, 2% for carcinomas elsewhere, for patients also receiving radiotherapy. Margins of more than 2mm in conjunction with radiotherapy showed better results (7% ipsilateral breast failure at 5 years, 9% at 10 years) than close or positive margins in a case series by Vicini et al. (2001). Yau et al. (2006) concluded that final resection margins of more than 2mm (mean and upper limit unclear) appears to be a reasonable alternative to mastectomy in view of a 100% 5 year survival rate and a 98% failure free rate. Neuschatz et al. (2002) found no tumours at reexcision in margins 2 to 10mm wide. The review by Kell and Morrow (2005) stated that radiotherapy with a margin of 2mm can achieve excellent local control. The data by Macdonald et al. (2005) showed that even without radiotherapy a local recurrence rate of only 11% was achieved. Ratanawichitrasin et al. (1999) reported 17% with residual disease, radiotherapy was not reported. Although Dillon et al. (2007) showed a high rate of successful breast conserving therapy without the need for mastectomy (88%, follow up

period unclear, radiotherapy co-treatment unclear) in patients with >2mm the authors recommend a 5mm resection margin.

Neuschatz et al. (2002) reported a 0% tumour rate at reexcision for margins between 2 and 10mm, the study did not report that the patients also received adjuvant radiotherapy. Goldstein et al. (1998) reported a 4% true recurrence rate and a 2% risk of a carcinoma elsewhere for patients treated with adjuvant radiation therapy. Goldstein et al. in a further publication (2000) reported a 5% recurrence rate and a 2% risk of a carcinoma elsewhere; the patients were also treated with radiation therapy. Vargas et al. (2005) reported 4% ipsilateral recurrence at five years, 9% at ten years, 3% true recurrences / marginal miss at five years, 7% at 10 years. Vicini et al. (2001) reported 9% ipsilateral breast failure, true recurrences or marginal miss rate at five and at ten years for patients treated with adjuvant radiation therapy. Chan et al. (2001) reported a 3.5% rate of patients with recurrences for margins between 1.1 and 5mm, several of the patients received adjuvant therapies, e.g. radiation or tamoxifen. Sahoo et al. (2005) showed a 10% local recurrence rate for margins between 1 and 5mm for patients receiving adjuvant radiation therapy, this study was also cited in the review by Kell and Morrow (2005). Yau et al. (2006) reported a 2% rate of local failure for margins above 2mm and in conjunction with radiotherapy and / or tamoxifen. Rodrigues et al. (2002) reported a 5% rate of recurrences for margins above 2mm in conjunction with radiotherapy. It is also possible to draw on those selected studies that report beneficial results for smaller margins to substantiate this statement, i.e. Neuschatz et al. (2001), Boland et al. (2003), Denoux et al. (2001), Boland et al. (2001), Holland et al. (1998) and Sahoo et al. (2005) report recurrence rates of under 10% for margins of ≥ 1 mm. Dillon et al. (2007) showed a 17% rate of residual disease, adjuvant therapies were not reported. Ratanawichitrasin et al. (1999) reported a 17% rate of residual disease at reexcisions; there was no information on adjuvant therapy. Macdonald et al. (2005) showed a 21% rate of recurrences for margins between 3 and 5.9mm for patients treated with excision alone.

Dillon et al. (2007) recommend a 5mm resection margin and indicated that in none of the patients with this margin distance residual disease was found, the role of adjuvant therapies is unclear. Sahoo et al. (2005) reported a 4% local recurrence rate for margins >5mm for patients receiving adjuvant radiation therapy, the study was also highlighted in the review by Kell and Morrow (2005). Vicini et al. (2001) reported a rate of 7% ipsilateral breast failure at five years, 9% at 10 years with only 3% true recurrences at five years, 5% at ten years, the patients received also radiotherapy. Chan et al. reported a 7% recurrence rate for patients with margins of 5.1 to 10mm, with a 6% recurrence rate were all events at ≥ 5 mm considered; the patients received adjuvant therapy.

It is also possible to draw on those selected studies that report beneficial results for smaller margins to substantiate this statement, i.e. Neuschatz et al. (2001), Boland et al. (2003), Denoux et al. (2001), Boland et al. (2001) and Holland et al. (1998) report recurrence rates of under 10% for margins of ≥ 1 mm, Yau et al. (2006), Neuschatz et al. (2002), Goldstein et al. (2000), Goldstein et al. (1998), Rodrigues et al. (2002) and Vargas et al. (2005) report recurrence rates of under 10% for margins of ≥ 2 mm.

Macdonald et al. (2005) data show that a margin of 6 to 9.9mm only carried a risk of 5% local recurrence for patients treated with excision alone. Dillon et al. (2007) reported no case of residual disease for margins above 5mm margins. Sahoo et al. (2005) reported a 4% local recurrence rate for margins above 5mm for patients also receiving radiation therapy. Vicini et al. (2001) found only a rate of 7% for ipsilateral breast failure and 3% true recurrence at five years for margins beyond 5mm. None of the 10 patients with margins of

2 to 10mm in Neuschatz et al. (2002) had a tumour at reexcision (follow up unclear). Chan et al. reported a 7% recurrence rate for patients with margins of 5.1 to 10mm. The review by Kell and Morrow (2005) stated that there is no difference between 10mm margins and 1 to 10mm margins and cited Silverstein et al. (1999).

Neuschatz et al. (2001) reported 3.7% crude local failure and 30% five year local failure rates for margins above 1 and 10mm. Boland et al. (2003) reported 6% recurrence for margins between 1 and 9mm in a group where some were only treated with excision. Denoux et al. (2001) reported a 7% recurrence rate. It is also possible to draw on those selected studies that report beneficial results for smaller margins to substantiate this statement, i.e. Boland et al. (2001) and Holland et al. (1998) report recurrence rates of under 10% for margins of ≥ 1 mm, Yau et al. (2006), Goldstein et al. (2000), Goldstein et al. (1998), Rodrigues et al. (2002) and Vargas et al. (2005) report recurrence rates of under 10% for margins of ≥ 2 mm. Silverstein et al. (1999) reported a local recurrence rate of 17% for a group where a subgroup did not receive radiotherapy and a rate of 15% in a further publication (Silverstein et al., 1997).

Denoux et al. (2001) found no local recurrence in this margin group (plus radiation therapy). Silverstein et al. (1999) reported a 2% local recurrence rate in a group where only some patients were treated with radiation therapy. Silverstein et al. (1997) showed a recurrence rate of 3% for a median follow up of 90 months. Boland et al. (2003) reported a 3% rate, only some patients received radiation therapy. Silverstein & Buchanan (2003) also report a 3% rate in a group where only some patients received radiation therapy. Macdonald et al. (2005) reported a 5% local recurrence rate for patients treated with excision alone. Chan reported a 5% recurrence rate; some patients received different adjuvant treatments. Macdonald et al. (2006) reported that a subgroup of excision alone patients showed a rate of 6% recurrences. Neuschatz et al. (2001) reported 7% crude local failure, 10% five year local failure, some patients received adjuvant treatment.

Wong et al. (2006) closed their study on patients receiving only wide excisions to accrual because the number of local recurrences exceeded a prespecified limit; they also reported a 2% first site treatment failure.

Cosmetic outcomes

Kell and Morrow (2005) stated that large margins lead to a greater deformity of the breast and patients will suffer a worse cosmetic outcome.

Only one case series (Yau et al., 2006) with 75 women living in Hong Kong reported cosmetic results and came to the conclusion that even final resection margins of more than 2mm (mean and upper limit unclear) achieve good to excellent cosmetic results in physician ratings (range only reported for whole sample).

Consideration of clinical and cosmetic outcomes

The case series by Yau et al. (2006) with 75 women in Hong Kong evaluated local recurrence and cosmetic results and came to the conclusion that final resection margins of more than 2mm (mean and upper limit unclear) appears to be a reasonable alternative to mastectomy regarding local recurrence rates and five year survival while achieving good to excellent cosmetic results in physician ratings.

Implications for co-interventions

Silverstein & Buchanan (2003) concluded from a case series that included 10 participants with ≥ 10 mm that there were so few local recurrences in these patients that the effect of

radiation therapy is of little practical importance. Cheng et al. (1997) concluded from their case series that although small tumours with clear margins of >1mm carry a low risk of local failure and can be treated with lumpectomy that large tumours pose a risk of residual disease independently of margin status and additional adjuvant therapy may be indicated. Hetelekidis et al (1999) report only a 8% actuarial five year local recurrence for margins above 1mm in patients treated without radiation therapy. Neuschatz et al. (2002) reported no tumours at reexcision for margins above 2mm; adjuvant therapy was not mentioned in the publication. Macdonald et al. (2006) showed a 6% rate of any recurrence for a group in which only some patients were additionally treated with radiation therapy. Wong et al. (2006) closed to accrual because the number of local recurrences met the predetermined stopping rules. Kell and Morrow (2005) approach the topic differently and stated radiotherapy may make the use of very wide margins redundant.

The European EORTC 10853 trial (Bijker et al., 2001) concluded that radiotherapy cannot compensate for positive margins although it should be noted that this is the result of a subgroup analysis and the trial did not randomise to margin status. Tunon-de-Lara et al. (2001) reported an 11% relapse rate for involved margins compared to 53% when radiotherapy is given, the corresponding rate for free margins and radiotherapy was 7.5%; the authors concluded that there is a need for clear margins but also emphasised that breast cancer mortality is extremely low regardless of the treatment method. Chan et al. (2001) compared the recurrence rates of the included subgroups and concluded that radiotherapy does not compensate for inadequate surgical clearance.

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Wong JS, Kaelin CM, Troyan SL (2006). Prospective study of wide excision alone for ductal carcinoma in situ of the breast. *Journal of Clinical Oncology*, 24 (7), 1031-1036.

Yau TK, Chan K, Chan M et al. (2006). Wide local excision and radiotherapy for the treatment of ductal carcinoma in situ of the breast. The Hong Kong experience. *Clinical Oncology*, 18, 447-452.

Updated 2018

Evidence Tables

MacDonald HR, Silverstein MJ, Mabry H et al. (2005). Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. American Journal of Surgery, 190 (4), 521-525.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=445 patients with DCIS and known margin widths

Intervention excision alone

Margin closest single distance between DCIS and inked margin; 0mm (tumour transected), 0.1-0.9mm, 1-1.9mm, 2-2.9mm, 3-5.9mm, 6-9.9mm and ≥ 10 mm as established by direct measurement or ocular micrometry

Follow up median: 57 months, median time to local recurrence: 26 months

Results

Margin	Results	Author's conclusion
overall	Margin width was associated with local recurrence in univariate ($p < .001$) and multivariate analyses ($p < 0.00001$) and was the most important predictor of local recurrence (relative HR 0.42). After adjusting for all other predictors the likelihood of local recurrence for patients with margins ≤ 10 mm was 5.39 times as much for patients with 10mm or more (CI: 2.68-10.64)	
positive	15/32 with local recurrence 48% probability of remaining free at 5yrs, 39% at 8yrs 0mm vs ≥ 10 mm: HR 7.69	Margin width is the single most important predictor of local recurrence, increasing margins decreases the risk for local recurrence.
0.1-0.9mm	18/53 with local recurrence [34%] 63% probability of remaining free at 5yrs 58% at 8yrs HR compared to 0mm: .61	
1-1.9mm	7/20 with local recurrence [35%] 73% probability of remaining free at 5yrs, 49% at 8yrs HR compared to 0mm: .58	
[<2mm]	[25/73 with local recurrence, 34%]	
2-2.9mm	20/82 with local recurrence [24%] 81% probability of remaining free at 5yrs, 78% at 8yrs HR compared to 0mm: .21	
[>2mm]	[39/340 with local recurrence, 11%]	
3-5.9mm	8/39 with local recurrence [21%] 64% probability of remaining free at 5yrs, 64% at 8yrs HR compared to 0mm: .35	
[>6mm]	[11/219 with local recurrence, 5%]	
6-9.9mm	2/22 with local recurrence [9%] 91% probability of remaining free at 5yrs, 61% at	

	8yrs HR compared to 0mm: .20
≥10mm	9/197 with local recurrence [5%] 93% probability of remaining free at 5yrs, 91% at 8yrs HR compared to 0mm: .07
General comments some patients may overlap with Macdonald et al (2006) and Silverstein et al. (1999)	

Updated 2018

Chan KC, Knox WF, Sinha G et al. (2001). Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. Cancer, 91(1), 9-16.

Design Case series **Evidence level** 3 **Country** UK

Population N=244 patients receiving breast conservative surgery for DCIS with a the maximum tumour diameter of 40mm and available margin information

Intervention wide local excision with the goal of obtaining clear margins and cavity shavings, tamoxifen (20mg, 5yrs), radiotherapy, tamoxifen + radiotherapy; involved margins or cavity shavings resulted in reexcision

Margin histologic margins measured by ocular micrometer, clear: >1mm, close: DCIS ≤1mm from inked margin, close: DCIS ≤ 1mm from any inked margin; involved: DCIS at any inked margin

Follow up at least 1 year for each patient

Results

Margin	Results	Author's conclusion
overall	The recurrence rates were different for margins of >1mm and ≤1mm (p<0.001), this was also true for the subgroup excision alone (P<0.001) and excision + tamoxifen (p<0.05) but not for excision + radiotherapy or excision + radiotherapy + tamoxifen (n.s.) Close margin width significantly predicted recurrence in uni- and multivariate analyses Recurrence free survival was different for margins >1mm and ≤1mm (p<0.001), but subgroups (1.1-5mm, 5.1-10mm, 10.1-40mm) of clear margins did not differ (n.s.)	Close margins were associated with a high risk of local recurrence, radiotherapy did not compensate for inadequate surgical clearance.
0.1-1mm	37.9% patients with recurrences, 22/66 DCIS, 3/66 invasive ductal carcinoma	
1.1-5mm	3.5% patients with recurrences, 2/89 DCIS, 2/89 invasive ductal carcinoma	
5.1-10mm	7.1% patients with recurrences, 2/28 DCIS, 0/28 invasive ductal carcinoma	
10.1-40mm	4.5% patients with recurrences, 0/22 DCIS, 1/22 invasive ductal carcinoma	
[≥5mm]	[3/50, 6% with recurrence]	
≤1mm	48.7% of nuclear grade 3 DCIS patients with recurrences, 15/37 DCIS, 3/37 invasive ductal carcinoma	
>1mm	7.9% of nuclear grade 3 DCIS patients with recurrences, 5/89 DCIS, 3/37 invasive ductal carcinoma	

General comments it is possible that some of the patients are also included

in Boland et al. (2003, 2001)

Updated 2018

Neuschatz AC, DiPetrillo T, Safaii H et al. (2001). Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. International Journal of Cancer, 96, 97-104.

Design Case series **Evidence level** 3 **Country** USA

Population N=125 patients with DCIS, (microinvasion excluded)

Intervention excision with rim of uninvolved tissue, excision + radiation therapy, mastectomy, (no tamoxifen)

Margin differentiation ≤ 1 vs > 1 and ≤ 1 mm vs 1-10mm vs > 10 mm; reexcision for margins ≤ 2 mm

Follow up 5 years

Results

Margin	Results	Author's conclusion
overall	Final margin status of ≤ 1 mm as compared to 1mm was associated with local failure (p=0.01) ≤ 1 mm vs 1-10mm vs > 10 mm: p=0.04* there were significant differences in local failure for different margin widths combined with different lesion diameters the addition of adjuvant radiotherapy suggested a delay to local failure in lesions with margins ≤ 1 mm	Large diameters (> 15 mm) and close surgical margins (≤ 1 mm) are dominant risk factors for local recurrence.
≤ 1 mm	25% crude local failure, 30% 5yr local failure	
> 1 -10mm	3.7% crude local failure, 5% 5yr local failure	
> 10 mm	7.3% crude local failure, 9.7% 5yr local failure	
> 1 mm	5.9% crude local failure, 8% 5yr local failure	

General comments *as reported in table 2; no formal statistical tests for interaction, rest not detailed

Boland GP, Chan KC, Knox WF et al. (2003). Value of the Van Nuys prognostic index in prediction of recurrence of ductal carcinoma in situ after breast conserving surgery. British Journal of Surgery, 90(4), 426-432.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** UK

Population N=237 patients with breast conserving surgery for DCIS and known margin measurements, (microinvasion excluded)

Intervention excision, some plus radiation therapy, some plus tamoxifen, some with all 3

Margin ocular micrometer measurement, clear: >1mm, close: DCIS ≤ 1mm from inked margin, involved: DCIS at any inked margin; involved margins resulted in reexcision and further shavings

Follow up median: 47 months, range: 12-197 months

Results

Margin	Results	Author's conclusion
overall	Excision margin was associated with recurrence in uni- and multivariate analyses (p<0.001)	
<1mm	38% with recurrence RR in comparison to ≥1mm: 9.8 RR in comparison to ≥10mm: 21	Excision width is the most important predictor of local recurrence.
≥1mm	5% with recurrence	
1-9mm	6% with recurrence RR in comparison to ≥10mm: 2.4	
≥10mm	3% with recurrence	

General comments it is possible that the patients from Boland et al. (2001) are also included in this analysis, overlap with Chan et al. (2001) is also possible

Dillon MF, Dermott EW O'Doherty A et al. (2007). Factors affecting successful breast conservation for ductal carcinoma in situ. Annals of surgical Oncology, 14(5), 1618-1628.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** Ireland

Population N=135 patients undergoing initial breast conserving procedures for DCIS, not all with definitive preoperative diagnosis

Intervention diagnostic or therapeutic operation, reexcision or mastectomy

Margin pathology margins, compromised (foci of DCIS found within 10mm) vs clear, ≤2mm, ≤2mm vs >2mm, 0mm vs 0-1mm vs 1-2mm vs 2-5mm vs >5mm

Follow up study period 6 years

Results

Margin	Results	Author's conclusion
overall	Underestimation of pathological size by mammography by >1cm occurred in more patients with compromised margins than in those with clear margins in univariate analyses (p=0.02) but the factor was not significant in a multivariate analysis Residual disease on re-operation and DCIS margin distance were associated (p=0.006) Margin width ≤2mm compared to >2mm was a predictor of residual disease in univariate (OR: 11.464, p<0.0001) and multivariate (OR: 6.694, p=0.032) DCSI margin distance affected the likelihood of whether breast conservation was successful or not (p<0.001)	Patients with margin distances of ≤2mm are at high risk of residual disease; a 5mm margin width is recommended.
0	64% with residual disease	
0-1mm	60% with residual disease	
1-2mm	64% with residual disease	
≤2mm	Of all people with residual disease 95% were in this margin group Of all patients with a successful breast conserving therapy, 33% were in this margin group, 88% of all patients with unsuccessful breast conserving therapy	
2-5mm	17% with residual disease	
>2mm	Of all the people with residual disease 5% were in this margin group	

Of all patients with a successful breast conserving therapy, 67% were in this margin group, 12% of all patients with unsuccessful breast conserving therapy

0% with residual disease

>5mm

General comments very different reporting compared to literature

Updated 2018

Silverstein MJ & Buchanan C (2003). Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. The Breast, 12, 457-471.

Design Case series **Evidence level** 3 **Country** USA

Population N=660 patients with DCIS treated with breast conserving therapy, typically with lesions ≤ 40 mm and clear margins ≥ 1 mm

Intervention excision alone, excision plus radiation therapy (40-50 Gy)

Margin < 1 mm, 1- < 10 mm, ≥ 10 mm, patients with reexcision without DCIS were scored as 10mm

Follow up mean: 88 months

Results

Margin	Results	Author's conclusion
overall	The differences between the local disease free survival curves for the 3 margins are significant ($p < 0.0001$) Margin width is the most important predictor of the USC/VNPI score / excellent predictor of local recurrence	As margin width increases, the probability of local recurrence decreases, 1mm margins are inadequate to ensure complete removal of DCIS, there are so few local recurrences in patients with margins of ≥ 10 mm that the effect of radiation therapy is of little practical importance.
< 1 mm	Different local recurrence free survival depending on treatment ($p < 0.0001$); 2.6fold increased risk of recurrence	
1-9mm	Different local recurrence free survival depending on treatment ($p < 0.03$); 2-fold increase in risk of local recurrence for patients with excision alone compared to plus radiation	
≥ 10 mm	No different local recurrence free survival depending on treatment (n.s.) 6/214 with local recurrence RR of local recurrence: 6%, relative risk of local recurrence decreased to 3% by adding radiation therapy (but n.s.) Tumour size groups and age groups n.s. differences	

General comments publication contains 24 graphs but few raw data, table 4 not extracted as unclear what was depicted / compared. It is possible that there is overlap with the patients reported in Silverstein et al. (1999)

Denoux Y, Marnay J, Crouet et al (2001). Evaluation of predictive factors, particularly the Van Nuys index, of local recurrence in ductal carcinoma in situ of the breast: study of 166 cases with conservative treatment and review of the literature. Bulletin du Cancer, 88(4), 419-425.

Design Case series **Evidence level** 3 **Country** France

Population N=166 patients with DCIS

Intervention lumpectomy + radiotherapy (6 patients lumpectomy only)

Margin excision presumably aiming at 10mm, histological slides and shames analysed, <1mm, 1-9mm, ≥10mm as proposed by the Van Nuys index

Follow up median: 75 months, range: 16-263, 5yr, 10yr

Results

Margin	Results	Author's conclusion
overall	Margin width did not predict local recurrence (n.s.)	Margin width was not a statistically significant predictor of recurrence but it should be noted that none of the patients with margins ≥10mm developed a local recurrence.
<1mm	16/82 with local recurrence [20%] 93% without local recurrence at 5yrs 82% without local recurrence at 10yrs	
1-9mm	5/70 with local recurrence [7%]	
≥10mm	0/14 with local recurrence 100% without local recurrence at 5yrs 1%(?) without local recurrence at 10yrs*	

General comments published in French; *as reported in table II, 100% is more likely; there appear to be several values missing in table II

Updated 2020

Silverstein MJ, Lagios MD & Groshen S (1999). The influence of margin width on local control of ductal carcinoma in situ of the breast. New England Journal of Medicine, 340(19), 1455-1461.

Design Cohort study **Evidence level** 2 **Country** USA

Population N=469 patients with DCIS treated with breast conserving therapy

Intervention excision alone, excision plus radiation therapy; treatment depending on patient and physician's choice

Margin <1mm, 1- <10mm, ≥10mm as established by direct measurement or ocular micrometry

Follow up mean: 81 months

Results

Margin	Results	Author's conclusion
<1mm	34/112 experience local recurrence [30%] probability of recurrence within 8yrs for excision alone: 0.58, excision plus radiation: 0.30 RR excision alone vs plus radiation: 2.54 (p=0.01)	Radiation does not lower the recurrence rate among patients with wide margins (≥10mm).
[≥1mm]	[41/357, 11%]	
1- <10mm	38/224 experience local recurrence [17%] probability of recurrence within 8yrs for excision alone: 0.20, excision plus radiation: 0.12 RR excision alone vs plus radiation: 1.49 (n.s.)	
≥10mm	3/133 experience local recurrence [2%] probability of recurrence within 8yrs for excision alone: 0.03, excision plus radiation: 0.04 RR excision alone vs plus radiation: 1.14 (n.s.)	

General comments 2 sites. It is possible that there is overlap with the patients reported in Silverstein & Buchanan (2003); the patients with ≥10mm are followed up in Macdonald et al. (2006)

Silverstein MJ, Beron P & Lewinsky BS (1997). Breast conserving therapy for ductal carcinoma in situ: The Van Nuys experience with excision plus radiation therapy. Breast Journal, 3(3 suppl), 36-41.

Design Case series **Evidence level** 3 **Country** USA

Population N=185 patients with DCIS treated with local excision and radiation therapy

Intervention excisional biopsy, reexcision became routine, radiation therapy

Margin <1mm, 1-9mm, ≥10mm

Follow up median: 90 months

Results

Margin	Results	Author's conclusion
<1mm	25% with recurrence	Local recurrence probability decreases as margin width increases, narrow margins amongst other factors may aid in selecting which patients benefit from radiation therapy.
[≥1mm]	[15/124, 12% with recurrence]	
1-9mm	15% with recurrence	
≥10mm	3% with recurrence	

General comments 2 sites. It is possible that there is overlap with the patients reported in Silverstein et al. (1999). Cosmetic results were assessed but not reported

Updated 2018

Boland G, Chan KC, Knox WF & Bundred NJ (2001). Comparison of margin status with van Nuys index to predict recurrence of ductal carcinoma in situ after breast conserving surgery. British Journal of Surgery, 88, 41.

Design Case series (regression) **Evidence level** 3 **Country** UK

Population N=228 patients treated with breast conserving surgery for unifocal DCIS

Intervention breast conserving surgery

Margin close: <1mm, not close: >1mm

Follow up median: 48 months

Results

Margin	Results	Author's conclusion
overall	Excision margin was associated with ipsilateral recurrence (p<0.001)	Close resection margins are a better predictor than the Van Nuys prognostic index for DCIS recurrence.
<1mm	36.9% with ipsilateral recurrence	
>1mm	5.8% with ipsilateral recurrence	

General comments Abstract only. It is possible that these patients are also part of Boland et al. (2003) and in parts of Chan et al. (2001)

Updated 2018

Hetelekidis S, Collins L & Manola J (1999). Predictors of local recurrence following excision alone for ductal carcinoma in situ. Cancer, 85 (2), 427-431.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=59 patients diagnosed with DCIS and negative margins of excision on review

Intervention excision alone, re-excision, (no radiation therapy)

Margin histologic slides, negative (>1mm), close (≤ 1 mm), (positive margins excluded)

Follow up median: 95.5 months, range: 34-141

Results

Margin	Results	Author's conclusion
overall	Margin size – local recurrence: n.s.	Margin status and nuclear grade may be useful to identify patients with DCIS who can be managed with excision alone.
≤ 1 mm	25% actuarial 5yr local recurrence	
>1mm	8% actuarial 5yr local recurrence	

General comments -

Updated 2018

Yau TK, Chan K, Chan M et al. (2006). Wide local excision and radiotherapy for the treatment of ductal carcinoma in situ of the breast: The Hong Kong experience. Clinical Oncology, 18, 447-452.

Design Case series (regression) **Evidence level** 3 **Country** China

Population N=75 consecutive women with DCIS treated with wide local excision and radiotherapy

Intervention excision + radiotherapy, tamoxifen possible but not standard (no interstitial brachytherapy, no regional node irradiation, no chemotherapy)

Margin close (≤ 2 mm but negative) vs > 2 mm

Follow up median: 5.1 years, range: 2-10.7

Results

Margin	Results	Author's conclusion
overall	Both groups differed in 5-yr actuarial local failure free rate ($p=0.02$) At 5yr follow-up all patients were still alive All women had good to excellent cosmetic scores (physician rating)	Wide local excision and radiotherapy appears a reasonable alternative, efforts are needed to achieve cosmetically acceptable tumour free margins greater than 2mm.
≤ 2 mm	3/20 patients with local failure [15%] 77% 5yr actuarial local failure free rate HR 9.083 ($p=0.056$)	
> 2 mm	1/55 patients with local failure [2%] 98.2% 5yr actuarial local failure free rate	

General comments mean and upper limit of applied margins unclear

Kell MR & Morrow M (2005). An adequate margin of excision in ductal carcinoma in situ: 2mm plus radiotherapy is as good as a bigger margin. BMJ, 331(7520), 789-790.

Design Non-systematic review **Evidence level** 4 **Country** USA

Population patients with DCIS, entire review on margins

Intervention excision + radiotherapy

Margin clear vs positive, 2mm vs >10mm, 0-1mm, 1-2mm, ≥2mm, 5mm, 1-10mm also cited

Follow up treatment failure, 10yrs

Results

Margin	Results	Author's conclusion
overall	<ul style="list-style-type: none"> -Definitions of negative vary, e.g. no tumour cells on the ink, 2mm free - Excisions of 5mm free seem unlikely to leave DCIS, even in patients with discontinuous growth, smaller margins may be appropriate for poorly differentiated DCIS - further disease is related to resection margin (Neuschatz et al. 2002 cited) - there is no difference between patients with 10mm margins and 1-10mm margins when treated with surgery and radiotherapy (Silverstein et al., 1999 cited) - the only benefit of >10mm could be in low risk patients in whom radiotherapy may be avoided but this is not empirically confirmed (Wong et al., 2003 cited) - radiotherapy reduces the risk of local recurrence even in studies that only look at negative margins without specifying margin width (3 studies cited including the EORTC trial) - Radiotherapy with a margin of 2mm can achieve excellent local control (Solin et al., 2005) - there is no convincing evidence that larger margins confer better rates of local control [presumably] than radiotherapy - large margins lead to a greater deformity to the breast and patients will suffer a worse cosmetic outcome (1 study cited) 	<p>Free margins should be obtained, when radiotherapy is given ≤2mm is as good as >10mm; there is an extremely low risk of death due to breast cancer associated with DCIS.</p>

General comments doesn't cite the American consensus conference but cites other studies from 1999

Neuschatz AC, DiPetrillo T, Steinhoff M et al. (2002). The value of breast lumpectomy margin assessment as a predictor of residual tumor burden in ductal carcinoma in situ of the breast. American Cancer Society, 94(7), 1917-1924.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=253 patients with DCIS treated with lumpectomy and reexcision, (microinvasion excluded)

Intervention initial excision, lumpectomy or reexcision, reexcisions typically for margins $\leq 2\text{mm}$; excision with normal margin of 5mm or more

Margin closest initial excision margin to DCIS specimen edge as measured by micrometer; positive focal margin (single microscopic focus in one histologic section), positive minimal (involvement in one low power field or 2-4 sections at one geographic edge), positive moderate (2-4 LPF / present in 5-7 sections), positive extensive (≥ 5 LPF / ≥ 8 sections), negative 0-1mm, negative 1-2mm, negative $>2\text{mm}$

Follow up ?

Results

Margin	Results	Author's conclusion
overall	Margin status significantly predict the presence of residual tumours in reexcision specimen ($p < 0.0001$) Margins significantly predict the presence of medium / large residual tumours ($p = 0.003$, < 0.0001 in uni- and multivariate analyses)	Margin status is the most important predictor for the presence and the amount of residual disease.
Positive-extensive	85% with tumour in reexcision	
Positive moderate	68% with tumour in reexcision	
Positive minimal	46% with tumour in reexcision	
Positive focal	30% with tumour in reexcision	
positive	63% with tumour in reexcision 11% with microscopic, 37% small, 10% medium, 5% large residual tumour	
0-1mm	41% with tumour in reexcision	
$>1-2\text{mm}$	31% with tumour in reexcision	
$>2-10\text{mm}$	0% with tumour in reexcision	
negative	63% no residual tumour, 10% with microscopic, 19% small, 4% medium, 3% large residual tumour	
$[\geq 1\text{mm}]$	$[4/23, 17\% \text{ with tumour in reexcision}]$	

Goldstein NS, Kestin L & Vicini F (2000). Intraductal carcinoma of the breast. American J of Surgical Pathology, 24(8), 1058-1067.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=132 consecutive patients with mammographically detected DCIS and inked final specimen margins treated with breast conserving therapy

Intervention local excision + radiation

Margin slide review, unknown (specimen fragmented or edges not inked), negative (all DCIS ducts more than 0.2cm away from inked margin edge), close (at least one DCIS duct within 0.2cm but margin did not transect DCIS duct), focally positive (margin edge transected DCIS duct), multifocal positive (margin transected by ≥ 2 DCIS separated by ≥ 5 cm or positive margin on ≥ 2 slides)

Follow up median: 84 months, range: 9-170.4, 78% followed for at least 5 years, 22% followed for at least 10 years

Results

Margin	Results	Author's conclusion
Overall	Margin status was not associated with true recurrences or marginal miss or 5yr actuarial recurrence rates in uni- or multivariate analyses (n.s.) No difference in true recurrences or marginal miss between patients with negative, close or positive final margins for patients with ≥ 5 DCIS ducts or terminal duct lobular units with cancerisation of lobules near final margin (n.s.)	Margin status is not associated with the analysed outcomes.
Multifocal positive	0/11 patients with recurrence 1 with carcinoma elsewhere	
Unifocal positive	1/5 patients with recurrence 0 with carcinoma elsewhere	
positive	1/16 patients with recurrence 1 with carcinoma elsewhere	
>0-2mm	2/25 patients with recurrence [8%] 1 with carcinoma elsewhere [4%]	
>2mm	4/88 patients with recurrence [5%] 2 with carcinoma elsewhere [2%]	
unknown	2/3 patients with recurrence 0 with carcinoma elsewhere	

General comments data may be open to alternative interpretation: there were only few patients with recurrences that could enter the analyses, close margins have almost twice the recurrence rate compared to wide margins (8% vs 4.5%). The patients may also be included in parts in Goldstein et al. (1998) and Goldstein et al (1999)

Goldstein NS, Lacerna M & Vincini F (1998). Cancerization of lobules and atypical ductal hyperplasia adjacent to ductal carcinoma in situ of the breast: Significance for breast conserving therapy. American J of Clinical Pathology, 110(3), 357-367.

Design Case series **Evidence level** 3 **Country** USA

Population N=94 consecutive patients with mammographically detected DCIS treated with breast conserving therapy

Intervention local excision + radiation

Margin final pathology margin; unknown (specimen fragmented or edges not inked), negative (all DCIS ducts more than 0.2cm away from inked margin edge), close (at least one DCIS duct within 0.2cm but margin did not transect DCIS duct), focally positive (margin edge transected DCIS duct), multifocal positive (margin transected by ≥ 2 DCIS separated by ≥ 5 cm or positive margin on ≥ 2 slides)

Follow up median: 78 months, range: 9-146, 70% followed for ≥ 5 years, 22% followed for ≥ 10 years

Results

Margin	Results	Author's conclusion
overall	Final margin status was not associated with true or recurrence elsewhere	
positive	No recurrence	
>0-2mm	3/16 patients with true recurrence, 1/16 with recurrence elsewhere [19%, 6%] 3/6 patients with in whom a true recurrence / marginal miss recurrent carcinoma developed were in this group 2/3 patient with recurrence elsewhere was in this margin group	DCIS may be inadequately excised if atypical ductal hyperplasia and DCIS or cancerisation of lobules and DCIS are near the margin.
>2mm	3/69 patients with true recurrence, 2/69 with recurrence elsewhere [4%, 3%] 3/6 patients with in whom a true recurrence / marginal miss recurrent carcinoma developed were in this group 2/3 patients with recurrence elsewhere were in this margin group	

General comments it is likely that these patients are also included in Goldstein et al. (2000), there may be overlap with Goldstein et al. (1999)

Holland P, Gandhi A, Knox WF et al. (1998). The importance of complete excision in the prevention of local recurrence of ductal carcinoma in situ. British Journal of Cancer, 77(1), 110-114.

Design Case series **Evidence level** 3 **Country** UK

Population N=129 women with localised screen-detected DCIS (including microcalcifications, mammographic mass lesions, in the majority impalpable) treated with breast conserving surgery

Intervention excision, involved margins underwent reexcision regardless of cavity shavings, some received also tamoxifen or breast irradiation or a combination of the two

Margin specimen or cavity shavings, clear (DCIS >1mm from any inked margin), involved (DCIS at any inked margin), close (DCIS ≤1mm from any inked margin)

Follow up every 3 months in the first year then annually, study period 58 months

Results

Margin	Results	Author's conclusion
overall	Ipsilateral recurrence was related to margin status (p<0.001)	Local relapses often represent residual DCIS rather than true recurrence, cavity shavings are ineffective in ensuring complete excision, 10mm margins around screen detected lesions are recommended.
positive	No recurrence	
≤1mm	36% with recurrence of all 12 recurrences 10 occur in these patients	
>1mm	2% with recurrence Of all recurrences 2/12 occur in these patients	

General comments

Cheng L, Al-Kaisi NK, Gordon NH et al. (1997). Relationship between the size and margin status of ductal carcinoma in situ of the breast and residual disease. Journal fo the National Cancer Institute, 89(18) 1356-1360.

Design Case series (multivariate) **Evidence level** 3 **Country** USA

Population N=232 consecutive patients diagnosed with mammary DCIS initially presenting with mammographic abnormality, palpable mass or other symptoms

Intervention excision, subsequent mastectomy, some with reexcision, some radiation therapy

Margin positive (tumour extending to or transacted by inked margin), close (tumour ≤ 1 mm or transacted by inked margin), negative (>1 mm from margin) in histologic biopsy specimen

Follow up median: 45 months, range: 3-171

Results

Margin	Results	Author's conclusion
overall	Residual disease was associated with positive margins in univariate ($p < 0.001$) and multivariate analyses ($p = 0.04$); OR for risk of residual disease 2.2 for patients with positive margins (CI: 1.02-4.55) compared to ≤ 1 mm or >1 mm margins residual disease risk for ≤ 1 mm margins was not different from that of >1 mm (n.s.) positive margins and tumour size appear to be positively correlated	Size of DCIS and margin status are independent predictors of residual disease, small tumours with negative margins carry a low risk of local failure and can be treated with lumpectomy, large tumours pose a risk of residual disease independently of margin status and additional adjuvant therapy may be indicated.
positive	39% with residual disease	
≤ 1 mm	19% with residual disease	
>1 mm	14% with residual disease	

General comments

Sahoo S, Recant WM, Jaskowiak N et al. (2005). Defining negative margins in DCIS patients treated with breast conservation therapy: The University of Chicago experience. The Breast Journal, 11(4), 242-247.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=103 consecutive patients with DCIS treated with breast conserving therapy and radiation therapy

Intervention excisional biopsy and external beam radiation (46 GY median plus boost therapy)

Margin final margins on slide review, positive (DCIS focus touched or was transected at inked margin), close (<1mm, 1-5mm, >5mm of uninvolved breast tissue from inked margin), free (negative but distance not known)

Follow up 63 months, range: 7-191, 5yrs

Results

Margin	Results	Author's conclusion
overall	Of the 13 patients that showed a recurrence, 5 had positive margins, 3 margins <1mm, 2 free margins, 2 with 1-5mm margins, 1 with >5mm Positive margin status was a predictor of local recurrence (p=0.008) compared to all other in univariate analyses, the survival curves of patients with positive margins compare to negative margins differed significantly; positive margin compared to all negative was a predictor in multivariate analyses with HR: 0.16 (CI: 0.04-0.63, p=0.009)	Excellent local control can be achieved by obtaining microscopically negative margins and radiation therapy.
positive	31% with local recurrence	
Clear but unknown	20% with local recurrence	
<1mm	8% with local recurrence	
1-5mm	10% with local recurrence	
>5mm	4% with local recurrence	
[≥1mm]	[3/42, 7%]	

General comments

Vicini FA, Kestin LL, Goldstein NS et al. (2001). Relationship between excision volume, margin status, and tumor size with the development of local recurrence in patients with ductal carcinoma in situ treated with breast conserving therapy. Journal of Surgical Oncology, 76, 245-254.

Design Case series (multivariate) **Evidence level** 3 **Country** USA

Population N=146 patients treated for DCIS with lumpectomy followed by radiation therapy with complete pathological review (no invasive carcinoma, no microinvasion)

Intervention excision + breast irradiation, reexcision due to close ($\leq 2\text{mm}$), positive, or uncertain margins

Margin pathology margin; unknown (specimen fragmented or not inked), negative (no DCIS within 0.2cm of inked margin), close (DCIS within 0.2cm but margin did not transected), unifocal positive (single DCIS duct transected at margin), multifocal positive (margin transected by ≥ 2 ducts separated by $\geq 5\text{cm}$ or positive margin on ≥ 2 slides)

Follow up 5yr, 10yr; every 3 months for 2 years, 6-monthsly after

Results

Margin	Results	Author's conclusion
overall	<p>close or positive margins combined and close, positive or uncertain margins combined differed in ipsilateral breast failures compared to $>2\text{mm}$ margins in univariate analyses ($p=0.24$, $p=0.09$) but not multivariate analyses (n.s.)</p> <p>Close or positive margins compared to $>2\text{mm}$ was associated with a HR of 4.47 ($p=0.03$) for true recurrences / marginal miss in a multivariate analysis, the corresponding values for all negative margins were HR of 2.59 ($p=0.07$) for ipsilateral breast failure, n.s. for true recurrences / marginal miss</p> <p>Close, positive or uncertain margins differed in true recurrences / marginal miss compared to $<5\text{mm}$ ($p=0.24$, $p=0.09$)</p> <p>Patients with reexcision and negative margin differed from patients with reexcision and close or positive margins in ipsilateral breast failure incidences ($p=0.02$) and true recurrences ($p=0.003$)</p>	Margin status alone may be suboptimal in defining excision adequacy.
Close or positive	<p>11.6% with ipsilateral breast failure at 5yrs, 14.7% at 10yrs, 9.5% true recurrence at 5yrs, 12.6% at 10yrs;</p> <p>Patients with reexcision: 23.4% with ipsilateral breast failure at 5yrs, 32% at 10yrs, 23.4% true recurrence at 5yrs, 32% at 10yrs</p>	
Close / positive / uncertain	<p>15.9% with ipsilateral breast failure at 5yrs, 18.7% at 10yrs, 14% true recurrence at 5yrs, 16.9% at 10yrs</p>	

>2mm	7.4% with ipsilateral breast failure at 5yrs, 9.3% at 10yrs, 4.4% true recurrence at 5yrs, 6.3% at 10yrs; Patients with reexcision 7% with ipsilateral breast failure at 5yrs, 9.4% at 10yrs, 4.3% true recurrence at 5yrs, 6.8% at 10yrs
2-5mm	9.1% with ipsilateral breast failure at 5yrs, 9.1% at 10yrs, 9.1% true recurrence at 5yrs, 9.1% at 10yrs
>5mm	6.8% with ipsilateral breast failure at 5yrs, 9.1% at 10yrs, 2.7% true recurrence at 5yrs, 5% at 10yrs
other	Negative margins at reexcision showed 7% ipsilateral breast failure at 5yrs, 9.4% at 10yrs, 4.3% true recurrence at 5yrs, 6.8% at 10yrs; Close or positive margins at reexcision showed 23.4% ipsilateral breast failure at 5yrs, 32% at 10yrs, 23.4% true recurrence at 5yrs, 32% at 10yrs

General comments these data have to be regarded with caution - due to the various groupings of patients and varying definitions of margin status and multiple subgroup analyses mistakes in the data extraction cannot be ruled out

Updated 2019

Rodrigues N, Carter D, Dillon D et al. (2002). Correlation of clinical and pathologic features with outcome in patients with ductal carcinoma in situ of the breast treated with breast conserving surgery and radiotherapy. International Journal of Radiation Oncology, Biology, Physics, 54(5), 1331-1335.

Design Case series **Evidence level** 3 **Country** USA

Population N=230 patients with DCIS treated with breast conserving surgery plus radiotherapy, margin status was only known for 42% of the patients

Intervention local excision + radiotherapy, 9% also hormonal therapy

Margin positive (DCIS extended to margin edge), close (DCIS present ≤ 2 cm from margin edge), negative (DCIS > 0.2 cm from margin edge or no tumour in reexcision)

Follow up median: 8.2 years; 3-6 months for 2-3 years then every year

Results

Margin	Results	Author's conclusion
overall	Ipsilateral breast tumour recurrence rate did not differ between patients with close / positive margins compared to negative / unknown margins	Positive or close margin status was not a significant predictor of local relapse.
unknown	9/97 with recurrence	
positive	0/8 recurrences	
≤ 2 mm	3/22 with recurrence [14%]	
> 2 mm	5/103 with recurrence [5%]	

General comments

Updated 2018

Ratanawichitrasin A, Rybicki LA, Steiger E et al. (1999). Predicting the likelihood of residual disease in women treated for ductal carcinoma in situ. J Am Coll Surg, 188(1), 17-21.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=112 patients who had undergone 2 or more operations for DCIS (i.e. 'consecutive paired interventions e.g. excision – reexcision'), including patients with microinvasion, (invasive cancer excluded)

Intervention excision biopsy, reexcision, subsequent reexcision, subsequent simple mastectomy, subsequent modified radical mastectomy

Margin surgical margin, positive (tumour found at the margin), close ($\leq 2\text{mm}$), negative ($>2\text{mm}$), unknown (margin status not reported)

Follow up [probably] within 21 months

Results

Margin	Results	Author's conclusion
overall	OR for residual disease: 7.7 (positive, $p=0.049$) 8.3 (unknown, $p=0.046$), 3.5 ($<2\text{mm}$, n.s.) compared to $>2\text{mm}$ in multivariate analysis (univariate analysis similar)	Positive or unknown biopsy margins are associated with higher risk of residual DCIS.
unknown	50% with residual disease	
positive	58% with residual disease	
$<2\text{mm}$	31% with residual disease	
$>2\text{mm}$	17% with residual disease	

General comments

Updated 2018

Sigal-Zafrani B, Lewis JS, Clough KB et al. (2004). Histological margin assessment for breast ductal carcinoma in situ: precision and implications. Modern Pathology, 17, 81-88.

Design Case series **Evidence level** 3 **Country** France

Population N=89 patients with screen detected DCIS (including DCIS + microinvasion), unifocal disease with <3cm on mammography and wide excision followed by reexcision

Intervention excision (aiming at complete removal of microcalcifications and/or mass) + reexcision or mastectomy, reexcision was performed when the lesion could be performed without leaving a major deformity, if not, mastectomy was recommended

Margin reexcision due to involved or close margins (<2mm), slices analysed in pathology, close with tumour cells present >1 from the inked surface, close with tumour cells present ≤1mm from but not involving the inked surface, focal involvement (<1mm of inked surface involved with tumour, minimal involvement (≥1<15mm of inked surface involved with tumour, extensive involvement (≥15mm of inked surface involved with tumour)

Follow up operations presumably close together

Results

Margin	Results	Author's conclusion
overall	<p>Presence of residual tumour correlated strongly with initial margin status (p=0.006) Margin status predicted the amount of residual tumour (p=0.009)</p> <p>Patients with greater involvement were more likely to end up with a mastectomy (p=0.007)</p>	
Positive ≥15mm involvement	<p>94% with residual tumour (33% small, 61% large)</p> <p>33% subsequent mastectomy, 9% further excision</p>	Margin status can be used to predict the presence and amount of residual tumour and guide management decision.
Positive ≥1<15mm involvement	<p>71% with residual tumour (30% small, 40% large)</p> <p>37% subsequent mastectomy, 32% further excision</p>	
Positive <1mm involvement	<p>67% with residual tumour (56% small, 11% large)</p> <p>9% subsequent mastectomy, 11% further excision</p>	
≤1mm	<p>45% with residual tumour (27% small, 18% large)</p>	

	21% subsequent mastectomy, 28% further excision
>1mm	44% with residual tumour (11% small, 33% large)
	0% subsequent mastectomy, 20% further excision
General comments	

Updated 2018

Vargas C, Kestin L, Go N et al. (2005). Factors associated with local recurrence and cause specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy. Int. J. Radiation Oncology Biol. Phys, 63(5), 1514-1521.

Design Case series (multivariate) **Evidence level** 3 **Country** USA

Population N=405 patients with DCIS

Intervention lumpectomy alone, lumpectomy + radiation therapy (median 45Gy), subsequent mastectomy, subsequent radiation therapy

Margin recorded for initial biopsy and reexcision, positive or close (≤ 2 mm from margin), negative (> 2 mm from margin), uncertain (not inked or fragmented specimen)

Follow up median: 7 years, mean: 6.1 years

Results

Margin	Results	Author's conclusion
overall	Margin status was related to an increase in ipsilateral recurrences ($p=0.02$) and true recurrences / marginal miss ($p=0.004$), positive / ≤ 2 mm was also a risk factor in multivariate analyses with a HR of 3.65 ($p=0.007$); using the categories positive, close, negative, or widely negative was also a predictor in multivariate analysis (HR1.82 per group, $p=0.04$)	Close or positive margins are associated with ipsilateral breast tumour recurrence, local therapy optimisation is crucial to improve local control and cause specific survival.
positive / ≤ 2 mm	13% with ipsilateral recurrence or true recurrence / marginal miss at 5yrs, 22% at 10yrs	
> 2 mm	4% with ipsilateral recurrence at 5yrs, 9% at 10yrs; 3% true recurrence / marginal miss at 5yrs, 7% at 10yrs	

General comments data extraction under the assumption that these were initial margin data; it is possible that some of the included patients were also part of Goldstein et al. (1998)

Boyages J, Delaney G & Taylor R. (1999). Predictors of local recurrence after treatment of ductal carcinoma in situ. A meta-analysis. Cancer, 85(2), p616-628.

Design Meta-analysis of observational studies **Evidence level 4** **Country** Australia

Population includes a section on resection margins and cites a number of relevant studies

Intervention conservative surgery alone, conservative surgery + radiotherapy, mastectomy

Margin differentiates clear vs positive, ≤ 1 mm, >1 mm

Follow up treatment failure as well as long term survival

Results

Margin	Results	Author's conclusion
overall	<ul style="list-style-type: none"> - there is no general consensus on what constitutes an adequate margin - most recurrences occur in the immediate vicinity of primary surgical site suggesting that recurrences arise from remaining tumour cells, i.e. incomplete surgical excision (15 references) - the presence of positive or close margins increases the risk of local recurrence irrespective of radiation therapy (4 studies cited) - margin status and the likelihood of residual disease are correlated (1 study) - 'free' should be differentiated, e.g. >1mm, <5mm, ≥ 10mm - margin measurements alone cannot guide decisions, other factors and modalities, e.g. presence of calcification, use of post-biopsy mammogram should be considered 	<p>Patients who may be suitable for conservative surgery alone may be those with low grade lesions with little or no necrosis, and with clear surgical margins.</p>

General comments

Tunon-de-Lara C, deMascarel I, MacGrogan G et al. (2001). Analysis of 676 cases of ductal carcinoma in situ of the breast from 1971 to 1995. Am J Clin Oncol, 24(6), 531-536.

Design Case series (includes 4 distinct cohorts) **Evidence level** 3 **Country** France

Population N=676 patients with DCIS, (contralateral infiltrative carcinoma excluded)

Intervention surgical biopsy / gross excision of primary tumour alone or excision + radiation therapy (50Gy), mastectomy, subsequent mastectomy, subsequent axillary lymph node dissection, subsequent radiation, subsequent lumpectomy

Margin histological sections analyses, free vs invaded margins

Follow up median: 86 months, range: 8-164, in subgroups median follow up 85.7, 78.8, 237*, 67.6 months

Results

Margin	Results	Author's conclusion
overall	Invaded margin status was predictive of recurrence (p=0.0073)	
free	38/312 relapses lumpectomy alone (n=192): 14.5% relapses (16 noninvasive, 12 invasive), 25 local recurrences, 3 axillary node recurrences, 0 metastasis 8-144 months delay breast cancer specific death: 0.52% 5yr local recurrence free rate: 89%, 10yr: 83% 10yr overall survival: 95.3% lumpectomy + radiation (n=120): 7.5% relapses (4 noninvasive, 6 invasive), 9 local recurrences, 0 axillary node recurrences, 0 metastasis 10-156 months delay breast cancer specific death: 0 5yr local recurrence free rate: 98.1%, 10yr: 87.8% 10yr overall survival: 96.9%	The data emphasize the need for clear margins; breast cancer mortality is extremely low regardless of the treatment method.
invaded	12/51 relapses lumpectomy alone (n=15): 53% relapses (3 noninvasive, 5 invasive), 8 local recurrences in same quadrant as original lesion, 0 axillary node recurrences, 0 metastasis 8-60 months delay breast cancer specific death: 13% 5yr local recurrence free rate: 51.4%, 10yr: - 10yr overall survival: 100% lumpectomy + radiation (n=36): 11% relapses (2 noninvasive, 2 invasive), 4 local recurrences in same quadrant as original lesion, 0 axillary node recurrences,	

0 metastasis

10-31 months delay

breast cancer specific death: 0

5yr local recurrence free rate: 89%, 10yr: -

10yr overall survival: 100%

General comments 12% of patients also included in EORTC trial; *as stated in table 6; the survival data cannot be attributed to the treatments excision alone or excision + radiation as patients received further treatments (including mastectomies) when recurrences occurred

Updated 2018

Solin LJ, Fourquet A, Vivini FA et al. (2005). Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma. Cancer, 103(6), 1137-1146.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=1003 women with unilateral mammographically detected DCIS (no microinvasion)

Intervention breast conserving surgery, definitive breast irradiation ($\geq 4000\text{cGy}$), (no adjuvant systemic chemotherapy or hormonal treatment)

Margin final pathology margin from reexcision or excision, reexcision in 47% (most commonly for positive margins or residual microcalcifications), negative (no tumour identified $>2\text{mm}$ or $\geq 2\text{mm}$); positive (tumour identified), close ($\leq 2\text{mm}$, $<2\text{mm}$ 2-3mm or 3mm as defined at individual institution)

Follow up median: 8.5 years, mean: 9 years, range: 0.2-24.6, 873/1003 alive and available at 5yrs, 363/1003 at 10yrs, 68/1003 at 15 years

Results

Margin	Results	Author's conclusion
overall	Final pathology margin status is associated with local recurrence in univariate ($p=0.024$) as well as multivariate analyses ($p=0.0026$); negative margin was associated with fewer local recurrence ($p=0.0026$)	Age $\geq 50\text{yrs}$ and negative margins are associated with a decreased risk of local failure.
negative	4% local failure at 5yrs, 8% at 10yrs	
close	7% at 5yrs, 13% at 10yrs HR 1.90 for local failure compared to negative margin ($p=0.027$)	
positive	11% at 5yrs, 15% at 10yrs HR 3.35 for local failure compared to negative margin ($p=0.00035$)	
unknown	6% at 5yrs, 14% at 10yrs	

General comments multi-site with varying margin cut-offs

Bijker N, Peterse JL, Duchateau L et al. (2001). Risk factors for recurrence and metastasis after breast conserving therapy for ductal carcinoma in situ: Analysis of European Organization for Research and Treatment of Cancer Trial 10853. Journal of Clinical Oncology, 19(8), 2263-2271.

Design RCT (not randomised to margin status) **Evidence level** 1- **Country** Europe

Population N=1010 women from 46 institutes enrolled in EORTC DCIS

Intervention excision alone vs excision + radiotherapy (47-55 Gy); excision was performed often together with reexcision of the biopsy cavity after diagnostic excision by shaving, margins were considered free if no DCIS was found in the multiple reexcision specimen

Margin pathology report, free with or without further specifications, close/involved; inking was mentioned in 25% of specimen

Follow up median: 5.4yrs

Results

Margin	Results	Author's conclusion
overall	Margin status was associated with local recurrence in univariate ($p < 0.0223$) and multivariate analyses ($p = 0.0008$) HR for unknown / close / involved margins compared to free margins: 2.07 (CI: 1.35-3.16, multivariate analysis) The time to local recurrence differed between the 4 groups excision+radiation-free margin, excision-free margin, excision+radiation-involved/nonspecified margin, excision-involved/nonspecified margin ($p = 0.0003$, Kaplan-Meier curves)	Involved, close, or nonspecified margins are related to the risk of recurrence; radiotherapy cannot compensate for involved margins.
free	15% local recurrence with further specified margins, 13% for free margins but not further specified, HR: 1.36 and 1.07 the group receiving excision only 18% or 14% experienced local recurrences, the excision + radiotherapy group had a 12% recurrence rate	
Close / involved	24% local recurrence, HR: 2.01 the group receiving excision only 32% experienced local recurrences, the excision + radiotherapy group had a 16%* recurrence rate	
unknown	28% local recurrence, HR: 2.11 the group receiving excision only 33% experienced local recurrences, the excision + radiotherapy group had a 22% recurrence	

rate

General comments multi-site; * the discussion implied that the recurrence rate was 20%; more information on excision and margin definitions were taken from the excluded paper by Bijker, Rutgers et al. (2001)

Updated 2018

Goldstein NS, Kestin L. & Vicini F (1999). Pathologic features of initial biopsy specimens associated with residual intraductal carcinoma on reexcision in patients with ductal carcinoma in situ of the breast referred for breast conserving therapy. American Journal of Surgical Pathology, 23(11), 1340-1348.

Design Case series (multivariate analysis) **Evidence level** 3 **Country** USA

Population N=98 patients with pure DCIS undergoing biopsy and reexcision with available inked initial biopsy specimen

Intervention biopsy, reexcision

Margin negative / close, unifocal positive or multifocal positive in initial biopsy

Follow up median: 84 months, range: 9-170.4, 78% followed for at least 5 years, 22% followed for at least 10 years

Results

Margin	Results	Author's conclusion
overall	<p>negative, close or unifocal positive margins vs multifocal positive margin showed differences in the presence of DCIS ($p < 0.01$)</p> <p>there was no difference between negative or close versus unifocal positive margins (n.s.)</p> <p>there was no difference between negative versus close or positive margins (n.s.)</p> <p>multifocal positive margins was associated with increasing number of slides with DCIS on reexcision ($p < 0.01$; only in univariate analysis)</p>	<p>Multifocal positive margins are associated with the presence of and an increasing amount of residual DCIS in reexcision specimens; the more DCIS and near the margin, the greater the chance of increasing amounts of DCIS in the adjacent breast.</p>
multifocal positive	79% with DCIS at reexcision	
unifocal positive	33% with DCIS at reexcision	
close or positive	56% with DCIS at reexcision	
negative, close or unifocal positive	42% with DCIS at reexcision	
negative or close	45% with DCIS at reexcision	
negative	43% with DCIS at reexcision	

General comments The patients may also be included in parts in Goldstein et al. (1998; 2000)

Silverstein, MJ, Gierson ED, Colburn WJ, et al. (1994). Can intraductal breast carcinoma be excised completely by local excision? Clinical and pathological predictors. Cancer, 73(12), 2985-2989.

Design Case series **Evidence level** 3 **Country** USA

Population N=181 patients with DCIS and excisional biopsy and subsequent reexcision or mastectomy

Intervention biopsy designed to remove lesion with excision leaving a rim of normal appearing tissue, subsequently reexcision or mastectomy

Margin microscopically differentiated between clear and positive

Follow up study period 14 years

Results

Margin	Results	Author's conclusion
overall	Positive initial biopsy margins can predict whether residual DCIS can be found at reexcision or mastectomy (p<0.0001) Tumour size was a predictor for DCIS independently of margin status	Inadequate excision may be the most important cause of local failure.
positive	76% with residual DCIS	
clear	43% with residual DCIS	

General comments

Updated 2018

Wong JS, Kaelin CM, Troyan SL (2006). Prospective study of wide excision alone for ductal carcinoma in situ of the breast. Journal of Clinical Oncology, 24 (7), 1031-1036.

Design Case series **Evidence level** 3 **Country** USA

Population N=158 patients with grade 1 or 2 DCIS

Intervention wide excision with or without reexcision, (no chemotherapy or tamoxifen)

Margin histologic margin ≥ 1 cm or a totally negative reexcision, reexcision if initial margins < 1 cm or not assessable

Follow up study closed after 3 years of recruiting, 477 patient years

Results

Margin	Results	Author's conclusion
≥ 10 mm	Study was closed to accrual at 158 patients because the number of local recurrences exceeded 7 before a total combined follow-up time of 100 patient years 2.4% first site treatment failure per patient-year (5 year rate 12%); recurrence of DCIS: in 69% of patients, recurrence with invasive disease: 31%	Despite margins of at least 10mm, local recurrence rate is substantial when treated with excision alone, the use of radiation therapy and / or tamoxifen should be assessed.

General comments -

Macdonald HR, Silverstein MJ, Lee LA et al. (2006). Margin width as the sole determinant of local recurrence after breast conservation in patients with ductal carcinoma in situ of the breast. The American Journal of Surgery, 192, 420-422.

Design Case series (includes 2 distinct cohorts) **Evidence level** 3 **Country** USA

Population N=272 patients diagnosed with DCIS and treated with breast conservation and margins of ≥ 10 mm, (microinvasion excluded)

Intervention excision alone, excision plus radiation therapy (no tamoxifen or other hormone therapy)

Margin ≥ 10 mm, determined by direct measurement or ocular micrometry, patients without DCIS at reexcision were scored ≥ 10 mm

Follow up median: 53 months

Results

Margin	Results	Author's conclusion
≥ 10 mm	12/212 excision alone patients experienced any recurrence, [6%] 3 invasive recurrences 13.9% probability of any recurrence at 12yrs, 3.4% for invasive recurrence 1/60 excision plus radiation patients experienced an invasive recurrence; 2.5% probability at 12yrs	Local recurrence compares favourably in patients treated with excision alone with margins of 10mm or greater to patients with nontransected margins and treated with radiation; the risk of invasive recurrence is extremely low.

General comments most patients also included in Silverstein et al. (1999), some overlap with Macdonald et al. (2005) and / or Silverstein & Buchanan (2003) possible

Cabioglu N, Hunt KK, Sahin AA et al. (2007). Role for intraoperative margin assessment in patients undergoing breast conserving surgery. Annals of Surgical Oncology, 14(4), 1458-1471.

Design Case series **Evidence level** 3 **Country** USA

Population sample of N=64 women diagnosed with DCIS undergoing primary tumour excision included in population

Intervention wide local excision including complete primary tumour removal plus adjuvant external beam radiation therapy, some received doxorubicin, tamoxifen, reexcision mainly for positive or close margins, subsequent mastectomy, level I and II axillary lymph node dissection with or without sentinel lymph node biopsy

Margin intraoperative assessment of gross tissue inspection, specimen radiography with or without frozen section

Follow up median: 6.4 years, range: 0.6-9.4; 5 years

Results

Margin	Results	Author's conclusion
Overall	DCIS patients with negative margins had a better 5yr ipsilateral recurrence free survival rate than patients with persistent positive / close margins after completion of all surgical treatment (86% versus 98%, p=0.017)	Intraoperative assessment assisted in identifying positive / close margins and enabled intraoperative reexcision and resulted in excellent local control.

General comments table 3 not extracted as number of patients with particular margin width missing

3.2 What is the role of mastectomy in patients with localised Paget's disease of the nipple?

Short Summary

There is a small volume of literature relating to Paget's disease of the nipple, with evidence comprising of mostly small retrospective, non-comparative case series.

11 observational studies provide data on breast cancer recurrence in patients treated with mastectomy or breast conserving surgery for Paget's disease (Sutton *et al.* 1999; Bijker *et al.* 2001; Dixon *et al.* 1991; Duff *et al.* 1998; Howard *et al.* 1989; Nicolosai *et al.* 1996; Polgar *et al.* 2002; Zurrida *et al.* 1993 Estabrook *et al.* 1996; Marshal *et al.* 2003). These data appear to show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis.

In 3 out of 4 studies in which survival data were reported for both mastectomy and breast conserving surgery, post-mastectomy breast cancer-specific survival was superior (Dixon *et al.* 1991; Howard *et al.* 1989; Polgar *et al.* 2002; Sutton *et al.* 1999).

A single study statistically compared survival following mastectomy or breast conserving surgery and found no statistical difference in breast cancer-specific survival at 15 years following treatment (Chen *et al.* 2006).

Cosmesis was assessed in one study only (Marshall *et al.* 2003). The treating radiation oncologist assessed cosmesis in 31 patients. These were rated as: excellent, 10 (32%; 4 patients underwent nipple reconstruction); good, 18 (58%); fair, 3 (10%). No data was identified for quality of life, based on assessment with a specific instrument, as an outcome in patients treated for Paget's disease by mastectomy or breast conserving surgery.

PICO

Population	Intervention	Comparison	Outcome
Patients with localized Paget's disease of the nipple	<ul style="list-style-type: none"> • Wide Local Excision (WLE) • Mastectomy 	Versus each other	<ul style="list-style-type: none"> • Recurrence • Disease Free Survival • Overall survival • Cosmesis • Patient Acceptability • Quality of Life

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There appears to be a relatively small literature base on Paget's disease of the nipple and for this reason no arbitrary threshold criteria were applied in selecting studies for appraisal.

The studies were predominantly small retrospective, non-comparative case series of which 15 reported on fewer than 50 cases. There was considerable heterogeneity in the included studies in terms of population size, follow-up intervals, methods of reporting disease recurrence and patient survival. For these reasons the results should be interpreted cautiously.

Of the outcome measures specified for this topic, recurrence (local/regional and distant metastases) and/or survival (disease-specific and overall) were addressed by all studies. Minimal information was reported on cosmesis (1 study) or post-operative complications relevant to patient quality of life (1 study; protracted chest wall pain, chronic breast infection and radiation dermatitis). No data were reported on patient acceptability.

The data appears to show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis.

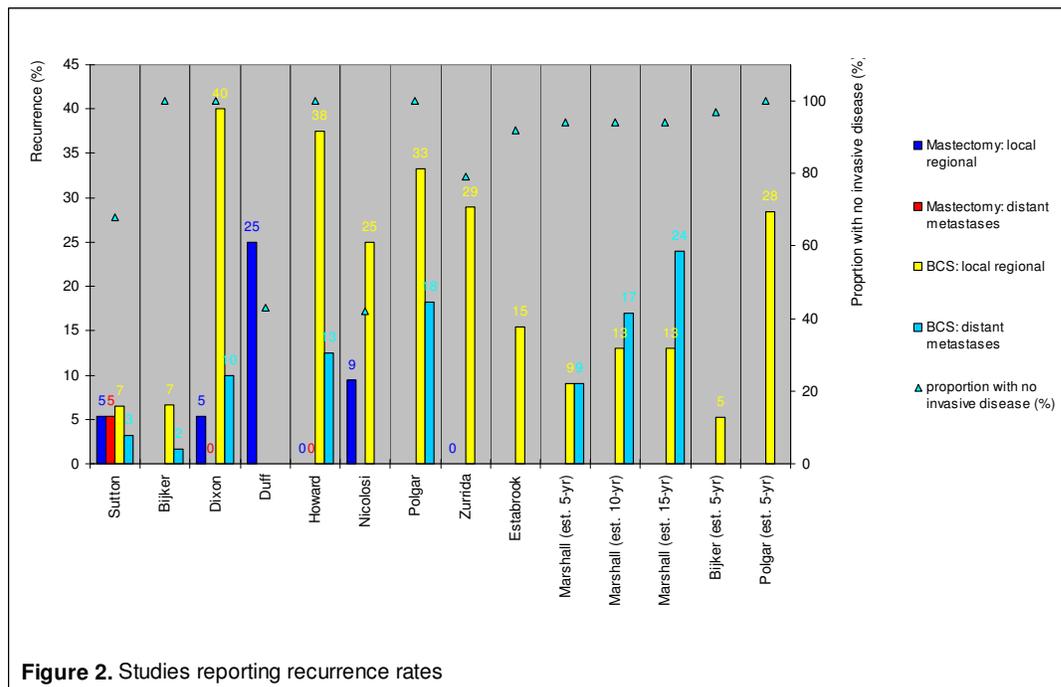
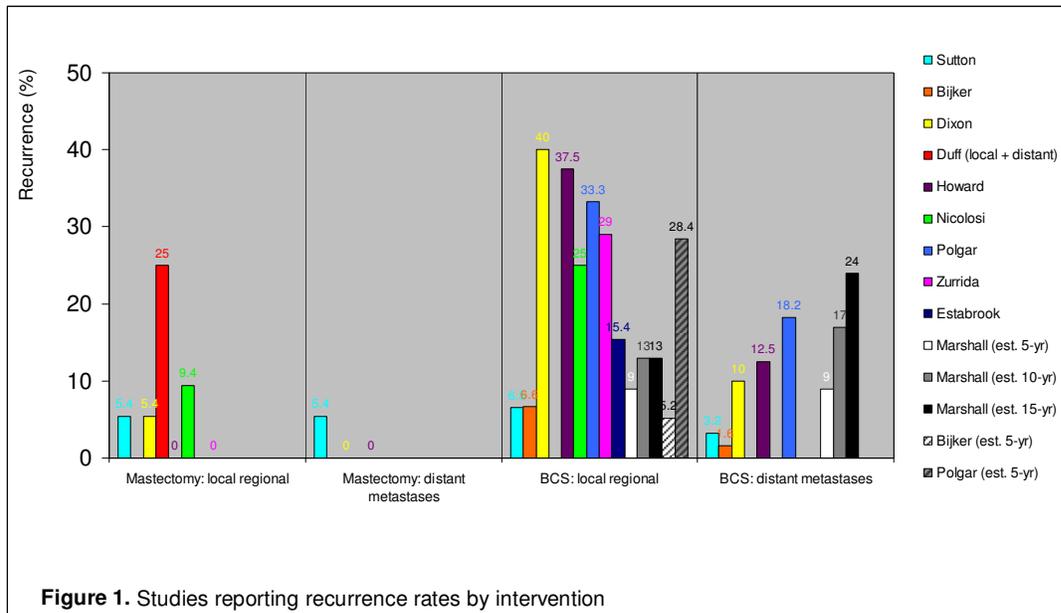
Data on crude rates of survival following mastectomy or breast conserving surgery in patients with Paget's disease comes from nine observational studies. In three of four studies that provided data on both procedures, survival was better in patients treated with mastectomy. However there is no other visible trend in the data and no conclusions on survival can be reliably made.

Disease-related events following surgical treatment for Paget's disease of the nipple

Disease recurrence

Eleven observational studies provide data on breast cancer recurrence in patients treated with mastectomy or breast conserving surgery for Paget's disease (Figure 1, Figure 2). These data appear to show higher rates of recurrence following breast conserving surgery compared to mastectomy, but no study provided a statistical analysis. Study size is small; 9 of the 11 observational studies comprised less than 50 cases. Therefore due to the poor quality of the data; no conclusions can be reliably drawn.

Eleven studies reported local and distant metastatic disease recurrence rates following surgery for Paget's disease of the nipple (Figure 1, Figure 2). All these studies reported recurrence rates following breast conserving surgery and six following mastectomy. In general the proportion of patients presenting with no evidence of underlying invasive breast cancer - therefore meeting the population criteria for this topic - was high (median = 92%, range, 42%-100%). The largest study in the series reported recurrence data comparing outcomes following mastectomy (n=74) and wide local excision (WLE, n=31) (Sutton *et al.* 1999). The data revealed similar but not statistically evaluated rates of local disease recurrence for mastectomy and WLE (5.4% vs. 6.5% respectively), but a higher distant metastatic disease recurrence rate following mastectomy (5.4% vs. 3.2%). Follow-up in this study was for 84 months and 60 months for mastectomy and WLE, respectively. In contrast, an earlier study (Dixon *et al.* 1991) reported local and distant disease recurrence rates markedly higher in patients who had undergone WLE (40%, 10%, respectively) compared with mastectomy (5.4%, 0%). However, although the follow-up interval for WLE was similar (56 months), follow-up for mastectomy was limited to 40 months, less than half the follow-up period reported by Sutton *et al.*



Disease recurrence in patients with Paget's disease of the nipple and no palpable underlying mass

One retrospective study analysed recurrence in the subgroup of patients with Paget's disease and no underlying palpable lump (Sutton 1999). In this study the crude rate of local recurrence was 1.9% following mastectomy and 6.9% following breast conserving surgery. Respective rates of distant recurrence were 5.7% and 3.4% respectively. With no statistical analysis and small numbers of patients, the data do not permit conclusions to be reliably drawn (Table 1).

Table 1. Post-operative breast cancer local and distant recurrence according to pre-existence/absence of a palpable mass

Study	Underlying palpability	Recurrence	Mastectomy				Breast conserving surgery			
			n ¹	d ²	Recurrence n÷d (%)	Follow-up ³ (months)	n ¹	d ²	Recurrence n÷d (%)	Follow-up ³ (months)
Sutton (1999)	Palpable lump	Local	3	21	14.3	84	0	2	0	60
	No palpable lump	Local	1	53	1.9	84	2	29	6.9	60
	Palpable lump	Distant	1	21	4.8	84	0	2	0	60
	No palpable lump	Distant	3	53	5.7	84	1	29	3.4	60

¹ number of patients with disease recurrence

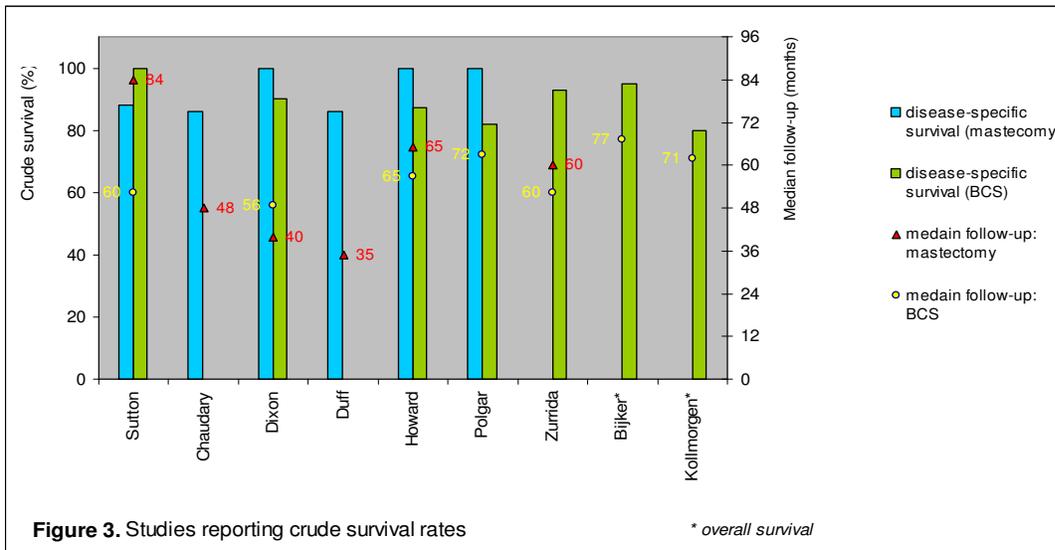
² number of patients followed-up

³ median follow-up

Patient survival - crude rates

Data on crude rates of survival following mastectomy or breast conserving surgery in patients with Paget's disease comes from nine observational studies (Figure 3). In three of four studies that provided data on both procedures, survival was better in patients treated with mastectomy. However there is no other visible trend in the data and no conclusions on survival can be reliably made.

Nine studies reported crude survival rates following either mastectomy or breast conserving surgery (BCS; Figure 3). Seven of these reported crude breast cancer-specific survival and 2 reported overall survival. The median follow-up period over which survivals were reported was 35-84 months for mastectomy and 56-77 months for BCS. In 3 out of 4 studies in which survival data were reported for both mastectomy and BCS, post-mastectomy breast cancer-specific survival was superior (figure 3) (Dixon et al. 1991; Howard et al. 1989; Polgar et al. 2002; Sutton et al. 1999). Sutton et al reported 100% (n = 29) patient survival at 84 months follow-up for patients with no pre-existing palpable mass who had received breast conserving surgery (Sutton et al. 1999). Likewise 100% survival was reported for patients who presented with a palpable mass although only 2 patients fell into this subgroup.

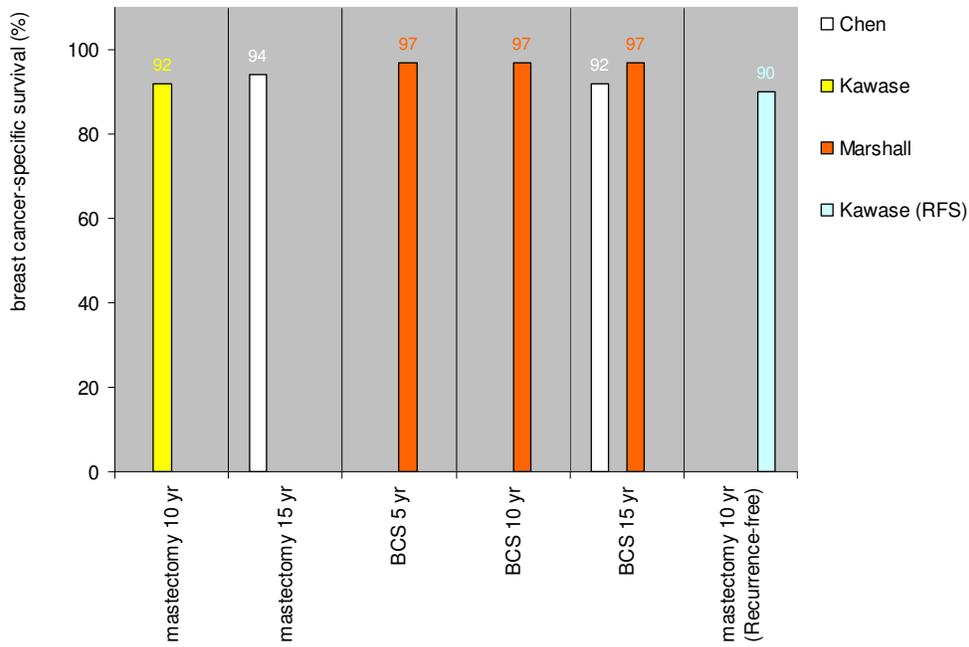


Patient survival - actuarial data

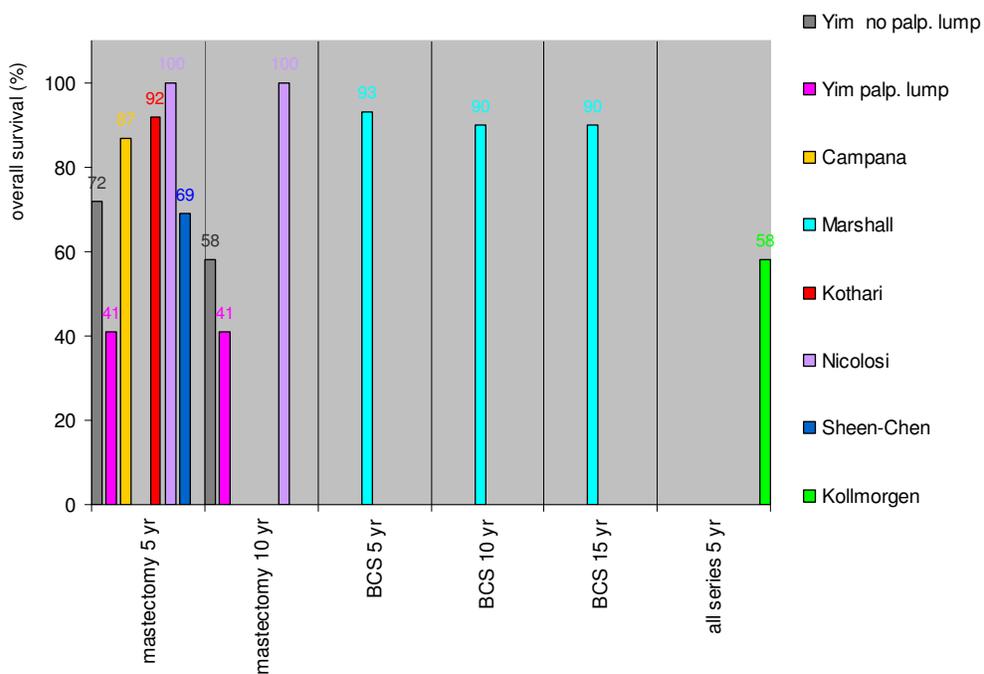
Nine observational studies provide estimated survival rates in patients with Paget's disease treated with mastectomy or breast conserving surgery based on time-to-event analyses (Figure 4). The only study that statistically compared survival following these procedures found no difference in breast cancer-specific survival at 15 years following treatment (Chen et al. 2006). The data from the remaining studies do not permit conclusions on the superiority of breast conserving surgery or mastectomy in terms of either breast cancer-specific survival or overall survival.

Nine studies reported actuarial (estimated) survival data for patients after mastectomy or breast conserving surgery. The results are presented for breast cancer-specific survival and for overall survival (Figure 4). The largest and most recently published study reported estimated breast-cancer specific survival rates for 350 mastectomies and 196 breast conserving surgery cases followed-up for 15 years (Chen *et al.* 2006). All patients were free of invasive disease at clinical presentation. Breast cancer-specific survival was not significantly different for the two treatment modalities (mastectomy, 94% [95% CI 88%-96%]; breast conserving surgery, 92% [95% CI 84%-96%], *P* not significant, log rank test). There is no visible pattern in the rate of breast cancer-specific survival following mastectomy compared to breast conserving surgery in the remaining studies reporting this outcome (Figure 4, a).

No study provided an analysis of overall survival, comparing mastectomy with breast conserving surgery, and the data are inadequate to indicate any difference in rates of survival arising from mastectomy or breast conserving surgery at respective follow-up periods (5-year, 10-year etc; Figure 4, b).



(a) Breast cancer-specific survival (BSS) and Recurrence-free survival



(b) Overall survival

Figure 4: Studies reporting estimated (actuarial) survival rates grouped by intervention

Cosmesis and patient quality of life

Cosmesis

Very few data were identified for cosmesis as an outcome measure. One small, retrospective case series study found that in 31 patients treated with predominantly complete excision of the nipple-areolar complex, cosmetic outcomes were assessed by the treating radiation oncologist as 'excellent' or 'good' in 90% of the series (Marshall *et al.* 2003).

Cosmesis was assessed in one study only (Marshall *et al.* 2003). The treating radiation oncologist assessed cosmesis in 31 patients. These were rated as: Excellent, 10 (32%; 4 patients underwent nipple reconstruction); Good, 18 (58%); Fair, 3 (10%).

Quality of life

No data was identified for quality of life, based on assessment with a specific instrument, as an outcome in patients treated for Paget's disease by mastectomy or breast conserving surgery.

No study evaluated quality of life using a specific assessment instrument. However post-operative complications relevant to patient quality of life were reported for 3 patients including protracted chest wall pain, chronic breast infection and radiation dermatitis (Marshall *et al.* 2003). Complications were assessed in 32 patients, of whom 29 (91%) had no long-term complications. Post-operative complications relevant to patient quality of life were reported for 3 patients including protracted chest wall pain, chronic breast infection and radiation dermatitis (Marshall *et al.* 2003).

Further Details

A retrospective case series study compared survival rates between women with Paget's disease of the breast treated by mastectomy or breast conserving surgery (BCS) (Chen *et al.* 2006). From 1704 patients with Paget's disease 546 included for study had no evidence of underlying invasive cancer and had undergone surgery. Of these 350 (64%) received mastectomy and 196 (36%) received BCS of varying types including partial mastectomy, lumpectomy, quadrantectomy, wedge resection, nipple resection and excisional biopsy. Estimated 15-year breast cancer-specific survival (Kaplan-Meier method) for mastectomy was 94% (95% CI 88%-96%) and 92% (95% CI 84%-96%) for BCS. Estimated 15-year breast cancer-specific survival by disease status was 94% (95% CI 89-97) for Paget's disease with DCIS and 88% (95% CI 77%-94%) for Paget's disease alone.

A retrospective case series study compared crude rates of local/regional disease recurrence, distant metastases, and disease specific deaths in 105 patients with histologically confirmed Paget's disease of the nipple treated either by mastectomy (n=74) or breast conserving surgery (BCS) (n=31) (Sutton *et al.* 1999). Patients were identified from a larger cohort treated within the years 1975-1997. Of these, 71/105 (68%) had no evidence of underlying invasive disease distributed between the 2 treatment intervention groups; 47/74 (64%) of mastectomy and 24/31 (77%) of BCS patients. Breast conserving surgery comprised wide local excision plus a wedge of underlying breast tissue. 14/31 BCS patients received post-operative radiotherapy (RT). Median follow-up was 7 years (mastectomy group) or 5 years (BCS group). Crude local and distant recurrence rates, and breast cancer-specific death rate following mastectomy were 5.4%, 5.4% and 12.2%, respectively and 6.5%, 3.2% and 0%, respectively following BCS. Recurrence and death rates were further stratified by presence or absence of palpable tumour at presentation (28% of mastectomy patients and 2% of BCS patients). Local or distant recurrence, and disease-specific death rates respectively were: (i) for mastectomy patients with no palpable mass; 1.9%, 5.7% and 9.4%, respectively; (ii) for BCS patients with no palpable

mass; 6.9%, 3.4% and 0%; (iii) for mastectomy patients with a palpable mass; 14.3%, 4.8% and 19%; and (iv) for BCS patients with a palpable mass; 0% throughout. Data presented were based on small subgroups and no statistical testing of the data was reported.

A prospective case series study assessed the feasibility of combined breast conserving surgery and radio-therapy for Paget's disease in 61 patients who had no associated invasive breast cancer (Bijker *et al.* 2001). All patients underwent cone excision of the nipple-areolar complex and subareolar breast tissue followed by 50 Gy X-rays in 25 fractions (no boost). Patients were followed-up for local recurrence (Kaplan-Meier method), distant disease recurrence, and breast cancer-specific deaths (median follow-up 6.4 years). At 5 years the estimated local recurrence rate was 5.2% (95% CI 1.8%-14.1%). Crude local and distant recurrence rates and disease-specific death rate were; 6.6%, 1.6% and 1.6%, respectively. The study group was carefully selected in terms of their suitability for breast conserving surgery, the majority of patients having no evidence of DCIS on preoperative mammography.

A prospective case series study reported comparative data on disease-specific and recurrence-free survival in 104 patients with Paget's disease of the nipple treated either by mastectomy (88%) or breast conserving surgery (BCS) (12%) within the years 1949-1993 (Kawase *et al.* 2005). 40% of patients had no invasive breast cancer of whom 15% had Paget's disease alone and 85% with associated DCIS). All patients treated by BCS and 20% of mastectomy patients received radiotherapy post-operatively. Kaplan-Meier estimated 10-year disease-specific survival and recurrence-free survival rates in patients with stage 0 (non-invasive disease) were 92% (95% CI 80%-100%) and 90% (95% CI 78%-100%), respectively. For the entire series disease-specific survival was 79% (95% CI 70%-88%) following mastectomy and 67% (95% CI 13%-100%) following breast conserving surgery ($P=0.697$, log rank test). Recurrence-free survival was 75% (95% CI 66%-84%) (mastectomy) and 61% (95% CI 10%-100%) (BCS) ($P=0.953$, log rank test).

A retrospective series of 37 cases of Paget's disease of the nipple treated by mastectomy (97%) or quadrantectomy (3%) reported survival rates over 150 months for patients with or without an associated palpable mass (Yim *et al.* 1997). 46% of patients presented with no associated palpable mass. Kaplan-Meier estimated overall survival rates at 5 years by presence/absence of a palpable mass were 41% (present) and 72% (absent). 10-year survival rates were 41% (present) and 58% (absent). There was a significant difference in overall survival between patients with or without a palpable mass on presentation ($P<0.05$, F test).

A retrospective case series reported survival data for 31 patients with Paget's disease of the nipple without an associated palpable mammary tumour who were treated by mastectomy between 1960 and 1984 (Campana *et al.* 1987). Estimated 5-year overall survival (Kaplan-Meier method) was 87% (median follow-up 7.5 years). 22 of the 31 patients (71%) in this series were confirmed as having no invasive disease on presentation.

A retrospective case series reviewed pathology and post-operative disease-related events for 35 women with biopsy-proven Paget's disease of the nipple treated between 1974 and 1984 (Chaudary *et al.* 1986). Of the 35 patients, 14 (41%) had Paget's disease with DCIS but no invasive disease. 32/35 (91%) of patients were treated by mastectomy, 2 by radiotherapy alone and 1 received no treatment. The crude survival rate (mean follow-up

48 months) for the series was 83% (29/35) and 86% (12/14) for patients with Paget's disease and associated DCIS.

A retrospective case series compared post-operative recurrence and survival for 48 patients with Paget's disease of the nipple who had no underlying palpable tumour and treated with either mastectomy or breast conserving surgery (Dixon *et al.* 1991). 39 patients (81%) who received surgery had no invasive component to their disease. 37 (77%) patients underwent mastectomy while 10 (21%) received breast-conserving wide local excision of the nipple-areolar complex including cone excision of underlying breast tissue. Patients were followed-up for a median 40 months post-mastectomy, or 56 months post-breast conserving surgery (BCS). Crude local/regional recurrence rates were 5.4% following mastectomy and 40% after BCS. Crude distant metastasis rates for the two groups were 0% and 10%, respectively and crude death rates were 0% and 10%, respectively.

A retrospective series of 28 histologically confirmed cases of Paget's disease of the nipple compared crude rates of recurrence and breast cancer-specific survival after mastectomy or breast conserving surgery (Duff *et al.* 1998). Patients were treated between 1983 and 1996 and followed-up over a mean period of 35 months. 12 (43%) patients had no associated invasive cancer and 12 (43%) patients had an associated palpable mass. 25 (89%) patients elected to undergo mastectomy, 1 received breast conserving surgery and 2 had no surgery. The crude recurrence rate was 25% for all patients, 50% for those with a palpable mass, and 6% with no palpable mass. The crude survival rate was 86% (all patients), 67% (palpable mass), and 100% (no palpable mass).

A small retrospective series of 13 cases of Paget's disease of the Breast, treated between 1990 and 1995, reported crude local recurrence data following surgical treatment (Estabrook *et al.* 1996). No patients had associated palpable masses or lymphadenopathy although 1 patient was recorded as having an associated invasive ductal breast carcinoma. Thus 12/13 (92%) of cases met the population criteria for this topic. All patients received breast conserving surgery (local excision) with 5 (38%) receiving post-operative radiotherapy. Crude local recurrence at a mean follow-up of 17.8 months was 2/13 (15.4 %); both being reported as ipsilateral recurrences.

A small retrospective case series reported crude 5-year and 10-year overall survival rates for patients with histologically proven Paget's disease of the breast treated during the period 1949 to 1972 (Freund *et al.* 1977). Of 29 patients 19 (66%) had no associated palpable lump and thus met the population criteria for this topic. 3/29 patients were reported to have no nipple abnormalities but had a breast tumour. 25/29 patients elected for mastectomy (21 radical Halstead's procedure, 4 simple mastectomy), and 4 received only radiotherapy due to the advanced stage of their cancer. 27 patients were available for follow-up. Overall survival at 5 years for the full cohort was 74%, falling to 69% at 10 years. When stratified by the presence/absence of a palpable mass there was a statistically significant improvement in survival for patients with no associated palpable mass at presentation; 40% (present) vs. 94% (absent) at 5 years; and 33% (present) vs. 91% (absent) at 10 years ($P < 0.001$, Fisher exact test).

A retrospective case series studying 17 patients with Paget's disease of the nipple (identified from a cohort of 78 patients with *in situ* breast carcinoma) treated between 1973 and 1985 reported post-operative recurrence and survival data over a mean follow-up period of 65 months (Howard *et al.* 1989). Nine patients (53%) elected to have simple mastectomy the remaining 8 having breast-conserving cone excision surgery. Crude rates

of local recurrence for the two treatment groups were 0% (mastectomy) and 37.5% (cone excision); Crude rates of distant metastases were 0% and 12.5%, respectively; and crude disease-specific survival rates were 100% and 12.5% respectively. No data on tumour palpability or invasive disease was provided.

A retrospective case series of 68 patients with Paget's disease of the nipple treated between 1963 and 1996 reported comparative data on survival rates for patients who elected for mastectomy or breast conserving surgery (lumpectomy or nipple excision/biopsy) (Kollmorgen *et al.* 1998). 25 patients (45%) had no associated invasive cancer on presentation. 58 patients underwent mastectomy and 10 had BCS and were followed-up for a median 61 months. The 5-year estimated survival rates (Kaplan-Meier method) were; 58% (entire series, n = 68), 35% (patients with a palpable mass at diagnosis, n = 30), and 75% (patient with no palpable mass, n = 38). Median survival for patients with palpable tumours was statistically significantly shorter than for those without (126 months; $P=0.007$, log rank test). Data was not reported for survival specific to histological evidence of invasive disease at diagnosis.

A retrospective study of 70 cases of histologically confirmed Paget's disease of the nipple treated between the years 1971 and 1999 reported survival data for patients who elected for treatment by mastectomy (Kothari *et al.* 2002). 23 patients (33%) presented with clinically apparent invasive disease and 15 (21%) presented with focal nodularity. 30 patients (43%) were reported as having no invasive disease, 29 of these having Paget's disease with associated DCIS. 2 patients were unfit for mastectomy and were therefore treated by local excision surgery. Estimated overall survival at 5 years (Kaplan-Meier method) for patients with DCIS (n = 29) was 92%. Although the number of patients with Paget's disease and DCIS who underwent mastectomy was not reported, that only 2/70 had conservative surgery indicates that between 93-100% would have received mastectomy.

A retrospective case series reported long-term follow-up of patients with Paget's disease of the breast without a palpable or mammographically identified mass and treated with combined breast conserving surgery and radiotherapy between 1980 and 2000 (Marshall *et al.* 2003). Of 36 patients with histologically proven Paget's disease 2 were classified as having associated invasive or microinvasive breast cancer, and therefore 34 (94%) met the population criteria for this topic. All patients received breast conserving surgery, either: complete excision of the nipple areolar complex (25/36); partial excision (9/36); or biopsy alone (2/36). All patients received post-operative radiotherapy of 50 Gy and boost radiation to the tumour bed in the majority of cases. Actuarial 5, 10 and 15 year local recurrence rates were reported in two ways; (i) as only site of first recurrence: 5 years = 9% [95% CI 0%-20%]; 10 years = 13% [95% CI 1%-25%]; 15 years = 13% [95% CI 1%-25%]; and (ii) as a component of all recurrences (i.e. includes regional and distant metastasis): 5 years = 9% [95% CI 0%-20%]; 10 years = 17% [95% CI 3%-31%]; 15 years = 24% [95% CI 6%-42%]. Disease-free survival at a median follow-up of 9 years was 89 (32/36 patients). This included patients with successfully treated recurrences. 2/4 patient deaths were not breast cancer-specific. Actuarial disease-specific and overall survival data were reported at 5, 10 and 15 years: (i) cause-specific survival (scores only breast cancer deaths as events): 5 years = 97% [95% CI 90%-100%]; 10 years = 97% [95% CI 90%-100%]; 15 years = 97% [95% CI 90%-100%]; and (ii) overall survival: 5 years = 93% [95% CI 84%-100%]; 10 years = 90% [95% CI 78%-100%]; 15 years = 90% [95% CI 78%-100%]. Cosmesis was assessed in 31 patients by the treating radiation oncologist: Excellent = 10 (32%; 4 patients underwent nipple reconstruction); Good = 18 (58%); Fair = 3 (10%). Complications were assessed in 32 patients, of whom 29 (91%) had no long-

term complications. Post-operative complications relevant to patient quality of life were reported for 3 patients including protracted chest wall pain, chronic breast infection and radiation dermatitis.

A retrospective case series study reported local recurrence rates and overall survival rates for patients with Paget's disease of the breast treated between 1973 and 1994 (Nicolosi *et al.* 1996). Of 38 patients included in the study, 16 (42%) had no histological evidence of invasive breast cancer and therefore met the population criteria for this topic. The majority of patients (32/38, 84%) underwent mastectomy, 4 (11%) elected for breast conserving surgery, and 2 (5%) received primary radiotherapy alone. Median follow-up was not reported but 5-year and 10-year actuarial overall survival of 100% was reported for patients with no invasive disease on presentation. Crude rates of local recurrence for the whole series were 9.4% (3/32) following mastectomy, and 25% (1/4) following breast conserving surgery.

A retrospective case series study of patients with Paget's disease of the nipple with no invasive disease and treated during the period 1980-1996 investigated the rate of local recurrence following cone excision breast conserving surgery (Polgar *et al.* 2002). Of 33 patients 30 (91%) had no palpable mass and in 30 evidence of limited DCIS was reported. No patients had invasive disease. All patients underwent breast conserving surgery (cone excision alone). Patient follow-up was for a median 6 years. The crude local recurrence rate was 33.3% (11/33) with 10/11 recurrences manifesting as invasive disease. This was compared with data from Bijker (Bijker *et al.* 2001) who reported a crude local recurrence rate of 6.6% ($P=0.0012$, Fisher exact test). Again comparing their data with that of Bijker *et al.*, The 5-year estimated local recurrence rates were 28.4% (this study) vs. 5.2% (Bijker). For distant recurrence the rates were 18.2% (this study) vs. 1.6% (Bijker) ($P=0.007$). Actuarial cancer-specific deaths were 18.2% (this study) vs. 1.6% (Bijker) ($P=0.007$).

A retrospective case series study of 31 patients for Paget's disease of the breast treated between 1986 and 1997 reported survival rates following mastectomy (Sheen-Chen *et al.* 2001). Fifteen patients (48%) had histological evidence of invasive disease, the remainder having either Paget's disease alone (4 = 13%) or co-presenting with DCIS (12 = 39%). Therefore 16/31 (52%) of patients met the population criteria for this topic. No palpable underlying tumour was found in 19 (61%) of patients. Each patient underwent mastectomy and was followed-up for a mean duration of 58 month. Estimated 5-year overall survival rates (Kaplan-Meier method) were: (i) 69% for all patients; and (ii) by tumour palpability: 19% (present) vs. 94% (absent) ($P<0.01$, log rank test). Patients with no palpable underlying tumours had significantly higher incidences of underlying non-invasive breast cancer than those with underlying palpable masses (73% vs. 8%, $P<0.01$, Chi square test).

A retrospective case series study of 35 patients with Paget's disease of the breast, identified from a larger cohort of 2261 breast cancer patients surgically-treated between 1989 and 1995 reported data on crude local and distant recurrence and survival rates following either radical mastectomy or breast conserving surgery (Stanislawek *et al.* 2002). Of 35 patients 28 (80%) had underlying intraductal breast cancer not classified as invasive, the remaining 8 patients (20%) having an underlying invasive cancer. Twenty nine patients (83%) elected for radical mastectomy and 6 (17%) had breast conserving surgery (type(s) not specified). Follow-up intervals were not reported for local recurrence, however, crude local recurrence rates by clinical presentation were reported: 1/28 (3.6%) for patients with no preoperative invasive disease, and 4/7 (57%) for patients with

infiltrating disease. Similarly, lymph node metastatic recurrence was reported: 0/29 (no invasive disease) and 4/7 (57%) (with invasive disease). No recurrence data were reported by intervention type. Crude 5-year survival rates by clinical presentation were reported but not defined as either disease-free, disease-specific or overall. Survival for patients with no preoperative invasive disease was 90%, and for patients with infiltrating disease survival was 49%.

A retrospective case series study of patients with Paget's disease of the breast treated between 1975 and 1989 reported follow-up recurrence and death rate data following either mastectomy or breast-conserving wide local excision surgery (Zurrida *et al.* 1993). Ten patients were reported as having involved focal areas of underlying nipple ducts but whether these were invasive disease was not specified. The remaining 39 (76%) patients had no associated invasive breast cancer. Pre-operative biopsy was used to confirm the presence of Paget's disease in 27/27 instances. Mastectomy was performed on 18/49 (37%) patients and wide local excision on 31 (63%), two of whom received post-operative radiotherapy. Patients were followed-up for a median 60 months. Crude rates of locally invasive cancer were 0/18 following mastectomy and 9/31 (29%) following wide local excision, one of the latter recurring in a patient who had received post-operative RT. Crude rates of death due to breast cancer were 0/18 following mastectomy and 2/31 (6.5%) following wide local excision.

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Evidence Tables

Retrospective comparative study

Chen, Sun & Anderson . Paget disease of the breast: Changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer* 107[7], 1448-1458. 2006.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

1704 women with Paget's disease of the nipple registered on the US Surveillance, Epidemiology and End Results (SEER) database in the period January 1988 - December 2002.

Distribution of histology:

Paget's disease + invasive ductal: 859 (50.4%)

Paget's disease + DCIS: 618 (36.3%)

Paget's disease alone: 227 (13.3%)

Exclusion criteria

Men with Paget's disease;

Patients with a history of any type of previous cancer;

Cases of Paget's disease of the nipple with underlying tumour other than ductal carcinoma (e.g. lobular carcinoma) since these cases were registered according to the underlying tumour and were not recorded as Paget's;

Cases of Paget's disease alone or Paget's disease with DCIS presenting with positive lymph nodes i.e. biologically questionable (n=34).

Population

number of patients = 845, median age = 64 years.

Interventions

Aim: to compare retrospectively survival between women with Paget's disease treated by mastectomy compared to women with Paget's disease treated by breast conserving surgery.

Of 845 patients with Paget's disease and no underlying invasive disease 546 (64.6%) were recorded as undergoing surgery:

Mastectomy: 350 (64%)

Breast conserving surgery: 196 (36%)

Outcomes

15-year breast cancer-specific survival (Kaplan-Meier method)

Follow up

Median not reported; study reports 15-year breast cancer-specific survival.

Results

Estimated 15-year breast cancer-specific survival:
Paget's disease + DCIS: 94% [95% CI 89%-97%]
Paget's disease alone: 88% [95% CI 77%-94%]

Estimated 15-year breast cancer-specific survival in patients with Paget's disease and no underlying invasive cancer by surgery performed:
Mastectomy: 94% [95% CI 88%-96%]
Breast conserving surgery: 92% [95% CI 84%-96%]
(p value not significant; log rank test)

General comments

A total of 845 patients represent the population of this question (for survival data), of whom 546 were recorded as undergoing surgery (for comparison of mastectomy versus breast conserving surgery).

'Breast conserving surgery' refers to a wide variety of procedures and includes nipple excisional biopsy: partial (less than total) mastectomy (including segmental mastectomy, lumpectomy, quadrantectomy, tylectomy, wedge resection, nipple resection, excisional biopsy and partial mastectomy).

Sutton, Singh, Baker & Sacks . Is mastectomy overtreatment for Paget's disease of the nipple? Breast 8[4], 191-194. 1999.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

105 patients with histologically proven Paget's disease of the nipple, identified from a larger series treated within the years 1975-1997 (see exclusion criteria).

No. patients with a history of previous breast cancer:

Mastectomy group: 5 (6.8%)

Breast conserving surgery group: 3 (9.7%)

Presence of palpable lump:

Mastectomy group: 21 (28%)

Breast conserving surgery group: 2 (6.5%)

Presence of mammographic abnormality:

Mastectomy group: 40 (54%)

Breast conserving surgery group: 11 (36%)

Underlying pathology:

Mastectomy group:

DCIS: 46 (62%)

Invasive carcinoma: 27 (36%)

No histological abnormality: 1 (1%)

Wide local excision group:

DCIS: 22 (71%)

Invasive carcinoma: 7 (23%)

No histological abnormality: 2 (6%)

Therefore in this series, 71/105 = 68% of all patients had no histological evidence of underlying invasive disease.

Exclusion criteria

Men: 5

No surgical treatment: 6

Metastatic disease at presentation: 10

Medical records untraceable: 14

Occurrence of Paget's after previous mastectomy: 6

Total: 41

Population

number of patients = 105, age range 24 to 94 years, median age = 57 years.

Interventions

Two groups were defined retrospectively according to surgical treatment:

Mastectomy group (n=74).

Breast conserving surgery group (n=31): underwent wide local excision plus excision of a wedge of underlying breast tissue. 14 patients in this group underwent RT in addition.

Outcomes

Crude rates of:

Breast recurrence;

Distant metastasis;

Breast cancer-related deaths [presented by subgroup according to tumour palpability]

Follow up

Mastectomy group: median 7 years (4 patients lost to follow-up)

Breast conserving surgery group: median 5 years (range 6 months-10 years)

Results

Incomplete excision:

In the breast conserving surgery group, 4/31 = 13% of tumours were incompletely excised on histological analysis, and were treated with RT.

Results for entire series (n=105)

1. Rate of breast recurrence

Mastectomy group: 4/74 = 5.4%

Breast conserving surgery group: 2/31 = 6.5%

2. Rate of distant metastasis

Mastectomy group: 4/74 = 5.4%

Breast conserving surgery group: 1/31 = 3.2%

3. Rate of breast cancer related deaths

Mastectomy group: 9/74 = 12.2 %

Breast conserving surgery group: 0/31 = 0%

Results for patients without a palpable tumour at presentation:

1. Rate of breast recurrence

Mastectomy group (median follow-up 7 years): 1/53 = 1.9%

Breast conserving surgery group (median follow-up 5 years): 2/29 = 6.9%

2. Rate of distant metastasis

Mastectomy group: 3/53 = 5.7%

Breast conserving surgery group: 1/29 = 3.4%

3. Rate of breast cancer related deaths

Mastectomy group: 5/53 = 9.4%

Breast conserving surgery group: 0/29 = 0%

Results for patients with a palpable tumour at presentation:

1. Rate of breast recurrence

Mastectomy group (median follow-up 5 years): 3/21 = 14.3%

Breast conserving surgery group (median follow-up 5 years): 0/2 = 0%

2. Rate of distant metastasis

Mastectomy group: 1/21 = 4.8%

Breast conserving surgery group: $0/2 = 0\%$

3. Rate of breast cancer related deaths

Mastectomy group: $4/21 = 19.0\%$

Breast conserving surgery group: $0/2 = 0\%$

General comments

All cases of Paget's disease were confirmed histologically by incision biopsy or scrape cytology of the nipple.

$71/105 = 68\%$ of all patients in this series represent the population specified for this question; 32% had invasive underlying disease revealed by definitive histology.

Crude rates of disease-related events reported are based on small subgroups. No evidence of statistical testing of differences between groups is provided.

Choice to perform mastectomy or breast conserving surgery (plus or minus RT) was not part of the study design and is likely to have depended heavily on prognostic information; a greater proportion of patients treated with mastectomy had palpable tumours and mammographic abnormalities than those treated by breast conserving surgery.

Prospective case series

Bijker, Rutgers, Duchateau, Peterse, Julien, Cataliotti & EORTC Breast Cancer Cooperative Group. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer* 91[3], 472-477. 2001.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: Europe, setting: Secondary care

Inclusion criteria

61 Women with histologically proven Paget's disease of the nipple and no invasive breast cancer:

Palpable mass present : 2 (3%)

Palpable mass absent: 59 (97%)

Histology:

Paget's without DCIS: 4 (7%)

Paget's with DCIS: 57 (93%)

Exclusion criteria

Evidence of invasive breast cancer;

DCIS extending >5cm from the nipple;

Involved margin following surgery;

Age > 75 years;

Pregnancy;

Previous or concomitant malignancy (except treated basal cell carcinoma of the skin or carcinoma in situ of the cervix);

Mental illness or other condition precluding long-term follow-up.

Population

number of patients = 61, age range 31 to 74 years, median age = 58 years.

Interventions

Aim: to assess the feasibility of breast conserving surgery plus RT in patients with Paget's disease of the nipple without associated invasive breast cancer.

All patients underwent:

Surgery: cone excision of the skin with the nipple-areolar complex and subareolar breast tissue (no axillary surgery).

RT: 50Gy to the whole breast in 25 fractions (no boost).

Outcomes

Time to local recurrence (Kaplan-Meier method);

Distant metastasis;

Death due to breast cancer.

Follow up

Median follow-up period: 6.4 years.

Protocol: clinical examination at 1 month, 3 months postoperatively, then 3 monthly for 3 years, 6 monthly until the 10th postoperative year, and annually thereafter.

Patients also received bilateral mammography 6 weeks postoperatively and annually thereafter.

Results

4 of 61 patients developed local recurrence (1 case of recurrent DCIS and 3 cases of recurrent invasive disease).

1 patient developed distant metastasis and died.

2 patients died of other causes than breast cancer.

At 5 years follow-up the estimated local recurrence rate (Kaplan-Meier) was 5.2% [95% CI 1.8%-14.1%].

General comments

Study group is carefully selected to be suitable for breast conserving surgery: extent of DCIS is limited and the majority of patients had no evidence of DCIS on preoperative bilateral mammography.

Surgical specimens were reviewed histologically for exclusion criteria based on tumour size and margin.

Median interval from nipple biopsy to surgery: 22 days (range 0-212 days).

Median interval from surgery to RT: 41 days (range 17-140 days).

Kawase, Dimaio, Tucker, Buchholz, Ross, Feig, Kuerer, Meric-Bernstam, Babiera, Ames, Singletary & Hunt . Paget's disease of the breast: there is a role for breast-conserving therapy. *Ann Surg Oncol* 12[5], 391-397. 2005.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

104 patients treated with surgery for Paget's disease of the nipple between the years 1949 and 1993.

Distribution of histology:

Invasive ductal:	43 (41%)
DCIS:	34 (33%)
Unspecified adenocarcinoma:	19 (18%)
Invasive lobular:	1 (1%)
Paget's alone:	7 (7%)

Distribution of stage:

Stage 0:	41 (39%)
Stage I:	23 (22%)
Stage II:	40 (38%).

Presence/absence of palpable mass:

Present:	36 (35%)
Absent:	68 (65%)

Diagnostic mammography was performed in 81 patients; results:

Normal mammography:	21 (26%)
Abnormality on mammography:	60 (74%)

Exclusion criteria

Patients with involvement of the nipple as part of locally advanced (Stage III) breast cancer (n=9)

Population

number of patients = 104, age range 24 to 90 years, median age = 57 years.

Interventions

Aim: to analyse survival and prognostic factors in patients with Paget's disease of the nipple.

Patients underwent surgery as follows:

Mastectomy:	92 (88.5%)
Breast conserving surgery):	12 (11.5%) (minimally, complete excision of the nipple-areolar complex)

30 patients received RT, including all patients treated primarily with breast

conserving surgery.

Outcomes

Estimated 10-year disease-specific and recurrence-free survival (Kaplan-Meier method).

Follow up

Median 7 years (range 10 months to 29 years).

Results

Estimated 10-year disease-specific survival in patients with stage 0 (non-invasive) disease: 92% [95% CI 80%-100%]

Estimated 10-year recurrence-free survival in patients with stage 0 (non-invasive) disease: 90% [95% CI 78%-100%]

For the whole series of patients (including the 61% with underlying invasive disease), 10-year disease-specific survival by type of surgery performed was as follows:

Mastectomy: 79% [95% CI 70%-88%]
Breast conserving surgery: 67% [95% CI 13%-100%]
p=0.697, Log rank test.

For the whole series of patients (including the 61% with underlying invasive disease), 10-year recurrence-free survival by type of surgery performed was as follows:

Mastectomy: 75% [95% CI 66%-84%]
Breast conserving surgery: 61% [95% CI 10%-100%]
p=0.953, Log rank test.

General comments

Discounting the cases of 'unspecified adenocarcinoma', 41 patients represent the population specified for this question (39% of the series). From data in the paper, these 41 patients appear to be those referred to in survival analyses as 'stage 0'.

Segmental mastectomy classed as breast conserving surgery.

Compared to mastectomy, fewer patients underwent breast conserving surgery; study may be underpowered to detect differences in survival arising from surgical procedure.

Retrospective case series

Yim, Wick, Philpott, Norton & Doherty . Underlying pathology in mammary Paget's disease. Ann Surg Oncol 4[4], 287-292. 1997.

Design

Design: Retrospective case series (therapy), evidence level:
Country: USA, setting: Secondary care

Inclusion criteria

37 patients with histologically proven Paget's disease of the nipple treated within the years 1979-1995.

Presence/absence of invasive tumour by definitive histology:

Present: 20 (54%)
Absent: 17 (46%)

Presence/absence of palpable mass:

Present: 20 (54%)
Absent: 17 (46%)

Exclusion criteria

1 patient who underwent local resection of the nipple, with no assessment of underlying histology.

Population

number of patients = 37, age range 28 to 88 years, median age = 63 years.

Interventions

Aim: to report on pathology and survival in patients treated for Paget's disease of the nipple.

Patients underwent surgery as follows:

Mastectomy: 36 (97%)
Quadrantectomy: 1 (3%)

Outcomes

Estimated overall survival (Kaplan-Meier method) by subgroup according to presence/absence of a palpable tumour.

Follow up

No median or mean reported. Range (from Kaplan-Meier curves) 0-150 months.

Results

Estimated 5-year overall survival by presence/absence of a palpable tumour:

Present: 41%
Absent: 72%

Estimated 10-year overall survival by presence/absence of a palpable tumour:

Present: 41%
Absent: 58%

Over a follow-up period of 150 months, patients with no palpable tumour had statistically significantly better overall survival than patients with a palpable tumour ($p < 0.05$, F test).

General comments

46% of patients in this series represent the population of patients specified for this question.

Campana, Vielh, Fourquet, Schlienger, Jullien, Durand, Salmon & Vilcoq . [Paget's disease of the nipple without any associated mammary tumor clinically or radiologically detectable. Apropos of 51 cases treated at the Curie Institute]. [French]. J Gynecol Obstet Biol.Reprod.(Paris) 16[8], 1069-1073. 1987.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: , setting: Secondary care

Inclusion criteria

31 patients with Paget's disease of the nipple and no palpable or mammographic mass, treated with mastectomy between 1960 and 1984.

Histology:

Paget's disease alone:	1 (3%)
Paget's + DCIS:	21 (68%)
Paget's + DCIS + microinvasion:	9 (29%)

Exclusion criteria

Study presents data for 20 further patients (total series size 51) treated with RT alone (17 cases) or breast conserving surgery plus RT (3 cases): not cited here.

Population

number of patients = 31, age range 40 to 90 years, median age = 58 years.

Interventions

Aim: to report on treatment and survival for 51 patients with Paget's disease of the nipple.

31 patients underwent mastectomy as primary treatment.

Outcomes

Estimated overall survival (Kaplan-Meier method).

Follow up

Median 7.5 years.

Results

Estimated 5-year overall survival in patients treated by mastectomy: 87%.

General comments

Of the 31 patients, 22 (71%) had no invasive disease and represent the population specified for this question.

Paper written in French; data cited are mostly from English abstract. In the main text, 'carcinome intracanalair' is assumed to represent DCIS, since patients with 'micro-infiltrants' are described separately.

Chaudary, Millis, Lane & Miller . Paget's disease of the nipple: a ten year review including clinical, pathological, and immunohistochemical findings. Breast Cancer Research & Treatment 8[2], 139-146. 1986.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

35 women with biopsy-proven Paget's disease of the nipple treated between 1974 and 1984.

Histology of the underlying breast tissue was available for 34 of 35 patients:

Paget's + pure DCIS: 14 (41%)
Paget's + DCIS + invasion: 20 (59%)

Exclusion criteria

Patients with Paget's disease as an incidental histological finding after mastectomy, but with no clinically apparent Paget's disease,

Population

, age range 31 to 88 years, mean age = 56 years.

Interventions

Aim: to review pathology and outcomes in a series of 35 patients with biopsy-proven Paget's disease of the nipple.

Patients received treatment as follows:

Mastectomy: 32 (91%)
RT alone: 2 (6%)
No treatment: 1 (3%)

Outcomes

Disease-related events.

Follow up

Mean 48 months (range 1-98 months).

Results

Crude rate of mortality due to breast cancer:

All patients: $6/35 = 17\%$
Patients with Paget's disease + pure DCIS: $2/14 = 14\%$
(2 deaths due to breast cancer in this latter subgroup followed mastectomy)

General comments

14 patients (41% of the series) had no evidence of underlying invasive disease and represent the population specified for this question.

1 patient received no radical treatment owing to general poor health.

All patients received either nipple biopsy or biopsy of the palpable breast lump, if present.

Study provides a very small amount of useful data for this question and results are highly susceptible to the effects of small sample size.

Dixon, Galea, Ellis, Elston & Blamey . Paget's disease of the nipple. Br J Surg 78[6], 722-723. 1991.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

48 patients with Paget's disease of the nipple no palpable underlying tumour, who were treated between the years 1973 and 1989.

Histology:

DCIS + invasive component: 8 (17%)

DCIS: 37 (79%)

No tumour: 2 (4%)

(1 patient received no surgery)

Pre-operative mammography was performed in 37 patients with results as follows:

Suspicious: 21 (57%)

Normal: 13 (35%)

Not reported: 3 (8%)

Exclusion criteria

Patients with Paget's disease in association with a palpable tumour.

Population

number of patients = 48, age range 35 to 85 years, median age = 62 years.

Interventions

Mastectomy: 37 (77%)

Wide local excision of nipple/areolar complex including a cone of underlying breast tissue: 10 (21%)

No surgery (tamoxifen alone) 1 (2%)

Outcomes

Incidence of disease related events.

Follow up

For patients treated by mastectomy: median 40 months (range 7-124 months);

For patients treated by breast conserving surgery: median 56 months (range 18-96 months).

Results

Crude rate of local-regional recurrence (breast or axilla):

Following mastectomy: $2/37 = 5.4\%$

Following breast conserving surgery: $4/10 = 40\%$

Crude rate of distant metastasis:

Following mastectomy: $0/37 = 0\%$
Following breast conserving surgery: $1/10 = 10\%$

Crude rate of death due to breast cancer:
Following mastectomy: $0/37 = 0\%$
Following breast conserving surgery: $1/10 = 10\%$

General comments

Of 48 patients in the series, 39 (81%) represent the population specified in the question, of which 38 underwent surgery.

Results are subject to the effects of small sample size and in particular, low event rates.

Duff, Hill, Shering, Nugent, Kennedy, McDermot & O'Higgins . Paget's disease of the nipple - A 14 year experience. Ir.Med J 91[4], 131-132. 1998.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Ireland, setting: Secondary care

Inclusion criteria

29 patients with histologically confirmed Paget's disease of the nipple treated between the years 1983-1996.

Histology:

Paget's disease alone:	4 (14%)
Paget's + DCIS:	8 (28%)
Paget's + LCIS:	1 (4%)
Paget's + invasive:	15 (54%)

Presence/absence of palpable mass:

Present:	12 (43%)
Absent:	16 (57%)

Exclusion criteria

1 patient who received treatment at a different centre.

Population

number of patients = 28, age range 30 to 74 years, mean age = 54 years.

Interventions

Aim: to report on presentation, treatment and outcomes for a series of patients treated for Paget's disease of the nipple.

Patients underwent surgery as follows:

Mastectomy:	25 (89%)
Breast conserving surgery:	1 (4%)
No surgery:	2 (7%)

Outcomes

Disease-related events.

Follow up

Mean 35 months (range 7-134 months).

Results

Crude rate of recurrence (any anatomical site):

All patients:	7/28 = 25%
Palpable mass:	6/12 = 50%
No palpable mass:	1/16 = 6%

Crude rate of deaths due to breast cancer:

All patients:	4/28 = 14%
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Palpable mass: 4/12 = 33%

No palpable mass: 0/16 = 0%

General comments

A total of 12 patients represent the population specified for this question (i.e. non-invasive disease, discounting 1 case of LCIS; 43% of the series). All 12 patients were treated with mastectomy.

2 patients underwent no surgery due to detection of disseminated disease at diagnosis. It is unclear whether these patients occur within the 6 cases of recurrent disease or 4 cases of mortality that were reported during the follow-up period.

Results reported are highly susceptible to the effect of small sample size.

Estabrook, Banerjee, Hibshoosh, Hans, Schnabel, Krementz & Kinne .
Conservative management of Paget's disease of the breast. Breast Cancer
Research & Treatment 37[Suppl], 43. 1996.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

Patients with Paget's disease of the breast with no associated palpable breast
lump or lymphadenopathy, treated between 1990 and 1995.

Paget's disease + focal intraductal breast Ca: 6/13 (46%)

Paget's disease + multifocal intraductal Ca: 6/13 (46%)

Paget's disease + invasive ductal Ca: 1/13 (8%)

Exclusion criteria

None specified.

Population

number of patients = 13, age range 45 to 87 years, mean age = 71 years.

Interventions

Breast conserving surgery (local excision): 8/13 (62%)

Breast conserving surgery (local excision) + Radiotherapy: 5/13 (38%)

Outcomes

Local disease recurrence rate.

Follow up

Mean 17.8 months (range 3-48 months)

Results

Crude local recurrence rate 15.4% (2/13) - 1 invasive ductal, 1 invasive
lobular, both ipsilateral.

General comments

Poster session abstract: small retrospective comparative case series with a
short mean follow-up period, 12/13 (92%) cases match the population criteria
for this topic.

Freund, Maydovnik, Laufer & Durst . Paget's disease of the breast. J Surg Oncol 9[1], 93-98. 1977.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Israel, setting: Secondary care

Inclusion criteria

Women with histologically proven Paget's disease of the breast, treated during the period 1949 and 1972.

Nipple changes only 19/29 (66%)
Nipple changes + palpable lump 7/29 (24%)
Breast tumour only 3/29 (10%)

Exclusion criteria

None specified

Population

number of patients = 29, age range 30 to 75 years, mean age = 54 years.

Interventions

Mastectomy: radical (classical Halsted) 21/29 (72%); simple 4/29 (14%)

RT only: 4/29 (due to advanced disease)

Outcomes

Crude overall survival rate at 5 years and 10 years

Follow up

Up to 10 years for 27 available patients

Results

Crude overall survival:

	n=	5 years (%)	10 years (%)
No palpable mass	17	94	91
Palpable mass	10	40	33
Total	27	74	69

Significant difference in survival rates between patients with or without a palpable mass at presentation ($P < 0.01$, Fisher exact test).

General comments

Small retrospective case series comparing survival rates between Paget's disease patients presenting with or without a palpable lump. Three patients had no nipple reported changes. The results are highly susceptible to the effects of a small sample size.

The authors also present tabulated 5 and 10 year survival data from previous studies of surgical interventions for Paget's disease from 1954 to 1970.

Howard, Locker, Dowle, Ellis, Elston & Blamey . In situ carcinoma of the breast. Eur J Surg Oncol 15[4], 328-332. 1989.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

17 Patients with Paget's disease of the nipple, identified retrospectively within a larger series of 78 patients with only in situ disease, treated between 1973 and 1985.

Mammography was performed in 8/17 patients with Paget's disease, with result as follows:

Indicative of DCIS: 4/8 = 50%

No abnormality: 4/8 = 50%

Exclusion criteria

Patients with invasive tumour revealed by histology.

Population

number of patients = 17, age range 28 to 81 years, mean age = 54 years.

Interventions

Aim: to review histological factors, method of treatment and outcomes in a series of patients treated for in situ breast cancer, including 17 patients with Paget's disease of the nipple.

17 patients with Paget's disease were treated with surgery as follows:

Simple mastectomy: 9 (53%)

Cone excision: 8 (47%)

Outcomes

Disease related events

Follow up

In the larger series: mean 65 months (range 18-144 months).

2 patients were lost to follow-up.

Results

Crude rate of local recurrence:

Following mastectomy: 0/9 = 0%

Following cone excision: 3/8 = 37.5%

Crude rate of distant metastases:

Following mastectomy: 0/9 = 0%

Following cone excision: 1/8 = 12.5%

Crude rate of deaths due to breast cancer:

Following mastectomy: $0/9 = 0\%$

Following cone excision: $1/8 = 12.5\%$

General comments

Tumour palpability is not reported for patients with Paget's disease.

Results are highly susceptible to the effects of small sample size and low event rates.

Kollmorgen, Varanasi, Edge & Carson . Paget's disease of the breast: a 33-year experience. J Am Coll.Surg 187[2], 171-177. 1998.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

68 patients diagnosed with Paget's disease of the nipple between January 1963 and June 1996:

Underlying tumour histology:

Invasive breast cancer:	25 (45%)
DCIS plus invasion:	6 (10%)
DCIS alone:	24 (43%)
Unknown:	1 (2%)

No. (%) of cases with palpable mass at time of diagnosis:

Present: 30 (44%)

Absent: 38 (56%)

Mammograms were available for 27/38 = 71% of patients without palpable tumours. Of these 27 patients 17 had normal mammograms and 10 showed mammographic abnormality.

Exclusion criteria

None reported.

Population

number of patients = 68, age range 23 to 85 years, median age = 57 years.

Interventions

Aim: To review retrospectively survival in patients treated for Paget's disease of the nipple.

Patients received surgery as follows:

58 (85%) patients underwent mastectomy;

5 (7%) patients underwent lumpectomy;

5 (7%) patients underwent nipple excision/biopsy alone.

Outcomes

Overall survival (Kaplan-Meier method).

Follow up

Median 61 months (range 2-288 months).

Results

5-year estimated survival rates:

Whole series (n=68): 58%

Patients with palpable tumours at diagnosis (n=30): 35%

Patients without palpable tumours at diagnosis (n=38): 75%.

The median survival for patients with palpable tumours (42 months) was statistically significantly shorter than for patients without palpable tumours (126 months; $p=0.007$, log rank test).

In the 10 patients treated with breast conserving surgery (5) or biopsy (5), 2 recurrences and 2 deaths occurred at a median follow-up of 71 months.

General comments

Study reports on an additional 12 patients in whom Paget's disease was an incidental histological finding after mastectomy; data not cited here. Therefore original series size was 80 patients.

Study does not report mammographic data for patients with palpable breast tumours at the time of diagnosis.

5 (7%) patients underwent nipple excision/biopsy alone, which is likely to be a less extensive procedure than wide local excision.

In this series only 25 (45%) patients had no histological evidence of invasive disease and represent the population specified for this question. Survival data is not reported for this subgroup, therefore applicability to this question is limited.

Kothari, Beechey-Newman, Hamed, Fentiman, D'Arrigo, Hanby & Ryder .
Paget disease of the nipple: a multifocal manifestation of higher-risk disease.
Cancer 95[1], 1-7. 2002.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

70 patients with clinically apparent and histologically confirmed Paget's disease of the nipple treated between the years 1971-1999.

Of the 70 patients, 23 (33%) patients presented with a palpable mass with clinical stage:

T1: 30%

T2: 53%

T3: 17%

A further 15 (21%) patients presented with focal nodularity, therefore 38 (54%) patients had a breast abnormality in addition to signs of Paget's disease.

Of 55 patients with a mammogram available for the time of diagnosis results were:

No abnormality: 12 (22%)

Abnormality present: 43 (78%)

The diagnoses for the whole series of 70 patients were as follows:

Paget's disease with pure DCIS tumour: 29 (41.4%)

Paget's disease with invasive tumour: 40 (57.1%)

Paget's disease with no underlying tumour: 1 (1.4%)

Exclusion criteria

Patients with Paget's disease that was an incidental histologic finding following mastectomy.

Population

number of patients = 29, age range 29 to 88 years, median age = 56 years.

Interventions

Aim: to examine pathologic tumour characteristics and overall survival in patients treated with mastectomy for Paget's disease of the nipple.

Outcomes

Overall survival estimated by Kaplan-Meier method.

Follow up

Median not reported. 5-year overall survival reported.

Results

Estimated overall survival at 5 years of patients with Paget's disease and DCIS was 92%.

General comments

Relevant information for this question is survival data for 29 patients with Paget's disease and DCIS.

The majority of patients in the larger series underwent mastectomy: 68/70 = 97%. 2 patients in the larger series underwent wide local excision since they were unfit for mastectomy.

Age data shown are for the larger series of 70 patients.

The proportion of patients with Paget's disease and DCIS who underwent mastectomy is not reported, however since only 2 patients in the larger series of 70 patients underwent wide local excision, the proportion with DCIS who received mastectomy must be between 93%-100%.

Marshall, Griffith, Haffty, Solin, Vicini, McCormick, Wazer, Recht & Pierce .
Conservative management of Paget disease of the breast with radiotherapy:
10- and 15-year results. Cancer 97[9], 2142-2149. 2003.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

36 patients with histologically proven Paget's disease of the breast without palpable or mammographic mass and treated with breast conserving surgery plus RT between the years 1980-2000.

Stage of disease (n cases):

TisN0M0, Stage 0: (33)

T1N0M0, Stage 1: (2; 1 pure DCIS, 1 microinvasive)

T2N0M0, Stage IIa: (1, i.e. invasive disease).

30 cases (83%) had an underlying breast malignancy.

Exclusion criteria

Follow up period < 12 months (2 patients)

Population

number of patients = 36, age range 33 to 79 years, median age = 51 years.

Interventions

Aim: to report long term follow-up of patients with Paget's disease of the breast treated with breast conserving surgery and RT.

All patients underwent surgery as follows:

Complete excision of nipple-areolar complex in 25 cases (69%);

Partial excision in 9 cases (25%);

Biopsy alone in 2 cases (6%).

All patients received RT to the whole breast: median 50 Gy; the majority received a boost to the remaining nipple or tumour bed.

Outcomes

Local recurrence

Cause-specific survival;

Overall survival.

[Analysis by Kaplan-Meier method, measured from the completion of RT]

Follow up

Median 113 months (range 17-257 months).

Results

Actuarial local recurrence rates:

1. As only site of first recurrence:

5 years: 9% [95% CI 0%-20%]
10 years: 13% [95% CI 1%-25%]
15 years: 13% [95% CI 1%-25%].

2. As a component of all recurrence (i.e. includes regional and distant metastasis):

5 years: 9% [95% CI 0%-20%]
10 years: 17% [95% CI 3%-31%]
15 years: 24% [95% CI 6%-42%].

Cosmesis:

Cosmesis was assessed in 31 patients by the treating radiation oncologist as follows:

Excellent: 10 (32%; 4 patients underwent nipple reconstruction)

Good: 18 (58%)

Fair: 3 (10%).

Complications were assessed in 32 patients, of whom 29 (91%) had no long-term complications. In 3 patients complications included protracted chest wall pain, chronic breast infection and radiation dermatitis.

Survival:

At a median follow-up of 9 years, 32 of 36 patients were alive with no evidence of disease (includes patients with successfully treated recurrence). 2 patients died of breast cancer and 2 died free of breast cancer.

Cause-specific survival (scores only breast cancer deaths as events):

5 years: 97% [95% CI 90%-100%]

10 years: 97% [95% CI 90%-100%]

15 years: 97% [95% CI 90%-100%]

Overall survival:

5 years: 93% [95% CI 84%-100%]

10 years: 90% [95% CI 78%-100%]

15 years: 90% [95% CI 78%-100%]

General comments

Small, retrospective study with long follow-up.

Of 36 patients, two had invasive disease, therefore 94% of the series represent the specified population for this question.

9 patients had mammographic abnormality: nipple thickening or microcalcifications.

15 patients (42%) underwent axillary surgery; all of whom had no axillary disease.

Method of assessment of cosmesis is cited, but is not accessible in this paper; clinician assessment is arguably less relevant than patient assessment.

Nicolosi, Mallocci, Calo & Tarquini . Paget's disease of the breast. Chirurgia (Bucur.) 9[4], 325-329. 1996.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria

38 female patients with Paget's disease, treated between 1973 and 1994.

Histology:

Paget's + invasive: 22

Paget's + DCIS: 7

Paget's alone: 9

Exclusion criteria

Not known.

Population

number of patients = 38, age range 34 to 88 years, median age = 60 years.

Interventions

Aim: to report treatment and disease-related events in 38 patients treated for Paget's disease of the nipple.

Patients underwent treatment as follows:

Mastectomy: 32 (84%)

Breast conserving surgery: 4 (11%)

No surgery/primary RT: 2 (5%)

Outcomes

Disease-related events;

Actuarial overall survival

Follow up

Median not known; 5-year and 10-year actuarial survival reported.

Results

Crude rates of local recurrence (whole series):

Following mastectomy: $3/32 = 9.4\%$

Following breast conserving surgery: $1/4 = 25\%$

Actuarial overall survival in patients with no evidence of invasive disease:

5-year: 100%

10 year: 100%

General comments

16/38 = 42% of patients in this series represent the population specified for this question, although survival is reported for this subset.

Paper written in Italian: data cited are mostly from the abstract.

Polgar, Orosz, Kovacs & Fodor . Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients¹⁴⁵. Cancer 94[6], 1904-1905. 2002.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Hungary, setting: Secondary care

Inclusion criteria

33 patients retrospectively identified as treated for Paget's disease of the nipple with limited DCIS between the years 1980-1996 by cone excision without RT.

The 33 patients were selected from a larger series of 62 patients with Paget's disease (see exclusion criteria).

30 patients had no palpable mass and a palpable mass was present in 3 patients.

In 30 patients DCIS was present and 3 patients had no evidence of DCIS.

Exclusion criteria

29 patients with Paget's disease plus extensive DCIS (n=12) or Paget's disease plus invasive disease (n=17).

Population

number of patients = 33, age range 35 to 80 years, median age = 65 years.

Interventions

Aim: to examine the rate of local recurrence in patients treated for Paget's disease (and no invasive tumour) with cone excision alone.

All patients underwent cone excision alone.

Outcomes

Local recurrence;
Distant metastasis;
Deaths due to breast cancer.

Follow up

Median 6 years (range 2-14 years)

Results

Local recurrence
The crude rate of local recurrence was $11/33 = 33.3\%$.

In 10 of 11 recurrences the recurrent tumour was invasive disease.

The estimated (actuarial method) 5-year local recurrence rate was 28.4%.

The comparison with the series reported by Bijker et al. 2002 was as follows:

Crude local recurrence rate:

This series: 33.3%

Bijker et al. 6.6% ($p=0.0012$, Fisher exact test)

Estimated (actuarial) local recurrence rate:

This series: 28.4%

Bijker et al. 5.2%

Distant metastasis:

This series: 6 (18.2%)

Bijker et al. 1 (1.6%) ($p=0.007$)

Deaths due to breast cancer:

This series: 6 (18.2%)

Bijker et al. 1 (1.6%) ($p=0.007$)

General comments

All 33 patients (100%) in this series represent the population specified for this question.

Threshold for 'extensive' DCIS (warranting mastectomy) as an exclusion criterion not reported.

Authors focus on a comparison between this series (treated with cone excision alone) and that of Bijker et al. 2001, who were treated with cone excision plus RT.

Whilst the comparison of this series with that of Bijker et al. 2002 is based on similar patient-disease variables (age, median follow-up time, histology and tumour palpability), the two groups represent two distinct, retrospectively defined groups, with possible further unknown differences.

Sheen-Chen, Chen, Chen, Eng, Sheen & Chou . Paget disease of the breast - An easily overlooked disease? J Surg Oncol 76[4], 261-265. 2001.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Taiwan, setting: Secondary care

Inclusion criteria

31 patients with histologically confirmed Paget's disease treated between 1986 and 1997.

Histology:

Paget's disease + invasive cancer:	15 (48%)
Paget's disease +DCIS:	12 (39%)
Paget's disease alone:	4 (13%)

Presence/absence of palpable underlying tumour:

Present:	12 (39%)
Absent:	19 (61%)

Exclusion criteria

None reported.

Population

number of patients = 31, age range 25 to 72 years, mean age = 51 years.

Interventions

Aim: to report survival rates of patients treated for Paget's disease of the nipple.

All patients underwent mastectomy.

Outcomes

Overall survival (Kaplan-Meier method)

Follow up

Mean 58 months (range 6-156 months).

Results

Estimated 5-year overall survival:
All patients: 69%

Estimated 5-year overall survival by subgroup for tumour palpability:
Palpable tumour present: 19%
Palpable tumour absent: 94%
($p < 0.01$, log rank test)

Proportion of patients with underlying pure DCIS by subgroup for tumour palpability (for 27 patients with an underlying tumour):
Palpable tumour present: 8%

Palpable tumour absent: 73%
($p < 0.01$, Chi square test)

General comments

Of the whole series 16 patients (52%) represent the population specified for this question.

Stanislawek, Kurylcio & Krasuska . Surgical treatment in Paget's disease of the breast. *Annales Universitatis Mariae Curie-Sklodowska - Sectio d - Medicina* 57[1], 444-448. 2002.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Poland, setting: Secondary care

Inclusion criteria

Identification of Paget's disease of the breast in a larger cohort of 2261 patients with breast cancer treated surgically in the interval 1989-1995

No statement on histopathological confirmation of disease

28/35 (80%) of patients had Paget's disease with underlying intraductal breast cancer (DCIS?)

7/35 (20%) had underlying invasive breast cancer

Exclusion criteria

None stated

Population

number of patients = 35, age range 42 to 71 years, mean age = 53 years.

Interventions

Radical mastectomy 29/35 (83%)

Breast conserving surgery 6/35 (17%)

Outcomes

Rates of local recurrence and lymph node metastasis (after ? years)

Crude 5-year survival

Follow up

Not stated, data presented on 5-year survival

Results

Crude local recurrence rate:

Paget's disease with intraductal (non-invasive) disease : 1/28 (3.6%)

Paget's disease with infiltration (invasive) disease: 4/7 (57%)

Crude lymph node metastatic recurrence rate:

Paget's disease with intraductal (non-invasive) disease: 0/28

Paget's disease with infiltration (invasive) disease: 4/7 (57%)

Crude survival at 5 years:

Paget's disease with intraductal disease (non-invasive): 90%

Paget's disease with infiltration (invasive) disease: 49%

General comments

Retrospective case series of Paget's disease of the breast identified from a

large cohort of surgically-treated breast cancer patients.

Eighty percent of the patients had no underlying invasive disease and therefore met the inclusion criteria for this topic.

Recurrence and survival data are given only by clinical presentation and not by intervention. The follow-up interval for recurrence is not stated. Survival rates are presumed to be overall survival.

Results are highly susceptible to the effects of a small sample size.

Zurrída, Squicciarini, Bartoli, Rovini & Salvadori . Treatment for Paget's disease of the breast without an underlying mass lesion: An unresolved problem. Breast 2[4], 248-249. 1993.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria

49 patients clinically diagnosed with Paget's disease between the years 1975 and 1989.

Pathology:

Paget's disease alone: 7 (14%)

Paget's plus DCIS: 32 (65%)

Paget's plus involvement of focal areas of breast and underlying nipple ducts: 10 (20%)

42 patients underwent a diagnostic mammography with results as follows:

Mammographic abnormality: 14 (34.2%)

Normal: 28 (68.3%)

Exclusion criteria

None reported.

Population

number of patients = 49, mean age = 60 years, median age = 62 years.

Interventions

Aim: to report on disease-related events in a small series of patients with Paget's disease of the nipple.

Patients received surgery as follows:

Mastectomy: 18 (36.7%)

Wide local excision: 31 (63.3%)

2 patients treated with wide local excision received RT in addition.

Outcomes

Local recurrence

Deaths due to breast cancer

Follow up

Median 60 months (range 20-179 months).

2 patients were lost to follow-up.

Results

Crude rates of locally recurrent invasive tumour:

Following mastectomy: 0/18 = 0%

Following wide local excision: $9/31 = 29\%$

Of 31 patients who underwent wide local excision, 8 cases of recurrence occurred in the subset of 29 patients who did not receive RT and 1 case of recurrence occurred in the subset of 2 patients who received RT.

Crude rates of death due to breast cancer:

Following mastectomy: $0/18 = 0\%$

Following wide local excision: $2/31 = 6.5\%$

General comments

Pre-operative biopsy was performed in 27 patients and confirmed Paget's disease histologically in all 27 cases.

Paper does not make clear whether 10 cases with definitive pathology of 'involvement of focal areas of breast and underlying nipple ducts' is invasive disease or in situ disease. However at least 39 cases (79% of the series) represent the population specified in the question.

Results are subject to the effects of small sample size and in particular, low event rates.

3.3 In patients with invasive breast cancer or DCIS when is sentinel lymph node biopsy justified as a staging procedure?

Short Summary - Invasive breast cancer SLNB versus axillary clearance or axillary sampling

There is a large volume of evidence on SLNB both from randomised controlled trials (RCTs) and case series studies (Agarwal *et al.* 2005, Blanchard *et al.* 2003, BMJ Clinical Evidence 2005; Carlo *et al.* 2005, Clarke *et al.* 2004, Cody *et al.* 1999, Cox. *et al.* 2000, Cserni *et al.* 2002, Fleissig *et al.* 2006 Giuliano *et al.* 1997, Haid *et al.* 2002, Imoto *et al.* 2004, Julian *et al.* 2004, Katz *et al.* 2006, Kim *et al.* 2006, Kokke 2005, Krag *et al.* 2001 and 2007, Langer *et al.* 2004, Langer *et al.* 2005, Leidenius 2004, Lucci *et al.* 2007, Mansel *et al.* 2006, Naik *et al.* 2004, Purushotham *et al.* 2005, Reitsamer *et al.* 2004, Rietman *et al.* 2003, Ung *et al.* 2004, Veronesi *et al.* 2003 and 2006, Zavagno *et al.* 2005a and 2005b and 2008)

A well conducted systematic review and meta-analysis of 69 studies (of mixed study design) was undertaken by Kim, Giuliano & Lyman (2006) with data from over 8000 patients. The overall sentinel lymph node localisation rate was 96.4%; the pooled estimate of false negative rate was 7.0% and the mean proportion of patients with positive sentinel lymph nodes was 42% and the post test probability negative was 4.6%. From other studies, the sentinel lymph node localisation rate ranged from 81.4% to 100%, (mean 94.0% and median 94.9%) (Agarwal *et al.* 2005, Carlo *et al.* 2005, Clarke *et al.* 2004, Cody *et al.* 1999, Cox. *et al.* 2000, Cserni *et al.* 2002, Giuliano *et al.* 1997, Haid *et al.* 2002, Imoto *et al.* 2004, Julian *et al.* 2004, Krag *et al.* 2001, Langer *et al.* 2004, Langer *et al.* 2005, Naik *et al.* 2004, Reitsamer *et al.* 2004, Ung *et al.* 2004, Veronesi *et al.* 2003).

The false negative rate of SLNB ranges from 0% to 10.7% (mean 5.8%, median 5.9%) (Agarwal *et al.* 2005, Clarke *et al.* 2004, Cody *et al.* 1999, Cox *et al.* 2000, Cserni *et al.* 2002, Giuliano *et al.* 1997, Julian *et al.* 2004, Krag *et al.* 2001, Langer *et al.* 2004, Ung *et al.* 2004, Veronesi *et al.* 2003). The accuracy of SLNB ranges from 94.6% to 100%, (mean 97.7% with a median of 98.3%) (Agarwal *et al.* 2005, Clarke *et al.* 2004, Cody *et al.* 1999, Cserni *et al.* 2002, Giuliano *et al.* 1997, Krag *et al.* 2001, Langer *et al.* 2004, Ung *et al.* 2004, Veronesi *et al.* 2003, Cox *et al.* 2000.) The prevalence of axillary disease has a mean of 39.1%, median 35.4% and a range from 28.8% to 57.6% (Agarwal *et al.* 2005, Clarke *et al.* 2004, Cody *et al.* 1999, Cserni *et al.* 2002, Giuliano *et al.* 1997, Krag *et al.* 2001, Langer *et al.* 2004, Leidenius *et al.* 2004, Ung *et al.* 2004, Veronesi *et al.* 2003 and 2006, Cox *et al.* 2000.)

The evidence on morbidity, including lymphoedema, favours SLNB over axillary clearance. (Mansel *et al.* 2006 and Fleissig *et al.* 2006; Purushotham *et al.* 2005; Lucci *et al.* 2007, Zavagno *et al.* 2008). The ALMANAC RCT (reported by Mansel, 2006 and Fleissig 2006) and the RCT by Purushotham *et al.* (2005) found little evidence, by intention to treat, that a difference exists in psychological morbidity between patients treated by SLNB compared to axillary clearance.

The follow-up periods in the studies ranged from a mean of 24 months from surgery (Blanchard *et al.* 2003) to a median of 60 months by Carlo *et al.* (2005) and up to 78 months as reported by Veronesi *et al.* (2006). The extent of follow-up is therefore immature and results should be interpreted with caution, however, findings showed that patients treated by SLNB do not appear to have poorer rates of: disease free survival or

overall survival, or of axillary recurrence in the short term, compared to patients treated by axillary clearance.

The retrospective review conducted by Katz *et al.* (2006) of SLNB procedures in 1,133 patients, the majority of whom had invasive disease, identified the following factors as risk factors for involvement of the sentinel lymph node: younger age; mastectomy as definitive surgery; larger tumour size; invasive histology; and tumour lymphovascular invasion. In the same study in patients with involved sentinel lymph nodes, the following factors were found to be risk factors for further axillary node involvement revealed by axillary clearance: tumour lymphovascular invasion; higher number of positive sentinel lymph nodes; larger sentinel lymph node deposits; and lower number of uninvolved sentinel lymph nodes. A RCT by Lucci *et al.* 2007 reported that the use of SLNB plus ALND resulted in more wound infections, axillary seromas, and paresthesias than SLNB alone. Lymphoedema was more common after SLNB plus ALND but was significantly different only by subjective report. The use of SLNB alone resulted in fewer complications. Zavagno *et al.* (2008) reported that the analysis of the Psychological General Well Being Index questionnaire showed a statistically more positive outcome in the anxiety domain and in the general index for the sentinel lymph node group.

Axillary sampling as staging surgery

In addition to SLNB, a literature search was performed to identify studies which evaluated axillary sampling as staging surgery in early breast cancer. 15 studies were identified: two RCTs: Chetty *et al.* 2000, Forrest *et al.* 1995 and 13 case series studies: Hadjiminias and Burke 1994, Rampaul *et al.* 2004, Tanaka *et al.* 2006, Thompson *et al.* 1995, Mathew *et al.* 2006, Sato *et al.* 2001; Ishikawa *et al.* 2005; Narredy *et al.* 2006; Macmillan *et al.* 2001; Hoar and Stonelake 2003, Gui *et al.* 2005; Cserni 1999, Kingsmore *et al.* 2003.

Staging performance: Staging data for axillary sampling were identified in five case series studies, most of which were very small in size. From these limited data, axillary sampling appears to have a median false negative rate of 3.6% (range 0%-6.5%) and a median accuracy of 98.5% (range 98%-100%). Although these values appear favourable to those of SLNB⁵ they should be interpreted with caution due to the small volume of low quality evidence. However the studies present no evidence that axillary sampling is inferior to SLNB in terms of detecting axillary disease.

Physical morbidity: Evidence from one RCT is suggestive of reduced morbidity from axillary sample over axillary clearance or axillary sample plus radiotherapy, expressed as greater arm flexion at six months from surgery and smaller forearm circumference at three years from surgery. There were no other significant differences in morbidity outcomes, including upper arm circumference and other arm movements. Evidence from three observational studies comparing axillary sampling with axillary clearance favours axillary sample in terms of arm volume increase. Two of these studies suggest that radiotherapy, when used after axillary sampling in patients with disease positive nodes, has an adverse effect on shoulder mobility and arm volume.

⁵ A meta-analysis by Kim, Giuliano & Lyman (2006) provided a pooled estimate of FNR for SLNB as 7.0% [95% CI 5.2%-8.8%]. In studies of SLNB reviewed for this guideline, the accuracy of SLNB had median 98.3% (range 94.6% to 100%), based on 10 series of patients (three series were within RCTs). The FNR of SLNB had median 5.9% (range 0% to 10.7%) based upon 11 series of patients (four series were within RCTs).

Recurrence and survival: Two RCTs comparing axillary sampling with axillary clearance found no significant difference in terms of survival or recurrence. One retrospective analysis of a large series of patients who were treated in the pre-SLNB era, concluded that survival is significantly improved if four or more nodes are sampled, compared to sampling fewer than four lymph nodes. This effect was demonstrated for patients with metastatic axillary lymph nodes and for patients with no detectable nodal metastases. A second observational study was suggestive of an inverse relationship between survival and the number of positive lymph nodes, with the best survival in patients with no detectable nodal disease.

Predictive factors for axillary metastases

Evidence on the risk factors for axillary metastases in patients with early invasive breast cancer was identified in 16 retrospective analyses. Although some studies represented large series of patients, the retrospective design constitutes poor quality evidence (Anan *et al.* 2000; Barth *et al.* 1997; Brenin *et al.* 2001; Cao *et al.* 2005; Chen *et al.* 2002; Cutuli *et al.* 2001; Giuliano *et al.* 1996; Grube *et al.* 2002; Houvenaeghel *et al.* 2003; Katz *et al.* 2006; Peters-Engl *et al.* 2004; Rivadeneira *et al.* 2000; Specht *et al.* 2005; Tan, Tan *et al.* 2005; Tan, Wu *et al.* 2005; Velanovich and Szymanski 1998).

The overall risk of axillary metastases in each of 13 studies had a median value of 27%. The most commonly reported risk factors for axillary metastases in 12 studies that performed multivariate analyses were larger tumour size (11 studies) presence of lympho-vascular invasion (8 studies), higher histological grade (5 studies) and younger patient age (5 studies), although other risk factors were reported.

The poor quality evidence from these studies does not permit definition of a distinct patient group with risk factors that indicate avoidance of SLNB in favour of axillary clearance.

Short Summary - DCIS

A limited volume of case series studies which address SLNB in patients with DCIS were identified. Ansari *et al.* (2008) conducted a meta-analysis (of observational studies) of the reported data on the incidence of sentinel lymph node metastasis in patients with DCIS. This analysis reported SLNB results in patients with the diagnosis of DCIS. The analysis showed the frequency of sentinel lymph node positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. With an overall positivity incidence of 7.4%. Postoperative overall positivity incidence was 3.7%. The overall frequencies of nodal metastasis between the two groups (preoperative versus definitive diagnosis) were significantly different. Evidence on a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component was reviewed and suggested that a palpable mass, a mammographic mass, a high-grade DCIS and a large size were associated with a significant risk of invasive disease in the final resection specimen.

In the other case series studies there was general consistency in differentiating between true DCIS, DCIS with microinvasion (DCIS_m) and invasive disease, usually based upon the definition of DCIS_m by the American Joint Committee on Cancer (i.e. invasive focus < 1mm in size on definitive histology). The overall rate of sentinel lymph node involvement for true DCIS was 1.8% (Veronesi *et al.* 2005) and 5% (Wilke *et al.* 2005). This evidence was drawn from observational studies which reported rates of detection of positive sentinel lymph nodes in patients with DCIS (with no detectable microinvasion) as 1.8% (Veronesi *et al.* 2005). The median value from 12 included observational studies was 5.4% (range 0% to 22%). Overall rate of sentinel lymph node involvement for DCIS_m from an

observational study by Wilke *et al.* (2005) showed that the subgroup of patients with DCISm represented only 51 individuals. Among these, the rate of detection of positive sentinel lymph nodes was 14%. The median value from 7 included observational studies is 11.1% (range 9.5% to 29.4%). From all other 16 case series studies the summary statistics for the rate of sentinel lymph node involvement in patients with DCIS (which represent patients with only true DCIS, only DCISm, or either of DCIS/DCISm) were: mean 7.6%; median 6.8%, range 0% to 22%. (Camp *et al.* 2005; Cox *et al.* 1998; Cserni *et al.* 2002; Farkas *et al.* 2004; Intra *et al.* 2003; Katz *et al.* 2006; Kelly *et al.* 2003; Klauber-DeMore *et al.* 2000; Liu, Yang and Chen 2003; Mittendorf *et al.* 2005; Pendas *et al.* 2000; Trisal, Qian and Wagman 2004; Veronesi *et al.* 2005; Wilkie *et al.* 2005; Zavagno *et al.* 2005 and b; and Zavotsky *et al.* 1999).

There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS grade. There was no evidence to suggest that a pattern exists between the rate of positive sentinel lymph nodes and DCIS tumour size. It was not possible to reliably estimate the proportion of patients with DCIS and positive sentinel lymph nodes who have further axillary nodal involvement from the studies identified, because of small numbers of patients in the series.

None of the selected studies (all retrospective) reported changes to treatment plans as a result of staging by SLNB, and all studies were retrospective in nature. However five studies provided data on patients who were upstaged from the stage attributed by primary tumour biopsy, in the light of final, primary tumour histology from definitive surgery: a retrospective case series study (Wilkie *et al.* 2005) provides evidence that 10% of patients staged by biopsy as having DCIS (including DCISm) and who undergo SLNB are found to have invasive disease by primary tumour histology revealed by definitive surgery.

PICO

Patients	Intervention	Comparator	Outcome
Patients with invasive breast cancer	SLNB	<ul style="list-style-type: none"> • ALND • Axillary node sampling 	<ul style="list-style-type: none"> • Sensitivity • Specificity • Axillary recurrence rate • Morbidity (short term) • Morbidity (long term) - Morbidity includes Lymphoedema and Psychological morbidity • QOL (to include function and activities of daily living) • Patient acceptability • Overall survival • Factors associated with high risk of nodal metastases (prior to definitive surgery)
Patients with DCIS or micro-invasive carcinoma (defined as invasive carcinoma <1mm)	SLNB	<ul style="list-style-type: none"> • No axillary surgery • Axillary node sample or ALND 	Rates of axillary positivity by subgroups: (1) low grade, vs. intermediate grade, vs. high grade DCIS (2) by size of DCIS

in size)			Change in treatment decisions
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This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Invasive breast cancer SLNB versus axillary clearance or axillary sampling -

Evidence Summary

There is a large volume of evidence on SLNB but the vast majority arises from numerous case series. Applicability to the UK is limited due to the variable techniques employed in different centres internationally.

A well conducted systematic review and meta-analysis of 69 studies (of mixed study design) was undertaken by Kim, Giuliano & Lyman (2006) with data from over 8000 patients. This study summarised the staging performance of SLNB as follows:

Overall SN localisation rate = 96.4%

Pooled estimate of FNR = 7.0% [95% CI 5.2%-8.8%, p<0.0001]
 Mean proportion of patients with positive SNs = 42%

Post test probability negative = 4.6%.

An earlier, smaller systematic review of 12 studies was performed by Cox et al. (2000) but the results are not summarised here since there is apparently overlap with the superior review by Kim, Giuliano & Lyman (2006). Otherwise in our review of the literature, data on the staging performance of SLNB comes from 17 original series of patients as follows:

Sentinel node localisation rate

The SN localisation rate had range 81.4% to 100%, mean 94.0% and median 94.9%, based upon 17 series of patients (four series were within RCTs):

Agarwal et al. 2005, Carlo et al. 2005, Clarke et al. 2004, Cody et al. 1999, Cox. et al. 2000, Cserni et al. 2002, Giuliano et al. 1997, Haid et al. 2002, Imoto et al. 2004, Julian et al. 2004, Krag et al. 2001, Langer et al. 2004, Langer et al. 2005, Naik et al. 2004, Reitsamer et al. 2004, Ung et al. 2004, Veronesi et al. 2003.

False negative rate

The FNR of SLNB had range 0% to 10.7% (mean 5.8%, median 5.9%) based upon 11 series of patients (four series were within RCTs):

Agarwal et al. 2005, Clarke et al. 2004, Cody et al. 1999, Cox et al. 2000, Cserni et al. 2002, Giuliano et al. 1997, Julian et al. 2004, Krag et al. 2001, Langer et al. 2004, Ung et al. 2004, Veronesi et al. 2003

Of these 11 studies 10 used axillary clearance as the gold standard and one (Agarwal et al. 2005) used FNS as the gold standard.

Accuracy

The accuracy of SLNB had range 94.6% to 100%, mean 97.7% and median 98.3% based on 10 series of patients (three series were within RCTs):

Agarwal et al. 2005, Clarke et al. 2004, Cody et al. 1999, Cserni et al. 2002, Giuliano et al. 1997, Krag et al. 2001, Langer et al. 2004, Ung et al. 2004, Veronesi et al. 2003, Cox et al. 2000.

Of these 10 studies 9 used axillary clearance as the gold standard and one (Agarwal et al. 2005) used FNS as the gold standard.

Prevalence of axillary disease

Prevalence of axillary disease had mean 39.1%, median 35.4% and range 28.8% to 57.6% based on 11 series of patients (three series were within RCTs):

Agarwal et al. 2005, Clarke et al. 2004, Cody et al. 1999, Cserni et al. 2002, Giuliano et al. 1997, Krag et al. 2001, Langer et al. 2004, Leidenius et al. 2004, Ung et al. 2004, Veronesi et al. 2003, Cox et al. 2000.

Of these 11 studies 10 used axillary clearance as the gold standard and one (Agarwal et al. 2005) used FNS as the gold standard.

Morbidity

Three RCTs and five observational studies compared morbidity outcomes between SLNB and axillary clearance.

Physical Morbidity

The majority of the evidence from 8 studies comparing physical morbidity, including lymphoedema, favours SLNB over axillary clearance. This was most effectively demonstrated by ITT analyses in two RCTs representing study situations where a proportion of patients randomised to SLNB actually underwent axillary clearance, which attenuates any advantage arising from SLNB (the ALMANAC RCT, reported by Mansel et al. 2006 and Fleissig et al. 2006 and a second RCT by Purushotham et al. 2005):

In Mansel et al. (2006) the ALMANAC trial demonstrated effects that were statistically significant and clinically important in favour of the SLNB arm for the trial outcome index (TOI) which was based on quality of life. Statistically significant effects in favour of SLNB were also demonstrated for arm sensory loss, lymphoedema, use of surgical drains and wound infection, at different time points up to one year post-surgery (RR of any lymphoedema in SLNB group compared to standard treatment group = 0.37 (95% CI 0.23-0.60). A significantly greater proportion of patients in the SLNB arm resumed normal activities within 3 months than did patients in the control arm. Fleissig (2006) demonstrated that patients in the SLNB group of the ALMANAC trial experienced statistically significantly better TOI at longer follow-up of 18 months from surgery. Older patients experienced statistically significantly better TOI than younger patients.

The RCT by Purushotham et al. (2005) also demonstrated significant advantages in favour of SLNB in the first year post-surgery in terms of physical morbidity: smaller mean increases in arm volume and lower odds of sensory loss in five different measurements were observed in the SLNB arm. Only one of five shoulder mobility outcomes were significantly better for the SLNB arm, with no significant differences detected in the remaining four by ITT.

Further evidence of less physical morbidity following SLNB compared to axillary clearance was provided (by non intention-to-treat (ITT) analysis) in the RCT by Veronesi et al. (2003) and also in observational studies by Haid et al. (2002), Blanchard et al. (2003), Langer et al. (2004) and Langer et al. (2005). These studies used a combination of subjective (mostly patient-reported) and objective measures and found that the effect in favour of SLNB was present from the short-term post-operative period, and was demonstrable at a mean follow-up period of 51 months (Langer et al. 2004). Only Rietman et al. (2003) found no significant difference in physical morbidity between SLNB and axillary clearance, at 6 weeks after surgery. Although not identified by the included studies, SLNB also carries a

risk of allergic reaction of 1.8% when blue dye is used (King 2004 cited by BMJ Clinical Evidence 2005b).

Psychological Morbidity

The ALMAMAC RCT (reported by Mansel, 2006 and Fleissig 2006) and the RCT by Purushotham et al. (2005) found little evidence, by ITT, that a difference exists in psychological morbidity between patients treated by SLNB compared to axillary clearance.

Mansel et al. (2006) found no significant difference between groups for a measure of state anxiety at any follow-up point up to 12 months post-surgery and concluded that this demonstrated that patients who undergo SLNB do not experience increased anxiety due to concerns of residual cancer being 'left behind'. Fleissig (2006) demonstrated a similar result that in the same study group considering only patients with positive nodes between randomised groups (non ITT) and also that older patients experienced statistically significantly less anxiety than younger patients.

Purushotham et al. (2005) found few significant differences between groups for psychological outcomes: There was one significant difference in favour of SLNB for a measure of 'clinically significant morbidity', but this did not remain significant when adjusted for trait anxiety.

Recurrence and survival

Twelve of the identified studies provide information on recurrence or survival after SLNB. The follow-up periods in the studies ranged from a mean of 24 months from surgery (Blanchard et al. 2003) to a median of 60 months by Carlo et al. (2005). The extent of follow-up is therefore immature although patients treated by SLNB do not appear to have poorer disease free or overall survival, or rates of axillary recurrence in the short term, compared to patients treated by axillary clearance.

Survival

Only three studies (Veronesi et al. 2003, Carlo et al. 2005 and Imoto et al. 2004) performed analyses using an actuarial method i.e. one which considers the time it takes for patients to reach the endpoints of interest:

The RCT by Veronesi et al. (2003) found no significant difference in overall survival by ITT, between randomised groups (intervention: SLNB with axillary clearance only if positive, versus control: SLNB plus axillary clearance), at a median follow up of 46 months, indicating no survival disadvantage in patients treated by SLNB in its operational setting. In the intervention group 0.8% of patients died of breast cancer compared with 0.4% of the control group ($p=0.15$, log rank test).

The case-series study by Carlo et al. (2005) estimated 5-year disease-free survival in patients who successfully underwent SLNB, at 94% (95% CI 91% to 97%). This result was for two patient groups together:

- i) patients with positive sentinel nodes who underwent axillary clearance
- ii) patients with negative sentinel nodes who did not undergo axillary clearance

5-year disease-free survival was significantly longer in patients in the second group (96%), compared to the first (89%, $p = 0.02$, log rank test), illustrating the prognostic value of the disease status of the axilla. The case-series study by Imoto et al. (2004) found no significant difference in disease-free survival between patients with negative sentinel nodes who underwent axillary clearance and patients with negative sentinel nodes who did

not undergo axillary clearance. The proportions of patients alive at a median follow-up of 52 months groups were 94% and 93% respectively ($p=0.78$, log rank test).

Recurrence

In the studies identified, axillary recurrence occurred with range 0% to 0.96% in patients with negative sentinel nodes who underwent no axillary clearance, with follow up periods ranging from 12 months (Mansel et al. 2006) to a median of 60 months (Carlo et al. 2005). These studies reported simple proportions of patients that had reached the event of interest and should be interpreted with caution due to the variability of follow-up periods.

In the ALMANAC RCT at 12 months from surgery 4 patients in the standard treatment group and 1 patient in the SLNB group experienced axillary recurrence (difference = 2.7%, 95% CI -1.5%-7.8%, Mansel et al. 2006).

In patients with positive sentinel nodes who received subsequent axillary clearance, axillary recurrence occurred with range 0% to 1.4%, with follow up periods ranging from median 31 months (Naik et al. 2004) to median 60 months (Carlo et al. 2005).

In patients with negative sentinel nodes who underwent axillary clearance in centres' validation periods, no axillary recurrences were reported with follow up ranging from a mean of 24 months (Blanchard et al. 2003) to a median of 52 months (Imoto et al. 2005).

Naik et al. (2004) demonstrated a higher proportion of patients with positive sentinel nodes who underwent no axillary clearance experiencing axillary recurrence (1.4%), than all other patients studied i.e. patients with positive sentinel nodes who underwent subsequent axillary clearance plus patients of with negative sentinel nodes, with or without subsequent axillary clearance (0.18%, $p=0.013$).

Patient acceptability

No studies were included that specifically address patient acceptability as an outcome measure.

Factors (identified prior to definitive surgery) that are associated with high risk of nodal metastases

The retrospective review conducted by Katz et al. (2006) of SLNB procedures in 1133 patients, the majority of whom had invasive disease, identified the following factors as risk factors for involvement of the sentinel node: younger age; mastectomy as definitive surgery; larger tumour size; invasive histology; tumour lymphovascular invasion. In the same study in patients with involved sentinel nodes, the following factors were found to be risk factors for further axillary node involvement revealed by axillary clearance: tumour lymphovascular invasion; higher number of positive sentinel nodes; larger sentinel node deposits; lower number of uninvolved sentinel nodes.

Axillary sample as staging surgery

An additional literature search was performed in addition to that for SLNB, on the MEDLINE and EMBASE databases. 15 studies were identified which evaluate axillary sample as staging surgery in patients with early breast cancer; 2 RCTs: Chetty et al. 2000, Forrest et al. 1995 and 13 case series studies: Hadjiminias and Burke 1994, Rampaul et al. 2004, Tanaka et al. 2006, Thompson et al. 1995, Mathew et al. 2006, Sato et al. 2001; Ishikawa et al. 2005; Narredy et al. 2006; Macmillan et al. 2001; Hoar and Stonelake 2003, Gui et al. 2005; Cserni 1999, Kingsmore et al. 2003.

Although all of the identified studies evaluate axillary sampling to stage the axilla, there is a high degree of inconsistency in the detail of the staging interventions (Table 1). Of the total of 15 studies, eight (including two RCTs) report on unguided axillary sample of four axillary nodes as the intended surgical procedure and two report on axillary sample of four nodes, guided by blue dye. In some studies there is an apparent blurring of the boundaries of axillary sample with SLNB (Hoar and Stonelake 2003, Gui et al. 2005).

Table 1. Consistency of axillary sample procedures

Staging intervention	Studies reporting
Unguided sample of a target/minimum of four axillary nodes, by palpation.	Chetty et al. 2000, Forrest et al. 1995, Hadjiminias and Burke 1994, Rampaul et al. 2004*, Tanaka et al. 2006, Thompson et al. 1995*, Mathew et al. 2006, Sato et al. 2001.
Dye assisted four node sample.	Ishikawa et al. 2005, Narredy et al. 2006.
Axillary clearance with retrospective analysis of the staging information provided by different numbers of nodes.	Cserni 1999, Kingsmore et al. 2003.
SLNB, extended to sample a minimum of four axillary nodes, using palpation.	Hoar and Stonelake 2003, Gui et al. 2005.
Unguided four node sample, but with preoperative injection of radiocolloid and analysis <i>ex vivo</i> of nodes identified as sentinel nodes.	Macmillan et al. 2001.

* Staging technique appears to be unguided sample, but details of the method were not specified.

Since 10 of the 15 studies are of patients treated in the UK (including two RCTs), applicability to the UK should be reasonable, noting inconsistencies discussed above.

Staging performance of axillary sample: Five observational studies provided complete staging performance data for axillary sample, compared to axillary clearance as gold standard (Hoar & Stonelake 2003, Ishikawa et al. 2005, Narreddy et al. 2006, Tanaka et al. 2006 and Sato et al. 2001). In general the studies represent small series of patients. For this reason the study by Tanaka et al. 2006 stands out with the largest series size of 237 patients. In this study, unguided axillary sample of four palpable nodes had a false negative rate of 6.5% and an accuracy of 98.3%.

False negative rate: The false negative rate of axillary sample had mean 2.9%, median 3.6% and range 0%-6.5% (Hoar & Stonelake 2003, Ishikawa et al. 2005, Narreddy et al. 2006, Tanaka et al. 2006 and Sato et al. 2001). Two studies reported false negative rates of zero (Ishikawa et al. 2005 and Narreddy et al. 2006), but these represented small series of patients (32 patients and 17 patients, respectively).

Accuracy: The accuracy of axillary sample had mean 99%, median 98.5% and range 98%-100%. Similar to above, two studies with very small series of patients reported accuracy values of 100% (Ishikawa et al. 2005 and Narreddy et al. 2006).

Prevalence of axillary disease: Prevalence of axillary disease as determined by axillary clearance as gold standard had a mean of 43.2%, median 39.8% and range 26.2%-76.5% (Hoar & Stonelake 2003, Ishikawa et al. 2005, Narreddy et al. 2006, Tanaka et al. 2006, Macmillan et al. 2001 and Sato et al. 2001). The highest prevalence of 76.5% was reported by Narreddy et al. 2006, who studied a small, selected series of 17 patients with multifocal breast cancer.

Other staging information: The case series study by Gui et al. 2005 studied the staging performance SLNB (with radiocolloid plus, in some cases, blue dye) extended where necessary, to an axillary sample of a minimum of four nodes. The study found that sampling a minimum of four nodes did not reveal, after SLNB, any cases of further positive nodes.

The retrospective review of pathology slides by Cserni 1999 examined the staging information provided by sampling the largest three, four, five and six axillary nodes in patients who underwent axillary clearance. Considering all cases, concordance of staging information with the axillary clearance was as follows:

- 3 nodes: 94-96%
- 4 nodes: 97-98%
- 5 nodes: 98-99%
- 6 nodes: 99%

Morbidity outcomes for axillary sample: The RCT reported by Chetty et al. 2000 compared axillary sample versus axillary clearance. Six months following surgery, arm flexion was statistically significantly lower in patients who received axillary clearance ($p=0.003$ ANCOVA) and in those who received axillary sample plus RT ($p=0.004$) compared to those who underwent axillary sample alone. There were no differences between groups in power to flex the shoulder or abduction, at any time point. There was no significant difference in the upper arm circumference between the three groups. At three years from surgery the forearm circumference was significantly greater after axillary clearance than after node sample ($p=0.005$) or node sample plus RT ($p=0.04$).⁶

The prospective case series study by Thompson et al. 1995 studied arm morbidity up to twelve months after surgery following axillary sample or axillary clearance. A greater proportion (42%) of patients who underwent axillary clearance had an arm volume increase $>200\text{ml}$ ⁷ compared to patients who underwent axillary sample (21%; difference 19%, 95% CI 1%-38%). RT was found independently to have a statistically significant adverse impact on shoulder mobility.

The prospective case series study by Hadjiminias and Burke 1994 measured the rate of lymphoedema at a median of 20 months following surgery. Lymphoedema was present in 14% of patients who underwent axillary sample followed by axillary clearance compared to 0% in patients who underwent axillary sample alone ($p<0.02$).

⁶ Morbidity outcomes were not analysed by intention to treat and although the forearm circumference difference is statistically significant, it is difficult to tell whether the difference is clinically important.

⁷ Regarded by the authors as a threshold for clinically important arm morbidity.

Mathew et al. 2006 studied the incidence of lymphoedema in patients who underwent axillary sample (with RT in cases with metastatic nodes) compared to patients who underwent axillary clearance, using two retrospectively defined groups. Axillary clearance was associated with a higher incidence of lymphoedema than axillary sample (12% and 2% respectively, $p=0.001$). This difference remained statistically significant when measured in node-negative patients only (removing the effect of RT), but statistical significance was lost when only node positive patients were analysed.

Recurrence and survival data for axillary sample: In the RCT of axillary sample versus axillary clearance after breast conserving surgery reported by Chetty et al. 2000, there was no statistically significant difference between randomised groups for overall survival or disease free survival at a median follow-up of 4.1 years. There was also no significant difference between randomised groups in the rate of axillary recurrence.

An earlier RCT reported by Forrest et al. 1995 compared axillary sample versus axillary clearance after mastectomy. At a median follow-up of 11 years there was no significant difference between groups for disease specific survival (Hazard ratio (HR) 1.11 in favour of axillary clearance; 95% CI 0.80-1.53), distant recurrence (HR 1.05 in favour of axillary clearance; 95% CI 0.74-1.5) or locoregional recurrence (HR 1.35 in favour of axillary sample; 95% CI 0.83-2.19).

Kingsmore et al. 2003 performed a retrospective analysis of a large series of patients who underwent axillary staging surgery in the pre-SLNB era, analysing survival against the number of axillary nodes examined. Patients who had examination of four or more axillary nodes had statistically significantly increased survival compared to patients who had 3 or less nodes examined, when node-negative patients were analysed (HR 1.34; 95% CI 1.09-1.65) and when node-positive patients were analysed (HR 1.20; 95% CI 1.02-1.41).

Rampaul et al. 2004 examined survival in a series of 852 patients who underwent axillary sample, with axillary RT given in cases with positive axillary nodes. At a median follow-up period of 7.5 years, axillary recurrence occurred at a rate of 0.66% per annum. Overall survival by the number of positive nodes was as follows:

- 0 nodes positive: 89%
- 1 nodes positive: 84%
- 2 nodes positive: 75%
- 3 nodes positive: 65%

Predictive factors for axillary metastases

There is a large volume of evidence on SLNB in general. 97 studies that address risk factors for axillary metastases were identified from within the list of studies identified for SLNB. All of the selected studies are retrospective analyses, usually performed by interrogating databases of routinely collected clinical and pathological data. Some of the studies report on large patient samples. However the quality of these studies is generally poor due to their retrospective nature.

There is likely to be inconsistency amongst the studies for the definition of a metastatic axillary node; SLNB is more likely to involve serial sectioning of nodes than is axillary dissection. Immunohistochemistry histology techniques, where used, are likely to be more sensitive than standard techniques. Studies also vary in terms of their methods of analysis and also the variables that authors chose to explore, and how results are presented (e.g. by continuous/categorical variables). Despite this, half or more of the studies report larger

tumour size and presence of tumour lympho-vascular invasion to be significant risk factors for axillary metastasis.

Studies are also inconsistent in the magnitude of risk conveyed by any particular risk factor (see Table 2: OR for axillary metastases by tumour size; Peters-Engl et al. 5004 and Rivadeneira et al. 2000).

Patient population:

The patient samples represented in the retrospective studies varied in terms of tumour size. Several studies are restricted to patients with tumour sizes below a stated maximum, notably T1 tumours in five studies (Anan et al. 2000, Barth et al. 1997, Brenin et al. 2001, Giuliano et al. 1996 and Rivadeneira et al. 2000). Other studies aimed to report on entire treated series and accordingly, patients were analysed without tumour size restrictions. Specht et al. 2005 state no T size criteria, but that all patients had clinically palpable axillary nodes. Table 1 provides a description of each patient series in terms of tumour size and also the surgical staging method used. Grube et al. 2002 report only on patients with invasive lobular carcinoma. Tan, Wu et al. 2005 studied only patients with metastatic sentinel nodes, demonstrated by SLNB.

Table 1 Tumour size and staging method

Study	T criteria	Staging method
Anan et al. 2000	T1	AC
Barth et al. 1997	T1	AC
Brenin et al. 2001	T1	AC
Cao et al. 2005	T1-2 (25mm or less)	SLNB
Chen et al. 2002	T1-T2	SLNB
Cutuli et al. 2001	T0-2 (3cm or less)	AC
Giuliano et al. 1996	T1	AC
Grube et al. 2002	ILC (size range 0.3-9.0cm)	SLNB
Houvenaeghel et al. 2003	T0-2, 3cm or less	AC
Katz et al. 2006	T1-T3 (upper T limit unknown)	SLNB
Peters-Engl et al. 2004	Largest tumour 8cm in size	SLNB
Rivadeneira et al. 2000	T1a-T1b	AC
Specht et al. 2005	palp nodes, T size range not reported.	SLNB
Tan, Tan et al. 2005	T1-2	AC
Tan, Wu et al. 2005	T1-2, N1	SLNB
Velanovich and Szymanski 1998	T1-3	AC

SLNB: Sentinel lymph node biopsy

AC: Axillary clearance/dissection

Risk of axillary metastases:

13 studies reported a prevalence of axillary disease, revealed by staging surgery (Anan et al. 2000, Barth et al. 1997, Brenin et al. 2001, Cao et al. 2005, Chen et al. 2002, Cutuli et al. 2001, Giuliano et al. 1996, Grube et al. 2002, Houvenaeghel et al. 2003, Katz et al.

2006, Rivadeneira et al. 2000, Specht et al. 2005 and Tan, Tan et al. 2005). In these 13 studies, summary statistics for the prevalence of axillary disease are as follows:

Mean: 31.4%
 Median: 27%
 Range: 18%-59%

Specht et al. 2005 reported a prevalence of 59%, but in a series of selected patients with clinically palpable axillary nodes. Discounting this value, the summary statistics become:

Mean: 29.1%
 Median: 27%
 Range: 18%-50%

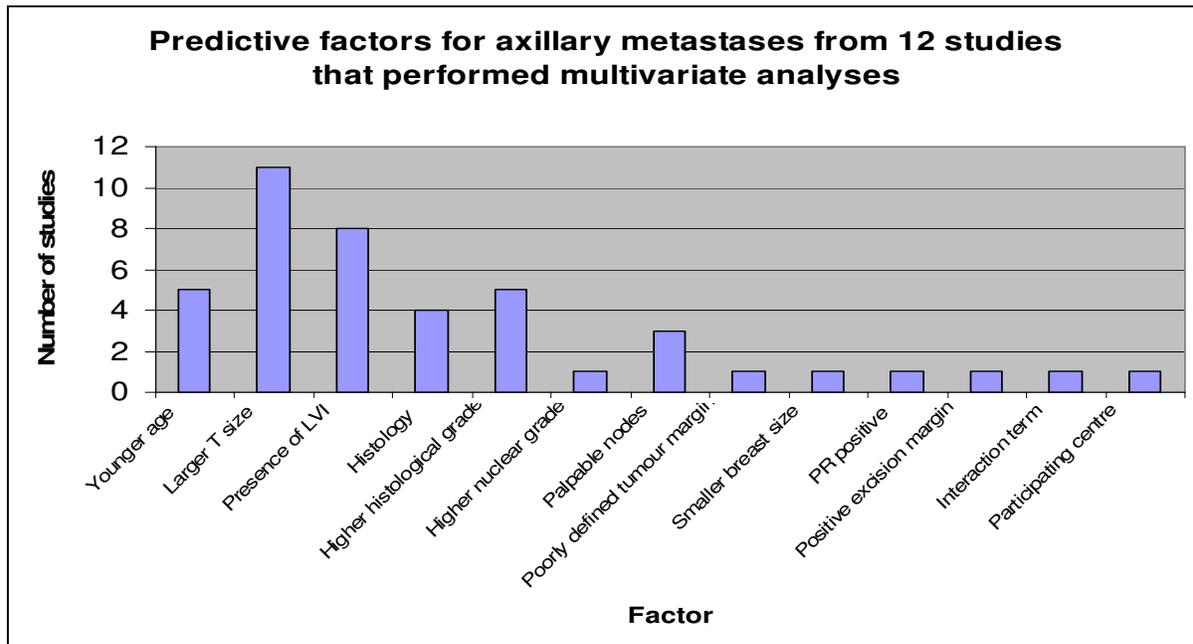
In either case, the mean and median values derived from these studies suggest that approximately 70% of patients who undergo surgical staging for early breast cancer have no axillary disease.

Predictive factors for metastatic axillary nodes

1. Studies that performed multivariate analysis

12 studies reported risk factors for the presence of any metastatic axillary nodes using multivariate analysis; that is, analysis which considers the action of each risk factor variable, independent of the action of other variables (Anan et al. 2000, Barth et al. 1997, Brenin et al. 2001, Cao et al. 2005, Chen et al. 2002, Cutuli et al. 2001, Houvenaeghel et al. 2003, Katz et al. 2006, Peters-Engl et al. 2004, Rivadeneira et al. 2000, Tan, Tan et al. 2005 and Velanovich and Szymanski 1998). The risk factors identified by multivariate analyses within these 12 studies are shown in Figure 1.

Figure 1



Tumour size

Larger tumour size was the most frequently identified (by 11 studies) risk factor for axillary metastasis. Odds ratios (OR) or relative risks (RR) for axillary metastasis by tumour size were reported as follows (Table 2):

Table 2 Tumour size as a risk factor for axillary metastases

Study	Measure	Value
Brenin et al. 2001	OR (T stage T1c>T1b>T1a)	2.9 [95% CI 1.9-4.3]
Cao et al. 2005	RR (for a 1mm increase in tumour size)	1.065 [95% CI 1.038-1.092]
Peters-Engl et al. 2004	OR (for a 1mm increase in tumour size)	1.06 [95% CI 1.05-1.08]
Rivadeneira et al. 2000	OR (for a 1mm increase in tumour size)	3.58 [95% CI 1.18-11.89]
Tan, Tan et al. 2005	OR (T1a relative to T2) OR (T1b relative to T2) OR (T1c relative to T2)	0.06 [95% CI 0.007-0.5] 0.18 [95% CI 0.065-0.49] 0.38 [95% CI 0.22-0.67]
Velanovich and Szymanski 1998	OR (no criterion reported)	1.5 [no 95% CI reported]

Lympho-vascular invasion

Presence of lympho-vascular invasion (LVI) was the second most frequently identified (8 studies) risk factor. Odds ratios (OR) or relative risks (RR) for axillary metastasis by LVI status were reported as follows (Table 3):

Table 3 LVI as a risk factor for axillary metastases

Study	Measure	Value
Brenin et al. 2001	OR (present:absent)	2.6 [95% CI 1.8-3.64]
Cao et al. 2005	RR (present:absent)	9.8 [95% CI 5.46-17.86]
Tan, Tan et al. 2005	OR (present:absent)	7.7 [95% CI 3.5-17]

Higher histological grade and younger age were equally the third most frequently identified factors (5 studies in each case):

Histological grade

Odds ratios (OR) for axillary metastasis by histological grade were reported as follows (Table 4):

Table 4 Histological grade as a risk factor for axillary metastases

Study	Measure	Value
Brenin et al. 2001	OR (Grade III>II>I)	1.6 [95% CI 1.2-2.1]
Peters-Engl et al. 2004	OR (Grade I:III)	0.55 [95%CI 0.32-0.81]
Rivadeneira et al. 2000	OR (Grade III:I)	2.45 [95% CI 1.27-4.68]

Age

Odds ratios (OR) for axillary metastasis by age were reported as follows (Table 5):

Table 5 Age as a risk factor for axillary metastases

Study	Measure	Value
Peters-Engl et al. 2004	OR (for a 1 year increase in age)	0.98 [95% CI 0.97-0.99]
Rivadeneira et al. 2000	OR (≥ 50 years: <50 years)	0.61 [95% CI 0.37-1.02]

Other risk factors

The remaining risk factors for axillary metastasis revealed by the studies included:

- Clinically palpable axillary lymph nodes: this risk factor was reported by three studies: Anan et al. 2000, Barth et al. 1997 and Peters-Engl et al. 2004; the latter study reported an OR (palpable:non-palpable) of 1.77 [95% CI 1.37-2.29].⁸
- Higher nuclear grade (Barth et al. 1997).
- Poorly defined tumour margin (Anan et al. 2000).
- Smaller breast size (Cutuli et al. 2001).
- Progesterone receptor (PR) positive tumour: Tan, Tan et al. 2005 reported OR (positive relative to negative): 1.8 [95% CI 1.0-3.0]
- Positive excision margin: Brenin et al. 2001 reported OR (present:absent) 23.8 [95% CI 5.6-101.2]
- Other factors: three other factors which warrant further explanation were also found to significantly influence the rate of axillary metastases; histological subtype, participating centre and an interaction term:

Histological subtype

The role of tumour histological type is unclear, based on four studies that found tumour histological type to be significantly associated with axillary metastases:

- Katz et al. 2006 found histology to independently predict SN involvement, but with no discernable pattern between histological subtypes, except for the lowest rate of axillary involvement in patients with DCIS.
- Peters-Engl et al. 2004 found ducto-lobular histology to be predictive of axillary metastasis relative to ductal histology (OR 2.16 [95% CI 1.48-3.16], $p=0.0001$).
- Tan, Tan et al. 2005 found that 'other' histology tumours (i.e. other than invasive lobular or invasive ductal carcinomas) were predictive of axillary metastases relative to invasive ductal carcinomas (OR 0.26 [95% CI 0.09-0.72], $p=0.04$).
- Velanovich and Szymanski 1998 found that invasive lobular carcinoma to be strongly predictive of axillary metastases, and tubular or medullary carcinoma to have the opposite effect (OR relative to invasive ductal carcinoma >400000 , $p=0.02$ and OR 0.000006, $p=0.02$, respectively).

Participating centre

⁸ The study by Specht et al. (2005) did not perform multivariate analysis but found that clinical palpation of the axilla had a positive predictive value (PPV) of 59% overall, and a PPV of 77% when only patients with unequivocally suspicious, palpable nodes were analysed.

The multicentre study by Peters-Engl et al. 2004 found that the rate of axillary metastases varied significantly by participating centre, of which there were 12, but with no clear pattern.

Interaction term

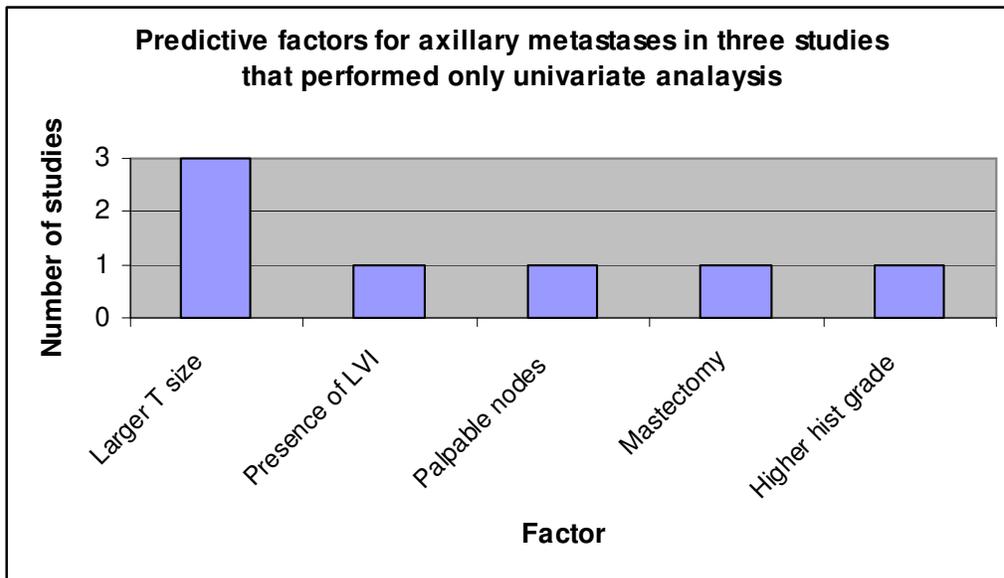
Brenin et al. 2001 modelled an interaction variable for the negative interaction between positive margin and T stage, with OR 0.34 [95% CI 0.2-0.6, p=0.0001]. This indicated that patients with positive margins had risks for axillary metastases largely unaffected by T stage, while increasing T stage conferred an increased risk for patients with negative margins.

2. Studies that performed only univariate analysis

Three studies (Giuliano et al. 1996, Grube et al. 2002 and Specht et al. 2005) reported risk factors for the presence of any metastatic axillary nodes using univariate analysis; that is, analysis which considers only one variable at a time. This analysis for risk factors has the disadvantage that the demonstrated effect of one variable will not take account of the effect of other variables which may also influence the outcome.

The risk factors identified by multivariate analyses within these three studies are shown in Figure 2.

Figure 2



Although the number of studies is small, larger tumour size remained the most frequently reported risk factor for axillary metastases (Giuliano et al. 1996, Grube et al. 2002 and Specht et al. 2005), with reported rates of axillary disease by tumour size as follows (Table 6):

Table 6 Incidence of axillary metastases by T stage

Study	Incidence of axillary disease by T stage
Giuliano et al. 1996	T1a: 10% T1b: 13% T1c: 30% (p<0.002)

Grube et al. 2002	pT1: 24% pT2: 59% pT3: 89% (p=0.001)
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Specht et al. 2005 found that in a series of patients with clinically palpable axillary nodes, mean tumour size was higher in patients with histologically positive axillary nodes compared to those with histologically negative axillary nodes (2.6cm and 1.6cm respectively, p=0.002).

Specht et al. 2005 also demonstrated in the same series that a higher proportion of patients with histologically positive axillary nodes had high grade tumours compared to those with histologically negative axillary nodes (77% and 43% respectively, p=0.002).

In addition to larger tumour size, Grube et al. 2002 found the presence of LVI, clinically palpable nodes and mastectomy surgery (as opposed to breast conserving surgery) to be factors significantly associated with axillary metastases.

Risk factors for macrometastatic sentinel nodes

Tan, Wu et al. 2005 studied risk factors for sentinel node macrometastases (2mm or more in size) in a selected series of patients with metastatic axillary nodes revealed by SLNB. In univariate analysis, the statistically significant risk factors for sentinel node macrometastases were larger tumour size, tubular carcinoma, presence of LVI and two or more positive sentinel nodes.

Risk factors for multiple positive axillary nodes

The study by Velanovich and Szymanski 1998 found, by multivariate analysis, statistically significant risk factors for 10 or more metastatic axillary nodes to be:

Larger tumour size, OR (no increment/category reported)14.8, p=0.026.

Oestrogen receptor (ER) negative tumour: OR 1.1, p=0.05.

DCIS - Evidence Summary

Only a small volume of studies which address SLNB in patients with DCIS were identified (28 studies in total). The best quality evidence comes from a meta analysis of observational studies and a number of case series, all of which provide retrospective analyses.

The meta-analysis showed the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS ranged from 0 to 16.7%. With an overall positivity incidence of 7.4%.

The case series studies vary in their methods of SLNB: six used radiocolloid to identify the sentinel node, nine used radiocolloid plus dye and one study used dye alone. The majority (14) report that immunohistochemistry is used to identify metastases in sentinel nodes. The studies are generally consistent in differentiating between true DCIS, DCISm and invasive disease, usually based upon the definition of DCISm by the American Joint Committee on Cancer: i.e. invasive focus <1mm in size on definitive histology.

No evidence was identified to suggest that a pattern exists between the rate of positive SNs and DCIS tumour grade.

No evidence was identified to suggest that a pattern exists between the rate of positive SNs and DCIS tumour size.

It is not possible to reliably estimate the proportion of patients with DCIS and positive SNs who have further axillary nodal involvement from the studies identified.

Rate of sentinel node involvement

1. Overall

'Pure' DCIS

Two reasonably sized, observational studies have demonstrated rates of detection of positive SNs in patients with DCIS (with no detectable microinvasion) as 1.8% (Veronesi et al. 2005) and 5% (Wilke et al. 2005). The median value from 12 included observational studies is 5.4% (range 0% to 22%).

DCISm

Even in one reasonably sized, observational study (Wilke et al. 2005), the subgroup of patients with DCISm represented only 51 individuals. Among these, the rate of detection of positive SNs was 14%. The median value from 7 included observational studies is 11.1% (range 9.5% to 29.4%).

The majority of the studies identified represent small series of patients, with a median series size of only 43.5 patients for all 16 studies. For this reason, the two studies by Wilkie et al. (2005) and Veronesi et al. (2005) stand out with much larger sizes of 675 patients and 508 patients, respectively. These two studies base their estimates of SN involvement on definitive primary tumour histology. Wilke et al. (2005) found the rate of SN involvement to be 5.6% in the whole series of patients, representing a rate of 5% in patients with pure DCIS and 14% in patients with DCISm. Veronesi et al. (2005) found the rate of SN involvement to be 1.8% in patients with pure DCIS.

All series

In all 17 series of patients the summary statistics for the rate of SN involvement in patients with DCIS are shown below, where the 16 series represent patients with only pure DCIS, only DCISm, or either of DCIS/DCISm:

Mean 7.6%

Median 6.8%

Range 0% to 22%.

[Camp et al. (2005), Cox et al. (1998), Cserni et al. (2002), Farkas et al. (2004), Intra et al. (2003), Katz et al. (2006), Kelly et al. (2003), Klauber-DeMore et al. (2000), Liu, Yang and Chen (2003), Mittendorf et al. (2005), Pendas et al. (2000), Trisal, Qian and Wagman (2004), Veronesi et al. (2005), Wilkie et al. (2005), Zavagno et al. (2005a) and Zavotsky et al. (1999)]

'Pure' DCIS

In the subgroup of patients without evidence of microinvasion (12 series), the summary statistics for the rate of SN involvement is as follows:

Mean 6.6%

Median 5.4%

Range 0% to 22%.

[Camp et al. (2005), Cserni et al. (2002), Katz et al. (2006), Kelly et al. (2003), Klauber-DeMore et al. (2000), Liu, Yang and Chen (2003), Mittendorf et al. (2005), Pendas et al. (2000), Trisal, Qian and Wagman (2004), Veronesi et al. (2005), Wilkie et al. (2005) and Zavagno et al. (2005a)].

DCISm

In the subgroup of patients with evidence of microinvasion (7 series), the summary statistics for the rate of SN involvement is as follows:

Mean 14%

Median 11.1%

Range 9.5% to 29.4%.

[Camp et al. (2005), Intra et al. (2003), Katz et al. (2006), Klauber-DeMore et al. (2000), Liu, Yang and Chen (2003), Wilkie et al. (2005) and Zavotsky et al. (1999)]

2. By tumour grade

Although a total of nine studies [Camp et al. (2005), Cserni et al. (2002), Intra et al. (2003), Katz et al. (2006), Kelly et al. (2003), Klauber-DeMore et al. (2000), Veronesi et al. (2005), Wilkie et al. (2005) and Zavotsky et al. (1999)] provide some data on the rate of positive SNs and primary DCIS tumour grade, the very small numbers of patients with positive SNs within subgroups based on tumour grade prevents meaningful analysis in the majority of studies.

The three studies that presented the rate of positive SNs for each tumour grade level found no pattern [Katz et al. (2006), Intra et al. (2003) and Veronesi et al. (2005)].

3. By tumour size

Similar to the data on DCIS tumour grade above, four studies provided some data on the rate of positive SNs [Katz et al. (2006), Klauber-DeMore et al. (2000), Veronesi et al. (2005) and

Zavotsky et al. (1999)], but the very small numbers of patients with positive SNs within subgroups based on tumour size prevents meaningful analysis in the majority of studies.

Katz et al. (2006) found no statistically significant relationship between the rate of positive SNs and primary DCIS tumour size.

Rate of further axillary node involvement in patients with positive sentinel nodes

The studies are inconsistent regarding whether all patients with DCIS and positive SNs underwent axillary clearance, but 9 studies provide data on the involvement of further axillary nodes [Camp et al. (2005), Cserni et al. (2002), Intra et al. (2003), Katz et al. (2006), Klauber-DeMore et al. (2000), Liu, Yang and Chen (2003), Mittendorf et al. (2005), Pendas et al. (2000) and Veronesi et al. (2005)].

The proportion of patients with further involved axillary nodes out of those with positive SNs *who undergo subsequent axillary clearance* is shown in the table below. Although this proportion has mean 0.1, median zero and mode zero, the numbers of patients represented are usually in single figures, so it is not reliable to rely on the data for this purpose.

Table: Proportion of patients with further involved axillary nodes out of those with positive SNs who undergo subsequent axillary clearance (values refer to number of patients)

Study	A n(positive SN)	B n(underwent axillary clearance)	C n(with further positive axillary node(s))	Proportion: C/B
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Camp et al. (2005)	6	4	0	0
Cserni et al. (2002)	1	1	0	0
Intra et al. (2003)	4	3	0	0
Katz et al. (2006)	10	3	1	0.33
Klauber-DeMore et al. (2000)	12	9	1	0.11
Liu, Yang and Chen (2003)	3	3	1	0.33
Mittendorf et al. (2005)	9	5	1	0.2
Pendas et al. (2000)	5	5	0	0
Veronesi et al. (2005)	9	8	0	0

Change in treatment decisions

None of the selected studies reported changes to treatment plans as a result of staging by SLNB, and all studies were retrospective in nature. However five studies provided data on patients who were upstaged from the stage attributed by primary tumour biopsy, in the light of final, primary tumour histology from definitive surgery:

Upstaging to invasive disease by definitive surgery

One single, retrospective case series study [Wilkie et al. (2005)] provides evidence that 10% [95% CI 7.8% to 12.2%]⁹ of patients staged by biopsy as having DCIS (including DCISm) and who undergo SLNB are found to have invasive disease by primary tumour histology revealed by definitive surgery.

Five of the selected studies report rates of upstaging by definitive surgery [Wilkie et al. (2005), (Camp et al. (2005), Mittendorf et al. (2005), Liu, Yang and Chen (2003) and Zavotsky et al. (1999)]. These data represent only patients with DCIS who were staged by SLNB, so more reliable data are probably available in the literature, which represent also patients with DCIS who are not staged by SLNB.

The largest series (n=675) in the studies selected is that studied by Wilkie et al. (2005). In this series 10% [95% CI 7.8% to 12.2%]⁹ of patients with a biopsy diagnosis of DCIS, including DCISm, were upstaged to invasive disease by definitive surgery.

The other series are much smaller and hence less reliable, but report upstaging from DCIS to invasive disease at rates of 4%, 7.3% and 12.5% [(Camp et al. (2005), Mittendorf et al.

⁹ 95% CI calculated using a spreadsheet constructed by Newcombe (2006), available online at:http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/index.htm. Last accessed: 3.10.06

(2005) and Liu, Yang and Chen (2003), respectively]. Liu, Yang and Chen (2003) also report a rate of upstaging from DCIS to DCISm of 12.5% and Zavotsky et al. (1999) report a rate of upstaging from DCISm to invasive disease of 28.6%, but based on only 14 patients.

Cost effectiveness

None of the selected studies reported cost effectiveness as an outcome measure.

EVIDENCE UPDATE

A meta-analysis (Ansari *et al.* 2008) of observational studies detailed reported data on the incidence of SLN metastasis in patients with DCIS. This analysis reported SLN biopsy results in patients with the diagnosis of DCIS.

Twenty-two publications reporting SLN biopsy results in patients with the diagnosis of DCIS were included giving a combined study population of 3166 patients.

- Studies that assessed the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS reported values from 0 to 16.7%
- The test for heterogeneity suggested that these 11 studies were not significantly heterogeneous ($\chi^2 = 16.07$, 10 df $P = 0.098$).
- A meta – analysis of the data on SLN positivity from these studies gave an overall positivity frequency (or overall incidence) = 7.4% (95 %CI 6.2 - 8.9)
- There was significant between study heterogeneity in the 11 studies of patients with a definitive (postoperative) diagnosis of DCIS ($\chi^2 = 27.82$, 10 df, $P = 0.002$).
- A meta-analysis of the data on SLN positivity from these studies showed an overall positivity frequency (or overall incidence) = 3.7% (95%CI 2.8 – 4.8)
- The overall frequencies of nodal metastasis between the two groups (preoperative versus definitive diagnosis) were significantly different with an odds ratio of 2.11 (95 %CI 1.15-2.93)
- A subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component were presented (from a literature search with some inconsistencies occurring between studies): Most of these studies suggested that a palpable mass; a mammographic mass; a high-grade lesion and a large size were associated with a significant risk of invasive disease in the final resection specimen.

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Evidence Tables

Invasive breast cancer SLNB versus axillary clearance or axillary sampling

Abbreviations:

SLNB technique:

Radiocolloid (R)

Lymphoscintigraphy (L)

Blue dye (D)

Histology technique:

Standard method e.g. Haematoxylin and Eosin, (S)

Frozen section (FS)

Immunohistochemistry (IHC)

Randomized controlled trials

Julian . Preliminary technical results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients. 2004.

Design: Randomized controlled trial (therapy), evidence level: 1

Country: United States, setting: Secondary care

Inclusion criteria Women with operable invasive breast cancer.

Exclusion criteria Not reported

Population number of patients = 5210.

Interventions NSABP B-32 RCT

Intervention:

SLNB. Patients with disease positive SN were treated with axillary clearance and patients staged as N0 had no further surgery.

Control:

SLNB with immediate conventional axillary clearance.

SLNB technique

R, D.

Histology

FS, S.

Outcomes RCT will measure morbidity, recurrence and survival.

Follow up Not reported

Results

STAGING

Sentinel node localisation rate (all patients) = 97%.

FNR (based on control group) = 9.7%.

General comments Staging data represent the performance achieved by 233 surgeons who had previously completed training cases to reach the standard to enrol patients to the RCT.

To date study has only reported preliminary technical results in abstract form.
Insufficient data available to calculate 95% confidence intervals.

Purushotham, Upponi, Klevesath, Bobrow, Millar, Myles & Duffy . Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23[19]. 2005.

Design: Randomized controlled trial (diagnosis, screening), evidence level: 1+
Country: United Kingdom, setting: Secondary care

Inclusion criteria Patients with breast cancer tumours of size 3 cm or less.

Exclusion criteria Not reported

Population number of patients = 298, mean age = 58 years.

Interventions Aim: to investigate physical and psychological morbidity following SLNB versus axillary clearance.

Intervention group: underwent SLNB. Patients with disease positive SNs were treated with axillary clearance and patients staged as N0 had no further surgery.

Control group: underwent axillary clearance.

SLNB technique

R, D.

Histology

S, IHC.

Outcomes

Physical morbidity:

Postoperative arm numbness, lymphoedema, paresthesia, swelling, shoulder mobility and seroma formation.

Psychological morbidity:

Beck depression Inventory (BDI)

State - trait anxiety inventory

Brief symptom inventory (BSI) and the closely related global severity index (GSI) to measure presence/absence of clinically significant psychological morbidity.

Mental adjustment to cancer scale (MAC) to measure psychological coping.

SF-36 quality of life scale

Visual analogue scale of quality of life i.e. patients self scored on a continuous scale of 0 to 100.

Follow up 12 months

Results

MORBIDITY

Assessment of outcome was taken at 1, 3, 6 and 12 months post-operatively.

Lymphoedema:

At 12 months follow-up the SLNB group had smaller mean increases in objectively measured arm volume than the axillary clearance group; at 12 months this difference was 37.8 ml in favour of SLNB ($p=0.004$).

Seroma:

The odds of seroma formation between groups were not statistically significantly different: the OR for seroma formation in SLNB group relative to axillary clearance group was given as 0.60 (95% CI 0.33 - 1.11) and $p=0.1$.

Sensory outcomes:

Patients in the SLNB group were statistically significantly less likely to experience numbness (OR 0.32, 95% CI 0.19 - 0.51), loss of sensation to pinprick (OR 0.38, 95% CI 0.22 - 0.64), loss of light touch (OR 0.39, 95% CI 0.23 - 0.65) and paresthesia (OR 0.36, 95% CI 0.20 - 0.66) in the year following surgery than patients in the axillary clearance group.

Shoulder mobility:

Shoulder mobility was assessed in five different arm movements: Only one of five arm movements (flexion) was significantly different between randomised groups, with a significant difference in mean reduction of movement of 6.3 (95% CI 0.1 - 12.6) degrees favouring SLNB ($p = 0.04$).

Psychological morbidity:

There was no significant difference between randomised groups in depressive symptoms or state anxiety during the one-year follow up period.

BSI & GSI:

The SLNB group consistently had lower mean global GSI score than the axillary clearance group, but this was significant only at the immediate postoperative assessment (i.e. SLNB: 49.7, axillary clearance: 52.9, $p=0.01$) and ceased to be significant when adjusted for trait anxiety.

There were no significant differences between SLNB and axillary clearance groups in MAC scores at any point by ITT.

In the immediate postoperative period the SF-36 physical combined score ($p=0.001$), physical functioning score ($p=0.003$) and vitality score ($p=0.004$) were significantly higher (reflecting better quality of life) in the SLNB group than the axillary clearance group.

Visual analogue scale:

In the immediate postoperative period, the QOL score was significantly higher (reflecting better quality of life) in the SLNB group than the axillary clearance. ($p = 0.01$).

General comments RCT was undertaken at 3 centres.

Random allocation was well conducted. It is not feasible that patients or surgeons remained blinded thereafter.

The authors report that there were no significant differences between study groups for patient and disease characteristics. However, no details were provided of statistical

testing.

57 patients in the SLNB group underwent subsequent axillary clearance (48 due to positive SN status and 9 SLNB failures). Since only ITT analyses are cited, the effect is to attenuate the often-observed differences in favour of SLNB.

Although many analyses were performed, alpha values were reduced a priori in some instances to reduce the risk of type I errors.

Losses to follow up and non-analysed patients were fully reported.

'Baseline' measurements were made at 7-14 days post surgery as a surrogate for a true baseline; considered by the authors to be more ethical than a preoperative assessment. It is possible, based on this range, that patients were assessed for baseline with up to a whole week's difference in time since surgery. It is not possible to tell to what extent the randomisation process was able to overcome this imprecision.

Veronesi, Paganelli, Viale, Luini, Zurrada, Galimberti, Intra, Veronesi, Robertson, Maisonneuve, Renne, De, De & Gennari . A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349[6]. 2003.

Design: Randomized controlled trial (diagnosis, screening), evidence level: 1+
Country: Italy, setting: Secondary care

Inclusion criteria Women patients with primary, unifocal breast cancer tumours ≤ 2 cm in diameter.

Eligible age range 40 to 75 years

Exclusion criteria Male patients and those scheduled to undergo mastectomy.

Population number of patients = 516.

Interventions

Aim: To evaluate the staging performance, side effects and disease-related events in patients staged by SLNB, compared to axillary clearance.

Intervention group: SLNB followed by axillary clearance if SN positive (n=259).

Control group: SLNB plus axillary clearance (n=257).

SLNB technique

L, R.

Histology

FS.

Outcomes

Diagnostic test parameters.

Overall survival (using Kaplan-Meier method and log rank test) and incidence of breast cancer-related events.

Surgical side effects:

Axillary pain;

Numbness ;

Arm mobility;

Arm swelling (by difference in circumference from that of untreated arm).

Follow up 24 months

Results STAGING

Data from entire study:

Sentinel node localisation rate (based on 532 randomised patients) = $527/532 = 99.1\%$ (95% CI 97.8% to 99.6%): the 5 cases of SLNB failure were among 16 cases not analysed for outcomes.

However in 649 patients considered for this RCT, the SN localisation rate was $638/649 = 98.3\%$ (95% CI 97.0% to 99.1%).

Number of SNs removed per patient: mean 1.7 (no range available).

Data from control group only:

Prevalence of axillary disease = $91/257 = 35.4\%$ (95% CI 29.8% to 41.4%).

Accuracy = $249/257 = 96.9\%$ (95% CI 94.0% to 98.4%).

FNR = $8/91 = 8.8\%$ (95% CI 4.5% to 16.4%).

MORBIDITY (non ITT analysis)

Assessment of outcome was made at 24 months after surgery.

The 259 patients who underwent axillary clearance stayed in hospital for an average (presumably mean) of 4.3 days, compared to 2.1 days for 167 patients who underwent SLNB only.

A sample of 100 patients who underwent SLNB only had less pain, numbness and arm swelling and better arm mobility at 2 years' follow up than a sample of 100 patients who underwent SLNB plus axillary clearance:

Respective percentages that were pain free were 92% and 61% (difference 31%, 95% CI 19.6% to 41.5%).

Respective percentages reporting numbness were 1% and 68% (difference 67%, 95% CI 56.4% to 75.4%).

Respective percentages with arm mobility =80% were 100% and 79% (difference 21%, 95% CI 13.2% to 30.0%).

Respective percentages with a difference in arm circumference =1cm compared to the other arm were 7% and 37% (difference 30%, 95% CI 18.9% to 40.4%).

RECURRENCE (ITT analysis)

Median follow up (of 516 patients) = 46 months.

15 breast cancer-related events occurred in the control group versus 10 in the intervention group, with no significant difference between groups in cumulative incidence of breast cancer related events ($p=0.26$, log rank test)

Recurrence of tumour in the treated breast occurred in 1 (0.4%) patient in the intervention group and 1 (0.4%) patient in the control group;

A primary tumour in the contralateral breast occurred in 2 (0.8%) patients in the intervention group and 3 (1.2%) patients in the control group;

Axillary recurrence occurred in 2 (0.8%) patients in the intervention group and 0 (0%) patients in the control group;

Distant metastases occurred in 10 (3.9%) patients in the intervention group and 6 (2.3%) patients in the control group.

SURVIVAL (ITT analysis)

There was no statistically significant difference in overall survival between the two groups. Overall, 8 patients died: 6 in the control group (2 (0.8%) from breast cancer) and 2 in the intervention group (1 (0.4%) from breast cancer, $p=0.15$, log rank test).

General comments

Subjects who were not eligible for the trial, who refused randomisation or who were not evaluable were fully reported. No subjects are reported as dropping out of the study.

Randomisation was well reported but blinding of patients or investigators was unlikely thereafter.

Informed consent and ethical approval were evident.

No significant differences were found between the intervention and control groups in terms of demography, tumour characteristics or prognostic factors.

Morbidity outcomes were not statistically tested, nor were confidence intervals provided.

Surgical side effects were compared between 100 consecutive patients from the control group (who underwent SLNB plus axillary clearance) with a sample of 100 patients from the intervention group who underwent SLNB only, using an interview at 6 months follow-up and a questionnaire at 24 months follow-up.

This non-ITT analysis was presumably restricted to 200 patients due to the large amount of effort required to interview patients and issue and collate questionnaires. 95% CIs were not constructed for these proportions reported in the paper since the proportions are of convenience samples and are of limited value.

There is little suggestion of bias in this study. The main limitation is that follow up period was relatively short such that survival and recurrence information was incomplete.

Fleissig, Fallowfield, Langridge, Johnson, Newcombe, Dixon, Kissin & Mansel . Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Research & Treatment 95[3]. 2006.

Design: Randomized controlled trial (diagnosis, screening), evidence level: 1++
Country: United Kingdom, setting: Secondary care

Inclusion criteria Patients with primary, invasive breast cancer of age <80 years and scheduled for mastectomy or breast conserving surgery.

Patients had to be clinically node negative but with any tumour size.

Exclusion criteria Multicentric cancer, previous ipsilateral breast or axillary surgery other than benign excision biopsy, previous ipsilateral radiotherapy to axilla or breast, pre-existing limb disease causing swelling, known allergy to patent blue dye/human albumin, pregnancy/breast feeding, inability to complete quality of life questionnaire in English.

Population number of patients = 829, age range 28 to 80 years, mean age = 57 years.

Interventions

Aim: to report fully on quality of life data from the ALMANAC RCT which compared standard axillary surgery (axillary clearance or FNS) with SLNB, and to report on the role of axillary node status, age, type of breast surgery and right/left handedness.

Intervention group (n=515) underwent SLNB. Patients with disease positive SN underwent axillary clearance or radiotherapy and patients staged as N0 had no further treatment.

Control group (n=516) underwent standard axillary management (axillary clearance or node sampling).

SLNB technique

L, R, D.

Histology

S.

Outcomes

Quality of life using:

Trial Outcome Index (TOI) = sum of FACT-B physical and well-being subscales NB: Maximum score 108 reflecting high quality of life, with a change in 5 points regarded as a meaningful difference.

Arm functioning subscale score (range 0-20) and FACT-B+4 score (range 0-160), reflecting global quality of life.

Spielberger State/Trait Anxiety Inventory (STAI), where higher scores indicate greater anxiety.

Follow up Follow up in this paper is longer than that reported by Mansel et al. (2006) i.e. to 18 months from surgery.

Outcomes were assessed at 1, 3, 6, 12 and 18 months, by questionnaire.

Results

Paper provides further information to that of Mansel et al. (2006) as follows:

TOI:

Two-way ANOVA examined the change in TOI from baseline to each study time point between randomised groups and in different age groups. This revealed a significant effect of treatment group (1 month $p<0.001$, 3 months $p=0.027$, 6 months $p=0.017$, 12 months $p=0.011$, 18 months $p=0.006$) in favour of the SLNB group and a significant effect of age ($p<0.001$) in favour of older patients for the first 6 months after surgery.

There was no significant interaction between treatment group and age.

Two-way ANOVA examined the mean change in TOI from baseline to each of the study time points between randomised groups and whether the patient had WLE or mastectomy. This

revealed a significant effect of treatment group in change of TOI from baseline to 1 month ($p=0.021$). There were no other significant effects.

ARM MORBIDITY

Arm functioning subscale:

Two-way ANOVA examined the change in arm functioning subscale score from baseline to each of the study time points between randomised groups and in each age group. This revealed a significant effect of treatment group ($p<0.001$) in favour of the SLNB group and a significant effect of age (1, 12 months $p=0.001$, 3 months $p=0.003$, 6, 18 months $p=0.002$) in favour of older patients. There was no significant interaction between randomised group and age.

Effect of surgery on the dominant arm:

Patients, who had surgery on the same side as their dominant arm, had similar arm functioning scores as patients, who had surgery on the contralateral side.

Two-way ANOVA examined the change in arm functioning in each randomised group and whether the operation was on the same or the opposite side to the dominant hand. There was a significant effect in the change of arm functioning by treatment group at each follow up ($p<0.001$), but no significant effects related to handedness and no significant interaction effects.

PATIENT REPORTED ARM PROBLEMS

(All proportions tested by Chi square)

Swollen/tender arm:

At each postal follow-up the proportion of patients reporting the problem (somewhat/quite a bit/very much) of a swollen or tender arm was significantly higher in the standard treatment group than in the SLNB group ($p<0.001$ at 1, 3, 6 months and $p=0.002$ at 12 and 18 months).

Numbness:

The proportion of patients reporting numbness in their arm on the operated side was also significantly higher in the standard treatment group than in the SLNB group ($p < 0.001$ at 1, 3, 6, 12, and 18 months).

Pain:

The proportion of patients reporting painful movement of the arm on the operated side was higher in the standard treatment group than in the SLNB group at 1, 3 months ($p < 0.001$) and 12 months ($p = 0.005$) after surgery, but not significantly different at 6 months ($p = 0.694$) or 18 months ($p = 0.159$) after surgery.

Poor range of movement:

The proportion of patients reporting poor range of movement on the operated side was significantly higher in the standard treatment group than in the SLNB group at the 1 month ($p < 0.001$) and 3 months ($p = 0.035$) postal follow-ups but differences between groups were no longer significantly different at later follow-ups (6 months $p = 0.167$, 12 months $p = 0.142$ and 18 months $p = 0.266$).

Stiffness:

At each postal follow-up the proportion of patients reporting stiffness of the arm on the operated side (somewhat/quite a bit/very much) was higher in the standard treatment group than in the SLNB group, but the difference between groups was not always statistically significant ($p < 0.001$ at 1 month, $p = 0.031$ at 3 months, $p = 0.089$ at 6 months, $p = 0.038$ at 12 months, $p = 0.051$ at 18 months).

QUALITY OF LIFE

FACT-B+4 score:

Two-way ANOVA examined change in FACT-B+4 from baseline to each of the study time points between randomised groups and in each age group (under 50, 50-64, 65 and older). This revealed a significant effect of treatment group (1 month $p < 0.001$, 3 months $p = 0.04$, 12 months $p = 0.024$, 18 months $p = 0.019$) except at 6 months ($p = 0.059$), in favour of the SLNB group and a significant effect of age ($p < 0.001$) in favour of older patients for the first 6 months after surgery. There was no significant interaction between treatment group and age.

Two-way ANOVA examined the mean change in FACT-B+4 from baseline to each of the study time points between randomised groups and in patients having WLE or mastectomy. This revealed a significant effect of treatment group on change in FACT-B+4 from baseline to 1 month ($p = 0.014$). There were no other significant effects.

Anxiety:

State anxiety scores at baseline and during the trial did not vary by randomised group. There were also no significant differences between the anxiety levels of patients in the SLNB group, with positive nodes, who went on to have axillary clearance at a second operation, compared with patients in the control (standard treatment) group who were node positive.

Two-way ANCOVA examining the effects of randomised group and age group on state anxiety demonstrated a significant effect of age on anxiety for the first 6 months after surgery (1 month $p < 0.001$, 3 months $p = 0.01$, 6 months $p = 0.007$, 12 months $p = 0.138$, 18 months $p = 0.302$) in favour of older patients. There were no significant effects of treatment

group and no significant interaction effects.

General comments

NB Same RCT as Mansel et al. (2006).

829 patients returned questionnaires: 424 in the SLNB group and 405 in the standard treatment group. 80% (662/829) of patients returned all 6 questionnaires. 32 questionnaires were invalid and were excluded from the analysis.

All analyses were by intention to treat unless otherwise stated.

Three age groups were analysed: under 50, 50-64, 65 and older.

The three age groups analysed differed with regard to tumour grade, proportion of screen detected cancers, proportion of breast conserving surgery operations and likelihood of receiving adjuvant therapy.

Mansel, Fallowfield, Kissin, Goyal, Newcombe, Dixon, Yiangou, Horgan, Bundred, Monypenny, England, Sibbering, Abdullah, Barr, Chetty, Sinnott, Fleissig, Clarke & Ell . Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial.[see comment]. J Natl Cancer Inst 98[9]. 2006.

Design: Randomized controlled trial (harm), evidence level: 1++
Country: United Kingdom, setting: Secondary care

Inclusion criteria Patients with primary, invasive breast cancer of age <80 years and scheduled for mastectomy or breast conserving surgery.

Patients had to be clinically node negative but with any tumour size.

Exclusion criteria Multicentric cancer, previous ipsilateral breast or axillary surgery other than benign excision biopsy, previous ipsilateral radiotherapy to axilla or breast, preexisting limb disease causing swelling, known allergy to patent blue dye/human albumin, pregnancy/breast feeding, inability to complete quality of life questionnaire in English.

Population number of patients = 991.

Interventions ALMANAC RCT

Aim: to compare morbidity following standard axillary surgery (axillary clearance or FNS) with SLNB.

Intervention group (n=515) underwent SLNB. Patients with disease positive SN underwent axillary clearance or radiotherapy and patients staged as N0 had no further treatment.

Control group (n=516) underwent standard axillary management (axillary clearance or node sampling).

SLNB technique

L, R, D.

Histology

S.

Outcomes Arm morbidity (including subjective and objective assessment of lymphoedema, the latter based upon % volume changes from baseline calculated from numerous circumference measurements, using the contralateral arm as a control)

Quality of life using:

An enhanced Functional Assessment of Cancer Therapy - Breast questionnaire, plus 4 additional arm morbidity items (FACT-B+4);

Trial Outcome Index (TOI) = sum of FACT-B physical and well-being subscales NB: Maximum score 108 reflecting high quality of life, with a change in 5 points regarded as a meaningful difference.

Spielberger State/Trait Anxiety Inventory (STAI).

Axillary recurrence rate

Follow up Patients were reviewed at 1, 3, 6, 12 and 18 months after surgery.

This paper reports data up to 12 months from surgery.

Results

STAGING

SN localisation rate was 504/515 = 97.9% (95% CI 96.2% to 98.8%).

44/468=9.4% of patients who underwent lymphoscintigraphy had SNs in the internal mammary chain. A further seven SNs in the internal mammary chain were revealed only with a gamma probe.

Number of SNs removed per patient: median 2, range 1-11.

In the control group 123 patients underwent FNS with a median of 5 ANs removed (range 2-25). 373 patients underwent axillary clearance;

Number of ANs removed per patient in axillary clearance: median 15, range 1-42).

Prevalence of axillary disease was similar between randomised groups: 26% in the intervention group and 23% in the control group (difference = 2.4%, 95% CI -3.0% to 7.7%).

MORBIDITY

Patient reported lymphoedema:

The proportion of patients reporting moderate or severe arm swelling was significantly greater in the standard treatment arm compared to the SLNB arm at 1, 3, 6 and 12 months follow up (e.g. 13% and 5% respectively at 12 months, $p < 0.001$, Chi square test).

RR of any lymphoedema in SLNB group compared to standard treatment group = 0.37 (95% CI 0.23-0.60)

Objectively assessed lymphoedema:

Patients in the standard treatment group had statistically significantly more arm swelling at 1, 3 and 6 months after surgery than patients in the SLNB group ($p < 0.001$, $p = 0.001$ and $p = 0.003$ respectively, t test; e.g. ratio of arm volume at 6 months to arm volume at baseline: 1.02 in the SLNB group and 1.06 in the standard treatment group). This difference ceased to be statistically significant at 12 months.

Sensory deficit:

At all time points a greater proportion of patients in the standard treatment group had physician assessed sensory loss than in the SLNB group ($p < 0.01$ for all, Chi square) e.g. at 12 months follow up, 31% of patients in the standard treatment arm had physician assessed sensory loss compared with 11% in the SLNB arm.

RR of sensory deficit at 12 months was 0.37 (95% CI 0.27-0.50) in favour of the SLNB group.

Patients in the standard treatment group had more extensive physician-assessed intercostal brachial nerve damage (based on mild, moderate, severe, $p < 0.001$ for all, Chi square); e.g. 9% of patients in the SLNB group had moderate or severe nerve damage compared with 31% in the standard treatment group.

Shoulder function:

Patients in the standard treatment group experienced statistically significantly more impairment of shoulder

flexion and abduction on the ipsilateral side at 1 month after surgery ($p = 0.004$ and $p = 0.001$, respectively, t test). However, shoulder flexion and abduction improved rapidly at

the subsequent time points in both groups, and differences between the groups were no longer statistically significant. There was no statistically significant difference in shoulder internal or external rotation between the two groups at any time point.

Other efficacy assessments:

A significantly greater proportion of patients in the standard treatment arm (79%) required surgical drains compared to the SLNB arm (17%) ($p < 0.0001$, Chi square test).

11% of patients in the SLNB group experienced an infection in hospital compared with 15% in the standard treatment group ($p = 0.051$, Chi square).

Patients in the SLNB arm returned to normal activities statistically significantly more quickly compared to the standard treatment arm ($p = 0.001$, Mann Whitney test); e.g. at 3 months the proportions, respectively in each group that had resumed their normal activities were 94% and 91%. There was no statistically significant difference between randomised groups in the time taken to return to paid work.

MEASURES OF QUALITY OF LIFE

The proportion of patients for whom the TOI score decreased from baseline by at least five points was statistically significantly higher in the standard treatment group than in the SLNB group at all time points ($p < 0.001$, at 1 and 3 months after surgery; $p = 0.002$, 6 months after surgery; $p = 0.001$, 12 months after surgery).

Arm functioning subscale:

Compared with baseline, arm functioning subscale score at 1, 3, 6, and 12 months after surgery was worse in both groups, but the impairment was greater in the standard group than in the sentinel lymph node biopsy group ($p < 0.0001$, t test).

FACT-B+4:

The change in scores from baseline was statistically significantly less favourable for the standard treatment group than for the SLNB group at 1 month ($p < 0.001$, t test), 3 months ($p = 0.001$), 6 months ($p = 0.003$), and 12 months ($p = 0.002$) after surgery e.g. at 12 months scores in each respective group were 130.5 (95% CI 128.4-132.6) and 132.7 (95% CI 130.9-134.6).

STAI:

There was no difference between randomised groups at any time point in the mean trait anxiety score or the mean state anxiety score.

RECURRENCE

At 12 months from surgery 4 patients in the standard treatment group and 1 patient in the SLNB group experienced axillary recurrence (difference = 2.7%, 95% CI -1.5%-7.8%).

SURVIVAL

There were 7 deaths in each group; 2 due to metastatic breast cancer in the standard treatment group and 2 due to metastatic breast cancer in the SLNB group.

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General comments Data on local recurrence and survival will be published at a later date with data from the ongoing NSABP-32 and ACOSOG trials.

After SLNB 92% of patients in each study arm received breast conserving surgery and 8% of patients in each study arm received mastectomy.

Power calculation performed. All analyses reported are by ITT.

Patients were randomised on a 1:1 basis to each group.

At baseline, the two groups were similar in terms of quality of life scores and patient and tumour characteristics.

The study benefited from a standardised validation phase across all 15 participating centres with the aim of standardising surgical competence (see Clarke, Newcombe and Mansel, 2004).

1031 patients were randomised. Due to patient ineligibility, refusal of initial management, 495 patients underwent SLNB and 496 patients underwent standard axillary surgery. Trial accrual stopped early due to concern with loss of equipoise in terms of morbidity.

17% of patients in the SLNB group underwent axillary clearance and 25% of the patients in the standard treatment group underwent FNS: this serves to attenuate the morbidity benefit of SLNB in the ITT analysis.

The finding of less surgical drain use in the SLNB group than in the standard treatment group is not surprising since the authors report that drain use is routine only following axillary clearance procedures.

Ung . Australasian experience and trials in sentinel lymph node biopsy: The. Asian Journal of Surgery 27[4]. 2004.

Design: Randomized controlled trial (diagnosis, screening), evidence level: 3
Country: New Zealand/Australia, setting: Secondary care

Inclusion criteria Women with invasive breast cancer and tumour size < 3.0 cm.
68% of patients were aged between 50 and 69 years.

Exclusion criteria -

Population number of patients = 150.

Interventions SNAC trial; in progress in 32 centres.

Aim: to compare SLNB with axillary clearance with regard to morbidity, recurrence and survival.

This paper reports on the staging performance based upon an interim analysis of the first 150 randomised patients.

Experimental group (n=75):

SLNB with subsequent axillary clearance if the SN is positive and no further surgery if the SN is negative.

Control group (n=75):

SLNB plus immediate axillary clearance.

SLNB technique

Varied by centre: combinations of L, R and D were employed.

Histology

S, IHC.

Outcomes Staging performance of SLNB reported here.

Follow up -

Results STAGING

Sentinel node localisation rate (in both groups combined) = 146/150 = 97.3% (95% CI 93.3% to 99.0%).

Number of SNs removed per patient: mean = 239/150 = 1.6.

Data from control group only:

Prevalence of axillary disease (based upon control group only) = 21/73 = 28.8% (95% CI 19.7% to 40.0%).

Accuracy = 70/71 = 98.6% (95% CI 92.4% to 99.8%).

FNR = 1/21 = 4.8% (95% CI 0.9% to 22.7%).

General comments Randomisation was undertaken centrally, with stratification for age (<50 versus =50 years), tumour palpability (palpable versus non-palpable), combinations of lymphatic mapping, gamma probe and blue dye to locate the SN and institution.

These data are not truly based upon RCT design, since staging information is largely derived from the control group alone. Study is graded accordingly here.

A validation phase preceded randomisation of patients: surgeons were required to demonstrate satisfactory performance in SLNB plus axillary clearance in 20 procedures with localisation rate =90%. Therefore, this study provides staging data using mature techniques, accepting some variability in precise method between centres.

Hung, Chan, Ying, Chong, Mak & Yip . Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. The British journal of surgery 92[12]. 2005.

Design

Randomized controlled trial (diagnosis, screening), evidence level: 1+
Country: Hong Kong, setting: Secondary care

Inclusion criteria

123 women with early breast cancer.

Exclusion criteria

Age over 70 years, tumour greater than 3cm in size, multicentric tumour, previous breast/axillary surgery, pregnancy.

Population

Mean age = 52 years.

Interventions

Aim: to compare the staging performance of SLNB when performed with radiocolloid plus dye versus SLNB when performed with dye alone.

Combined technique group (n=61): underwent SLNB with radiocolloid and dye (including lymphoscintigraphy) and immediate axillary clearance to level I/II.

Blue dye group (n=57): underwent SLNB with dye alone and immediate axillary clearance to level I/II.

Outcomes

Staging performance of SLNB.

Follow up

Not reported.

Results

Staging performance; blue dye technique:

SN localisation rate = 49/57 = 86%

Mean no. SNs removed per patient = 1.8

Prevalence of axillary disease = 25/57 = 44%

FNR = 1/22 = 4.5%

Accuracy = 48/49 = 98%

Staging performance; combined technique:

SN localisation rate = 61/61 = 100%

Mean no. SNs removed per patient = 2.1

Prevalence of axillary disease = 33/61 = 54%

FNR = 0/33 = 0%

Accuracy = 61/61 = 100%

The SN localisation rate was significantly higher with combined technique (100%) compared to blue dye technique (86%), p=0.002, Chi square. Accuracy and FNR were not statistically significantly different between the two techniques.

General comments

A power calculation performed indicated a target size of 70 subjects in each group.

Each group was comparable for patient/tumour factors that could be expected to affect the SLNB procedure (statistically tested).

FNR reported here (based on 2:2 table) is $c/(a+c)$ whereas authors reported FNR as $c/(\text{total patients with identified SNs})$ which is the complement of accuracy.

Prevalence for the dye only group is based on whole group including patients in whom SLNB failed.

Of 123 patients randomised, 5 were excluded due to definitive diagnosis of DCIS and two due to inappropriate administration of blue dye .

Case control study

Leidenius, Krogerus, Tukiainen & Von . Accuracy of axillary staging using sentinel node biopsy of diagnostic axillary lymph node dissection - A case-control study. APMIS 112[4-5]. 2004.

Design: Case control study (diagnosis, screening), evidence level: 2-
Country: Finland, setting: Secondary care

Inclusion criteria Patients with histologically unifocal, invasive breast cancer with tumour size \leq 30mm.

Exclusion criteria -

Population number of patients = 332.

Interventions Aim = to examine whether higher prevalence is detected by SLNB than axillary clearance based on a more exhaustive histology technique employed in SLNB. 166 patients staged by SLNB were matched 1:1 with 166 patients staged by axillary clearance.

Matching factors included age, tumour size, histological type and grade.

SLNB technique

L, R, D.

Histology

SLNB: FS, S, IHC.

axillary clearance: S.

Outcomes Difference in attributed axillary disease prevalence between groups, by analysis of discordant pairs i.e. proportion of patients staged as axillary positive by SLNB, compared to axillary clearance.

Follow up -

Results STAGING

Number of SNs removed per patient: mean 2.6 (range 1 to 9)

Number of ANs removed per patient: mean 13.8 (range 6 to 27).

Axillary metastases were detected in 62 (37.4%) of SLNB patients and 51 (30.7%) of axillary clearance patients i.e. an apparent upstaging effect of 6.7% (difference 6.7%, 95% CI -3.6% to 16.6%) arising in SLNB patients.

57 pairs were discordant in relation to detection of axillary metastases. In 34 discordant pairs the SLNB patient had axillary metastasis detected and in 23 discordant pairs the axillary clearance patient had axillary metastasis detected ($p=0.19$, Chi square McNemar). Therefore, no group emerged as significantly more likely to be staged as axillary positive.

In the 57 discordant pairs, mean tumour size was 15.1mm (range 6 to 30 mm) in axillary node positive patients and 15.4 (range 7 to 28) mm in axillary node negative patients ($p = 0.81$, Mann-Whitney U).

Mean age was 59.9 (range 42 to 86) years in axillary node positive patients and 59.4 (range 36 to 83) years in axillary node negative patients ($p = 0.98$, Mann-Whitney U). Therefore, neither tumour size nor age appeared to explain positive axillary status.

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General comments No SN localisation rate reported since only patients with successful SLNB procedures were eligible for inclusion.

Case control study design crucially assumed that groups had equal true prevalence: patients in each group were satisfactorily matched for many prognostic factors (statistically tested).

There was no apparent risk of 'over matching' for the procedure performed, assuming that no disease factor determined performance of SLNB or axillary clearance. The two groups arose from standard practice at the centre at different times.

All SLNB patients from original series of 191 were accounted for; no matching pairs were found for 25 SLNB patients (excluded from analysis).

Prospective case series

Agarwal, Kakkos, Cunningham, Darzi, Lee, Rajan & Hadjiminias . Sentinel node biopsy can replace four-node-sampling in staging early breast cancer. Eur J Surg Oncol 31[2]. 2005.

Design: Prospective case series (other), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria Patients with primary, unifocal, invasive breast cancer.
Tumour size = 25mm.
Disease grade I-III.
Disease stage T1-3.

Exclusion criteria -

Population number of patients = 234.

Interventions Single centre case series study

Aim: to compare the staging information provided by SLNB, with FNS as gold standard.

All patients underwent SLNB plus FNS (validation period).

Patients with metastatic disease in the axillary node field identified by either method underwent axillary clearance.

SLNB technique

R, D

Histology

FS, S

Outcomes Diagnostic test parameters.

Follow up -

Results STAGING

Sentinel node localisation rate = 221/234 = 94.4% (95% CI 90.7% to 96.7%)

Number of sentinel nodes removed per patient: mean = 1.4 (range, 1-4).

Prevalence of axillary disease in patients with localised SN = 77/221 = 34.8% (95% CI 28.8 to 41.3%).

Accuracy = 221/221 = 100% (95% CI 98.3% to 100%).

FNR = 0/77 = 0% (95% CI 0% to 0.02%).

Authors concluded that SLNB could replace FNS to stage the axilla for patients with early stage breast cancers.

-

General comments The 'gold standard' of FNS may not have been applied in its usual situation since the presence of blue dye and/or radioactive tracer from SLNB may have influenced which subsequent nodes were sampled.

Carlo, Grant, Knox, Jones, Hamilton, Livingston & Kuhn . Survival analysis following sentinel lymph node biopsy: a validation trial demonstrating its accuracy in staging early breast cancer. Baylor University Medical Center Proceedings 18[2]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with primary, unifocal, invasive breast cancer.
Primary tumour size <5cm (mean 1.42cm. range 0 to 4.05cm).

Exclusion criteria -

Population number of patients = 345, age range 29 to 85 years, mean age = 567 years.

Interventions Aim: to evaluate the performance of SLNB in an operational setting by measuring 5-year disease free survival.

All patients underwent SLNB. Patients with positive SN underwent axillary clearance (cohort 1) and patients staged as N0 by SLNB underwent no further surgery (cohort 2).

SLNB Technique

R, D.

Histology

FS, S, IHC.

Outcomes Disease free survival estimated at 5 years, by Kaplan-Meier method with log rank test.

Follow up -

Results STAGING

Sentinel node localisation rate = 315/345 = 91.3% (95% CI 87.9% to 93.8%).

A mean of 2.4 sentinel nodes were removed from each patient.

RECURRENCE

Median follow up was 60 months.

Axillary recurrence occurred in 0/222 =0% of patients staged as N0 by SLNB (cohort 2).

SURVIVAL

Estimated 5-year disease free survival in 315 patients who successfully underwent SLNB was 94% (95% CI 91% to 97%).

Estimated 5 year disease free survival was significantly longer in the 222 patients with negative SNs (cohort 2, 96%), compared to the 93 patients with positive SNs (cohort 1, 89%), (p = 0.02).

Estimated 5 year disease free survival by disease stage based upon SLNB differed significantly:

Stage I: 97%

Stage IIa: 90%

Stage IIb: 85%

Stage IIIa: 78% (p < 0.001, percentages read from graph).

-

General comments The analysis excluded patients who underwent SLNB, but in whom the SLNB was a technical failure.

SNs were considered positive if any malignant cells were present by the highly sensitive IHC histology.

The median follow up period after surgery was 60 months, with no patients lost to follow up.

The Kaplan Meier analysis and log rank test used in the analysis were appropriate to the setting. The study made one minor numerical error and did not consistently report confidence intervals with proportions.

Patient and disease characteristics were reported for the whole study group together.

The survival analysis by disease stage took account of the important tumour size prognostic variable.

Clarke, Newcombe & Mansel . The learning curve in sentinel node biopsy: The ALMANAC experience. Ann Surg Oncol 11[3]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria Patients with primary, invasive breast cancer.

Patients were eligible for this study with no upper limit on tumour size specified, provided tumours were of stage T3 or less.

Exclusion criteria -

Population number of patients = 520, age range 27 to 82 years, mean age = 57.6 years.

Interventions Study represents the ALMANAC RCT validation phase, undertaken in 14 centres in the UK.

Aim: to evaluate the competence of surgeons in performing SLNB prior to embarking on a RCT.

All patients underwent SLNB plus either FNS or axillary clearance as 'gold standard'.

The standard for surgeons to proceed to RCT phase was a SN localisation rate of =90% and a false negative rate of <5% in 40 procedures.

SLNB technique

L, R, D.

Histology

S.

Outcomes Sentinel node localisation rate.

False negative rate (against standard surgery as 'gold standard').

Follow up -

Results STAGING

Sentinel node localisation rate = 96.3% (95% CI 94.4% to 97.7%).

Mean number of sentinel nodes sampled per patient = 2.1 (range 1 to 9).

Prevalence of axillary disease in the entire study group = 169/520 = 32.5% (95% CI 28.6% to 36.6%).

Accuracy = 510/520 = 98.1% (95% CI 96.5% to 99.0%).

FNR = 10/169 = 5.9% (95% CI 3.2% to 10.5%).

Higher rates of failed SN localisations and a higher FNR were observed in surgeons' first procedures than in subsequent procedures.

-

General comments Study sets a standard for the calculation of valid staging outcome measures, considering case mix in the series. MORE HERE

Cody, Hill, Tran, Brennan & Borgen . Credentialing for breast lymphatic mapping: how many cases are enough? Ann Surg 229[5]. 1999.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with biopsy proven, invasive breast cancer.

8 patients with DCIS were excluded from analysis.

Exclusion criteria -

Population number of patients = 500, age range 21 to 87 years, mean age = 56 years.

Interventions Prospective, single-centre, case series study.

Aim: To examine the staging performance of SLNB, according to the experience of the surgeon.

Most data are of 104 patients who underwent SLNB with immediate axillary clearance.

SLNB technique

R, D.

Histology

Not reported.

Outcomes Staging performance of SLNB using axillary clearance as gold standard.
SLNB failure rate and FNR, examined by the experience of surgeons.

Follow up -

Results STAGING

Sentinel node localisation rate in larger series = $458/492 = 93.1\%$ (95% CI 90.5% to 95.0%).

Number of SNs removed per patient: no data available.

Data for 104 patients (who underwent SLNB plus axillary clearance):

Prevalence of axillary disease = $47/104 = 45.2\%$ (95% CI 36.0% to 54.8%).

Accuracy = $99/104 = 95.2\%$ (95% CI 89.2% to 97.9%).

FNR = $5/47 = 10.6\%$ (95% CI 4.6% to 22.6%).

Effect of surgeons' experience:

A higher SN localisation rate was seen in more experienced surgeons (94%) than in less experienced surgeons (86%, $p=0.012$, Fisher's exact test).

In the larger case series, the SLNB failure rate fell as the series of procedures were completed: there were 10 failures in the first 100 patients and 8, 6, 6 and 4 failures in each subsequent 100 patients.

Most SLNB false negative cases occurred early in the surgeons' experience.

-

General comments In the whole series of 500 patients, 423 procedures were performed by 3 surgeons with experience of SLNB (mean of 140 procedures per surgeon).

The remaining 5 surgeons (with less experience) performed a mean of 16 procedures each.

Therefore, two 'experience' groups emerged, although not clearly defined. An analysis was performed between these groups for SN localisation rate, but FNR was assessed between groups by narrative alone.

It is unclear why axillary clearance was performed in 104 patients, but possibly represents a validation period.

However, it cannot be ruled out that patients with poorer prognoses based upon tumour characteristics, were more likely to undergo axillary clearance, with the effect of raising the prevalence of axillary disease in these 104 patients.

The reported SN localisation rate is for the larger series of patients (n=492) representing greater surgical experience than for the 104 patients described above.

Although data were presented for FNR in each surgeon according to surgical experience, no analysis was performed.

Haid, Kuehn, Konstantiniuk, Kobere-Wuhrer, Knauer, Kreienberg & Zimmermann .
Shoulder-arm morbidity following axillary dissection and sentinel node only biopsy for
breast cancer. Eur J Surg Oncol 28[7]. 2002.

Design: Prospective case series (harm), evidence level: 3
Country: Germany, setting: Secondary care

Inclusion criteria Patients with invasive breast cancer.

SLNB group: patients staged as N0.

Mean tumour diameter 17.4mm.

axillary clearance group: no stage stipulated.

Mean tumour diameter 23.3mm.

Exclusion criteria Patients who received axillary radiotherapy were excluded.

Population number of patients = 151, mean age = 57 years.

Interventions Aim: to examine morbidity following SLNB only, compared to that following
axillary clearance.

Compares two groups:

SLNB group: patients who underwent SLNB only (n=66)

axillary clearance group: randomly selected patients who underwent routine axillary
clearance only (n=85).

Groups were defined retrospectively but assessment of outcome was prospective.

SLNB technique

Not reported.

Histology

S, IHC.

Outcomes Morbidity, using a summation score (range 0 to 100), which was 60% based
upon patient reported information and 40% upon clinically assessed information and
considered pain, lymphoedema, loss of strength, range of motion and sensitivity to touch.

Follow up -

Results STAGING

Sentinel node localisation rate (based on larger series) = 219/237 = 92.4% (95% CI 88.3%
to 95.1%).

Mean number of SNs removed per patient in SLNB group= 1.8.

A mean of 13 nodes were removed in the axillary clearance group.

MORBIDITY

Follow-up ranged from a minimum of 2 months to a maximum of 48 months from surgery
(no median reported).

The total summation score was significantly higher (representing better functioning) in the
SLNB group (92.8) compared to the axillary clearance group (80.6, $p < 0.001$). All individual
measures were statistically significant (with $p < 0.05$) except for abduction ($p = 0.8$).

Patients in the SLNB group had significantly higher score for subjective outcomes (54.1)
compared to patients in the axillary clearance group (45.5, $p < 0.001$).

Patients in the SLNB group had significantly higher score for objective outcomes (38.6)

compared to patients in the axillary clearance group (34.7, $p < 0.001$).

With the analysis stratified by primary surgical procedure, these differences remained statistically significant in patients who underwent breast conserving surgery but statistical significance was lost for the majority of measures in patients who underwent mastectomy.

-

General comments No clear criteria were set to identify the two study groups from the larger series. It was not reported whether the axillary clearance group patients had nodal disease. Patients with knowledge of more extensive disease may have over-reported their morbidity.

The axillary clearance group had generally more advanced disease at the outset including significantly larger tumours ($p = 0.019$) greater likelihood of receiving adjuvant chemotherapy ($p < 0.001$) and mastectomy (no p value) compared to the SLNB group.

One cannot be certain that the two groups compared were similar at the beginning of the study.

The number of patients lost to follow up and the median follow-up period were not reported.

All patients were evaluated in the spring of 2001, and hence at different times in their recovery from surgery.

Many p values were reported, with increasing likelihood of a type I error. No multivariate analysis was performed which may have adjusted for the effects of different variables.

Krag, Harlow, Weaver & Ashikaga . Radiolabeled sentinel node biopsy: collaborative trial with the National Cancer Institute. World J Surg 25[6]. 2001.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with operable, invasive breast cancer.

Exclusion criteria -

Population number of patients = 145, mean age = 53 years.

Interventions Aim = to test the staging performance of SLNB.
All patients underwent SLNB plus immediate axillary clearance.
SLNB technique
R.
Histology
S.

Outcomes Staging performance of SLNB compared to axillary clearance as gold standard.

Follow up -

Results STAGING

Sentinel node localisation rate = $127/145 = 87.6\%$ (95% CI 81.2% to 92.0%).

Number of SNs removed per patient: mean 2.8, SD 1.8.

Number of ANs removed per patient in axillary clearance: mean 15.6, SD 6.5.

Prevalence of axillary disease = $45/127 = 35.4\%$ (95% CI 27.7% to 44.1%).

Accuracy = $125/127 = 98.4\%$ (95% CI 94.4% to 99.6%).

FNR = $2/45 = 4.4\%$ (95% CI 1.2% to 14.8%).

In 8.6% of patients, internal mammary SNs were identified and removed.

-

General comments Patient characteristics were analysed between successful SLNB localisations and failures: no patient or disease factor was found to be significantly associated with SN localisation.

This study represents a series of patients treated at a centre, which had already performed studies of radioactive tracers and adopted the use of a single tracer for this study. However, no formalised training period for the two participating surgeons had been implemented.

Langer, Marti, Guller, Moch, Harder, Oertli & Zuber . Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: Prospective analysis of 150 patients after SLN biopsy. Ann Surg 241[1]. 2005.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Switzerland, setting: Secondary care

Inclusion criteria Patients with palpable breast tumours.

Mean age was 59.9 (SD 11.7) years in patients who underwent axillary clearance and 63.5 (SD 12.0) years in patients who underwent only SLNB.

Exclusion criteria -

Population -

Interventions Aim: to evaluate axillary recurrence in patients staged as N0 by SLNB without axillary clearance.

All patients underwent SLNB. Two study groups were defined:

1. Patients with no detectable SN metastases or SN micrometastases of size ≤ 2 mm by SLNB, were staged as N0 and did not undergo axillary clearance (cohort 2, n=150).
2. Patients with SN metastases of size > 2 mm by SLNB, were considered SN positive and underwent axillary clearance (cohort 1, n=74).

SLNB technique

L, R, D.

Histology

FS, S, IHC.

Outcomes Morbidity

Local recurrence

Axillary recurrence

Distant metastasis

Disease-related deaths

Follow up -

Results STAGING

SN identification rate was $224/236 = 94.9\%$ (95% CI 91.3% to 97.1%).

A mean of 2.1 (SD1.4) SNs were removed per patient.

MORBIDITY

15/74 (20.3%) patients who underwent axillary clearance developed axillary complications: seroma (n=8), wound infection (n=2), chronic lymphoedema (n=5).

1/150 (0.7%) of patients who underwent SLNB alone experienced complications: haematoma (n=1).

The difference in the proportion of patients in each group with complications was 19.6% (95% CI for difference 11.4% to 30.1%).

RECURRENCE

Median follow-up was 42 months (range 12 to 64 months) overall. 2 patients were lost to follow up.

Local recurrence (breast)

6/149 = 4.0% of patients who underwent SLNB alone (cohort 2) had local recurrence in the breast compared with 4/73 = 5.5% of patients who underwent axillary clearance (cohort 1).

Axillary recurrence

The axillary recurrence rate in patients treated with SLNB alone (cohort 2) was 1/149 = 0.7% compared to 1/73 = 1.4% in patients who underwent axillary clearance (cohort 1).

Distant metastasis

3/149 (2.0%) of patients staged as N0 by SLNB (cohort 2) developed distant metastases compared with 7/73 (9.6%) of patients who underwent axillary clearance (cohort 1).

SURVIVAL

11 patients died; 5/11 deaths were related to metastatic breast cancer (not reported by group).

-

General comments Data represent 236 procedures in 234 patients.

Reporting of absolute numbers of patients was rigorous throughout.

The study used highly sensitive IHC histology.

This study considered patients with small metastases (≤ 2 mm) in the SN to have stage N0, with omission of axillary clearance with the use of adjuvant therapy.

Only 2 patients were lost to follow up (one in each analysis group). These were excluded from the analyses.

In the 'SLNB only' group, subgroup analysis of N0 stage patients with small SN metastases of size 0 to 0.2mm versus 0.2 to 2mm revealed no significant differences in disease related events. This may be because so few events were observed in the follow-up period, or may be due to the protective role of adjuvant therapy.

The authors consider their rate of axillary recurrence in cohort 2 of 0.7%, with rates from other published studies, which have range 0.1% to 1.5%.

Reitsamer, Peintinger, Prokop, Rettenbacher & Menzel . 200 Sentinel lymph node biopsies without axillary lymph node dissection - No axillary recurrences after a 3-year follow-up. Br J Cancer 90[8]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Austria, setting: Secondary care

Inclusion criteria Patients with invasive breast cancer.

Mean tumour size was 16.5 (range, 1 to 50) mm in patients who underwent SLNB only and 20.5 (range, 5 to 55) mm in patients who underwent SLNB plus axillary clearance.

Exclusion criteria -

Population number of patients = 333.

Interventions Aim: to measure the rate of axillary recurrence in patients staged as N0 by SLNB, without axillary clearance.

Two groups were defined:

Cohort 1: patients with disease positive SLNB result who underwent subsequent axillary clearance (n=128);

Cohort 2: patients staged as N0 by SLNB (n=200).

SLNB technique

L, R, D.

Histology

FS, S, IHC

Outcomes Axillary recurrence rate

Also provides information on upstaging by FS, S and IHC histology

Follow up -

Results STAGING

SN localisation rate = $328/333 = 98.5\%$ (95% CI 96.5% to 99.4%).

Mean number of SNs removed per patient in cohort 2= 2.1.

Mean number of ANs removed per patient in cohort 1= 20.8.

The SN was the only positive node in $77/128 = 60.2\%$ (95% CI 51.5% to 68.2%) of patients with positive SLNB result.

$15/215 = 7.0\%$ (95% CI 4.2% to 11.2) of patients staged as N0 by standard histology were upstaged by the use of IHC histology.

$104/128 = 81.3\%$ (95% CI 73.6% to 87.1%) of patients with positive SNs who underwent axillary clearance did so in the same operation as SLNB due to intraoperative histology by FS.

RECURRENCE

Median follow-up was 36 (range 22 to 56) months.

There were no local or axillary recurrences in either group (cohorts 1 and 2) at a median follow-up of 36 months.

-

General comments All patients from the original series were accounted for; 5 cases of SLNB failure underwent immediate axillary clearance (excluded from follow-up data). Patient characteristics, exclusion criteria and follow-up practice thoroughly reported. Patients were attributed positive SN status using the highly sensitive IHC technique.

Rietman, Dijkstra, Geertzen, Baas, de, Dolsma, Groothoff, Eisma & Hoekstra . Short-term morbidity of the upper limb after sentinel lymph node biopsy or axillary lymph node dissection for Stage I or II breast carcinoma.[see comment][erratum appears in Cancer. Cancer. 2004 May 1;100(9):1991]. Cancer 98[4]. 2003.

Design: Prospective case series (harm), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria Patients with invasive breast cancer.

Exclusion criteria -

Population number of patients = 204, mean age = 56 years.

Interventions Aim: to prospectively compare short-term morbidity between SLNB and axillary clearance.

Two groups of patients were defined:

1. Patients who underwent SLNB alone (n=66).
2. Patients who underwent axillary clearance alone or SLNB and subsequent axillary clearance (n=138). axillary clearance was performed to level I-II.

SLNB technique

R, D.

Histology

Not reported.

Outcomes Surgical complications.

Patient-reported pain (visual analogue scale [VAS] with range 0 to 10cm).

Numbness (yes/no).

Upper limb mobility and strength (using instruments).

Arm circumference.

Activities of daily living (ADL) using the Shoulder disability questionnaire (SDQ) and the Groningen activity restriction scale (GARS).

Follow up -

Results MORBIDITY

Surgical complications:

Seroma lasting 4 weeks or more occurred in 3/60 = 5.0% of SLNB patients and in 18/119 = 15.1% of axillary clearance patients (difference 10.1%, 95% CI -0.08% to 18.3%) (p=0.051).

Wound infection necessitating antibiotic treatment occurred in 6/63 = 9.5% of SLNB patients and 20/121 = 16.5% of axillary clearance patients (difference, 7.0%, 95% CI -4.2% to 16.2%) (p=0.265).

Outcomes measured at follow-up point (6 weeks after surgery):

In the study group as a whole, patient-assessed pain increased from a score of mean 0.5 (SD 1.2) preoperatively to mean 1.3 (SD 1.3) at follow-up (p<0.001). 67.6% of all patients

experienced numbness at follow-up.

In the study group as a whole, upper limb morbidity was significantly reduced at follow-up compared to preoperative levels in terms of forward flexion, abduction and external rotation, with $p < 0.05$ for these parameters. Neither external rotation nor grip strength was significantly reduced.

In the study group as a whole, arm circumference was not significantly increased at follow-up.

In the study group as a whole, the mean SDQ score and the mean GARS score significantly increased (worsened) at follow-up compared to the preoperative scores ($p < 0.001$).

There were no significant differences between the SLNB group and the axillary clearance group for any outcome measure at follow-up. However, the sizes of changes were generally larger in the axillary clearance group compared to the SLNB group.

-

General comments The study reported exclusion of 1 patient; otherwise, all patients treated at the 2 centres appear to be included. Only three patients were lost to follow up.

Unusually, this study prospectively included patients with clinically suspicious nodes.

The axillary clearance group includes patients who underwent axillary clearance up to two weeks after SLNB, which introduces variability with regard to the targeted 6-week follow-up point.

Statistical methods were partially described, although no statistical test was described for the proportion outcomes, where Chi square may have been suitable.

The outcome measures provided meaningful objective and subjective information on the effect of surgery on patients' everyday activities.

The use of a preoperative baseline meant that patients were in the same state at the study outset.

No patient had started adjuvant therapy prior to the follow-up assessment at 6 weeks post surgery.

Morbidity in the axillary clearance group may have been accentuated by a greater proportion ($68/138 = 49.3\%$) of patients receiving mastectomy, than in the SNB group ($17/66 = 25.8\%$; difference 23.5%, 95% CI 9.3% to 35.7%).

Torrença, Fabry, Van, Van Diest, Pijpers, Meijer & Nieweg . Omitting axillary lymph node dissection in sentinel node negative breast cancer patients is safe: A long term follow-up analysis. J Surg Oncol 88[1]. 2004.

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria Patients with breast cancer.

Mean tumour size 1.5 (range 0.4 to 5.0) cm.

Exclusion criteria -

Population number of patients = 104, age range 32 to 81 years, mean age = 55 years.

Interventions Prospective, single-centre, case series study

Aim: to measure axillary recurrence and survival in patients staged as N0 by SLNB without axillary clearance (Cohort 2).

SLNB technique

L, R, D.

Histology

S, IHC.

Outcomes Disease free survival and overall survival.

Follow up -

Results STAGING

A mean of 1.3 SNs (range, 1 to 3) were excised per patient.

RECURRENCE

Median follow-up was 57 (range 48 to 83) months.

Axillary recurrence occurred in 1/104 = 0.96% of patients.

Distant metastases occurred in 3/104 = 2.9% of patients.

SURVIVAL

Proportion of patients alive at 4 years from point of surgery = 102/104 = 98.1%.

Proportion of patients alive and disease free at 4 years from point of surgery = 101/104 = 97.1%, including the 1 patient with treated recurrence in the denominator.

-

General comments The study includes all patients representing cohort 2, treated at the centre.

The SN localisation rate was not reported in this follow up study, but use of the triple technique (L, R, D) gives confidence of a high rate of 'true SN' detection, assuming that surgeons were adequately trained.

A mean of 1.25 SNs were excised per patient. Interestingly 82 of the total 104 SN negative patients were staged based on 1 SN.

In all patents N0 stage was attributed detection of no cancer cells by IHC histology; a

highly sensitive technique.

Retrospective case series

Blanchard, Donohue, Reynolds & Grant . Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. Arch Surg 138[5]. 2003.

Design: Retrospective case series (harm), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with primary, invasive breast cancer; staged as N0.

Exclusion criteria -

Population -

Interventions Retrospective, single centre case series study with prospective survey of a subgroup.

Aim: to measure axillary recurrence rates and physical morbidity in patients staged by SLNB, with or without axillary clearance.

(n=776)

Of 1253 patients treated by SLNB, 894 patients staged as N0 were contacted by questionnaire. 776 patients responded, representing two retrospectively defined groups:

axillary clearance group: (cohort 4) patients treated by SLNB plus axillary clearance (validation period, n=91)

SLNB group: (cohort 2) patients treated by SLNB only (after validation period, n= 685).

SLNB Technique

Variable: initially D; thereafter L, R, D.

Histology

FS, S, IHC.

Outcomes Patient-reported rates of lymphoedema, seroma, pain and infection.

Axillary recurrence.

Follow up -

Results STAGING

A mean of 2.3 (SD 1.3) SNs were removed in patients in the SLNB group and a mean of 1.8 (SD 1.0) SNs were removed in patients in the axillary clearance group.

Questionnaire results

Mean follow up was 2.4 years (SD 0.9 years).

MORBIDITY

Lymphoedema was reported by 39/683 = 6% of SLNB group patients, compared to 31/91 = 34% of axillary clearance group patients (difference 28.3%, 95% CI 19.2% to 38.7%).

Lymphoedema was reported as severe (necessitating use of a support sleeve) in 4/683 =

0.6% of SLNB group patients compared with 8/91 = 9% of axillary clearance group patients (difference 8.2%, 95% CI 3.8% to 15.8%) ($p < 0.001$).

Pain was reported by 95/681 = 14% of SLNB group patients, compared to 35/91 = 38% of axillary clearance group patients (difference 24.5%, 95% CI 14.8% to 35.1%). Pain was reported as severe (necessitating use of analgesia for more than one month after surgery) in 6/681 = 0.9% of SLNB group patients compared with 4/91 = 4% of axillary clearance group patients (difference 3.5%, 95% CI 0.7% to 9.9%) ($p < 0.001$).

Seroma necessitating aspiration was reported by 50/681 = 7% of SLNB group patients, compared to 21/89 = 24% of SLNB plus axillary clearance patients (difference 16.3%, 95% CI 8.3% to 26.2%) ($p < 0.001$).

Infection requiring treatment with antibiotics was reported by 20/681 = 3% of SLNB only patients, compared to 8/88 = 9% of axillary clearance group patients (difference 6.2%, 95% CI 1.5% to 14.1%) ($p = 0.006$).

52/505 = 10% patients reporting lymphoedema 10% (52) reported receiving radiotherapy, which was not significantly different to 18/247 = 7% who reported lymphoedema with no radiotherapy (difference 3%, 95% CI -1.6% to 7.0%), $p = 0.18$). A similar, non-significant result was obtained for pain, by radiotherapy. However, the authors did not differentiate between radiotherapy to the breast from the axilla.

RECURRENCE

1/685 = 0.15% of SLNB group patients (cohort 2) experienced axillary recurrence.

-

General comments The two analysis groups were similar in terms of many disease and treatment characteristics. However patients in the SLNB group were older than those in the axillary clearance group (mean 61.6 years versus 58.3 years respectively, $p = 0.03$), had less advanced disease stage ($p = 0.01$).

This study does not report exactly which data originated from a retrospective review of medical notes, rather than the questionnaire.

Histology was highly sensitive.

The SLNB method changed over time, but is poorly reported. Non-standardised SLNB may have affected the reported outcomes.

No survival data are cited since the reporting was inadequate.

The axillary clearance group included some patients with clinically palpable, suspicious nodes.

The questionnaire was not included in the paper.

The study did not consistently report multivariate analyses, raising suspicion that only significant findings were reported.

Cserni, Rajtar, Boross, Sinko, Svebis & Baltas . Comparison of vital dye-guided lymphatic mapping and dye plus gamma probe-guided sentinel node biopsy in breast cancer. World J Surg 26[5]. 2002.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Hungary, setting: Secondary care

Inclusion criteria Patients with invasive breast cancer.

Exclusion criteria -

Population number of patients = 184, mean age = 59 years, median age = 60 years.

Interventions Retrospective, single-centre case series.

Aim = to evaluate the staging performance of SLNB during a validation period.

All patients underwent SLNB plus axillary clearance.

Different patient groups were defined according to practice at the centre over time (from 201 procedures in 199 patients).

SLNB technique

Initially D, later R, D.

Histology

S, IHC.

Outcomes Staging performance of SLNB based upon axillary clearance as gold standard.

Follow up -

Results STAGING

Data from whole series (including learning phase and period where SLNB was performed with blue dye alone):

Sentinel node localisation rate = $184/201 = 91.5\%$ (95% CI 86.9% to 94.7%).

Number of SNs removed per patient: mean 1.4, median 1.

Prevalence of axillary disease = $106/184 = 57.6\%$ (95% CI 50.4% to 64.5%).

Accuracy = $176/184 = 95.7\%$ (95% CI 91.7% to 97.8%).

FNR = $8/106 = 7.5\%$ (95% CI 3.9% to 14.2%).

Data for subgroup of 72 patients staged by SLNB using blue dye plus radioactive tracer (excludes surgical training phase):

Sentinel node localisation rate = $72/72 = 100\%$ (95% CI 94.9% to 100%).

Number of SNs removed per patient: mean 1.4, median 1.

Prevalence of axillary disease = $30/72 = 41.7\%$ (95% CI 31.0% to 53.2%).

Accuracy = $71/72 = 98.6\%$ (95% CI 92.5% to 99.8%).

FNR = $1/30 = 3.3\%$ (95% CI 0.6% to 16.7%).

Learning curve:

The SN identification rate for the first six groups of ten procedures was 50%, 80%, 90%, 80%, 90% and 100%, respectively. The accepted standard of 90% localisation rate was achieved for the previous 30 procedures at the 53rd procedure.

-

General comments The study group was poorly defined: an undisclosed number of

patients with in situ disease were included.

Also, during the study period, the centre was performing SLNB alone in some patients, staged as N0. Hence, this group did not undergo axillary clearance and could not occur in the series reported, possibly contributing to the high prevalence reported.

In all sentinel nodes, any malignant cells detected by highly sensitive IHC warranted a positive status, which may also serve to raise the prevalence.

The subgroup of 72 patients represented those treated by surgeons who had completed training in SLNB. By this time, the centre used both radioactive tracer plus blue dye. This provides data for a centre, which has reached maturity in performing SLNB.

This Hungarian centre did not appear to draw a clear distinction between a validation period and an operational period: it is not possible to clearly define the effect of surgical competence, technical method for SLNB and practice setting.

Giuliano, Jones, Brennan & Statman . Sentinel lymphadenectomy in breast cancer. J Clin Oncol 15[6]. 1997.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with invasive breast cancer.
Mean tumour size was 2.11 (SD 1.38) cm.

Exclusion criteria -

Population number of patients = 107.

Interventions Aim: to report on the staging performance of SLNB during a validation period.

All patients underwent SLNB plus axillary clearance.

SLNB technique

D.

Histology

S, IHC.

Outcomes Staging performance of SLNB based on axillary clearance as 'gold standard'.

Follow up -

Results STAGING

Sentinel node localisation rate = $100/107 = 93.5\%$ (95% CI 87.1% to 96.8%).

Number of SNs removed per patient: mean 1.8 (range 1 to 8), SD 1.8.

Number of ANs removed per patient: 20.3 (range 7 to 60), SD 7.8.

Prevalence of axillary disease = $42/100 = 42\%$ (95% CI % 32.8% to 51.8%).

Accuracy = $100/100 = 100\%$ (95% CI 96.3% to 100%).

FNR = $0/42 = 0\%$ (95% CI 0% to 8.4%).

-

General comments Results represent performance attained at a centre of excellence, which developed the technique.

Based on these results the centre omitted axillary clearance in all cases of SLNB.

All patients accounted for in original series, to illustrate how 107 patients were identified.

8 patients with clinically suspicious nodes were included; introducing a bias towards better performance based upon prior knowledge, and also through raising the prevalence (see discussion).

Imoto, Wada, Murakami, Hasebe, Ochiai & Ebihara . Prognosis of breast cancer patients treated with sentinel node biopsy in Japan. Jpn.J Clin Oncol 34[8]. 2004.

Design: Retrospective case series (prognosis), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria Patients with unilateral, invasive breast cancer staged as N0.

Exclusion criteria -

Population number of patients = 209.

Interventions Aim: to measure recurrence and survival in patients who were surgically staged as N0 by SLNB compared to axillary clearance.

Study compares two groups treated at a single centre:

SLNB group: Patients staged as N0 by SLNB (cohort 2, n=112).

axillary clearance group: Patients staged as N0 by SLNB plus axillary clearance (cohort 4, validation period, n=97).

SLNB technique

L, R, D.

Histology

FS, S.

Outcomes Disease-related events.

Relapse-free survival, by Kaplan Meier survival analysis and log rank test.

Follow up -

Results STAGING

SLNB localisation rate was 79/97=81.4% (95% CI 72.6% to 88.0%) in the validation phase and 111/112= 99.1% (95% CI 95.1% to 99.8%) thereafter.

RECURRENCE

Median follow-up in all patients was 52 months.

In all patients, 18 (9%) experienced disease relapse.

Loco-regional recurrence was seen in 5/97 = 5.2% of patients in the axillary clearance group (cohort 4) and 5/112 = 4.5% patients in the SLNB group (cohort 2).

Distant metastases were seen in 5/97 = 5.2% of patients in the axillary clearance group (cohort 4) and 3/112 = 2.7% of patients in the SLNB group.

3 (3.1%) deaths due to breast cancer occurred in the axillary clearance group (cohort 4) compared to 1 (0.9%) in the SLNB group (cohort 2).

SURVIVAL

The relapse-free survival rates in the axillary clearance (cohort 4) and SLNB (cohort 2) groups were 94% and 93% respectively (p=0.78, log rank test).

-

General comments The study provided details of how the two groups were derived from a

series of 391 patients; criteria for exclusion from the analysis were clearly defined. Differences in prognostic variables were statistically tested between groups: the axillary clearance group had significantly larger tumour size ($p=0.008$), greater likelihood of mastectomy ($p=0.01$) and more advanced disease stage ($p=0.015$) than the SLNB group. However, the groups were clearly defined by the change in practice from validation period to operational period. The reported loco-regional recurrence rate of 4.5% for cohort 2 presumably includes axillary recurrence plus local recurrence in the breast.

Katz, Niemierko, Gage, Evans, Shaffer, Fleury, Smith, Petrucci, Flax, Drogula & Magnant . Can axillary dissection be avoided in patients with sentinel lymph node metastasis?[see comment]. [Review] [46 refs]. J Surg Oncol 93[7]. 2006.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients treated with SLNB between 1998 and 2003.

110 patients had DCIS
1034 patients had invasive disease

307 patients underwent mastectomy and 833 breast conserving surgery. In 8 patients the type of definitive surgery was unknown.

Exclusion criteria Retrospective study: none reported.

Population number of patients = 1133, age range 30 to 96 years, median age = 57 years.

Interventions Retrospective analysis of 1148 SLNB procedures in 1133 patients treated at a single centre and recorded on a pathology database.

SLNB technique: R, D
Histology: FS, S, IHC

Outcomes Risk factors for the presence of SN metastases.

Risk factors for the presence of further axillary node metastases in patients who undergo axillary clearance for positive SLNB result.

Follow up No follow-up reported, study assesses predictive factors for SN and non SN axillary nodal involvement.

Results 246 patients had involved SNs and underwent axillary clearance.
121 patients had involved SNs and did not undergo axillary clearance.

Prevalence of axillary disease = $367/1148 = 32\%$

A median of 2 SNs were identified per procedure (range 1-15)

RISK FACTORS FOR SN INVOLVEMENT

By Pearson Chi square the proportion of patients with positive SNs varied significantly by subgroup for the following variables (as categorical variables):

Age (higher rates of SN involvement in younger patients, $p < 0.001$);
Type of surgery (higher rates of SN involvement after mastectomy, $p < 0.008$);
Tumour size (higher rates of SN involvement with larger tumours, $p < 0.001$);
Histology (higher rates of SN involvement for invasive histology, $p < 0.001$);
Invasion of lymphovascular space (higher rates of SN involvement when present, $p < 0.001$).

By Pearson Chi square the proportion of patients with positive SNs did not vary significantly by subgroup for the following variables (as categorical variables):

Number of SNs identified;
ER receptor status;
PR receptor status.

The statistical significance observed was the same whether SN positivity was determined by H&E histology or by any technique (including more sensitive techniques).

On multiple logistic regression analysis age, histology, type of surgery, primary tumour size and lymphovascular invasion were statistically significantly associated with SN involvement (no further details reported).

RISK FACTORS FOR INVOLVEMENT OF ADDITIONAL NON-SENTINEL NODES

By Pearson Chi square the proportion of patients with positive further nodes varied significantly by subgroup for the following variables (as categorical variables):

Presence of lymphovascular invasion ($p=0.001$);

Number of SNs examined (higher rates of further nodal involvement where fewer SNs were examined, $p=0.03$);

Histological method to detect SN metastasis (higher rates of further nodal involvement for H&E, $p=0.03$);

Number of involved SNs (higher rates of further nodal involvement where ≥ 3 SNs involved, $p=0.002$ for H&E histology and $P=0.05$ for any histological technique);

Number of uninvolved SNs (higher rates of further nodal involvement where fewer SNs uninvolved, $p<0.001$);

Size of the largest SN metastasis (higher rates of further nodal involvement for larger SN metastases, $p<0.001$).

By Pearson Chi square the proportion of patients with further involved axillary nodes did not vary significantly by subgroup for the following variables (as categorical variables):

Age;

Type of definitive surgery;

Tumour size;

Histology.

On multiple logistic regression analysis the presence of lymphovascular invasion, increasing number of positive SNs, increasing size of the largest SN metastasis and decreasing number of negative SNs were statistically significantly associated with further axillary node involvement (no further details reported).

-

General comments It is not reported, but this series of patients appear to have been treated in an operational phase for SLNB i.e. without planned axillary clearance for any patients irrespective of SN status.

Kokke, Jannink, Barneveld, van der Linden, Gelderman, Wissing & Bosscha . Incidence of axillary recurrence in 113 sentinel node negative breast cancer patients: A 3-year follow-up study. Eur J Surg Oncol 31[3]. 2005.

Design: Retrospective case series (therapy), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria Women with invasive breast cancer, stage N0 by SLNB.
Mean tumour size 14.0 (range 2 to 35) mm.

Exclusion criteria -

Population number of patients = 113.

Interventions Aim: To measure the axillary recurrence rate in patients staged as N0 by SLNB (cohort 2).

SLNB technique

L, R, D.

Histology

S.

Outcomes Disease-related events; primarily, axillary recurrence.

Follow up -

Results RECURRENCE

Mean follow-up was 37.5 (range 24.1 to 53.6) months.

1 patient developed an axillary recurrence: $1/113 = 0.9\%$. Review of the original pathology slides showed metastasis in the SN.

1 patient developed supraclavicular lymph node metastasis (outside the axilla): $1/113 = 0.9\%$.

2 patients developed a further primary tumour in the contralateral breast $2/113 = 1.8\%$.

-

General comments 113 patients were drawn from an original series of 197 treated by SLNB at a single centre. The 84 patients excluded were accounted for with suitable reasons e.g. history of cancer in the bilateral breast.

Study implies 1 case of false negative result from the pathology laboratory.

Follow-up examination was by clinical examination exam only: no use of ultrasound imaging was reported, which is a more sensitive technique. The frequency of follow-up examinations was 3 monthly in the first year and 6 monthly thereafter.

Langer, Guenther, Haigh & DiFronzo . Lymphatic mapping improves staging and reduces morbidity in women undergoing total mastectomy for breast carcinoma. Am Surg 70[10]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with biopsy proven breast cancer, who had mastectomy as primary surgery.

Mean tumour size 2.5 (range 0.3 to 8.0) cm.

Exclusion criteria -

Population number of patients = 99, age range 34 to 87 years, mean age = 59 years.

Interventions Aim: to compare morbidity between SLNB and axillary clearance.

Patients who underwent mastectomy were identified from a larger series and two groups were defined:

1. Patients who underwent SLNB plus axillary clearance
2. Patients who underwent SLNB only.

SLNB technique

D.

Histology

FS, S, IHC.

Outcomes Staging performance of SLNB compared to axillary clearance as gold standard in subset of 56 patients.

Post operative morbidity, including:

Paresthesia;

Restricted arm movement;

Lymphoedema;

Infection;

Seroma.

Follow up -

Results STAGING

Sentinel node localisation rate (based upon whole series of 100 procedures) = 96/100 = 96% (95% CI 90.1% to 98.4%).

Number of SNs removed per patient: mean 1.7, range 1 to 5.

Data from 56 patients who underwent SLNB plus axillary clearance:

Prevalence of axillary disease = 28/56 = 50% (95% CI 37.3% to 62.7%).

Accuracy = 53/56 = 94.6% (95% CI 85.4% to 98.2%).

FNR = 3/28 = 10.7% (95% CI 3.7% to 27.2%).

MORBIDITY

Mean follow up was 51 months (range 6 to 107) months.

A smaller proportion of patients who underwent SLNB alone experienced adverse events, compared to patients who underwent SLNB plus axillary clearance.

These differences were statistically significant for paresthesia (25% versus 78% respectively, $p < 0.0001$), restricted arm movement (0% versus 16% respectively, $p < 0.0054$) and lymphoedema (0% versus 13% respectively, $p < 0.0202$) but not for infection (0% versus 3% respectively, $p < 0.5152$) or seroma (0% versus 5% respectively, $p < 0.0813$, Fisher's exact test).

-

General comments Data represent 100 procedures in 99 patients.

Patients who provide staging outcomes ($n=56$) underwent axillary clearance either in the validation phase ($n=34$) or based on a positive SN by intraoperative histology. The latter case introduced further patients with positive axillary status, thus raising the prevalence.

Since this series underwent mastectomy, and included patients with tumours that were large (8cm) or of advanced stage (T4). This may also increase the prevalence of axillary disease.

Assessment of morbidity outcomes was based upon clinical follow-up.

Some numerical errors were evident and no confidence intervals were reported. Statistical methods were otherwise adequately reported.

100 SLNB procedures were performed in 99 patients: therefore, one patient with two SLNB procedures yielded a greater influence than the 98 others with regard to morbidity outcomes.

Patient and tumour characteristics were reported for the whole series.

Naik, Fey, Gemignani, Heerdt, Montgomery, Petrek, Port, Sacchini, Sclafani, VanZee, Wagman, Borgen, Cody III, Bland, Ross, Leong, Morrow & Strasberg . The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: A follow-up study of 4008 procedures. Ann Surg 240[3]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with invasive, unilateral breast cancer, of tumour size T3 or less.

Exclusion criteria -

Population -

Interventions Aim: to measure the rate of axillary recurrence in different cohorts of patients staged by SLNB with or without axillary clearance.

(n=4008, selected from a total series of 6278 patients).

Patients were analysed in four groups:

Cohort 1: patients with positive SN result who underwent axillary clearance (n=1132)

Cohort 2: patients with negative SN result who did not undergo axillary clearance (n=2340)

Cohort 3: patients with positive SN result who, unconventionally, did not undergo axillary clearance (n=210). This decision was based upon clinical judgment and/or patient preference.

Cohort 4: patients with negative SN result who underwent axillary clearance (n=326) in the validation period.

SLNB technique

R, D.

Histology

FS, S, IHC.

Outcomes Rate of axillary local recurrence

Follow up -

Results STAGING

SN localisation rate reported as 97.3 %.

RECURRENCE

Median follow-up was 31 months (minimum 12 months).

There was axillary recurrence in 10 patients overall, out of 4008 patients (0.25%). In 3 patients (0.07%), the axillary recurrence was the sole initial site of treatment failure.

Axillary recurrence occurred in 4/1132 = 0.35% of patients cohort 1.

Axillary recurrence occurred in 3/2340 = 0.13% of patients cohort 2.

Axillary recurrence occurred in 3/210 = 1.4% of patients cohort 3.

Axillary recurrence occurred in 0/326 = 0% of patients cohort 4.

The axillary recurrence rate was 0.18% in the three conventionally treated cohorts (1, 2 and 4) compared to 1.4% in the unconventionally treated cohort 3 (p=0.013).

Of the 210 patients in cohort 3, 53 (25.2%) received adjuvant radiotherapy. Of these 23/53

(43%) underwent radiotherapy to the breast only and 30/53 (57%) underwent radiotherapy extended to the axilla: there was no recurrence in this sub group of 30 patients.

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General comments The study had the advantage of a large sample size with the aim of recording a rare occurrence.

Given that as many as 23 SNs were removed in SLNB, the researchers set a threshold value of 10 nodes removed, above which patients were analysed as receiving axillary clearance, and below which patients were analysed as not receiving axillary clearance irrespective of whether the surgeon recorded axillary clearance as a procedure.

The Fisher exact test was used for the categorical variable of whether axillary recurrence occurred. No confidence intervals were reported.

The length of follow-up period was acknowledged by the authors as inadequate to detect all recurrence that may arise, since breast cancer has a long natural history.

Veronesi, Galimberti, Mariani, Gatti, Paganelli, Viale, Zurrada, Veronesi, Intra, Gennari, Rita, Luini, Tullii, Bassani & Rotmensz . Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection.[see comment]. Eur J Cancer 41[2]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria Women with invasive breast cancer; mean tumour size 1.2 cm.

Exclusion criteria -

Population number of patients = 953, age range 24 to 86 years, mean age = 55 years.

Interventions Aim: to measure disease related events in a series of patients staged as N0 by SLNB, without axillary clearance (Cohort 2).

SLNB technique

L, R.

Histology

FS.

Outcomes Disease-related events, particularly axillary recurrence rate.
Survival, estimated by Kaplan-Meier method.

Follow up Median follow-up was 38 months.

Results 55 unfavourable events occurred:

Axillary recurrence occurred in 3/953 = 0.3% of patients;

Local recurrence occurred in 12/953 = 1.3% of patients;

Contralateral breast cancer occurred in 5/953 = 0.5% of patients;

Distant metastases occurred in 20/953 = 2.1% of patients;

New primary tumours occurred in 13/953 = 1.4% of patients.

There were 6 deaths (5 due to breast cancer); 5-year mortality was estimated at 1.4% (standard error of mean: 0.6%).

-

General comments No exclusions from the analysis are reported, so the 953 patients reported appear to represent the entire cohort 2 for the centre.

198 women had already undergone an excisional breast biopsy prior to sentinel node biopsy, which would warrant exclusion from some SLNB studies.

Zavagno, Carcoforo, Franchini, Renier, Barutta, De Salvo, Maravegias, Capitanio, Nitti & Lise . Axillary recurrence after negative sentinel lymph node biopsy without axillary dissection: a study on 479 breast cancer patients. Eur J Surg Oncol 31[7]. 2005a.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria Patients with primary tumour size \leq 3cm.

Exclusion criteria -

Population number of patients = 479, age range 31 to 86 years, median age = 61 years.

Interventions Aim: To measure the rate of axillary recurrence in cohort 2: patients staged as N0 by SLNB without axillary clearance.

SLNB technique

L, R.

Histology

FS, S, IHC.

Outcomes Rate of axillary recurrence.

Follow up -

Results Median follow up was 35.8 months (range 12 to 68 months).

No axillary recurrences were observed (rate = zero).

Authors conclude that patients with negative SLNB result are not exposed to increased risk of evident axillary recurrence in the short term.

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General comments The study excluded 70/549 (12.8%) patients staged as N0 by SLNB who either underwent axillary clearance as a precaution or were lost to follow up. Only patients with 'successful' SLNB were eligible to be analysed so the study provided no estimate of the failure rate of SLNB. Therefore, the selection of cases appears to be justifiable.

Prognostic and demographic variables were well reported for the whole study group.

Systematic review of diagnostic studies

Kim, Giuliano & Lyman . Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: A metaanalysis. Cancer 106[1]. 2006.

Design: Systematic review of diagnostic studies (diagnosis, screening), evidence level: 2++

Country: United States, setting: Secondary care

Inclusion criteria Studies reporting original series of patients who underwent both SLNB plus axillary clearance as planned procedures, regardless of the result of SLNB.

Exclusion criteria -

Population number of patients = 8059, mean age = 57 years.

Interventions SLNB with planned axillary clearance (representing 'validation phase' for SLNB).

Of 69 included studies, SLNB technique was as follows:

R (16 studies)

D (18 studies)

Combined (34 studies)

Outcomes False negative rate (FNR)

Post-test probability negative (PTPN)

Diagnostic odds ratio (OR)

SN localisation rate

Follow up No follow-up reported; study assesses staging outcomes for SLNB.

Results 69 studies were included. Study quality, on a scale of 0-5 was ≤ 2 in 50% of studies and varied inversely with FNR ($p=0.002$): FNR was 14% in the studies with the poorest quality score of zero.

Identification of SN:

SN localisation rate = $7765/8059 = 96.35\%$

Mean number of SNs reported = 1.92 (median 2, mode 2)

Mean proportion of patients with positive SNs = 42% (median 40%, mode 50%, range 17%-74%)

FNR:

Reported FNR had mean 8.4%, median 7%, range 0%-29.4%

The observed FNR decreased with increasing study size ($p=0.046$) and there was a statistically significant inverse correlation between FNR and SN localisation rate ($p=0.001$).

Pooled estimate of FNR = 7.0% [95% CI 5.2%-8.8%, $p<0.0001$]

PTPN:

There was a statistically significant inverse correlation between PTPN and SN localisation rate ($p=0.0001$).

Pooled estimate of PTPN = 4.6% [95% CI 3.8%-5.4%, $p < 0.0001$]

SLNB technique:

SN localisation rate varied by SLNB technique: 83.1% for dye alone, 89.2% for radiocolloid and 91.9% for combined technique ($p = 0.007$).

FNR varied by SLNB technique: 10.9% for dye alone, 8.8% for radiocolloid and 7.0% for combined technique ($p = 0.047$).

Multivariate analysis:

Statistically significant, independent predictors of the FNR in linear regression analysis (adjusted for study size) included:

Reporting of measures of test performance ($p = 0.009$);

SN localisation rate ($p = 0.011$)

Proportion of positive lymph nodes ($p = 0.013$).

Statistically significant predictors of a FNR $< 10\%$ included:

Reporting of patient characteristics (OR=5.8);

Description of reasons for study withdrawal (OR=6.6);

SN localisation rate $> 90\%$ (OR= 3.5).

Statistically significant, independent predictors of the PTPN in linear regression analysis (adjusted for study size) included:

Proportion of positive lymph nodes ($p = 0.003$);

Reporting of measures of test performance ($p = 0.010$);

SN localisation rate ($p = 0.013$).

Statistically significant predictors of a PTPN $< 10\%$ included:

$< 50\%$ positive lymph nodes (OR=17.3);

SN localisation rate $> 90\%$ (OR=17.5);

Reporting of patient characteristics (OR=9.7).

-

General comments Included studies represent 'validation phase' of SLNB i.e. with immediate axillary clearance as gold standard.

Review does not comment on the threshold used in each study to determine positive nodal status, particularly SN; i.e. related to histology technique.

Quality assessment of included studies considered:

Description of patient characteristics;

Reasons for study withdrawal;

Measures of test performance;

Measures of variability;

Description of the technique used (R, D or both).

Study quality assessment and data extraction was performed by two independent reviewers.

Rigorous assessment of study heterogeneity performed and appropriate methods used accordingly, for meta-analysis.

Cox, Bass, McCann, Ku, Berman, Durand, Bolano, Wang, Peltz, Cox, Salud, Reintgen & Lyman . Lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer. Annu.Rev Med 51[pp 525-542]. 2000.

Design: Systematic review of diagnostic studies, evidence level: 2-
Country: US/various, setting: Secondary care

Inclusion criteria Case series: 1147 women, mean age 58.5 years, median 57 years, SD 13.2 years

Systematic review: Studies with original study populations, axillary clearance performed as well as SLNB, with description of surgical/statistical methodology.

Total number of patients: 1842 in 12 series.

Exclusion criteria Case series: Pregnancy

Population -

Interventions Case series:

SLNB technique: R, D

Histology : FS (rarely), S, IHC

Systematic review:

SLNB technique: combined (4 studies), R (4 studies), D (4 studies)

Outcomes Staging performance of SLNB including:

Pre-test probability (= prevalence of axillary disease by gold standard, axillary clearance)

Post-test probability negative (PTPN) (= probability of an axillary lymph node involvement in patients with a negative SN result).

PTPN = pre-test odds/[1 + post-test odds] where:

Post-test odds = pre-test odds x likelihood ratio (LR)

LR = [1 - sensitivity]/specificity

Pre-test odds = prevalence/[1 - prevalence]

Follow up Not reported: Study reports staging outcomes

Results Case series:

SN localisation rate = 1098/1147 = 95.7%

Number of SNs per patient = 2395/1098 = 2.2

Pre-test probability = 54/173 = 31.2%

FNR = 1/54 = 1.85%

Accuracy = 172/173 = 99.4%

PTPN = 0.83%

Systematic review:

SN localisation rate = 1534/1717 = 91.5%

Pre-test probability = 37.6% [95% CI 35.3% to 39.9%]

PTPN = 4.17% [95% CI 2.99% to 5.35%]

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General comments Systematic review: Chi square test revealed low heterogeneity between 12 included studies therefore meta-analysis appears justified.

Update of 6A – SLNB invasive BC

<p>Veronesi, U., Paganelli, G., Viale, G., Luini, A., Zurrada, S., Galimberti, V., Intra, M., Veronesi, P., Maisonneuve, P., Gatti, G., Mazzarol, G., De, C. C., Manfredi, G. & Fernández, J. R. (2006) Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. <i>The lancet oncology</i>, 7: 983-990.</p>
<p>Design: RCT (extended follow-up from original Veronesi 2003 study), 1+</p>
<p>Country: Italy</p>
<p>Aim: to update the original Veronesi 2003 with results from longer follow-up, .</p>
<p>Inclusion criteria</p> <ul style="list-style-type: none">• Women with breast tumours of diameter 2 cm or less were randomly assigned after breast-conserving surgery either to SLNB and total ALND (ALND group), or to SLNB followed by ALND only if the SLN was involved (SLN group).• Analysis was restricted to patients whose tumour characteristics met eligibility criteria after treatment.
<p>Exclusion criteria</p> <p>Multicentric cancer or previous excisional biopsy</p>
<p>Population</p> <p>Women with breast tumours of diameter 2 cm or less. Women aged 40–75 years with invasive breast carcinoma and no history of any other cancer, except skin cancer, were eligible for inclusion.</p>
<p>Interventions</p> <p>Women were randomly assigned after breast-conserving surgery either to SLNB and total ALND (ALND group), or to SLNB followed by ALND only if the SLN was involved (SLN group). 257 patients in the ALND group 259 patients in the SLN group</p>
<p>Outcomes</p> <p>The main outcomes were: the number of axillary metastases in women in the SLN group with negative SLNs, staging power of SLNB, disease-free and overall survival (defined as time from surgery until the date of death (from any cause) or until the date of last follow-up.)</p> <p>Secondary outcomes: the development of any breast cancer- related event (reappearance of tumour within the breast; axillary, supraclavicular, or distant metastases)</p> <p>Associations between the status of the axillary nodes and the characteristics of the primary tumour were assessed by Fisher's exact test. Logistic regression was used to assess the association between various clinico-pathological characteristics (age, tumour size, location, grade, presence of peritumoral lymphatic and vascular invasion, oestrogen-receptor status, and proliferative rate) and SLN metastases.</p> <p>Mean follow-up of 78 months (median 79, range 15–97)</p>
<p>Results</p>

n=516 evaluable patients

Of the 257 patients in the ALND group, 83 (32%) had a positive SLN and 174 (68%) had a negative SLN;

8 (5%) of those with negative SLNs were found to have false-negative SLNs.

Of the 259 patients in the SLN group, 92 (36%) had a positive SLN, and 167 (65%) had a negative SLN;

1 case of overt clinical axillary metastasis was seen in the follow-up of the 167 women in the SLN group who did not receive ALND (ie, one false-negative).

After a median follow-up of 79 months (range 15–97), 34 events associated with breast cancer occurred: 18 in the ALND group, and 16 in the SLN group (log-rank $p=0.6$).

The overall 5-year survival of all patients was 96.4% (95% CI 94.1–98.7) in the ALND group and 98.4% (96.9–100) in the SLN group (log-rank $p=0.1$).

Characteristics predictive of SLN status:

- peritumoral vascular invasion (linked to a very high rate of SLN metastases (61 of 87 patients; 70%))
- size of primary carcinoma (the prevalence of SLN metastases varied from 22% (28 of 130 patients) in tumours less than 1.0 cm in diameter to 38% (55 of 143 patients) in tumours larger than 1.5 cm.
- Age, site of primary carcinoma, oestrogen-receptor status, grade, and proliferative fraction did not show any significant relation with involvement of SLNs.

General comments

SLNB can allow total ALND to be avoided in patients with negative SLNs, while reducing postoperative morbidity and the costs of hospital stay. The finding that only one overt axillary metastasis occurred during follow-up of patients who did not receive ALND (whereas eight cases were expected) could be explained by various hypotheses, including those from cancer-stem-cell research.

Krag, D. N., Anderson, S. J., Julian, T. B., Brown, A. M., Harlow, S. P., Ashikaga, T., Weaver, D. L., Miller, B. J., Jalovec, L. M., Frazier, T. G., Noyes, R. D., Robidoux, A., Scarth, H. M., Mammolito, D. M., McCready, D. R., Mamounas, E. P., Costantino, J. P., Wolmark, N. & National Surgical Adjuvant Breast and Bowel Project (2007) Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *The lancet oncology*, 8: 881-888.

Design: RCT, 1+

Country: US

Aim: To evaluate the efficacy and safety of SLN biopsy compared to ALND.

Inclusion criteria

Women with operable invasive primary breast cancer and clinically negative nodes.

The randomisation was stratified according to age at entry (≤ 49 years or ≥ 50 years); surgical treatment plan (lumpectomy or mastectomy); and clinical tumour size (≤ 2.0 cm, 2.1–4.0 cm, or > 4.0 cm).

Exclusion criteria

Population

5611 women with invasive breast cancer were randomly assigned to receive either SLN resection followed by immediate conventional ALND (n=2807; group 1) or SLN resection without ALND if SLNs were negative on intraoperative cytology and histological examination (n=2804; group 2)

Patients in group 2 underwent ALND if no SLNs were identified or if one or more SLNs were positive on intraoperative cytology or subsequent histological examination.

Interventions

Women were randomised into SLN biopsy associated with ALND (ALND group) or SLN biopsy followed by ALND only if the SLN was metastatic (SLN group)

Outcomes

- Accuracy and technical success of SLN resection plus ALND versus SLN resection alone
- Side effects

Results

Technical success (defined as the ability to identify and remove at least one SLN)

- 97.3% (2672 of 2746) in group 1: 74 patients in group 1 did not have SLNs identified
- 97% (2707 of 2790) in group 2: 83 patients in group 2 did not have SLNs identified.

Overall nodal status was established from the histological status of all examined lymph nodes:

- For 766 patients (29.2%) overall nodal status was positive; for the remaining 1853 patients it was negative (70.8%).
- **Of the 1928 SLN negative patients, 1853 (96.1%) were confirmed to be node negative by ALND (negative predictive value).**
- **75 patients classified as node negative by SLN biopsy were node positive on subsequent**

ALND:

- false-negative rate = 9.8% (75 of 766; 95% CI 7.8–12.2)
- sensitivity = 90.2% (691 of 766; 87.8–92.2).

- Overall accuracy of SLN resection in this group of patients was 97.1% (2544 of 2619; 96.4–97.7).

Assessment for possible association with false-negative rates:

- Differences in tumour location when assessed by region, type of previous diagnostic biopsy, and number of SLNs removed statistically affected false-negative rates.
- Data on the relation between intraoperative cytology and subsequent histological examination were available for 2697 patients in group 2.
- Overall accuracy of intraoperative cytology = 89.7% (2418 of 2697; 95% CI 88.4–90.8%).
- The negative predictive value of intraoperative cytology = 88.1% (86.7–89.4).
- The positive predictive value = 97.5% (95.4–98.7).
- The false-negative rate for intraoperative cytology = 38.6% (268 of 694; 35.0–42.4).
- Sensitivity of intraoperative cytology = 61.4% (426 of 694; 57.6–65.0).
- Only 11 of the 2003 patients deemed to have negative nodes on histological examination were classified as having positive nodes on intraoperative cytology (0.5%; 0.3–1.0).

Of the 5379 patients who had at least one SLN removed, similarities in those who were SLN positive, across groups, were observed: (26.0% [694 of 2672] in group 1 and 25.7% [696 of 2707] in group 2; $p=0.85$).

Of the 5536 patients who had an SLN procedure done (with or without technical success):

- 28.5% (783 of 2746) in group 1 were identified as node positive,
- 25.6% (715 of 2790) of patients in group 2,
- a difference of 2.9% ($p=0.02$)

Author claim: Because this was a randomised trial, it maybe assumed that about 2.9% of positive-node patients in group 2 were misclassified as node negative because their positive nodes were not removed by ALND.

- In 61.4% (426 of 694) of SLN-positive patients in group 1, positive SLNs were the only positive nodes identified. Although the nodal status of the remaining SLN-positive patients was correctly established by doing an ALND, 38.6% (268 of 694) of the SLN-positive patients would have had at least one unresected positive node if completion ALND had not been done.
- In the patients with pathologically positive SLNs, the pathologically positive SLN specimens were located exclusively outside axillary levels I and II in 1.4% of cases. Because conventional ALND would not have identified these patients as node positive, they would have been incorrectly classified as node negative if only ALND had been done.

Adverse Events:

- Allergic reactions were associated with blue dye injections: Out of 5588 patients with data on toxic effects: 0.4 % ($n=25$) had grade 1 or 2 allergic reactions and 0.2% ($n=12$) had grade 3 or 4 allergic reactions.
- No deaths due to allergic reactions were reported.

General comments

Summary from Abstract:

Findings

Data for technical success were available for 5536 of 5611 patients; 75 declined protocol treatment, had no SLNs removed, or had no SLN resection done. SLNs were successfully removed in 97.2% of patients (5379 of 5536) in both groups combined. Identification of a

preincision hot spot was associated with greater SLN removal (98·9% [5072 of 5128]). Only 1·4% (189 of 13171) of SLN specimens were outside of axillary levels I and II. 65·1% (8571 of 13171) of SLN specimens were both radioactive and blue; a small percentage was identified by palpation only (3·9% [515 of 13171]). The overall accuracy of SLN resection in patients in group 1 was 97·1% (2544 of 2619; 95% CI 96·4–97·7), with a false-negative rate of 9·8% (75 of 766; 95% CI 7·8–12·2). Differences in tumour location, type of biopsy, and number of SLNs removed significantly affected the false-negative rate. Allergic reactions related to blue dye occurred in 0·7% (37 of 5588) of patients with data on toxic effects.

Interpretation

The findings reported here indicate excellent balance in clinical patient characteristics between the two randomised groups and that the success of SLN resection was high. These findings are important because the B-32 trial is the only trial of sufficient size to provide definitive information related to the primary outcome measures of survival and regional control. Removal of more than one SLN and avoidance of excisional biopsy are important variables in reducing the false-negative rate.

Zavagno, G., De Salvo, G. L., Scalco, G., Bozza, F., Barutta, L., Del, B. P., Renier, M., Racano, C., Carraro, P., Nitti, D. & GIVOM, T. (2008) A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Annals of Surgery*, 247: 207-213.

Design: RCT 1+

Country: Italy

Aim: To evaluate the effectiveness of SLN biopsy followed by standard ALND with SLN biopsy followed by ALND (only if the SLN was found to be positive at histology)

Inclusion criteria

Patients with invasive breast cancer ≤ 3 cm and clinically negative axilla.

Exclusion criteria

Nonpalpable tumors, multiple tumors, ductal carcinoma in situ, tumors ≥ 3 cm, clinically positive axilla, distant metastases, previous neoadjuvant therapy, pregnancy, age >80 years

Population

697 patients available for the analysis.

Interventions

1. Patients in the first arm (ALND group) underwent SLN biopsy immediately followed by standard ALND.
2. Patients in the second arm (SLN group) underwent SLN biopsy with frozen section examination and ALND was performed only in patients with metastatic SLN. In cases with negative SLN frozen section examination but positive definitive histology, a delayed ALND was performed.

Outcomes

disease-free survival (DFS), overall survival (OS), physical morbidity, and quality of life.

Results

Identification and Removal of the SLNs:

SLNs were identified in 662 cases (95.0%).

The rate of identification was similar in the 2 arms (94.9% in the ALND arm and 95.1% in the SLN arm).

SLN Status and False Negative Rate:

Of the 334 patients with identified SLNs in the ALND group, 90 had a positive SLN at definitive histology (26.9%, 95% CI 22.3–32.0)

Among the 328 patients with identified SLNs in the SLN group, 99 had a positive SLN at definitive histology (30.2%, 95% CI 25.3–35.5)

Among the 323 patients who underwent ALND in this group, 90 had a positive SLN and 233 had a negative SLN at the definitive histology.

- 18 of 233 patients with negative SLNs were found to have other nodal metastases in the ALND specimen: negative predictive value = 92.3% (215 of 233 patients, 95% CI 88.1–95.4),
- overall accuracy of the SLN status = 94.4% (305 of 323 patients, 95% CI 91.3–96.7)
- sensitivity was 83.3% (90 of 108 patients, 95% CI 74.9–89.8)
- specificity was 100% (by definition)
- The false negative rate was 16.7% (18 of 108 patients, 95% CI 10.2–25.1).

Side Effects and Quality of Life Evaluation

Women in the SLN group had significantly less lymphoedema ($P = 0.01$), restrictions of shoulder mobility ($P = 0.016$), and numbness ($P < 0.0001$) compared with those in the ALND group.

No differences were found between the 2 groups in all HRQOL domains of the SF-36.

The analysis of the Psychological General Well Being Index questionnaire showed a more positive outcome in the anxiety domain and in the general index for the SLN group ($P = 0.013$ and $P = 0.015$, respectively).

Unfavorable Events (Disease recurrence and Survival)

Median follow up = 55.6 months.

At the time of analysis, there were 51 events, 22 in the ALND group and 29 in the SLN group

- Locoregional recurrences have occurred in 3 patients in the ALND group and in 16 patients in the SLN group (Local recurrences in the SLN group: 8 ipsilateral breast and 4 thoracic wall recurrences compared with 2 ipsilateral breast and 1 thoracic wall recurrences in the ALND arm).
- 5 cases of contralateral breast cancer (3 in the ALND group and 2 in the SLN group)
- Distant metastases in 16 patients in the ALND group and in 11 patients in the SLN group
- Other primary tumors were detected in 1 patient in the ALND group and 3 patients in the SLN group.

- 35 patients died, 18 from metastatic breast cancer (8 in the ALND group and 10 in the SLN group) and 17 from other causes (6 in the ALND group and 11 in the SLN group).

At 5 years, the Kaplan-Meier estimates of DFS:

- ALND 89.9% (95% CI 85.3–93.1)
- SLN group 87.6% (95% CI 83.3–90.9)

The difference was 2.3% ($P = 0.7692$) with a 95% CI ranging from -3.1% to 7.6%.

(Because the upper bound is more than the acceptable difference of 6%, it can not exclude the possibility of a worse DFS in the SLN arm.)

The 5 years Kaplan-Meier estimates of OS:

- 95.5% (95% CI 92.2–97.5) in the ALND group
- 94.8% (95% CI 91.6 –96.8) in the SLN group

General comments

The high false negative rate was explained as an consequence of inexperienced and untrained surgeons conducting the procedure. The authors claim that this would probably reflect standard practice and that the levels reported in other studies was probably higher than the reality.

Lucci, A., Mccall, L. M., Beitsch, P. D., Whitworth, P. W., Reintgen, D. S., Blumencranz, P. W., Leitch, A. M., Saha, S., Hunt, K. K., Giuliano, A. E. & American College of Surgeons Oncology Group (2007) Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 25: 3657-3663.

Design: RCT, 1

Country: US

Aim: To compare the complications associated with SLN dissection (SLND) plus ALND, versus SLND alone.

Inclusion criteria

All participants were women at least 18 years old undergoing breast conservation therapy who had clinical T1 or T2, N0, M0 breast cancer; one or two positive SLNs; and an Eastern Cooperative Oncology Group/Zubrod functional status ≤ 2

Exclusion criteria

Patient withdrawal before surgery; nodes not positive on examination of HE-stained samples; too many positive SLNs; distant metastatic disease; unclear margins; presence of gross extra capsular invasion; and various other reasons.

Population

group 1 (SLND+ALND; n=445)

group 2 (SLND alone; n=446)

Interventions

- SLN dissection (SLND) plus ALND, versus SLND alone.
- SLNDs were performed with isosulfan blue, a radiopharmaceutical, or both.
- Patients with a medial hemisphere lesion had preoperative lymphoscintigraphy to confirm axillary drainage. After the blue and/or hot nodes were removed, any remaining axillary nodes were palpated; if suggestive of disease, they were considered SLNs and removed.
- ALND was defined as the removal of all anatomic level I and II nodes on the affected side, with at least 10 identified nodes per axillary specimen.

Outcomes

- Adverse effects for all operative procedures were recorded at 30 days, every 6 months until year 3, and then annually.
- Surgical effects assessed at day 30 included wound infections, axillary seroma, axillary paresthesia, and brachial plexus injury (BPI).
- Surgical effects documented every 6 months included axillary paresthesia, Lymphoedemas and BPI.

Results

Adverse surgical effects:

- 70% (278 of 399) of patients after SLND+ ALND
- 25% (103 of 411) after SLND alone ($P \leq 0.001$)

Wound Infection:

On multivariate analysis, both greater BMI ($P=0.0113$) and having had an ALND ($P=0.0026$) were significant predictors for developing a wound infection, but age and number of nodes removed were not significant predictors.

Axillary Seromas at 30 Days:

- Having had an ALND was a significant predictor ($P \leq 0.0001$) for axillary seroma at 30 days
- Older age was a significant predictor of seroma formation ($P= 0.028$) in the SLND+ALND arm but not in the SLND-alone arm.
- When age, BMI, and linked age and study group were included in a model to evaluate association; the age and age/study group linkage were significant predictors of seroma.
- BMI and number of nodes removed were not significant in any of the models.

Axillary Paresthesias

- At day 30 : Axillary paresthesias were the most common surgical effect
- Having had an ALND was the only factor that predicted axillary paresthesias at any time point ($P<0.0001$)
- The number of nodes removed was a significant predictor of paresthesia 30 days after an ALND but not after SLND alone
- There was no significant decline in reported axillary paresthesias at 6 or 12 months compared with rates at 30 days.
- Younger age remained a significant predictor for paresthesia 1 year after ALND ($P=0.0131$), but the number of nodes removed did not remain a significant predictor (from multivariate analysis).

Lymphoedema

- From multivariate analysis, having ALND was not a significant predictor of lymphoedema at 6 months, but it was significant at 1 year ($P< 0.0001$) and after 12 months ($P,0.0001$)
- When subjective data from all follow-ups were combined, having had an ALND was also a significant predictor of lymphoedema ($P \leq 0.0001$).
- Based on proximal arm measurement data, no clinical factors (including number of nodes removed) reliably predicted lymphoedema at 30 days, 6 months, or 1 year. (arm measurements were not always recorded at these follow-up times and the number of patients for whom data were available was much lower than the number of assessable patients).

BPI

- True overall BPI incidence = 8 of 821 (0.97%)
- 18 BPIs were reported originally, but when re-evaluated, 10 should have been more accurately classified as axillary paresthesias.
- 88% of all BPIs were resolved at last follow-up

General comments

Authors' conclusion:

In this trial Z0011, the use of SLND + ALND resulted in more wound infections, axillary seromas, and paresthesias than SLND alone. Lymphoedema was more common after SLND + ALND but was significantly different only by subjective report. The use of SLND alone resulted in fewer complications.

Evidence Tables

Axillary sampling

Randomized controlled trials

Chetty, Jack, Prescott, Tyler & Rodger . Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. Edinburgh Breast Unit.[see comment]. Br J Surg 87[2]. 2000.

Design

Randomized controlled trial (therapy), evidence level: 1+
Country: United Kingdom, setting: Secondary care

Inclusion criteria

Patients of age <70 years with unilateral invasive breast cancer of clinical size <=4cm and no evidence of metastatic disease.

Exclusion criteria

Patients with clinically multicentric or inoperable tumours or those with fixed nodes or history of previous malignancy except skin basal cell carcinoma.

Population

Number of patients = 466, median age = 54 years.

Interventions

Axillary sample group (n=234): underwent breast conserving surgery plus removal of a minimum of four nodes by incision and palpation [without any localisation aid].

Axillary clearance group (n=232): underwent breast conserving surgery plus level III axillary clearance.

Outcomes

Overall survival
Disease free survival
Axillary recurrence free survival

Arm volume and circumference
Shoulder mobility and muscle power

Follow up

Median follow-up was 4.1 years

Results

There was no statistically significant difference between randomised groups for overall survival [p=0.2, log rank test] or disease free survival [p=0.68, log rank test].

Survival:

The estimated 5 year survival rate was 88.6% (SD 2.5%) in the axillary sample group and 82.1% (SD 3.1%) in the axillary clearance group. 5 year estimated disease free survival rates were 79.1% (3.1%) and 76.0% (3.5%) respectively.

Axillary recurrence:

There was no significant difference between randomised groups in axillary recurrence ($p=0.94$, log rank test).

Morbidity:

At 6 months from surgery, arm flexion was statistically significantly lower in the axillary clearance group ($p=0.003$ ANCOVA) and in the axillary sample plus RT group ($p=0.004$) compared to the axillary sample group.

There were no differences between groups in power to flex the shoulder at any time point, nor in abduction.

There was little difference in the upper arm circumference between the three groups. At three years from surgery the forearm circumference was significantly greater after axillary clearance than after node sample ($p=0.005$) or node sample plus RT ($p=0.04$).

General comments

For axillary sample, nodes were identified starting at the axillary tail and working upwards.

Patients received/did not receive radiotherapy (RT) on an individual basis according to clinical judgement/standard practice at the time, and not by random allocation:

All but 48 patients received breast RT

5/232 patients in the axillary clearance group received axillary RT.

91/234 patients in the axillary sample group received RT.

29 patients did not receive their randomised treatment. 12 patients were found to have benign or non-invasive disease.

Survival analyses are by ITT.

Morbidity analyses are by treatment received [3 groups]:

Axillary clearance;

Axillary sample plus axillary RT;

Axillary sample.

Study does not appear to provide compelling evidence on morbidity due to non-ITT analysis, numerous assessment points, 3 analysis groups and incomplete reporting.

A median of 15 nodes were removed in the axillary clearance group (range 4-36) and a median of 5 (range 2-12) in the axillary sample group.

Forrest, Everington, McDonald, Steele, Chetty & Stewart . The Edinburgh randomized trial of axillary sampling or clearance after mastectomy. Br J Surg 82[11]. 1995.

Design

Randomized controlled trial (diagnosis, screening), evidence level: 1+
Country: United Kingdom, setting: Secondary care

Inclusion criteria

Patients with clinically operable invasive breast cancer (T1-2 or operable T3, N0-1, M0).

Median ages in randomised groups were 58.7 and 57.

Exclusion criteria

Patients unlikely to participate in continuous follow up, those with Paget's disease of the nipple, insitu disease or multifocal or contralateral breast cancer.

Population

number of patients = 417.

Interventions

Intervention group (n=203): Total mastectomy plus removal of a target of four nodes by incision and palpation [without any localisation aid].

Control group (n=203): Total mastectomy plus axillary clearance.

Outcomes

Survival
Recurrence

Follow up

Median 11 years (range 2-13 years)

Results

Disease specific survival

There was no significant difference between groups for disease specific survival at a median of 11 years follow up: 57/203 patients died due to breast cancer in the axillary sample group compared to 54/203 in the axillary clearance group, HR 1.11 [95% CI 0.80-1.53].

Distant recurrence

There was no significant difference between groups for distant recurrence at a median of 11 years follow up: HR as above 1.05 [95% CI 0.74-1.5].

Locoregional recurrence

There was no significant difference between groups in terms of locoregional recurrence: 29 patients had locoregional recurrence in the axillary sample group compared with 38 in the axillary clearance group (HR 1.35 in favour of axillary sample group [95% CI 0.83-2.19]).

General comments The last 135 randomised patients all underwent axillary sample prior to randomisation in theatre, with axillary clearance performed

immediately where allocated.

Analysis of reported outcomes was by ITT. 11 patients were ineligible and excluded and 23 patients had protocol violations but were analysed as per ITT.

Time to event analysis was by Kaplan-Meier curves and Cox survival models.

A mean of 6 nodes (median 4) were removed in the axillary sample group and a mean of 20 (median 20) were removed in the axillary clearance group.

82/86 patients with involved nodes in the axillary sample group received RT to the chest wall and axilla; no patients in the axillary clearance group received RT.

Retrospective comparative studies

Cserni . The reliability of sampling three to six nodes for staging breast cancer. J Clin Pathol 52[9]. 1999.

Design

Retrospective comparative study (diagnosis, screening), evidence level: 3
Country: Hungary, setting: Secondary care

Inclusion criteria

499 patients with pathological nodal stage pN0-1, identified from a consecutively treated series.

Exclusion criteria

None stated.

Population

Number of patients = 499.

Interventions

Aim: to assess the optimal number of axillary nodes that are required to stage the axilla.

A retrospective review of pathology reports was performed. Patients underwent axillary clearance with nodes numbered consecutively in order of their size, based on the blue staining area on haematoxylin and eosin histology.

Outcomes

Rate of concordance of sampling 3, 4, 5 and 6 nodes, based on size order, with axillary clearance.

Follow up

Not reported.

Results

Mean no. of lymph nodes per axillary specimen was 10.7 (range 1-45).

The rates of concordance (%) of the information provided by limited sampling of nodes with that of axillary clearance were as follows:

Based on definitively positive axillae:

3 nodes: 89-93%

4 nodes: 94-97%

5 nodes: 95-98%

6 nodes: 97-98%

Based on all axillae:

3 nodes: 94-96%

4 nodes: 97-98%

5 nodes: 98-99%

6 nodes: 99%

General comments

Ranges in results arise from cases where nodes were of similar size such that they were allocated size rank jointly e.g. 3 nodes of similar size, each labelled, '2-4'.

It appears that patients did not undergo limited sampling, but axillary clearance: the analysis considered information provided by a limited number of nodes compared to that provided by axillary clearance.

Kingsmore, Ssemwogerere, Hole, Gillis & George . Increased mortality from breast cancer and inadequate axillary treatment. Breast 12[1]. 2003.

Design

Retrospective comparative study (therapy), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

4637 patients who received axillary staging with number of nodes examined stated, out of a consecutive series of 7144 patients with invasive breast cancer, identified from a cancer registry.

Exclusion criteria

364 patients who underwent staging surgery but with no report of the number of nodes examined.

Population

Number of patients = 4637.

Interventions

Aim: to derive the minimum number of nodes required to safely stage the axilla in patients with breast cancer.

Survival and pathological data were retrospectively reviewed in a large series of patients with breast cancer and also in a reference group of patients in whom 10 or more lymph nodes were removed for staging (considered to be adequate staging based on previous literature).

Outcomes

Survival (based on breast cancer specific mortality)

Follow up

Mean 9.5 years, range 3-18 years

Results

Compared to the reference group, node negative patients had significantly greater survival at 5 and 10 years where 4 or more nodes were examined, compared to where 1-3 nodes were examined (hazard ratio [HR] 1.31 [95% CI 1.07-1.60], $p < 0.01$).

Compared to the reference group, node positive patients had significantly greater survival at 5 and 10 years where 4 or more nodes were examined, compared to where 1-3 nodes were examined (HR 1.85 [95% CI 1.54-2.21], $p < 0.01$).

Application of 4 node threshold to series of 4637 patients:

In node-negative patients, those who had examination of four or more axillary nodes had statistically significantly increased survival compared to patients who had 3 or less nodes examined (87% and 81% respectively, at 5 years; 76% and 70% respectively, at 10 years, HR 1.34 [95% CI 1.09-1.65]).

In node-positive patients, those who had examination of four or more axillary

nodes had statistically significantly increased survival compared to patients who had 3 or less nodes examined 59% and 53% respectively, at 5 years; 42% and 35% respectively, at 10 years, HR 1.20 [95% CI 1.02-1.41]).

General comments

No information on tumour grade was analysed.

The effects of adjuvant RT, chemotherapy and hormone therapy were not accounted for.

Variation in pathology technique was not accounted for.

No details are provided about intended surgical staging techniques e.g. whether axillary clearance, unguided sample or blue dye guided sample. Patients were treated prior to 1994; hence no patients underwent SLNB.

The reference group was verified by demonstrating that node positivity varied by tumour size, and that these factors were associated with survival. Size of reference group not reported.

Prospective case series

Hadjiminas & Burke . Intraoperative Assessment of Nodal Status in the Selection of Patients with Breast-Cancer for Axillary Clearance. Br J Surg 81[11]. 1994.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

114 patients with operable breast cancer of stage I-II.

Exclusion criteria

None stated.

Population

Number of patients = 114.

Interventions Aim: to report on a centre's experience with axillary sample as an alternative procedure to automatic axillary clearance.

All patients underwent an unguided axillary sample of four nodes. Patients with disease revealed by intra-operative contact cytology underwent axillary clearance. Patients with negative contact cytology underwent no further surgery.

Outcomes

Objective arm lymphoedema, defined as: difference between the sum of the circumferences of the normal and affected arm, measured at 2 points, was 4cm or more.

Objective shoulder stiffness, defined as: maximum abduction of 160 degrees or less.

Follow up

Mean 18.7 months, median 20 months.

Results

43 patients underwent axillary clearance in addition to axillary sample due to positive cytology and 71 patients axillary sample only due to negative cytology.

Rate of lymphoedema:

After axillary clearance: $6/43 = 14.0\%$

After axillary sample alone: $0/71 = 0\%$ ($p < 0.02$, Fishers exact test).

General comments

No patients received axillary RT.

Paper does not state that 5 patients with apparent falsely negative contact

cytology result underwent axillary clearance.

The result may be confounded by the effect of having two surgical procedures rather than one.

Very little data reported on shoulder stiffness: no statistical test reported.

Hoar & Stonelake . A prospective study of the value of axillary node sampling in addition to sentinel lymph node biopsy in patients with breast cancer. Eur J Surg Oncol 29[6]. 2003.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

66 consecutive patients with primary, operable, invasive breast cancer.
1 patient had bilateral breast cancer and so 67 axillae represent the cases.

Exclusion criteria

No exclusions were made on the basis of tumour size or patient age.

Population

Number of patients = 66, age range 27 to 86 years, mean age = 55 years.

Interventions

Aim: to assess the staging performance of SLNB plus axillary sample as a staging procedure, compared to axillary clearance as gold standard.

All patients underwent SLNB, extended where necessary such that all patients had a minimum of 4 nodes removed as the 'SLNB plus axillary sample' procedure. If 4 or more SNs were removed, then only suspicious further nodes were removed as the 'SLNB plus axillary sample' procedure.

All patients then underwent a level II axillary clearance.

SLNB technique: radiocolloid, dye, lymphoscintigraphy.
Histology technique: all nodes were examined by a single, standard section.

Outcomes

Staging performance (against axillary clearance as gold standard) of:
SLNB alone;
SLNB extended to axillary sample (reported by whether additional sampled nodes were palpably suspicious during surgery).

Follow up

Not reported

Results

Median no. of SNs removed per case in SLNB= 2 (range 1-8).
Median no. of nodes removed in SLNB plus axillary sample = 5 (range 2-14).
Median total no. of nodes removed (SLNB plus axillary sample plus axillary clearance) = 16 (range 7-35).

Staging performance of SLNB alone:
SN identification rate = 65/67 = 97%
No. SNs removed per patient = median 2 (range 1-8)
Prevalence of axillary disease = 29/67 = 43.3%, or amongst patients with localised SNs, 28/65 = 43.1%.
FNR = 4/28 = 14.3%

Accuracy = $[24+37]/65 = 93.8\%$

Staging performance of SLNB extended to axillary sample of a minimum of 4 nodes where further sampled nodes included palpably suspicious nodes:

FNR = $1/28 = 3.6\%$

Accuracy = $[27+37]/65 = 98.5\%$

Staging performance of SLNB extended to axillary sample of a minimum of 4 nodes where further sampled nodes did not include any palpably suspicious nodes:

FNR = $1/28 = 3.6\%$

Accuracy = $[27+37]/65 = 98.5\%$

i.e. staging performance of SLNB plus axillary sample did not vary by whether the further sampled nodes were palpably suspicious.

General comments

8 patients had undergone excision biopsy or wide local excision prior to SLNB, for presumed DCIS and one patient had received neoadjuvant chemotherapy.

The 'SLNB plus axillary sample' procedure may not be independent of the SLNB procedure and the research setting is not as rigorous as one where axillary sample is the first procedure performed.

In some cases a procedure was classified as both a SLNB and a 'SLNB plus axillary sample'; hence the sample was a guided sample by radiocolloid, lymphoscintigraphy and dye.

SLNB did not use serial sectioning, but all nodes received the same histological technique.

High FNR may be related to the patients in the series: 27.7% of patients had tumours >30mm in size.

Ishikawa, Momiyama, Hamaguchi, Tanabe, Tomita, Ichikawa, Nakatani, Sasaki, Nozawa, Inayama, Inui & Shimada . Blue-dye technique complements four-node sampling for early breast cancer. Eur J Surg Oncol 31[10]. 2005.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria

33 consecutive patients with breast cancer of clinical stage N0-1

Exclusion criteria

None stated.

Population

Number of patients = 33, age range 26 to 75 years, mean age = 53 years.

Interventions

Aim: to evaluate the staging performance of dye assisted axillary sample compared to axillary clearance as gold standard.

All patients underwent a dye-assisted axillary sample of a target of four nodes, including non-blue-staining, palpable nodes, followed by a level II axillary clearance.

Outcomes

Staging performance of dye-assisted axillary sample.

Follow up

Not reported.

Results

Mean no. of blue stained nodes per patient (range) = 1.7 (0-4).

Mean no. of nodes sampled per patient (range) = 3.4 (0-7).

Total no. of nodes removed, including axillary clearance (range) = 18 (0-32).

Prevalence of axillary disease = 11/32 = 34.4%

FNR = 0/11 = 0%

Accuracy = 32/32 = 100%

General comments

Study is hampered by small series size.

Study represents a validation period for dye-assisted axillary sample.

13 patients underwent preoperative excisional biopsy, which may hamper the identification rate of nodes by blue dye.

Inclusion of clinically N1 patients may act to increase prevalence of axillary disease by gold standard assessment.

32/33 patients underwent axillary clearance as gold standard: 1 patient with non-invasive DCIS did not undergo axillary clearance. Therefore staging

results are based on 32 patients.

Results shown are for a dye-assisted axillary sample, with palpation to include a target of four nodes, even if non-blue nodes are included.

A larger observational study was also initiated of axillary sample with axillary clearance only in cases of positive sample: only minimal results available with unspecified follow-up; not reported here.

Macmillan, Barbera, Hadjiminias, Rampaul, Lee & Pinder . Sentinel node biopsy for breast cancer may have little to offer four-node-samplers: Results of a prospective comparison study. Eur J Cancer 37[9]. 2001.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

200 consecutive patients with biopsy-proven primary invasive breast cancer of clinical stage T1-2, N0, M0.

Exclusion criteria

Not reported.

Population

Number of patients = 200.

Interventions

Aim: to compare the staging performance of SLNB with axillary sample.

All patients received preoperative injection of radiocolloid.

During surgery all patients underwent axillary sample of a minimum of four nodes, based on palpation.

SNs were identified ex vivo using a gamma probe and the operated axilla was also probed for potentially remaining SNs. Any such SNs found in vivo were also removed.

SN identification technique: radiocolloid

Histology technique: 3-5mm intervals with standard (haematoxylin and eosin) assessment.

Outcomes

Explores relationship between SNs and nodes examined by axillary sample.

Follow up

Not reported.

Results

A mean of 1.5 SNs were identified in total (ex vivo plus in vivo) per patient (range 1-3).

In 153/191 = 80.1% of patients with one or more SNs identified, all of the SNs were removed within the axillary sample.

In 38/191 = 19.9% of patients with one or more SNs identified, SNs were identified in the axilla after performing axillary sample.

Prevalence of axillary disease = 60/200 = 30%.

In 1 patient the axillary sample did not include a SN that was histologically positive for disease.

Other staging performance outcomes not reported since study does not evaluate true SLNB.

General comments

Study does not evaluate true performance of SLNB, but an artificial alternative.

The first SN was classed as the 'hottest' node ex vivo. Further SNs were defined by demonstrating 25% of the radioactivity of the first SN.

15 patients underwent preoperative scintigraphy.

Study design assumes:

that the preoperative scintigraphy did not influence which nodes were excised;
that SN identification can be performed ex vivo to the same standard as in vivo;

that the axillary sample surgery does not affect the identification of further SNs in vivo.

Narreddy, Govindarajulu, Cawthorn & Sahu . Sentinel node biopsy in multifocal breast cancer: Accuracy of blue dye assisted four node sample. Ejc Supplements 4[2]. 2006.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

17 patients with multifocal breast cancer, identified from a series of 74 patients who underwent axillary sample with blue dye and subsequent axillary dissection.

Exclusion criteria

None reported

Population

Number of patients = 17, mean age = 57 years.

Interventions

Aim: to report on the centre's validation period for axillary sample of four nodes with blue dye in patients with multifocal breast cancer.

All patients underwent axillary sample of four nodes with blue dye plus immediate axillary clearance.

Outcomes

Staging performance of axillary sample with axillary clearance as gold standard.

Follow up

Not reported.

Results

Authors report SN localisation rate as 17/17 patients in this subgroup and 97% for the larger series of 74 patients.

4 or more blue stained nodes were sampled in 13/17 cases.

Number of nodes removed per patient: not reported.

Prevalence of axillary disease = 13/17 = 76.5%

FNR=0/13=0%

Accuracy = 17/17=100%.

The axillary node sample included all the positive nodes in 7/13 cases, therefore 6/13 patients with positive axillary sample had further involved nodes revealed by axillary clearance.

General comments

Only abstract available. Small series represented.

Only patients with multifocal breast cancer are represented [higher risk group than other studies?].

Patients appear to have been treated in the centre's validation period.

Authors describe the four node axillary sample with blue dye procedure as 'SLNB'.

SN localisation rate reported should be interpreted with caution here since the procedure differs from SLNB as usually practiced in the UK.

Due to the very small series size, all staging outcomes should be interpreted with caution. Prevalence of axillary disease is much higher than in other series (usually of patients with unifocal disease).

Rampaul, Pinder, Mitchell, Morgan, Ellis, Blamey & MacMillan . Long-term regional recurrence and survival after axillary node sampling for breast cancer. Breast Cancer Res Treat 88. 2004.

Design

Prospective case series (diagnosis, screening), evidence level: 3

Country: United Kingdom, setting: Secondary care

Inclusion criteria

852 patients with primary operable breast cancer.

Exclusion criteria

None stated.

Population

Number of patients = 852.

Interventions

Aim: To report regional recurrence and survival in a series of patients who underwent axillary sample.

All patients underwent axillary sample.

Patients with no axillary disease (stage I) underwent no further axillary treatment.

Patients with axillary disease revealed by axillary sample (stage II: 1-3 nodes positive, stage III: 4 or more nodes positive) underwent axillary RT.

Outcomes

Axillary recurrence

Overall survival

Follow up

Median 7.5 years

Results

Axillary recurrence:

42 axillary recurrences occurred, at a rate of 0.66% per annum.

Stage III patients had a higher rate of axillary recurrence than than stage II or stage I patients ($p < 0.001$)

Overall survival:

At a median follow-up of 7.5 years, OS was as follows:

0 nodes positive: 89%

1 nodes positive: 84%

2 nodes positive: 75%

3 nodes positive: 65%

General comments

Abstract only. Abstract does not mention details of surgical technique e.g. whether blue dye is used.

No overall survival result is provided for the whole series combined.

Tanaka, Yamamoto, Kanematsu, Okugawa & Kamiyama . A four node axillary sampling trial on breast cancer patients. Breast 15[2]. 2006.

Design

Prospective case series (diagnosis, screening), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria

237 patients with primary breast cancer of stage T1-2, N0-1: 23 patients had clinical stage N1 disease by preoperative assessment.

Exclusion criteria

None stated.

Population

Number of patients = 237, mean age = 57 years.

Interventions

Aim: to evaluate the staging performance of unguided axillary sample compared to axillary clearance as gold standard.

All patients underwent either mastectomy or breast conserving surgery followed by axillary sample of four palpable nodes and then axillary clearance.

Histology technique: study reports that 'all lymph nodes were examined by multiple sections'; exact technique not reported.

Outcomes

Staging performance of axillary sample compared to axillary clearance as gold standard.

Follow up

Not reported.

Results

A mean of 18.4 axillary nodes per patient were removed.

Prevalence of axillary disease = $62/237 = 26.2\%$

FNR = $4/62 = 6.5\%$

Accuracy = $(58+175)/237 = 98.3\%$

General comments

204/237 = 86% of patients underwent axillary clearance to level I-II and 33/237 = 14% to level III.

Histopathological assessment appears to have been equal for all examined nodes.

The mean/median no. of nodes sampled per axillary sample procedure is not reported, but may be four exactly.

Thompson, Air, Jack, Kerr, Rodger & Chetty . Arm morbidity after breast conservation and axillary therapy. Breast 4[4]. 1995.

Design

Prospective case series (harm), evidence level: 3
Country: UK/Australia, setting: Secondary care

Inclusion criteria

121 consecutive patients who opted for breast conserving surgery for unilateral breast cancer of clinical stage T1-T2, M0

Exclusion criteria

Patients who underwent mastectomy.

Population

Number of patients = 121.

Interventions

Aim: to measure upper limb morbidity in patients who received different surgical/RT treatment strategies to the axilla.

Morbidity outcomes were assessed in 4 groups:

1. Axillary sampling (n=28)
2. Axillary sampling plus axillary RT (n=61)
3. Axillary clearance of levels I, II and III (n=19)
4. Axillary clearance of levels I-II and axillary RT (n=13)

Outcomes

Upper limb volume, by water displacement:
Change in arm volume on the treated side from preoperative volume, adjusting for changes in opposite arm;
Upper limb circumference;

Shoulder mobility:
abduction with external rotation;
adduction with internal rotation;
flexion;
pure glenohumeral abduction.

Follow up

Outcomes were assessed preoperatively and 12 months post-operatively.

Results

Arm volume:
At 12 months since surgery, arm volume had increased in all four groups of patients, with mean change in ipsilateral volume (cm³) as follows:
Axillary sampling: +108 (t test, p=0.004)
Axillary sampling plus axillary RT: +81 (t test, p=0.003)
Axillary clearance of levels I-III: +75 (t test, p=0.39)
Axillary clearance of levels I-II plus axillary RT: +216 (t test, p=0.064).

Number (%) of patients with an increase in arm volume >200ml:
Axillary sampling: 6/28 = 21%

Axillary sampling plus axillary RT: $18/61 = 30\%$

Axillary clearance of levels I-III: $8/19 = 42\%$

Axillary clearance of levels I-II plus axillary RT: $7/13 = 54\%$

This proportion was significantly greater in patients who underwent axillary clearance than in patients who underwent axillary sample (unpaired difference between two proportions: axillary clearance minus axillary sampling = $42\% - 21\% = 19\%$ [95% CI 1.0%-38.4%])

Arm circumference:

The mean increase in arm circumference was significantly greater in patients in the two axillary clearance groups (Group 3: 0.65cm; Group 4: 1.1cm) than patients in the two axillary sample groups (Group 1: 0.35cm; Group 2: 0.25; ANOVA, $F=7.94$, $df=1$, $p=0.006$).

Upper limb mobility:

Patients who had RT after axillary node sample had statistically significantly reduced mean upper limb elevation (minus 6cm) compared with those who had no RT (minus 1cm t test, $p=0.005$).

There was no statistically significant difference in terms of flexion between the two axillary clearance groups.

Rotary movements at the shoulder were statistically significantly reduced by the addition of radiotherapy to either axillary sample or axillary clearance (Group 2: -1cm; Group4: -1.5cm versus Group 1: zero, Group 3: -0.4; ANOVA $F=7.88$, $df=1$, $p=0.006$ for abduction; Group 2: -2cm; Group4: -2.5cm versus Group 1: zero, Group 3: -0.4; ANOVA $F=4.83$, $df=1$, $p=0.03$ for adduction).

General comments Study is hampered by small numbers in comparison groups: has potential for wide variation in results due to limited sample size; neither mean arm volume increase in the two groups of patients treated by axillary clearance were statistically significant.

With regard to axillary clearance versus axillary sample comparisons, a greater proportion of patients received RT within the axillary sample groups than within the axillary clearance groups (this would work to attenuate the reported effect in favour of axillary sampling for arm circumference and % of patients with an increase in arm volume >200ml).

Authors regard an increase in arm volume of >200ml as a threshold for clinically important morbidity.

Study only assesses arm morbidity at the 12 month post-treatment stage and does not assess morbidity that may occur later.

95% CI for unpaired difference between two proportions calculated with spreadsheet available from Cardiff University (Newcombe, 2006), available online at:

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls

Retrospective case series

Gui, Joubert, Reichert, Ward, Lakhani, Osin, Nerurkar, A'Hern, Benson & Underwood . Continued axillary sampling is unnecessary and provides no further information to sentinel node biopsy in staging breast cancer. Eur J Surg Oncol 31[7]. 2005.

Design

Retrospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

168 patients with primary breast cancer tumours of 3cm or less in size.

Exclusion criteria

Neoadjuvant chemotherapy;
Age >75 years at time of surgery;
DCIS with no invasive component;
Locally recurrent breast cancer;
Metastatic disease.

Population

Number of patients = 168, age range 27 to 75 years, mean age = 54 years.

Interventions

Aim: to assess the staging performance of SLNB against axillary sample of a minimum of four nodes, and against axillary clearance.

82 patients underwent SLNB followed by axillary sample and, in cases with axillary disease revealed by either procedure, axillary clearance.

86 patients underwent SLNB followed by axillary clearance.

SLNB technique: Radiocolloid plus dye, or dye alone.

Histology technique: standard, with selective use of IHC in sentinel nodes.

Outcomes

Staging performance of SLNB, with interest focused on additional information provided by axillary sample.

Follow up

Not reported.

Results

SN localisation rate = $165/168 = 98.2\%$

Median (range) no. of SNs removed per patient:

Axillary sample group: 3 (1-5)

Axillary dissection group: 2 (1-8)

No. of axillary nodes removed by axillary clearance:

Axillary sample group: 12.5 (6-32) NB: represents only patients with positive axillae

Axillary clearance group: 8 (4-21)

Staging performance of SLNB [using either axillary clearance or sample as gold standard, n=165]:

Prevalence of axillary disease = $44/165 = 26.7\%$

FNR = $2/44 = 4.5\%$ [95% CI 0.6-15.5%]

Accuracy = $(42+121)/165 = 98.8\%$

Staging performance of SLNB [using only axillary clearance as gold standard, n=84]:

Prevalence of axillary disease = $26/84 = 31.0\%$

FNR = $2/26 = 7.7\%$ [95% CI 0.9%-25.1%]

Accuracy = $(24+58)/84 = 97.6\%$

Extending SLNB where necessary to sample a minimum of four nodes did not reveal any cases of further positive nodes.

General comments

SLNB method changed during this series, with the introduction of radiocolloid in addition to blue dye.

In all cases of axillary sample, presence of blue dye (or radiocolloid) is likely to have influenced choice of which nodes to remove and may enhance staging performance compared to unguided sampling.

The two FNRs reported are similar, noting their 95% CIs and limited series sizes.

Mathew, Barthelmes, Neminathan & Crawford . Comparative study of lymphoedema with axillary node dissection versus. Eur J Surg Oncol. 32[7]. 2006.

Design

Retrospective case series (therapy), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

Group 1 was defined from a total of 770 patients who underwent surgery for invasive breast cancer between Jan 1994-Dec 1998 and group 2 from 546 patients who underwent surgery for invasive breast cancer between Jan 2000-Dec 2002.

Mean age was 59 in group 1 and 58 in group 2.

Exclusion criteria

Previous breast cancer surgery;
Neoadjuvant chemotherapy.

6 patients with incomplete records plus one patient lost to follow-up were excluded from analyses.

Interventions

Aim: to compare the incidence of lymphoedema in node positive patients treated by breast conservation and axillary sample plus RT compared to breast conservation and axillary clearance.

Retrospective review of two series as follows:

Group 1 (n=312): underwent axillary sampling of a target of 6 nodes, with a stipulated minimum of 4 nodes. Patients with involved nodes underwent axillary RT.

Group 2 (n=194): underwent axillary clearance to level II or III without RT.

Outcomes

Incidence of lymphoedema.

Follow up

Minimum follow-up periods of two years were available for both groups.

Results

Mean no. of nodes removed (range):

Group 1: 8 (3-17)

Group 2: 10 (4-27)

Prevalence of axillary disease at staging was 26% in group 1 and 20% in group 2. Therefore 26% of patients in group 1 would have received RT.

Incidence of lymphoedema (all patients):

Group 1: 7/312 = 2.2% [95% CI 1.1%-4.6%]

Group 2: 24/194 = 12.4% [95% CI 8.5%-17.8%]
(p=0.001, Chi square)

Incidence of lymphoedema (node-negative patients; no RT in group 1):

Group 1: 2/231 = 0.87% [95% CI 0.24%-0.31%]

Group 2: 18/155 = 11.6% [95% CI 7.5%-17.6%]

(p=0.001, Chi square)

Incidence of lymphoedema (node-positive patients; RT given in group 1):

Group 1: 5/81 = 6.2% [95% CI 2.6%-13.7%]

Group 2: 6/39 = 15.4% [95% CI 7.3%-29.7%]

(p=0.17, Chi square)

General comments

Criterion used for lymphoedema: difference of 2cm or more in arm circumference between affected and non affected limbs.

All patients received RT breast.

95% CI for single proportion calculated with spreadsheet from Cardiff University (Newcombe, 2006), available online at: http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/CIPROPORTION.xls

Sato, Tamaki, Takeuchi, Tsuda, Kosuda, Kusano, Hiraide & Mochizuki . Management of the axilla in breast cancer: a comparative study between sentinel lymph node biopsy and four-node sampling procedure. Jpn.J Clin Oncol 31[7]. 2001.

Design

Retrospective case series (diagnosis, screening), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria

206 patients with operable breast cancer with tumour size 5cm or less.

Exclusion criteria

Previous neoadjuvant chemotherapy, patients with large biopsy cavity or clinical evidence of axillary involvement.

Population

Number of patients = 206, age range 28 to 87 years, mean age = 54 years.

Interventions

Aim: to compare the efficacy of SLNB and axillary sample of a target of four nodes.

110 patients underwent SLNB and immediate axillary clearance to level I or II.

98 patients underwent axillary sample without localisation aid, with a target of 4 nodes sampled from the axillary tail upwards, and immediate axillary clearance.

SLNB technique: Radiocolloid plus dye.

Histology technique: not reported specifically for SLNB; standard methods for axillary nodes.

Outcomes

Staging performance of SLNB and axillary sample compared to axillary clearance as gold standard.

Follow up

Not reported

Results

Staging performance of SLNB:

SN localisation rate = 108/110 = 98.2%

Mean no. SNs removed per patient = 1.7 (range 1-7)

Prevalence of axillary disease = 41/108 = 38%

FNR = 1/41 = 2.4%

Accuracy = 107/108 = 99%

Staging performance of axillary sample:

Mean no. nodes removed per patient = 4 (range 2-7)

Prevalence of axillary disease = 48/98 = 49%

FNR = 2/48 = 4.2%

Accuracy = 96/98 = 98%

General comments The two retrospectively defined groups were similar for patient and tumour characteristics.

Evidence Tables

Predictive factors for axillary metastases

Retrospective case series studies

Anan, Mitsuyama, Tamae, Nishihara, Iwashita, Abe, Ihara & Toyoshima . Axillary lymph node metastases in patients with small carcinomas of the breast: is accurate prediction possible? Eur J Surg 166[8]. 2000.

Design: Retrospective case series (therapy), evidence level: 3
Country: Japan, setting: Secondary care

Inclusion criteria

1003 patients with invasive breast cancer of tumour size 2cm or less on gross pathological examination.

Exclusion criteria

None stated.

Population

number of patients = 1003, age range 24 to 89 years, mean age = 53 years, median age = 51 years.

Interventions

Aim: to examine the value of 10 clinical and pathological factors in predicting metastatic involvement of the axilla.

All patients underwent axillary clearance.

Histology technique: standard

Outcomes

Association between variables and metastatic axillary nodes.

Factors examined were: age, palpability and size of tumour, macroscopic classification of tumour margin (well-defined, moderately defined or ill-defined), clinical axillary status, radiating spiculation on a mammogram, histological type, lymphatic invasion, oestrogen and progesterone receptor status.

Follow up

Not reported.

Results

255 patients had metastatic lymph nodes therefore prevalence of axillary disease = $255/1003 = 25.4\%$.

Univariate analysis showed that clinical axillary status, macroscopic classification of tumour margin, lymphatic invasion and age were significant predictors of metastatic axillae ($p < 0.01$, Chi square).

Multivariate analysis was performed for clinical axillary status, macroscopic classification of tumour margin, lymphatic invasion, age, radiating spiculation on mammography and tumour size, due to p values below 0.2. The same four

variables as above were independent predictors of axillary node metastases:

Proportion of patients with metastatic axillae by clinical node status:

N0: 32/159 = 20%

N1: 38/89 = 43%

N2: 7/7 = 100% ($p < 0.0001$)

Proportion of patients with metastatic axillae by tumour margin classification:

Well-defined: 34/50 = 17%

Moderately defined: 25/106 = 26%

Ill-defined: 33/99 = 33% ($p < 0.0001$)

Proportion of patients with metastatic axillae by tumour lymphatic invasion:

Present: 25/62 = 41%

Absent: 44/193 = 23% ($p < 0.0001$)

Proportion of patients with metastatic axillae by age:

≤ 34 : 7/16 = 41%

35-49: 26/104 = 25%

50-64: 32/106 = 30%

65+: 4/29 = 15% ($p = 0.003$).

General comments

analysis was initially by univariate Chi square and then, for factors with a significant association ($p < 0.2$), multiple logistic regression, with an alpha value of 0.05 for statistical significance.

Tumour margin classification is designed to be a measure of the extent of tumour invasion.

Barth, Craig & Silverstein . Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer 79[10]. 1997.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

918 patients with T1 tumours who underwent treatment for breast cancer between 1979-1995.

Exclusion criteria

None stated.

Population

number of patients = 918.

Interventions

Aim: to determine the association between metastatic axillae and 11 clinical and pathologic factors.

All patients underwent axillary clearance.

Histology technique: standard.

Outcomes

Association between clinical and pathologic factors and metastatic axillae.

Factors examined were: tumour size, lympho-vascular invasion, nuclear grade, S-phase, ploidy, palpability, age, estrogen receptor status, progesterone receptor status, HER-2 status and histology.

Follow up

Not reported.

Results

Prevalence of axillary disease: 218/918 = 22.6%.

On univariate analysis, tumour size, tumour palpability, lympho-vascular invasion and nuclear grade were significantly associated with metastases in the axillary nodes (each with $p < 0.0001$).

By multivariate analysis, the same four variables were independent predictors of axillary lymph node metastases:

Proportion of patients with metastatic axillary nodes by tumour lympho-vascular invasion:

Present: 53/116 = 46%

Absent: 143/74 = 19% ($p = 0.0000001$)

Proportion of patients with metastatic axillary nodes by tumour palpability:

Palpable: 183/656 = 28%

Non-palpable: 26/262 = 10% ($p = 0.00004$)

Proportion of patients with metastatic axillary nodes by nuclear grade:

1: 13/148 = 9%

2: 107/510 = 21%

3: 78/237 = 33% (p=0.0004)

Proportion of patients with metastatic axillary nodes by tumour size:

T1a: 4/92 = 4%

T1b: 42/245 = 17%

T1c: 163/581 = 28% (p=0.01)

Among 117 patients with nonpalpable, non high nuclear grade tumours ≤ 1 cm in size without lympho-vascular invasion, the incidence of axillary was 3%. Among 43 patients with T1c tumours and all three other risk factors, incidence was 49%.

General comments

Clinical assessment of the axilla was not always recorded; however the majority of patients were of clinical stage N0.

Statistical analysis was by univariate analysis (log rank test) and, for variables showing a statistically significant association with axillary involvement, multivariate analysis (Cox proportional hazards regression model).

Brenin, Manasseh, El-Tamer, Troxel, Schnabel, Ditkoff & Kinne . Factors correlating with lymph node metastases in patients with T1 breast cancer. Ann Surg Oncol 8[5]. 2001.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

1416 patients with breast cancers of stage T1 who were treated at a single centre between 1989 and 1998.

Exclusion criteria

Patients with multifocal tumours.

Population

number of patients = 1416, age range 23 to 88 years, mean age = 58 years.

Interventions

Aim: to examine the relationship between patient and tumour variables and incidence of axillary metastases.

All patients underwent axillary clearance.

Histology technique: standard, with immunohistochemistry only in equivocal cases.

Outcomes

Association between patient and tumour variables and axillary metastases. Variables examined were: age, race, height, weight, menopausal status, palpability, tumor size, positive margin on initial excision, histology, histological grade, lympho-vascular invasion (LVI), oestrogen receptor status (ER), progesterone receptor status, S-phase, and ploidy.

Follow up

Not reported.

Results

Prevalence of axillary disease: 326/1416 = 23%

On univariate analysis, the following variables were statistically significantly associated with the presence of axillary metastases: tumour palpability [palpable > non-palpable], T size [T1c > T1b > T1a], LVI [present > absent], histology [infiltrating ductal > lobular > other > tubular], histological grade [III > II > I], ER status, and positive margin on initial excision [positive > negative], all with p<0.05, Chi square.

On multivariate analysis, the following variables were found to be independent predictors of axillary metastasis:

Larger Tumour size:

Proportion of patients with axillary metastases by tumour size:

T1a: 14/131 = 10.7%

T1b: 67/435 = 15.4%

T1c: 245/850 = 28.8%
OR 2.9 [95% CI 1.9-4.3, p=0.0001].

Presence of LVI:

Proportion of patients with axillary metastases by presence of LVI:

Present: 94/219 = 43%

Absent: 143/792 = 18%

OR 2.6 [95% CI 1.8-3.64, p=0.0001].

Histological tumour grade:

Proportion of patients with axillary metastases by tumour grade:

III: 128/399 = 32%

II: 119/543 = 22%

I: 16/146 = 11%

OR (III>II>I) 1.6 [95% CI 1.2-2.1, p=0.0004].

Positive margin on initial biopsy:

Proportion of patients with axillary metastases by positive/negative margin on initial biopsy:

Positive: 140/538 = 26%

Negative: 181/862 = 21%

OR (present:absent) 23.8 [95% CI 5.6-101.2, p=0.0001].

Interaction variable for the negative interaction between positive margin and T stage:

OR 0.34 [95% CI 0.2-0.6, p=0.0001]

This indicates that patients with positive margins had risks largely unaffected by T stage, while increasing T stage conferred an increased risk for patients with negative margins.

Based on the multivariate analysis, risk of axillary metastases varied as follows:

LVI absent, margin negative, Grade I, T size T1a: 2% risk.

LVI present, margin positive, Grade III, T size T1c: 51% risk.

General comments

Analysis was by Chi square for univariate analysis, and then by logistic regression using backward selection to eliminate statistically insignificant variables from the models.

Some data are missing for some variables since totals do not equal the total number of patients in the series (1416).

Re: positive margins, 'initial excision' and 'initial biopsy' appear to be interchangeable terms, which probably mean definitive treatment of the tumour.

NB grade = histological grade.

Cao, Paner & Rajan . Sentinel node status and tumor characteristics: A study of 234 invasive breast carcinomas. Archives of Pathology & Laboratory Medicine Vol 129(1)(pp 82-84), [1]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: US/UK, setting: Secondary care

Inclusion criteria

234 patients with unifocal breast cancer with tumour size 25 mm or less treated between May 1998 and December 2002.

Age data not reported.

Exclusion criteria

None stated.

Population

number of patients = 234.

Interventions

Aim: to examine the relationship between the status of the sentinel node (SN) and tumour size, grade and presence or absence of lympho-vascular invasion (LVI).

All patients underwent SLNB. Patients with metastatic SNs underwent axillary clearance.

SLNB technique: not reported.

Histology technique: intra-operative, standard and selectively, immunohistochemistry.

Outcomes

Relationship between SN status and tumour size, grade and LVI.

Follow up

Not reported.

Results

STAGING

SN localisation rate: 221/234 = 94.4%

No. of SNs removed per patient: mean 1.38; range 1-4.

Rate of positive SNs = 77/221 = 34.8% [no gold standard reported].

RISK FACTORS

Univariate analysis:

LVI:

Proportion of patients with metastatic SNs by presence/absence of LVI:

Present: 30/46 = 76%

Absent: 42/175 = 24% (p<0.001)

Tumour grade:

Proportion of patients with metastatic SNs by tumour grade:

I: 13/78 = 16.7%

II: 49/108 = 45.4%

III: 14/31 = 45.2%

OR of positive SNs in grade II or III relative to grade I: 4.15 [95% CI 2.1-8.2].

Tumour size:

The median tumour size in cases of metastatic SNs was 20mm, compared to 15mm for negative SNs ($p < 0.001$).

Multivariate analysis:

In logistic regression, increasing tumour size and presence of LVI were statistically significant independent predictors of SN metastasis:

LVI present: RR 9.8 [95% CI 5.46-17.86, $p < 0.001$]

Increasing tumour size: RR (for an increment of 1mm) 1.065 [95% CI 1.038-1.092, $p < 0.001$].

General comments

Paper has exact same staging data as Agarwal et al. (2005) and may be the same series of patients.

Statistical analysis was by Mann-Whitney test for SN status and tumour size and Chi square for tumour grade and LVI. Binary logistic regression was performed to examine which factors were independent predictors of metastatic SNs.

The rate of positive SNs cannot be taken for true prevalence of axillary disease since no gold standard staging data are reported re: falsely negative SNs. However the RR values are prevalence dependent, i.e. upon the value of 34.8%.

Tumour grade data were available for 217 of 221 patients in whom SNs were identified.

NB grade = histological grade.

Chen, Palleschi, Khoynzhad, Gecelter, Marini & Simms . Role of primary breast cancer characteristics in predicting positive sentinel lymph node biopsy results - A multivariate analysis. Arch Surg 137[5]. 2002.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

257 patients who underwent SLNB. Eligibility for SLNB included patients with:
no palpable axillary nodes;
no previous history of axillary surgery;
no contra-indications to radiocolloid.

Exclusion criteria

Stated above.

Population

number of patients = 257, age range 31 to 84 years, mean age = 62 years.

Interventions

Aim: to identify characteristics of primary breast tumours that are predictive of metastatic sentinel nodes.

Patients underwent SLNB and a medical database was retrospectively reviewed.

SLNB technique: radiocolloid, dye.

Histology technique: intra-operative, standard plus immuno-histochemistry.

Outcomes

Association between tumour variables and metastatic SNs.

Factors analysed were: age, tumour size, histological type, presence/absence of DCIS, architectural pattern of DCIS, extensive DCIS, presence/absence of LCIS, border of neoplasm, lympho-vascular invasion, host lymphoid reaction, grade, ER status and HER-2 status.

Follow up

Not reported.

Results

Prevalence of axillary disease = $73/257 = 28.4\%$

In both univariate and multiple logistic regression, tumour size and lympho-vascular invasion were the only variables predictive of positive SNs:

Rate of SN involvement by tumour size:

T1a: $5/37 = 13.5\%$

T1b: $19/93 = 20.4\%$

T1c: $37/103 = 35.9\%$

T2: $12/24 = 50\%$

Rate of SN involvement by presence/absence of lympho-vascular invasion:

LVI present: 8/13 = 61.5%

LVI absent: 58/213 = 27.2% (p=0.02)

General comments

Analysis was univariate, then multivariate. Not all tests performed nor all p values are reported.

LVI data was available for only 226 patients.

Cutuli, Velten & Martin . Assessment of Axillary lymph node involvement in small breast cancer: Analysis of 893 cases. Clinical Breast Cancer 2[1]. 2001.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: France, setting: Secondary care

Inclusion criteria

893 women with breast cancer of clinical stage T0-2 (<3cm), N0-1, treated at a single centre between January 1980 and December 1991.

Exclusion criteria

None stated.

Population

number of patients = 893, median age = 52 years.

Interventions

Aim: to measure the risk of axillary metastasis in patients with small tumours, based upon clinical and histological parameters.

All patients underwent axillary clearance.

Histology technique: standard.

Outcomes

Association between the proportion of patients with axillary metastases according to subgroups based on: clinical tumour size (T0, T1, T2 <3cm), histological tumour size (0-9.9mm, 10-14.9mm, 15-19.9mm, 20-24.9mm, 25-29.9mm), histological subtype (infiltrating ductal carcinoma [IDC] grade I, II and III, infiltrating lobular carcinoma [ILC], other), age (<40 years, 40-60 years, >60 years), tumour location (inner, medial or outer quadrant), breast size (small, medium or large).

Follow up

Not reported.

Results

Prevalence of axillary disease was 25.3%

In multivariate analysis, clinical tumour size, histological subtype (including grade) and breast size were statistically significant independent predictors of axillary node metastasis:

Proportion of patients with axillary metastases by clinical tumour size:

T0: 21/152 = 13.8%

T1: 78/394 = 19.8%

T2 <3cm: 127/347 = 36.6% (p<0.0001)

Proportion of patients with axillary metastases by histological subtype:

IDC grade I: 32/175 = 18.3%

IDC grade II: 101/371 = 27.2%

IDC grade III: 65/172 = 37.8%

ILC: 17/75 = 22.7%

Other: 10/100 = 10% (p=0.0005)

Proportion of patients with axillary metastases by breast size:

Small (<10cm): 40/133 = 30.1%

Large (>10cm): 185/760 = 24.4% (p=0.004).

General comments

Statistical analysis was by Chi square test for each parameter in turn and then by multivariate analysis by logistic regression.

Breast size was based upon dosimetric size for RT.

Paper does not report any results of univariate analyses.

Giuliano, Barth, Spivack, Beitsch & Evans . Incidence and predictors of axillary metastasis in T1 carcinoma of the breast.[see comment]. J Am Coll.Surg 183[3]. 1996.

Design: Retrospective case series (harm), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

259 patients with T1 invasive breast cancer treated at a single centre between January 1988 and June 1994.

Exclusion criteria

Patients with incomplete data for any of the following parameters: tumour size, age, hormone receptor status, presence of DCIS and histology.

Population

number of patients = 259, age range 31 to 85 years, median age = 55 years.

Interventions

Aim: to examine the incidence and predictive variables of axillary lymph node metastasis in patients with breast cancer of stage T1.

All patients underwent axillary clearance.

Histology technique: standard.

Outcomes

Relationship between patient/tumour parameters and incidence of axillary node metastases. Parameters examined were: tumour size, age, hormone receptor status, presence of DCIS, histology, ploidy, and S-phase.

Follow up

Not reported.

Results

Presence of axillary disease was 69/259 = 27%.

In univariate analysis, only tumour size was statistically significantly associated with axillary node metastasis:

Proportion of patients with axillary metastases by tumour size:

T1a: 2/20 = 10%

T1b: 9/68 = 13%

T1c: 51/171 = 30% (p<0.002).

General comments

Statistical analysis was by Fisher's exact test.

Tumour ploidy and phase data were available in 64% of patients.

A subset of 114 patients underwent SLNB plus axillary clearance as part of a pilot study, with blue dye and immunohistochemistry. Staging data from the same centre have been reported by Giuliano et al. (1997) so are not cited here. Rates of metastatic axillary nodes reported here are by standard

histology techniques.

Grube, Hansen, Ye & Giuliano . Tumor characteristics predictive of sentinel node metastases in 105 consecutive patients with invasive lobular carcinoma. Am J Surg 184[4]. 2002.

Design: Retrospective case series (harm), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

103 cases of ILC in 102 patients (including 1 patient with metachronous, bilateral ILC) treated between October 1991 and May 2001. Patients were identified from a larger series of 121 patients with ILC.

Mean age was 60 in patients with positive SNs and 61 in patients with negative SNs.

Exclusion criteria

3 patients with failed SN localisation.
16 patients enrolled in clinical trials: ACS Z0010 and Z0011.

Population

number of patients = 102, age range 42 to 87 years.

Interventions

Aim: to identify patient and tumour factors that are predictive of SN metastasis in patients with invasive lobular carcinoma (ILC).

All patients underwent SLNB.

SLNB technique: dye; radiocolloid only in some cases.
Histology technique: standard; immunohistochemistry.

Outcomes

Compares prognostic factors between patients with SN metastases and patients without SN metastases. Factors examined were: tumour differentiation, grade, lympho-vascular invasion (LVI), ER status, PR status, HER-2 status, DNA index, S phase.

Follow up

Mean 39 months for patients with positive SNs.
Mean 48 months for patients with negative SNs (follow up is not very relevant to cited outcomes).

Results

There were 51 cases (50%) with a positive SN and 52 cases (50%) with a negative SN.

Factors found by univariate analysis to vary statistically significantly by SN status were as follows:

Factors reported as 'demographic factors':

Proportion of patients with positive SNs by tumour palpability:
Palpable: 40/68 = 59%

Not palpable: 11/35 = 31% ($p=0.048$, Chi square).

Proportion of patients with positive SNs by type of surgery:

Breast conservation: 36/81 = 44%

Mastectomy: 15/22 = 68% ($p=0.048$, Chi square).

Proportion of patients with positive SNs by pT size:

pT1: 11/45 = 24%

pT2: 23/39 = 59%

pT3: 16/18 = 89% ($p=0.001$, Chi square).

Mean tumour size by SN status:

SN positive: 3.9cm

SN negative: 1.9cm ($p=0.0001$, t test).

Factors investigated as prognostic factors:

Proportion of patients with positive SNs by presence/absence of LVI:

Present: 9/11 = 82%

Absent: 42/92 = 46% ($p=0.023$, Fisher's exact test).

LVI was the only prognostic factor defined a priori to be significantly associated with metastatic SNs, so no multivariate analysis was performed.

General comments

Study provides some narrative staging data for SLNB, but not cited here due to high likelihood of duplication with Giuliano et al. (1997).

Statistical analysis was univariate: by t test, Chi square or Fisher's exact test. Study therefore does not take account of the individual role of each variable by controlling for variation in other variables.

Authors decided not to investigate 'demographic' factors as prognostic factors per se e.g. pT stage, but variables found to be significantly associated with positive SNs are cited.

Houvenaeghel, Martino, Jacquemier, Moutardier, Tallet, Viens, Puig & Bardou . Risk of stage underestimation of breast cancer by sentinel lymph node biopsy method. Bull.Cancer (Paris) 90[5]. 2003.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: France, setting: Secondary care

Inclusion criteria

1,636 patients treated with axillary clearance for breast cancer of clinical stage T0, T1 or T2 <30 mm, N0 breast cancer between 1975 and 1999.

Exclusion criteria

Not known.

Population

number of patients = 1636.

Interventions

Aim: to measure the relationship between prognostic factors and the rate of metastatic axillary lymph nodes in patients with breast cancer.

All patients underwent axillary clearance.

Outcomes

Association between prognostic factors and axillary metastasis. Factors examined were: pathologic diameter, grading, lympho-vascular invasion (LVI), hormone receptor status, menopausal status and age.

Follow up

Not known.

Results

Prevalence of axillary disease: 444/1636 = 27%

Prevalence of axillary disease by T stage:

T0: 74/437 = 17%

T1: 202/766 = 26%

T2 <30mm: 168/433 = 39%

The following variables were statistically significantly associated with the rate of axillary metastases:

Proportion of patients with metastatic axillary nodes by presence/absence of LVI (univariate analysis):

LVI absent: 166/845 = 19.6%

LVI present: 208/506 = 41.1% (p<0.000001)

RR by multivariate analysis: 2.2 [95% CI 1.7-2.9], p<0.0001.

Proportion of patients with metastatic axillary nodes by tumour grade (univariate analysis):

I: 84/444 = 18.9%

II: 213/743 = 28.7%

III: 126/283 = 44.5% (p<0.00001)

RR by multivariate analysis, Grade III relative to grade I-II: 2.3 [95% CI 1.7-3.3], $p < 0.0001$.

Proportion of patients with metastatic axillary nodes by menopausal status (univariate analysis):

Post-menopausal: 247/1019 = 24.2%

Pre-menopausal: 197/617 = 31.9% ($p = 0.0007$)

RR by multivariate analysis: not provided.

Proportion of patients with metastatic axillary nodes by age group (univariate analysis):

≤ 50 years: 180/551 = 32.7%

> 50 years: 264/1085 = 24.3% ($p = 0.0003$)

RR by multivariate analysis: 1.4 [95% CI 1.0-1.8], $p = 0.024$.

Proportion of patients with metastatic axillary nodes by pathological tumour diameter (univariate analysis):

≤ 30 mm: 348/1295 = 26.9%

> 30 mm: 57/121 = 47.1%

RR by multivariate analysis: 2 [95% CI 1.3-3.1], $p = 0.0014$.

General comments

LVI data was available for 1351 patients; 285 patients had unclear LVI results and were excluded from the LVI analyses.

Grade data was available for 1470 patients; 166 patients had unclear grade results and were excluded from the grade analyses.

Pathological tumour size data was available for 1416 patients; 220 patients were excluded from the pathological tumour size analysis.

Grade is reported as 'grade'; therefore assumed to represent histological grade.

Katz, Niemierko, Gage, Evans, Shaffer, Fleury, Smith, Petrucci, Flax, Drogula & Magnant . Can axillary dissection be avoided in patients with sentinel lymph node metastasis?[see comment]. [Review] [46 refs]. J Surg Oncol 93[7]. 2006.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients treated with SLNB between 1998 and 2003.

110 patients had DCIS
1034 patients had invasive disease

307 patients underwent mastectomy and 833 breast conserving surgery. In 8 patients the type of definitive surgery was unknown.

Exclusion criteria Retrospective study: none reported.

Population number of patients = 1133, age range 30 to 96 years, median age = 57 years.

Interventions Retrospective analysis of 1148 SLNB procedures in 1133 patients treated at a single centre and recorded on a pathology database.

SLNB technique: R, D
Histology: FS, S, IHC

Outcomes Risk factors for the presence of SN metastases.

Risk factors for the presence of further axillary node metastases in patients who undergo axillary clearance for positive SLNB result.

Follow up No follow-up reported, study assesses predictive factors for SN and non SN axillary nodal involvement.

Results 246 patients had involved SNs and underwent axillary clearance.
121 patients had involved SNs and did not undergo axillary clearance.

Prevalence of axillary disease = $367/1148 = 32\%$

A median of 2 SNs were identified per procedure (range 1-15)

RISK FACTORS FOR SN INVOLVEMENT

By Pearson Chi square the proportion of patients with positive SNs varied significantly by subgroup for the following variables (as categorical variables):
Age (higher rates of SN involvement in younger patients, $p < 0.001$);
Type of surgery (higher rates of SN involvement after mastectomy, $p < 0.008$);
Tumour size (higher rates of SN involvement with larger tumours, $p < 0.001$);
Histology (no discernable pattern by histological subtype except for lowest rate in patients with DCIS, $p = 0.001$);
Invasion of lymphovascular space (higher rates of SN involvement when present, $p < 0.001$).

By Pearson Chi square the proportion of patients with positive SNs did not vary significantly by subgroup for the following variables (as categorical variables):

Number of SNs identified;
ER receptor status;
PR receptor status.

The statistical significance observed was the same whether SN positivity was determined by H&E histology or by any technique (including more sensitive techniques).

On multiple logistic regression analysis age, histology, primary tumour size and lymphovascular invasion were statistically significantly associated with SN involvement (no further details reported).

RISK FACTORS FOR INVOLVEMENT OF ADDITIONAL NON-SENTINEL NODES

By Pearson Chi square the proportion of patients with positive further nodes varied significantly by subgroup for the following variables (as categorical variables):

Presence of lymphovascular invasion ($p=0.001$);
Number of SNs examined (higher rates of further nodal involvement where fewer SNs were examined, $p=0.03$);
Histological method to detect SN metastasis (higher rates of further nodal involvement for H&E, $p=0.03$);
Number of involved SNs (higher rates of further nodal involvement where ≥ 3 SNs involved, $p=0.002$ for H&E histology and $P=0.05$ for any histological technique);
Number of uninvolved SNs (higher rates of further nodal involvement where fewer SNs uninvolved, $p<0.001$);
Size of the largest SN metastasis (higher rates of further nodal involvement for larger SN metastases, $p<0.001$).

By Pearson Chi square the proportion of patients with further involved axillary nodes did not vary significantly by subgroup for the following variables (as categorical variables):

Age;
Type of definitive surgery;
Tumour size;
Histology.

On multiple logistic regression analysis the presence of lymphovascular invasion, increasing number of positive SNs, increasing size of the largest SN metastasis and decreasing number of negative SNs were statistically significantly associated with further axillary node involvement (no further details reported).

General comments It is not reported, but this series of patients appear to have been treated in an operational phase for SLNB i.e. without planned axillary clearance for any patients irrespective of SN status.

Peters-Engl, Konstantiniuk, Tausch, Haid, Hoffmann, Jagoutz-Herzlinger, Kugler, Redtenbacher, Roka, Schrenk & Steinmassl . The impact of preoperative breast biopsy on the risk of sentinel lymph node metastases: analysis of 2502 cases from the Austrian sentinel node biopsy study group. Br J Cancer 91[10]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Austria, setting: Secondary care

Inclusion criteria

2328 patients with early, invasive breast cancer treated with SLNB in 12 contributing centres and identified from a larger series of 2500 patients.
1890 patients yielded complete data for the analyses. Tumour size had range 0.5-80mm.

Exclusion criteria

Preoperative systemic treatment;
Multifocal disease;
In situ disease.

Population

number of patients = 1890, age range 23 to 96 years, median age = 60 years.

Interventions

Aim: to evaluate the impact of preoperative fine needle aspiration (FNA) or core biopsy of the primary tumour on the rate of metastasis to the SN of patients with early breast cancer.

All patients underwent SLNB.

SLNB technique: dye or radiocolloid or both.

Histology technique: intra-operative, standard, immunohistochemistry.

Outcomes

Proportion of patients with metastatic SNs by subgroup analysis for clinicopathologic factors:

Age, tumour size, histology, grade, location of tumour in breast, tumour palpability, performance of FNA/core biopsy, treatment within a validation period, contributing centre, SLNB technique, timing of SLNB (1st or 2nd procedure) and whether data on patients was collected prospectively or retrospectively.

Follow up

Not reported.

Results

STAGING

SN localisation rate: 2079/2328 = 89.3%

RISK FACTORS

230/1890 = 12.1% of patients underwent FNA.

818/1890 = 43.3% of patients underwent core biopsy.

842/1890 = 44.6% of patients underwent neither FNA nor core biopsy.

In univariate analysis, the following factors were statistically significantly associated with metastatic SNs:

Larger tumour size ($p < 0.0001$), age ($p = 0.002$), preoperative biopsy ($p = 0.001$), histological type ($p < 0.0001$), grade ($p < 0.0001$), palpability ($p < 0.0001$), timing of SLNB ($p = 0.008$) and participating centre ($p = 0.003$).

In multivariate analysis the following factors were statistically significantly associated with metastatic SNs:

Increasing tumour size:

OR 1.06 [95% CI 1.05-1.08], $p < 0.0001$.

Tumour grading:

Proportion of patients with metastatic SNs by tumour grade:

I: 53/293 = 18%

II: 360/1001 = 36%

III: 232/596 = 39%

OR, grade I relative to grade III: 0.55 [95%CI 0.32-0.81], $p = 0.002$.

Histological type:

Proportion of patients with metastatic SNs by histological type:

Ductal: 406/1230 = 33%

Ducto-lobular: 80/163 = 49%

Lobular: 92/235 = 39%

Other: 66/262 = 25%

OR, ducto-lobular relative to ductal histology: 2.16 [95% CI 1.48-3.16], $p = 0.0001$.

Age:

OR 0.98 [95% CI 0.97-0.99], $p < 0.0001$.

Palpability:

Proportion of patients with metastatic SNs by tumour palpability:

Palpable: 520/1270 = 41%

Not palpable: 124/620 = 20%

OR 1.77 [95% CI 1.37-2.29], $p < 0.0001$.

Participating centre (No data cited, $p = 0.001$).

Notably, FNA/core biopsy was not found to have a statistically significant relationship with metastatic SNs.

General comments

An unspecified number of patients underwent excisional biopsy of the breast tumour prior to SLNB, with immediate SLNB (as 1st procedure) if intra-operative histology revealed malignancy in the breast, or SLNB as 2nd procedure if standard histology revealed malignancy at a later date. SLNB as a 2nd procedure occurred in 140 (7.4%) patients overall, 32 (3.1%) in the biopsy group and 108 (12.8%) in the 'no biopsy' group. This implies that at least 140 patients underwent excisional breast biopsy. However excisional

breast biopsy was not analysed as a specific clinicopathologic factor, even though it may confound the effect of the factor of particular interest, FNA/core biopsy.

Analysis groups were compared for similarity:

Patients in the biopsy group had larger tumours than those in the 'no biopsy' group: mean 17.8mm versus 14.9mm respectively ($p < 0.0001$, t test).

There were more cases of ductal and lobular tumours and less ducto-lobular and other subtypes in the biopsy group compared to the 'no biopsy' group ($p = 0.006$, Chi square).

More patients in the 'no biopsy' group were treated during the SLNB validation phase compared to the biopsy group: 28% versus 17% respectively ($p < 0.0001$, Chi square).

More patients in the biopsy group had palpable tumours compared to the 'no biopsy' group: 74% versus 58% respectively ($p < 0.0001$, Chi square).

More patients in the biopsy group underwent SLNB with combined radiocolloid plus dye compared to the 'no biopsy' group: 69% versus 34% respectively ($p < 0.0001$, Chi square).

In all analyses, SN metastases were defined as metastases detected by either of standard histology/immunohistochemistry.

Grade reported as 'tumour grade': assumed to be histological grade.

Rivadeneira, Simmons, Christos, Hanna, Daly & Osborne . Predictive factors associated with axillary lymph node metastases in T1a and T1b breast carcinomas: analysis in more than 900 patients. J Am Coll.Surg 191[1]. 2000.

Design: Retrospective comparative study (diagnosis, screening), evidence level: 3

Country: United States, setting: Secondary care

Inclusion criteria

919 patients with invasive T1a-T1b breast cancer tumours (i.e. <=1cm in size), treated at a single institution between 1990 and 1996.

199 patients had T1a tumours.

720 patients had T1b tumours

Exclusion criteria

None stated.

Population

number of patients = 919, age range 24 to 90 years, mean age = 58 years, median age = 57 years.

Interventions

Aim: to determine clinical and pathologic factors predictive of axillary lymph node metastases in patients with invasive breast cancer and tumours <= 1cm in size.

All patients underwent axillary clearance.

Histology technique: standard.

Outcomes

Relationship between clinical and pathological variables and the rate of axillary metastasis. Factors examined were: age, race, tumour size, tumour palpability, histologic type, histologic grade, oestrogen and progesterone receptor status, and lympho-vascular invasion (LVI).

Follow up

Not reported.

Results

Prevalence of axillary disease was 165/919 = 18%

In the univariate analysis, the following factors were found to be statistically significantly associated with the presence of axillary metastases: age (p=0.01), tumour diameter (p=0.01), tumour grade (p=0.003) and LVI (p=0.0001).

Proportion of patients with metastatic axillary nodes by presence/absence of LVI (univariate analysis):

LVI present: 14/28 = 50%

LVI absent: 68/450 = 15%

OR 5.52 [95% CI 2.51-12.19], p=0.0001.

In the multivariate analysis the following variables were found to be independently statistically significantly associated with the presence of axillary metastases: age, tumour diameter and tumour grade:

Age:

OR (>=50 years relative to <50 years): 0.61 [95% CI 0.37-1.02], p=0.05*

Tumour size:

OR (continuous variable, for each 1mm increase): 3.58 [95% CI 1.18-11.89], p=0.03

Tumour grade:

Proportion of patients with axillary metastases by tumour grade:

I: 27/205 = 13%

II: 38/240 = 16%

III: 22/76 = 29%

OR (grade III relative to grade I): 2.45 [95% CI 1.27-4.68], p=0.01

General comments

Analysis was by univariate analysis: Chi square and Chi square for a trend, and also by multivariate analysis: logistic regression.

In the multivariate analysis the LVI variable could not be modelled due to insufficient data (478 patients in total).

*95% CI and p value appear to conflict.

Some analyses appear to be affected by missing data: i.e. between 398-566 patients.

NB Grade = histological grade.

Specht, Fey, Borgen & Cody . Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? J Am Coll.Surg 200[1]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

106 patients with breast cancer and clinically palpable axillary nodes who underwent SLNB between September 1996 and August 2003, performed by two surgeons.

Exclusion criteria

Previous history of breast cancer;
Earlier axillary surgery;
Breast irradiation;
Neoadjuvant chemotherapy;
Cases not performed by two surgeons stated above.

Population

number of patients = 106, age range 26 to 88 years, median age = 51 years.

Interventions

Aim: to examine the role of SLNB in patients with clinically palpable axillary lymph nodes.

All patients underwent SLNB. Two groups were defined:

1. Patients with moderately suspicious nodes by palpation (n=62);
2. Patients with unequivocally suspicious nodes by palpation (n=44).

SLNB technique: dye, radiocolloid.

Histology technique:

Outcomes

Positive predictive value (PPV) of clinically palpable nodes, against axillary node status by definitive histology.

Patient/tumour factors compared between patients with falsely positive palpable axillae and those with truly positive palpable axillae. Factors compared were: age, previous surgical biopsy, body mass index, tumour size, histological grade.

Follow up

Not reported.

Results

Positive SNs were found in 63/106 = 59% of all patients with clinically palpable nodes.

In patients with moderately suspicious nodes by palpation, the rate of positive SNs was 29/62 = 48%.

In patients with unequivocally suspicious nodes by palpation, the rate of

positive SNs was 34/44 = 77%.

PPV (all patients) = 59%

PPV (patients with moderately suspicious nodes) = 47%

PPV (patients with unequivocally suspicious nodes) = 77%.

In patients with truly positive nodes by palpation, the following variables were statistically significantly different than in patients with falsely positive nodes by palpation:

Tumour size: mean 2.6cm and 1.6cm respectively, (p=0.002);

Proportion of patients with high histologic grade: 77% and 43% respectively (p=0.002).

General comments

'Moderately suspicious' nodes were defined as firm, shotty and more prominent than on the contralateral side.

Subgrouping of clinical suspicion of nodes based upon palpation appears to be vague and subjective, even assuming that two operating surgeons reported above, performed the examination.

Tan, Tan, Heng & Chan . Predictors of axillary lymph node metastases in women with early breast cancer in Singapore. Singapore Med J 46[12]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Singapore, setting: Secondary care

Inclusion criteria

380 cases (in 373 patients) of early breast cancer of stage T1-2, N0-1, M0, treated between January 1999 and August 2002.

Exclusion criteria

Patients with missing data on factors examined.

Population

number of patients = 380, age range 24 to 87 years, median age = 52 years.

Interventions

Aim: to investigate the relationship between preoperative factors and the status of axillary lymph nodes.

All patients underwent axillary clearance

Outcomes

Relationship between preoperative/pathological factors and incidence of positive axillary nodes. Factors examined were: age, race, parity, menopausal status, family history of breast cancer, tumour stage/grade, histology, lympho-vascular invasion (LVI) and ER/PR status.

Follow up

Not reported.

Results

Prevalence of axillary disease = $136/380 = 35.8\%$.

In univariate analysis the following factors were significantly associated with axillary metastases: multiparity ($p=0.03$), higher tumour stage ($p<0.0001$), higher tumour grade ($p=0.0003$), invasive ductal histology ($p=0.0003$) and presence of LVI ($p<0.0001$).

In multivariate analysis the following variables were independent predictors of axillary metastases: higher tumour stage, invasive ductal histology and presence of LVI. PR negative tumours were predictive of axillary metastases, but only with borderline statistical significance:

Proportion of patients with metastatic axillary nodes by tumour stage:

T1a: $1/23 = 4.3\%$

T1b: $7/37 = 18.9\%$

T1c: $45/163 = 27.6\%$

T2: $83/157 = 52.9\%$

OR (T1a relative to T2): 0.06 [95% CI 0.007-0.5]

OR (T1b relative to T2): 0.18 [95% CI 0.065-0.49]

OR (T1c relative to T2): 0.38 [95% CI 0.22-0.67], $p=0.0001$.

Proportion of patients with metastatic axillary nodes by tumour histology:

Invasive ductal: 128/322 = 39.6%

Invasive lobular: 4/13 = 30.8%

Other: 5/45 = 10.9%

OR (invasive lobular relative to invasive ductal): 0.9 [95% CI 0.24-3.4]

OR (others relative to invasive ductal): 0.26 [95% CI 0.09-0.72], p=0.04.

Proportion of patients with metastatic axillary nodes by LVI status:

LVI present: 43/57 = 75.4%

LVI absent: 91/317 = 28.7%

OR (present relative to absent): 7.7 [95% CI 3.5-17], p<0.0001.

Proportion of patients with metastatic axillary nodes by PR receptor status:

PR positive: 73/193 = 37.8%

PR negative: 58/154 = 37.7%

OR (positive relative to negative): 1.8 [95% CI 1.0-3.0], p=0.05.

General comments

Analysis was univariate (simple log regression) and multivariate for all factors (multiple log regression).

Tan, Wu, Fan, Hwang, Ewing, Lane, Esserman, Lu, Treseler, Morita & Leong . Primary tumor characteristics predict sentinel lymph node macrometastasis in breast cancer. Breast Journal 11[5]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

NB NODE POSITIVE POPULATION

122 patients with primary invasive breast cancer who underwent SLNB between November 1997 and August 2003 and in whom one or more positive SNs were identified, out of a total of 644 patients.

Mean tumour size was 21.1mm (range 2-82mm)

Exclusion criteria

Palpable axillary nodes;
Noninvasive tumours;
Recurrent breast cancer;
Failed preoperative lymphoscintigraphy.

Population

number of patients = 122, age range 25 to 83 years, median age = 53 years.

Interventions

Aim: to examine factors that may be predictive of sentinel node macrometastases in patients with breast cancer.

All patients underwent SLNB and had at least one positive SN identified.

SLNB technique: lymphoscintigraphy, radiocolloid (and sometimes dye)
Histology technique: standard, immunohistochemistry (IHC).

Outcomes

Relationship between SN tumour burden (micrometastases or macrometastases) and tumour characteristics as follows: tumour size, tumour grade, nuclear grade, mitotic count, tubular formation, histology, lympho-vascular invasion (LVI), ER status, PR status, HER-2 status, number of positive SNs.

Follow up

Not reported.

Results

79/122 = 65% patients had macrometastases.
43/122 = 35% patients had micrometastases.

In univariate analysis, the following factors were found to be statistically significantly associated with the finding of SN macrometastases: tumour size >15mm, tubular formation >=2, presence of LVI and no. positive SNs >=2:

Proportion of patients with macrometastatic SN by tumour size:

$\leq 15\text{mm}$: $22/42 = 52\%$

$>15\text{mm}$: $57/80 = 71\%$ ($p=0.038$).

Proportion of patients with macrometastatic SN by tubular formation:

1: $3/10 = 30\%$

≥ 2 : $76/112 = 68\%$ ($p=0.033$).

Proportion of patients with macrometastatic SN by LVI:

LVI present: $29/36 = 81\%$

LVI absent: $50/85 = 59\%$ ($p=0.022$).

Proportion of patients with macrometastatic SN by no. of positive SNs:

1: $48/87 = 55\%$

≥ 2 : $31/35 = 89\%$ ($p=0.00035$).

General comments

SN tumour burden was defined as follows:

Macrometastases: $\geq 2\text{mm}$ on H&E

Micrometastases: $< 2\text{mm}$ on H&E

Smaller metastatic deposits seen only on IHC were classed as negative.

Analysis was univariate; Chi square and Fisher's exact tests. Without multivariate analysis the effect of any one variable may depend on that of another.

Velanovich & Szymanski . Lymph node metastasis in breast cancer: common prognostic markers lack predictive value. Ann Surg Oncol 5[7]. 1998.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

851 patients with invasive breast cancer who underwent treatment with axillary clearance.

Exclusion criteria

None stated.

Population

number of patients = 851.

Interventions

Aim: to examine whether tumour factors are predictive of axillary metastases in patients with breast cancer.

All patients underwent axillary clearance.

Outcomes

Relationship between lymph node status and tumour factors. Results were reported by:

1. Presence of any lymph node metastasis;
2. Presence of 10 or more lymph node metastases.

Tumour factors examined were: histological type (infiltrating ductal or lobular carcinoma, medullary carcinoma), site of primary lesion in the breast (central, upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant), ER and PR status, DNA index, S-phase fraction, nuclear grade, and extensive intraductal component.

Follow up

Not reported.

Results

1. Presence of any lymph node metastasis:

Tumour size:

Univariate analysis:

Proportion of patients with axillary lymph node metastases by tumour size:

T1a: 8%

T1b: 15%

T1c: 30%

21-30mm: 53%

31-40 mm: 52%

41-50 mm: 67%

>51mm: 76% (p<0.0001)

Multivariate analysis: increasing tumour size had OR 1.5, p=0.04 (no increment reported).

Tumour location within the breast:

Univariate analysis:

There was a statistically significant difference in the proportion of patients with any axillary lymph node metastases by tumour location category ($p=0.02$), but there was no discernable pattern.

Multivariate analysis did not reveal any tumour location as predictive of axillary metastasis.

Histological type:

Univariate analysis: there was no statistically significant association between axillary metastases and histological tumour type.

Multivariate analysis: Invasive lobular pathology was strongly independently predictive of axillary lymph node metastases: OR >400000, $p=0.02$, whereas tubular and medullary histology were strongly associated with lower odds of axillary metastasis: OR 0.000006, $p=0.02$.

ER and PR status:

In both univariate and multivariate analysis, there was no statistically significant association between any axillary metastases and ER/PR status.

Nuclear grade:

Univariate analysis:

Proportion of patients with one or more metastatic axillary nodes by nuclear grade:

I: 19%

II: 32%

III: 43% ($p=0.0004$)

Multivariate analysis: nuclear grade was not a statistically significant predictor of axillary lymph node metastasis.

2. Presence of 9 or more positive lymph nodes

Tumour size:

Univariate analysis:

Proportion of patients with 9 or more metastatic axillary lymph nodes by tumour size:

T1a: 0%

T1b: 1%

T1c: 4%

21-30mm: 6%

31-40 mm: 11%

41-50 mm: 16%

>51mm: 34% ($p<0.0001$)

Multivariate analysis: increasing tumour size had OR 14.8, $p=0.026$ (no increment reported).

ER status:

Univariate analysis: ER status was not statistically significantly associated with the presence of 9 or more metastatic axillary nodes.

Multivariate analysis: Patients with ER negative tumours were statistically

significantly more likely to have 9 or more metastatic axillary nodes; OR 1.1, $p=0.05$.

General comments

Analysis was univariate (Chi square) and multivariate (logistic regression).

Summary statistics for the number of lymph nodes excised is not reported; regarding the outcome for 10 or more metastatic nodes, this is not possible if 9 nodes or fewer are examined.

On univariate analysis, tumour size, tumour location and nuclear grade were significantly associated with axillary node status.

The multivariate analysis for histological type doesn't seem plausible and is inconsistent with other studies; odds ratios do not state relative category, but appears to be ductal carcinoma.

Paper does not provide patient numbers for percentage proportions, nor 95% confidence intervals for odds ratios. Most percentages cited are read from graphs.

Authors report that in the multivariate analysis, the variables that are statistically significantly predictive of 1) one or more metastatic axillary lymph nodes; 2) 9 or more metastatic axillary lymph nodes; account for respectively 5.6% and 19.5% of the log likelihood of the regression in each case, implying that most of the metastases were unexplained by the factors analysed.

Evidence table**Abbreviations:**

DCIS: ductal carcinoma in situ
 DCISm: ductal carcinoma in situ with microinvasion
 SLNB: sentinel lymph node biopsy
 SN: sentinel node

Retrospective case series studies (16)

Camp, Feezor, Kasraeian, Cendan, Schell, Wilkinson, Copeland & Lind .
 Sentinel lymph node biopsy for ductal carcinoma in situ: an evolving approach
 at the University of Florida. Breast Journal 11[6]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, **setting:** Secondary care

Inclusion criteria Patients with DCIS and DCISm

Exclusion criteria None stated: retrospective review

Population number of patients = 43.

Interventions Aim = to retrospectively review the experience of a single
 centre of SLNB in patients with DCIS including DCISm.

All patients underwent SLNB.

SLNB technique: radiocolloid.

Histology technique: standard method, immunohistochemistry.

Outcomes Rates of SN positivity by final histological diagnosis.

Follow up None stated.

Results In total 7/43=16.3% of patients had positive SNs:

Final histology:

DCIS: 1/25=4% had positive SNs

DCISm: 5/17=29.4% had positive SNs

Invasive: 1/1=100% had positive SNs

SN positivity by tumour grade:

Of 13 patients with high nuclear grade, 1 [8%] was SN positive and 12 [92%]
 were SN negative.

Upstaging to invasive disease:

1 patient with a biopsy diagnosis of DCIS was upstaged to invasive disease
 after definitive surgery, representing:

1/25=4% of patients with DCIS;

1/43=2.3% of all patients in the series [DCIS+DCISm]

4 patients with positive SNs underwent axillary clearance and none had any
 further positive axillary nodes.

General comments

Series represents patients with DCIS who underwent SLNB because they
 were considered to be at high risk for invasive disease due to microinvasion,

comedo necrosis, multifocal, extensive or high grade DCIS, or the presence of a mass.
Paper does not report rate of SN positivity by tumour size.
Small series size.

Cox, Bass, Ku, Berman, Shons, Yeatman & Reintgen . Sentinel lymphadenectomy: a safe answer to less axillary surgery? Recent Results Cancer Res 152. 1998.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Series of patients with DCIS is a subset of 167 patients treated for breast cancer [mean age 58.5, SD 14.2 years].

17 patients had DCIS

Exclusion criteria None stated.

Population number of patients = 17.

Interventions Aim = to report on a centre's validation period for SLNB. All patients underwent SLNB plus axillary clearance.

SLNB technique: radiocolloid, dye.

Histology technique: intraoperative, standard method, immunohistochemistry.

Outcomes Rate of SN positivity by tumour size, reported for the whole patient series (n=167)

Follow up Not reported.

Results 1/17=5.9% of patients with DCIS had a positive SN

-

General comments Small number of patients with DCIS.
Study does not report rate of SN positivity by tumour size or grade for patients with DCIS.

Cserni . Sentinel lymph node biopsy as a tool for the staging of ductal carcinoma in situ in patients with breast carcinoma. Surg Today 32[2]. 2002.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Hungary, setting: Secondary care

Inclusion criteria Patients with pure DCIS on final histology.

Exclusion criteria None stated: retrospective review, although patients with invasive disease are excluded from the analysis and no data are provided for patients with DCISm [it is possible that no cases occurred].

Population number of patients = 10.

Interventions To retrospectively review the experience of a single centre in SLNB in patients with DCIS.

SLNB technique: dye or radiocolloid plus dye.

Histology technique: standard method, immunohistochemistry.

Outcomes Rate of SN positivity by tumour grade and nodal pathological stage.

Follow up Not reported.

Results 1/10=10% of patients with pure DCIS had positive SNs:

SN positivity by tumour grade:

Low: 0/3=0%

Intermediate: 1/2=50%

High: 0/4=0%

Not reported: 0/1=0%

6 patients underwent axillary clearance including the patient with a positive SN. No patient had further positive axillary nodes.

-

General comments Small series of patients [10]

The one patient with no tumour grade reported had an intracystic papillary carcinoma.

Since 5 patients underwent axillary clearance following SLNB with negative result, these patients were apparently treated in the centre's validation period for SLNB.

Farkas, Stolier, Teng, Bolton & Fuhrman . An argument against routine sentinel node mapping for DCIS. Am Surg 70[1]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Patients with pure DCIS.

Exclusion criteria Cases of DCIS diagnosed by biopsy at outside institutions

Cases of DCIS by biopsy that were revealed by definitive histology to be cases of invasive disease or DCISm.

Population number of patients = 44, age range 46 to 81 years, mean age = 63 years.

Interventions Aim: to determine the rate of positive SNs in patients with DCIS based on the experience of a single centre.

All patients underwent SLNB.

SLNB technique: mostly radiocolloid, dye.

Histology technique: standard method, immunohistochemistry.

Outcomes Rate of SN positivity.

Follow up Not reported.

Results 46 cases of DCIS were analysed in 44 patients.

The rate of SN positivity was zero.

The binomial probability of observing 0 positive SNs in 46 cases of SLNB, assuming a rate of SN positivity of 13% [see comment] was $p < 0.01$.

-

General comments Exclusion criteria are likely to produce a low rate of SN positivity compared to other series in the literature. Exclusion of cases of DCIS diagnosed by biopsy at outside institutions seeks to reduce the fallibility of diagnosis.

The rate of SN positivity of 13% was based upon that measured by Cox et al [2001]:

Cox CE; Nguyen K; Gray RJ; Salud C; Ku NN; Dupont E; Hutson L; Peltz E; Whitehead G; Reintgen D; Cantor A. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001 Jun ;67(6):513-519.

This paper was not included since later follow up by Wilke et al. [2005] was included.

Design: Retrospective case series (diagnosis, screening), evidence level: 3

Country: Italy, setting: Secondary care

Inclusion criteria Patients with DCISm

Exclusion criteria Not specified: implied by inclusion criteria.

Population number of patients = 41, age range 29 to 67 years, mean age = 36 years.

Interventions Retrospective review of patients with DCISm treated with SLNB.

SLNB technique: preoperative lymphoscintigraphy, radiocolloid.

Histology technique: standard method, immunohistochemistry.

Outcomes Clinical presentation and pathological findings, including rate of SN positivity by tumour grade.

Follow up Not reported.

Results Rate of axillary positivity:

4/41 = 9.7% of patients with DCISm had positive SNs.

Rate of axillary positivity by tumour grade:

2/4=50% of patients with positive SNs had Grade I tumours compared to 5/37=13.9% of patients with negative SNs.

2/4=50% of patients with positive SNs had Grade II tumours compared to 12/37=33.3% of patients with negative SNs.

0/4=0% of patients with positive SNs had Grade III tumours compared to 19/37=52.8% of patients with negative SNs.

The SNs were the only affected node in 3 patients who underwent subsequent axillary clearance. In 1 patient axillary clearance revealed 4 further positive axillary nodes.

-

General comments Small series of patients with DCISm: higher risk group than pure DCIS.

Study appears to be retrospective in nature due to the definitive diagnosis of DCISm.

Small series size: no statistical testing performed and interpretation of small subgroups is difficult.

Study does not report rates of SN positivity by T size.

Katz, Gage, Evans, Shaffer, Fleury, Smith, Flax, Drogula, Petrucci & Magnant . Sentinel lymph node positivity of patients with ductal carcinoma in situ or microinvasive breast cancer. Am J Surg 191[6]. 2006.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 109 patients had DCIS.
21 patients had DCISm.

Exclusion criteria None specified.

Population number of patients = 130, age range 33 to 86 years, median age = 55 years.

Interventions Aim = to measure the rate of SN positivity in patients with DCIS, based on retrospective review of 131 SLNB procedures in 130 patients.

All patients underwent SLNB.

SLNB technique: dye initially, then radiocolloid, dye.
Histology technique: standard method, immunohistochemistry.

Outcomes Rates of SN positivity.

Correlation of patient/tumour subgroups with SN positivity based upon standardised histological records.

Follow up Median follow-up 22 months, range 1 to 75 months.

Results ALL PATIENTS

Overall 10/131=7.6% of patients with DCIS including those with DCISm had positive SNs.

PURE DCIS

8/110=7.2% of patients with pure DCIS had positive SNs.

Of these, 2 patients underwent subsequent axillary clearance; no further positive axillary nodes were found.

Grade:

In patients with pure DCIS SN positivity by tumour grade was as follows:

Well differentiated: 2/8=25%

Moderately differentiated: 4/45=9%

Poorly differentiated: 2/55=4% p=ns [Chi square]

Tumour size:

In patients with pure DCIS SN positivity by tumour size was as follows:

<= 1.0 cm: 1/26=4%

1.1-2.0cm: 3/21=14%

2.1-5.0cm: 3/36=8%

>5.0cm: 1/21=5%

Unknown: 0/6=0% p=ns [Chi square]

In patients with pure DCIS, no patient, tumour or treatment related factor was predictive of SN involvement (including age, presentation, T size, grade, presence of necrosis, histological subtype, margin status, type of surgery, number of SNs identified).

PATIENTS WITH DCISm

2/21=9.5% of patients with DCISm had positive SNs.

Of these two patients one underwent axillary clearance and 1 further positive axillary node.

Grade:

In patients with DCISm SN positivity by tumour grade was as follows:

Well differentiated: 0/3=0%

Moderately differentiated: 1/9=11%

Poorly differentiated: 0/6=0%

Unknown: 1/3=33% p=ns [Chi square]

In patients with DCISm, no patient, tumour or treatment related factor was predictive of SN involvement (including age, presentation, T size, grade, presence of necrosis, histological subtype, hormone receptor status, margin status, type of surgery, number of SNs identified).

-

General comments

1 patient underwent bilateral SLNB for DCIS.

Pathology reported appears to be definitive, since a large pathology database was interrogated for the data.

Analysis used Chi square test.

DCIS grade was attributed using Van Nuys classification.

No tumour size subgroup data provided for patients with DCISm.

Kelly, Kim, Patrick, Grundfest & Crowe . Axillary lymph node metastases in patients with a final diagnosis of ductal carcinoma in situ. Am J Surg 186[4]. 2003.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 134 patients with definitive diagnosis of pure DCIS underwent axillary surgery:

93 patients underwent axillary clearance only

14 patients underwent SLNB only

27 patients underwent SLNB plus axillary clearance

Exclusion criteria Patients with DCISm

Population number of patients = 134, mean age = 54 years.

Interventions Aim = to measure the incidence of axillary node metastases in patients with DCIS, prior to and after the introduction of SLNB and immunohistochemistry histology.

Patients underwent SLNB and/or ALND.

SLNB technique: dye or radiocolloid plus dye

Histology technique: immunohistochemistry for SNs. Standard method for axillary nodes from axillary clearance.

Outcomes Rate of detection of axillary disease, reported by axillary surgery procedure.

Follow up -

Results 3/134=2% of patients with pure DCIS had axillary disease.

In all 3 patients with pure DCIS and axillary disease, the tumour grade was grade II.

-

General comments 'Axillary clearance' in this study refers to removal of level I and II axillary nodes.

Study does not report axillary involvement by tumour size.

Klauber-DeMore, Tan, Liberman, Kaptain, Fey, Borgen, Heerdt, Montgomery, Paglia, Petrek, Cody III & Van Zee . Sentinel lymph node biopsy: Is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? Ann Surg Oncol 7[9]. 2000.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 76 patients with DCIS [median age 56 years, range 38-81 years]

31 patients with DCISm [median age 51 years, range 31-80 years]

Exclusion criteria None specified.

Population number of patients = 107.

Interventions Aim: to retrospectively report the rate of axillary metastasis in patients with high risk DCIS and DCISm who underwent SLNB.

SLNB technique: radiocolloid, dye

Histology technique: standard method, immunohistochemistry.

Outcomes Rate of SN positivity

Follow up Not reported.

Results

All patients:

12/107=11.2% of all patients with DCIS (including DCISm) had positive SNs.

Pure DCIS:

9/76=12% of patients with pure DCIS had positive SNs.

Of these 9 patients, 6 underwent axillary clearance and further axillary nodal involvement was found in 1 patient.

In these 9 patients, tumour grade was high in 7 patients, intermediate in 2 patients and low in 1 patient. Tumour size [on mammography] had mean 4.5cm, median 3.2cm and range 0.6-13.5cm.

DCISm:

3/31=10% of patients with DCISm had positive SNs.

All 3 patients underwent axillary clearance and no further positive axillary nodes were found.

In these 3 patients tumour grade was high in all 3 cases and tumour size [on mammography] was 0.3, 1.2 and 0.6cm respectively.

-

General comments Patients with DCIS or DCISm underwent SLNB only if they were considered high risk for metastatic disease. Retrospectively, patients had at least one of the following: palpable mass, mammographic mass, suspicious histology, multicentric disease, high nuclear grade, necrosis.

Pathology reported appears to be definitive, since a large pathology database was interrogated for the data.

Study does not report SN positivity by tumour size/grade subgroups, but describes these characteristics in SN positive patients.

Accordingly 21% of all patients with DCIS underwent SLNB and 82% of all patients with DCISm.

Liu, Yang & Chen . Sentinel lymph node mapping with emulsion of activated carbon particles in patients with pre-mastectomy diagnosis of intraductal carcinoma of the breast. Journal of the Chinese Medical Association: JCMA 66[7]. 2003.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: China (PRC), setting: Secondary care

Inclusion criteria 24 patients with DCIS by biopsy
19 patients with DCISm by biopsy

Age not reported.

Exclusion criteria Not reported.

Population number of patients = 33.

Interventions

All patients underwent SLNB and further axillary surgery to some extent: dissection to level I/sampling of level II if the SN was negative and axillary clearance if the SN was positive.

SLNB technique: radiocolloid.

Histology technique: standard method.

Outcomes Rate of positive SNs/axillary nodes.

Follow up Not reported.

Results Rate of positive SNs:

Overall 3/33=9% of patients had positive SNs.

In patients with DCIS by biopsy, 2/24=8.3% had positive SNs.

In patients with DCISm by biopsy, 1/9=11.1% had positive SNs.

Of 3 patients with positive SNs, 1 patient had 1 further positive axillary node.

Upstaging by definitive surgery:

In 24 patients with DCIS by biopsy, 3 [12.5%] were upstaged to DCISm and 3 [12.5%] were upstaged to invasive disease.

In 9 patients with DCISm by biopsy, 3 [33.3%] were upstaged to invasive disease.

-

General comments In this series of patients the surgical team used activated carbon as the radiotracer.

All three patients with positive SNs were upstaged to invasive disease by definitive surgery.

Mittendorf, Arciero, Gutchell, Hooke & Shriver . Core biopsy diagnosis of ductal carcinoma in situ: An indication for sentinel lymph node biopsy. Curr.Surg 62[2]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 44 patients with biopsy diagnosis of DCIS but without evidence or suspicion of DCISm, who underwent SLNB, with successful SLNB in 41 patients.

Exclusion criteria Patients with biopsy diagnosis of DCISm; data for patients in whom SLNB was unseccessful (4/44=9.1%) is not reported.

Population number of patients = 41.

Interventions SLNB technique: radiocolloid.
Histology technique: standard method, immunohistochemistry.

Outcomes Rate of positive SNs and further axillary nodes.

Rate of upstaging to invasive disease by biposy method (not shown).

Follow up Not reported.

Results 9/41=22% patients had positive SNs.

Of 9 patients with positive SNs, 5 underwent axillary clearance, of whom 1/5=20% had further involved axillary nodes.

Upstaging to invasive disease by definitive surgery:
3/41=7.3% patients with biopsy diagnosis of DCIS who underwent successful SLNB had invasive disease revealed by definitive surgery.

-

General comments The 44 patients described above were identified form a series of 85 with biopsy diagnosis of DCIS. Therefore no SLNB was attempted in 41 patients.

Study does not report rate of positive SNs by tumour size or grade.

Pendas, Dauway, Giuliano, Ku, Cox & Reintgen . Sentinel node biopsy in ductal carcinoma in situ patients.[see comment]. Ann Surg Oncol 7[1]. 2000.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 87 patients with pure DCIS by biopsy diagnosis.

No age data provided.

Exclusion criteria Patients with DCISm by biopsy diagnosis [n=9].

Pregnant women.

Patients with clinically palpably suspicious axillae.

Population number of patients = 87.

Interventions All patients underwent SLNB. Patients with any evidence of a metastatic SN underwent axillary clearance.

SLNB technique: radiocolloid, dye.

Histological technique: standard method, immunohistochemistry.

Outcomes Rate of positive SNs.

Histological features of tumours.

Follow up Not reported.

Results 5/87=5.7% of patients had positive SNs.

These 5 patients underwent axillary clearance; no further metastatic axillary nodes were identified.

-

General comments No information provided on whether definitive surgery revealed any invasive focus in the primary tumour.

Rate of positive SNs is not reported by tumour size or grade.

Trisal, Qian & Wagman . Axillary recurrence in DCIs: is axillary lymphadenectomy warranted? Am Surg 70[10]. 2004.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria Retrospective analysis of 171 patients with pure DCIS, of which 15 (9%) underwent SLNB.

Age data for the whole series of 171 patients: median 55 years, range 27-93 years.

Exclusion criteria None stated: implied by inclusion criteria.

Population -

Interventions Aim: to retrospectively evaluate recurrence and survival in patients with pure DCIS treated over a 14 year period at a single centre.

15 patients underwent SLNB.

SLNB technique: radiocolloid, dye.

Histological technique: standard method, immunohistochemistry.

Outcomes Survival.

Recurrence.

Histological outcomes.

Follow up Mean follow up 70 months for the whole series of 171 patients.

Results The rate of positive SNs was 0/15=0%.

At a mean follow up of 70 months for the larger series of 171 patients, no cases of axillary recurrence was seen, including in the 15 patients treated with SLNB.

-

General comments Small subset of patients underwent SLNB (n=15) .

Pathology reported appears to be definitive, since a large pathology database was interrogated for the data, plus medical notes.

Study does not report rates of positive SNs by tumour grade or size.

Veronesi, Intra, Vento, Naninato, Caldarella, Paganelli & Viale . Sentinel lymph node biopsy for localised ductal carcinoma in situ? Breast 14[6]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria Patients with pure DCIS

Exclusion criteria Patients with DCISm

Population number of patients = 508.

Interventions Retrospective review of 508 patients with definitive diagnosis of DCIS who underwent SLNB.

SLNB technique: radiocolloid

Histology technique: not reported.

Outcomes Rate of positive SNs by tumour and treatment variables.

Follow up Study reports at 46 months of follow up for the 9 SN positive patients [not stated as minimum, median, etc.]

Results 9/508=1.8% of patients with pure DCIS had positive SNs and 499/508 patients had negative SNs.

8 of these patients underwent axillary clearance and in all 8 the SN was the only positive axillary node.

No pattern was observed between rate of positive SNs and grade:

Grade I: 2/9 = 22.2% of SN positive patients had Grade I disease compared to 90/499 = 18.1% of SN negative patients.

Grade II: 4/9 = 44.4% of SN positive patients had Grade I disease compared to 245/499 = 49.1% of SN negative patients.

Grade III: 3/9 = 33.3% of SN positive patients had Grade I disease compared to 164/499 = 32.8% of SN negative patients.

Similarly no correlation was observed between rate of positive SNs and clinical presentation, hormone receptor status, proliferative index or type of surgery.

T size had median 22.3mm in the 9 SN positive patients compared to median 12.1mm in the 499 SN negative patients.

2/9=22.2% of SN positive patients had comedo DCIS compared to 51/499 = 10.2% of SN negative patients.

-

General comments Diagnosis of DCIS appears to be definitive, based upon final histology and study hence retrospective.

Small number [9] of patients with pure DCIS and positive SNs: no statistical testing was performed.

Wilkie, White, Dupont, Cantor & Cox . An update of sentinel lymph node mapping in patients with ductal carcinoma in situ. Am J Surg 190[4]. 2005.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 675 patients with biopsy diagnosis of DCIS [613] or DCISm [62].

Exclusion criteria None reported - retrospective review of whole series.

Population number of patients = 675.

Interventions Aim = to clarify the incidence [amongst patients with biopsy diagnosis of DCIS or DCISm] who are upstaged to invasive ductal carcinoma at the time of definitive resection.

All patients underwent SLNB.

SLNB technique: radiocolloid, dye

Histology technique: Intra-operative, standard method, immunohistochemistry

Outcomes Rate of change of diagnosis to invasive disease.

Rates of positive SNs by definitive diagnosis.

Follow up None reported.

Results Upstaging to invasive disease:

66/675 = 10% of patients were upstaged to invasive disease after definitive surgery [Of these 66 patients 58 had T1 tumours, 7 had T2 tumours and 1 had a T3 tumour].

Of 613 patients with biopsy diagnosis of DCIS 55 [9%] were upstaged to invasive disease.

Of 62 patients with biopsy diagnosis of DCISm 11 [18%] were upstaged to invasive disease.

Rates of positive SNs:

Of 559 patients with a definitive diagnosis of DCIS 27 [5%] had a positive SN.

Of 51 patients with a definitive diagnosis of DCISm 7 [14%] had a positive SN.

Therefore these rates combined reflect the rate of SN positivity in patients with DCIS, including DCISm: 34/610=5.6%.

Of 66 patients with a definitive diagnosis of invasive disease 15 [23%] had a positive SN.

Upstaging to invasive disease by grade of DCIS:

603 patients had biopsy grade data.

21/313 = 7% of patients with DCIS grade I, I-II or II were upstaged to invasive disease compared to 30/228 = 13% of patients with DCIS grade II-III or III [p=0.003, Chi square].

-

General comments Attributed grade was the highest grade seen by

histology.

603 patients had grade data. Grade data is dichotomised for Chi square analysis of rates of upstaging to invasive disease.

Study provides no data on rate of SN positivity by grade of DCIS, nor by size of DCIS tumour.

Zavagno, Carcoforo, Marconato, Franchini, Scalco, Burelli, Pietrarota, Lise, Mencarelli, Capitanio, Ballarin, Pierobon, Marconato & Nitti . Role of axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. BMC Cancer 5. 2005b.

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria 102 patients with a definitive diagnosis of pure DCIS who underwent SLNB.

Exclusion criteria Patients with DCISm

Population , age range 37 to 85 years, median age = 59 years.

Interventions Aim = to measure the incidence of SN metastases in patients with a definitive diagnosis of pure DCIS.

All patients underwent SLNB.

SLNB technique: radiocolloid.

Histology technique: standard method, immunohistochemistry.

Outcomes Rate of SN positivity.

Follow up Not reported.

Results 1/102=0.98% patients with pure DCIS had a positive SN.

In this patient the primary tumour was grade II and 16mm in diameter (T1c).

The tumour size and grade of 101 patients with negative SNs was as follows:

T size

0-5mm:	14 [13.9%]
5-10mm:	40 [39.6%]
10-15mm:	19 [18.8%]
15-20mm:	13 [12.9%]
20-30mm:	10 [9.9%]
>30mm:	2 [2.0%]
Unknown:	3 [3.0%]

Grade:

I:	21 [20.8%]
II:	36 [35.6%]
III:	44 [43.6%]

-

General comments -

Zavotsky, Hansen, Brennan, Turner & Giuliano . Lymph node metastasis from ductal carcinoma in situ with microinvasion. Cancer 85[11]. 1999.

Design: Retrospective case series (prognosis), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria 14 patients with DCISm who underwent SLNB, identified from a larger series.

DCISM was defined as follows (on the basis of initial triple assessment):

Single focus of size $\leq 2\text{mm}$

≤ 3 foci of size $\leq 1\text{mm}$

Exclusion criteria -

Population number of patients = 14.

Interventions Aim = to examine the role of SLNB in patients with DCISM.

All patients identified underwent SLNB.

SLNB technique: dye.

Histology technique: standard method, immunohistochemistry.

Outcomes Rate of positive SNs by size of tumour, size of invasive element of DCIS and tumour grade.

Follow up Not reported.

Results 2/14=14.3% of patients with DCISM had positive SNs:

SN positivity by T size:

$\leq 2\text{cm}$: 0/5=0%

2-5cm: 2/5=40%

$>5\text{cm}$: 0/4=0%

SN positivity by Tumour grade:

Grade I: 0/1=0%

Grade II: 0/2=0%

Grade III: 2/11=18.2%

Upstaging to invasive disease by definitive surgery:

4/14=28.6% of patients staged by SLNB were found, by definitive surgery, to have invasive foci of 1mm or more.

-

General comments The definition of true DCISM used is that of the American Joint Committee on Cancer: i.e. invasive focus $<1\text{mm}$ in size on definitive histology.

Very small series of patients.

Update 6B

Ansari, B., Ogston, S. A., Purdie, C. A., Adamson, D. J., Brown, D. C. & Thompson, A. M. (2008) Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast. *British Journal of Surgery*, 95: 547-554.

Design: Meta-analysis of case series studies, Evidence level 3

Aim: This study is a meta-analysis of the reported data on the incidence of SLN metastasis in patients with DCIS.

Some studies of SLN biopsy in DCIS assess the sentinel node biopsy-positive frequency in patients with a definitive (postoperative) diagnosis of DCIS, whereas others report this frequency in patients using the preoperative initial core biopsy diagnosis of DCIS. Given that 10–30 per cent of patients with a preoperative core biopsy diagnosis of DCIS will eventually turn out to have invasive cancers, the frequency of SLN metastatic involvement in these two patient groups may be different. Therefore, a meta-analysis of these two different sets of publications was performed separately.

Inclusion criteria

- Case series studies that reported percentage SLN positivity in patients with a diagnosis of DCIS were included in the meta-analysis.
- Patients: patients with DCIS who were considered to be at high risk of having an invasive component, such as those with adverse clinical or histological features (large, palpable tumours, mammographic mass, high grade)

Exclusion criteria

Publications that had not reported percentage SLN positivity data, review articles and editorials were excluded.

Population

22 publications reporting SLN biopsy results in patients with the diagnosis of DCIS were included.

The combined study population = 3166 patients.

Interventions

A comprehensive search was conducted for the studies: Medline, Embase, CINHALL, Ovid and The Cochrane Library, up to August 2007

Outcomes

SLN positivity data

Results

Studies that assessed the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS reported values from 0 to 16.7%

The test for heterogeneity suggested that these 11 studies were not significantly heterogeneous ($\chi^2 = 16.07$, 10 df $P = 0.098$).

A meta – analysis of the data on SLN positivity from these studies gave an overall positivity frequency (or overall incidence) of 7.4% (95 %CI 6.2 to 8.9)

There was significant between study heterogeneity in the 11 studies of patients with a definitive (postoperative) diagnosis of DCIS ($\chi^2 = 27.82$, 10 df, $P = 0.002$).

A meta-analysis of the data on SLN positivity from these studies showed an overall positivity frequency (or overall incidence) = 3.7% (95%CI 2.8 – 4.8)

The overall frequencies of nodal metastasis between the two groups (preoperative versus

<p>definitive diagnosis) were significantly different with an odds ratio of 2.11 (95 %CI 1.15-2.93)</p> <p>From a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component were presented (from a literature search with some inconsistencies occurring between studies):</p> <p>Most of these studies suggested that a palpable mass; a mammographic mass; a high-grade lesion and a large size were associated with a significant risk of invasive disease in the final resection specimen.</p>
<p>General comments</p> <p>Authors note that “Small patient numbers, evolving techniques of SLN biopsy and variations in methods of pathological examination, including differences in extent of tissue sampling and methods of metastasis detection, may all contribute to the variability in the reported frequencies of node positivity.”</p> <p>Conclusion: Patients with a preoperative diagnosis of DCIS should be considered for SLN biopsy.</p>
<p>Julian, T. B., Land, S. R., Fourchette, V., Haile, S. R., Fisher, E. R., Mamounas, E. P., Costantino, J. P. & Wolmark, N. (2007) Is sentinel node biopsy necessary in conservatively treated DCIS? <i>Annals of Surgical Oncology</i>, 14: 2202-2208.</p>
<p>Design: RCT – extended report of 2 RCTs (National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-17 and NSABP trial B-24)</p> <p>Country: US</p> <p>Aim: To identify the risk of axillary node involvement in patients with ductal carcinoma in situ (DCIS) and to determine whether axillary node assessment is necessary in these patients.</p>
<p>Inclusion criteria</p> <p>Patients included in the trials (NSABP trial B-17 and NSABP trial B-24): localised DCIS and disease-negative margins after local excision (LE)</p>
<p>Exclusion criteria</p>
<p>Population</p> <ul style="list-style-type: none"> • 813 patients with localised DCIS and disease-negative margins after LE (NSABP) trial B-17 • 1799 patients with DCIS treated with LE and radiotherapy (NSABP trial B-24)
<p>Interventions</p> <ul style="list-style-type: none"> • NSABP trial B-17 : records of 813 patients with localised DCIS and disease-negative margins after LE who were randomly assigned to no further therapy or to breast irradiation (ALND was performed in 253 patients, 31.1%) • NSABP trial B-24: 1799 patients randomised to receive placebo or tamoxifen after LE + radiotherapy (An ALND was performed in 162 in NSABP B-24, 9%)
<p>Outcomes</p> <ul style="list-style-type: none"> • Ipsilateral nodal recurrence (INR) rate • Pathological features for INR (assessed with standard hematoxylin and eosin staining)
<p>Follow – up: 15 years for B17 and 11 years for B-24</p>
<p>Results</p> <p>INR:</p>

In the NSABP trial B-17: Overall ipsilateral nodal recurrence (INR) rate = 0.83/1000 patient-years. (0.86%

In NSABP B-24: Overall INR rate = 0.36/1000 patient-years.

Pathology:

- Pathology was available for 76.6% of patients in the B-17 trial and 81% in the B-24 trial.
- Margins were involved in 17.2% of patients in B-17 trial and 29.5% in B-24 trial (with 9.3% unknown).
- For both trials: margin status; comedo necrosis; gross tumour size; nuclear grade and focality were assessed as a risk factor for nodal recurrence and no factor was statically significant related.

General comments

Authors' comments: INR can be considered a surrogate for axillary involvement at the time of DCIS diagnosis. INR in patients with DCIS treated conservatively is extremely rare. Findings from this study do not support the routine use of SNB in patients with conservatively treated, localised DCIS

Health Economics Summary

The volume of economic evidence on SLNB is limited and refers only to question 6.a (i.e. it considered patients with invasive breast cancer but not those with DCIS). From a total of 80 references obtained from the search, six studies were identified that addressed topic 6.a from a health economics point of view: one of these studies was a full economic evaluation (Jeruss et al 2006), two of them were partial economic evaluations (Fortunato et al 2004 and Ronka et al 2004), and three of them were cost studies (Chirikos et al 2001, Gemignani et al 2000 and Perrier et al 2004). The identified studies do not provide a clear, reliable answer for the PICO question here presented. A full description of all these studies has been presented in the accompanying document containing the HE Evidence Tables.

The only economic evaluation identified in relation to this topic assessed two alternative ways of conducting SLNB (rather than comparing SLNB with ALND or axillary node sampling): intraoperatively and postoperatively, using analytic modelling techniques, and concluded that intraoperative SLNB seems to be cost-effective when compared to postoperative SLNB, although results were sensitive to the utilities used to estimate QALYs. The partial economic evaluation by Fortunato et al 2004 concluded that intraoperative SLNB resulted in significant cost savings derived from avoiding a second surgery on a subgroup of patients (i.e. those with negative nodes), although the comparator used in this study was not explicitly stated. Ronka et al (2004) compared three ways of conducting SLNB with ALND and found a false negative rate for SLNB of 13.24%, while ALND was the least costly staging strategy in terms of hospital costs; the authors mentioned that the benefits of intraoperative SLNB are likely to be found in the long-term (i.e. decreased arm morbidity) may be worth at relatively low false-negative rates because it avoids secondary surgery in patients undergoing staging.

None of the identified cost studies was conducted in UK. Two of these cost studies were conducted in the USA (Chirikos et al. 2001, and Gemignani et al 2000) and considered billing charges rather than costs for the estimation of the costs related to SLNB (which may not be representative of the UK setting and of the true costs of the intervention). The other study was conducted in France (Perrier et al. 2004). It was unclear whether SLNB was more or less expensive compared to ALND: Perrier et al (2004) concluded that SLNB seemed to be less expensive than ALND; according to Gemignani et al (2000), SLNB did not seem to result in significantly higher hospital-related charges compared to ALND; Chirikos et al (2001) highlighted that, although SLNB appeared to be more expensive procedure than ALND from the results of their study, the potential cost-savings they would expect from SLNB are likely to be observed in the long term. None of these studies considered the costs of post-operative complications, whose inclusion would have been required for an accurate cost assessment. Therefore, the studies seem to present limitations and to be either with limited applicability or non-applicable to the UK setting.

Summary of individual studies

The only full economic evaluation identified (Jeruss et al 2006) was a cost-utility analysis conducted in USA that compared the cost-effectiveness of two alternative methods to carry out SLNB: intraoperative touch imprint cytology (TIC) and standard postoperative SLNB. No comparison was conducted with any of the comparators stated in the PICO question of the topic (i.e. no axillary surgery, axillary node sample or axillary lymph node dissection). A decision tree was constructed to estimate the incremental cost per QALY at 6 months. The baseline data used to populate the model was derived from a prospective cohort study developed at the authors' institution, although the parameters' ranges used in the sensitivity analyses were identified from the published literature. Health care resource utilisation and unit costs are likely to have reflected the clinical practice of the authors'

institution, and no statistical or sensitivity analyses were conducted for the estimated costs. Utility scores for the estimation of QALYs were obtained by surveying 4 surgical oncologists using the EuroQol-5D. The results of the analysis concluded that TIC was cost-effective compared to standard postoperative SLNB, with an incremental cost-per-QALY equal to: \$13,731 for T1 tumours and \$7,102 for T2 tumours for 2005 prices (equivalent to £8,497 and £4,395, respectively), and it was dominant (i.e. more effective and less costly) for T3 and T4 tumours, compared to standard postoperative SLNB. The results of the sensitivity analyses showed that the cost-effectiveness results were sensitive to the utility scores used for the estimation of QALYs.

The study by Fortunato et al (2004) was a cost-consequences analysis (CCA) conducted in Italy. The study assessed the accuracy of SLNB and the savings to the Italian Health System that could be achieved from avoiding second surgeries by means of SLNB. The reference standard used to assess SLNB accuracy was not explicitly stated, although it may have been ALND. The authors concluded that SLNB, with a sensitivity equal to 68% and a specificity of 99%, could result in significant cost savings for the Italian NHS derived from avoiding second surgeries. However, the cost estimation presented relevant limitations since the costs of SLNB were not included, only those of second operations; therefore, there is uncertainty regarding the reliability of the study results.

The study by Ronka et al (2004) was a CCA as well, and it was conducted in Finland. It assessed the number of patients that would undergo either 1, 2 or 3 surgeries depending on the staging strategy followed (i.e. ALND, SLNB with frozen section, SLNB without frozen section or SLNB as day care surgery), and the associated hospital costs per patient. The data were derived from a prospective cohort study evaluating SLNB frozen section, and from authors' assumptions about the other three staging strategies based on the results of this study. The accuracy of SLNB frozen section was additionally reported using the postoperative assessment as the reference standard. The authors concluded that ALND was the least costly strategy in terms of hospital costs, and that SLNB with frozen section may be worth at relatively low false-negative rates. The cost estimation did not include any long-term cost related to the alternative staging strategies (e.g. post-operative complications); therefore, it is likely not to accurately reflect the costs related to the staging strategies considered at analysis.

References

Chirikos, T.N., et al., Cost consequences of sentinel lymph node biopsy in the treatment of breast cancer. A preliminary analysis. *International Journal of Technology Assessment in Health Care*, 2001. 17(4): p. 626-631.

Fortunato, L., et al., Intraoperative examination of sentinel nodes in breast cancer: Is the glass half full or half empty? *Annals of Surgical Oncology*, 2004. 11(11): p. 1005-1010.

Gemignani, M.L., et al., Impact of sentinel lymph node mapping on relative charges in patients with early-stage breast cancer. *Annals of Surgical Oncology*, 2000. 7(8): p. 575-580.

Jeruss, J.S., et al., Is intraoperative touch imprint cytology of sentinel lymph nodes in patients with breast cancer cost-effective? *Cancer*, 2006. 107(10): p. 2328-2336.

Perrier, L., et al., Cost comparison of two surgical strategies in the treatment of breast cancer: Sentinel lymph node biopsy versus axillary lymph node dissection. International Journal of Technology Assessment in Health Care, 2004. 20(4): p. 449-454.

Ronka, R., et al., The impact of sentinel node biopsy and axillary staging strategy on hospital costs. Annals of Oncology, 2004. 15(1): p. 88-94.

Chapter 3.3) In patients with invasive breast cancer when is SLNB justified as a staging procedure?

Full Economic Evaluations

Jeruss JS et al. Is intraoperative touch imprint cytology of sentinel lymph nodes in patients with breast cancer cost-effective? Cancer, 2006. 107(10): p. 2328-2336.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. decision tree).

Clinical effectiveness:

From a prospective study conducted at their centre, assumptions, estimates of utilities from surgeons and some data from published literature.

Cost estimation:

Costs included were those of the procedures (TIC, postoperative SLNB, ALNC, either immediate or delayed) and postoperative complications.

Country: USA, **setting:** Hospital

Inclusion criteria

Breast cancer patients undergoing SLNB as staging procedure

Exclusion criteria

Not stated

Population number of patients = 342 patients from prospective study, 5 patients for cost estimation.

Interventions

Intraoperative touch imprint cytology (TIC) of SLNs

Standard postoperative SLNB

Follow up

Time horizon = 6 months

Data used to populate the model

Assumptions:

- Patients with positive TIC would undergo immediate ALND
- Patients with metastases noted on standard postoperative SLNB have delayed ALND within 4 weeks after initial SLNB
- Probability of short-term surgical complications (e.g. infection and seroma) after ALND is 15%.

Health states: awaiting surgery, waiting for results of standard postoperative SLNB, recovering from ALND and recovering from ALND complications.

Data from prospective study:

OUTCOME OF INTEREST	TIC	Postoperative SLNB
Sensitivity	0.43	-
Specificity	0.99	-
Prevalence of SLN metastasis		
T1 tumours		0.17
T2 tumours		0.27
T3 tumours		0.40

T4 tumours

0.42

Utilities and costs: estimated by surveying 4 surgical oncologist, using EQ-5D:

Health States	Utility	Cumulative cost (2005 US\$)	Cumulative cost (2005 UK£)
TIC(+), Immediate ALND, No complications	0.71	8154	5046
TIC(+), Immediate ALND, Complications	0.56	8604	5324
TIC(-), SLNB(+), Delayed ALND, No complications	0.71	12040	7450
TIC(-), SLNB(+), Delayed ALND, Complications	0.62	12490	7729
TIC(-), SLNB(-), no ALND	0.89	5240	3243
Standard SLNB(+), Delayed ALND, No complications	0.66	11443	7081
Standard SLNB(+), Delayed ALND, Complications	0.58	11893	7359
Standard SLNB(-), No ALND	0.84	4643	2873

Health care resource utilisation and costs: To extract resource utilisation only 5 patients were identified, according to each treatment undergone and scenario proposed in the model.

Unit costs	2005 US\$	2005 UK£
TIC	600	371
Standard postoperative SLNB	4700	2908
ALND	6800	4208
TIC/Standard postoperative SLNB/Immediate ALND*	8200	5074
Postoperative complications	450	278

* Not sure why they would conduct postoperative SLNB after having performed ALND

Results

OUTCOME OF INTEREST	T1 tumours		T2 tumours		T3 tumours		T4 tumours	
	SLNB*	TIC	SLNB*	TIC	SLNB*	TIC	SLNB*	TIC
Average cost (2005 US\$)	5831	6160	6484	6652	7356	7311	7534	7445
Average cost (2005 UK£)	3608	3812	4012	4116	4552	4524	4662	4607
QALYs	0.4	0.43	0.39	0.42	0.38	0.41	0.38	0.4
Cost/QALY (2005 US\$)	14456	14415	16445	15914	19252	18026	19849	18474
Cost/QALY (2005 UK£)	8945	8920	10176	9848	11913	11155	12283	11432
ICER (2005 US\$)	-	13731	-	7103	-	Dominant	-	Dominant
ICER (2005 UK£)	-	8497	-	4395	-	Dominant	-	Dominant
# Procedures required to avoid one ALND	-	14	-	9	-	6	-	6
Patients with nodal metastasis	17%		27%		40%		42%	

*SLNB = Standard postoperative SLNB

Sensitivity analysis:

The results were robust to changes in sensitivity and specificity of TIC, prevalence of metastases, probability of complications and most of the costs. TIC would not be longer cost-effective in the following analysed situations:

- When the cost for TIC with immediate ALND varied to 200% above the baseline estimate (presenting an ICER > £30,000 , or > US\$ 50,000).
- When the utility associated with postoperative SLNB was ≥ 0.9 .

Authors' conclusions:

Overall, TIC is cost-effective in patients with clinically node-negative BC, and especially for those patients with larger tumours (who are more likely to have node metastasis and require ALND, in which case TIC would be less costly than postoperative SLNB).

General comments –

There were some limitations in the cost analysis due to the small patients sample considered to collect cost data. The authors mentioned that the lower incidence of nodal metastasis and the lower sensitivity found for TIC may be due to the fact that the standard practice at their

centre is to use pre-treatment US+FNA in an initial stage to identify patients with positive nodes that can spare the SLNB procedure; these patients will typically receive preoperative chemotherapy (reducing or eradicating nodal metastasis before SLNB); therefore the patients included in this study are more likely to present micro metastasis, which are more difficult to detect through TIC.

Partial Economic Evaluations

Fortunato L et al. Intraoperative examination of sentinel nodes in breast cancer: Is the glass half full or half empty? *Annals of Surgical Oncology* 2004; 11(11):1005-1010.

Design:

Type of economic evaluation:

Partial economic evaluation (due to limitations in cost estimation)

Clinical effectiveness:

Derived from a prospective diagnostic study

Cost estimation:

It considered the savings to the Italian Health System derived from avoiding a second operation (i.e. ALND) for those patients with negative SLNs as identified through SLNB, minus the cost of the ALND on those false-positive cases.

Country: Italy, **setting:** Hospital

Inclusion criteria BC patients

Exclusion criteria Not stated

Population number of patients = 236 patients (median age = 64 years; median tumour diameter = 1.5cm): 201 (85%) of patients with ductal cancer, 21 (9%) with lobular and rest with other types of tumour (e.g. mucinous, tubular, medullary, metaplastic).

Interventions SLNB during surgical treatment for BC

The reference standard may have been ALND but this was not explicitly stated in the paper. (The authors mentioned that in addition to SLNB, non-SLNs were removed and analysed, and intra-operative SLNB accuracy was based on definitive pathological results).

Follow up Until test results

Results

97% of patients had SLNs identified, with a median of 2 SLNs identified per patient. A median of 17 non-SLNs were removed in positive cases, and 2 in negative cases.

Accuracy = 86.5593% $((52+157)/(77+159))$

Sensitivity = 67.5325% $(77/52)$

Specificity = 98.7421% $(157/(157+2))$

False negative = 13.7% $(25/(157+25))$

False positive = 3.7% $(2/(52+2))$

PPV = 96.2963% $(52/(52+2))$

NPV = 86.2637% $(157/(157+25))$

The savings to the Italian Health System were estimated to be €198,040 (or £164,162), based on 20% of patients (48/236) that avoided a second operation (i.e. ALND) due to the intraoperative SLNB minus the cost of the ALND for the two false-positive cases.

Authors' conclusions:

Intraoperative SLNB resulted in significant cost savings derived from avoiding a second operation for completion lymphadenectomy on a subgroup of patients.

General comments –

The study may have been subject to bias since it was not clearly identified how the validation of the SLNB results was conducted (i.e. there was not an explicit identification of the reference standard used for validation of SLNB results, although as previously stated, the authors mentioned that in addition to SLNB, non-SLNs were removed and analysed). The authors mentioned they did not intend to conduct a cost-effectiveness analysis. For the estimation of the savings to the Italian Health System, not all the essential relevant costs were considered in the estimation (i.e. the costs of the SLNBs were excluded) and therefore there is uncertainty regarding the reliability of this cost estimation. They mentioned that there may be relevant differences in costs at the international level and therefore the results may not be generalisable to other settings.

Ronka, R., et al., The impact of sentinel node biopsy and axillary staging strategy on hospital costs. *Annals of Oncology*, 2004. 15(1): p. 88-94.

Design:Type of economic evaluation:

Partial economic evaluation: cost-consequences analysis that used modelling (i.e. decision tree).

Clinical effectiveness:

Prospective cohort study and authors' assumptions

Cost estimation:

Unit costs from Helsinki University Hospital.

Costs included:

- Hospital inpatient care (i.e. room and board, medication, blood products, laboratory costs, pre- and post-operative nursing care).
- Outpatient visits (i.e. pre- and post-operative check ups).
- Lymphoscintigraphy.
- Surgery (i.e. operation, anesthesia and recovery room).
- Pathological analysis (i.e. intra-operative frozen section, postoperative histological examination, breast specimens and ALND if conducted).

Price year: 2001.

Country: Finland, **setting:** Hospital

Inclusion criteria Patients with clinical T1-2, node-negative BC that underwent lymphatic mapping and SLNB at the authors' institution between September 2000 and August 2001.

Exclusion criteria Not stated

Population number of patients = 237

Interventions

- SLNB with intraoperative frozen section diagnosis (previous lymphoscintigraphy was conducted and Patent Blue dye was used), followed by ALNC (levels I and II) when there was evidence of axilla involvement (either after frozen section or after identifying a false negative result), SLNs not identified or were blue only without radioactivity, or if the tumour proved to be multifocal. ALNC (level III) was performed for palpable nodes suspicious of metastatic involvement.

Patients admitted to hospital in same day of surgery and discharged on first day after surgery for SLNB and second day after ALNC. Drainage removed by a breast nurse on fifth day after surgery.

Three hypothetical interventions were additionally assessed:

- Diagnostic ALND
- SLNB as day case surgery prior to breast surgery
- SLNB without frozen section diagnosis

Follow up Staging process

Results

OUTCOME OF INTEREST:	SLNB	SLNB	Total
Intraoperative and postoperative histological	Frozen	Frozen	

diagnosis in SLN metastases in 204 patients with successful identification of SLN	section (+)	section (-)	
Involved SLN	59	9	68 (33.33%)
Uninvolved SLN	1	135	136 (66.67%)
	60 (29.41%)	144 (70.59%)	204 (100%)

False negative rate for intraoperative SLNB = 9/68 = 13.24%

OUTCOME OF INTEREST	Diagnostic ALND	SNLB with frozen section	SLNB without frozen section	SLNB as day care surgery
Hospital costs per patient (€ 2001)	3020	3750	4087	4573
Hospital costs per patient (£ 2006)	2372	2945	3210	3592
Number (%) of patients with one operation	231 (97%)	218 (92%)	118 (49%)	-
Number (%) of patients with two operations	6 (3%)	19 (8%)	119 (51%)	237 (100%)
Number (%) of patients with three operations	-	-	-	13 (5%)

Authors' conclusions –
ALND was the least costly staging strategy in terms of hospital costs. Intraoperative diagnosis of SLN metastases may be worth in the long terms, at relatively low false-negative rates, since the benefits of SLNB are likely to be observed in the long term. Further evaluation is required to identify long-term benefits of SLNB.

General comments –
There was a clear description of the health care resource utilisation and unit costs used in the model, which would allow replications of the model using UK data. It seemed that the clinical parameters used in the model for the hypothetical staging/diagnostic strategies were inferred from the prospective cohort study. The lower costs found in this study for ALND were not consistent with the results of other studies (e.g. Gemignani et al 2000), which may have been due to differences in the type of patients included at analysis and to the fact that SLNB patients in this study had one day of hospitalisation after the staging procedure.

Cost studies

Chirikos, T.N., et al., Cost consequences of sentinel lymph node biopsy in the treatment of breast cancer. A preliminary analysis. *International Journal of Technology Assessment in Health Care*, 2001. 17(4): p. 626-631.

Design:

Type of study:

Cost study.

Multivariate analysis was conducted to identify the net effect of SLNB on charges, after controlling for other variables (e.g. age, number of cancers, stage at diagnosis, histology, node status, treatment and outcomes).

Cost estimation:

Data collected from cancer registry and from charge/billing system (to identify patients undergoing SLNB). Charges were considered for the cost estimation, which included: service encounters and charges for hospital room, board, outpatient visits, supplies, drugs, procedures, tests, etc.

Country: USA, **setting:** Hospital

Inclusion criteria All patients diagnosed of BC and who received the first course of treatment at the authors' centre between August 1995 and March 1998.

Exclusion criteria Patients who did not undergo any surgery, those treated by blood/marrow transplantation, and those diagnosed with stage IV.

Population number of patients = 555 in the SLNB group, 256 in the control group

Interventions SLNB versus Non-SLNB (not clearly specified)

Follow up From diagnosis to 44 months after diagnosis or death.

Results

OUTCOME OF INTEREST	SLNB (n = 555)	Control (n = 256)	P-value
Unadjusted average cumulative charges (\$)*	26,200	28,700	ns
Unadjusted average cumulative charges (UK£ 2006)*	23,046	25,245	-
Unadjusted SLNB charges as % of comparison group charges (%) at all follow up times	91.3	100	-
Adjusted SLNB charges as % of comparison group charges (%) at all follow up times	111.2	100	P < 0.01

*Price year assumed to be 1998 for adjustments to UK£ 2006

Authors' conclusions

It is likely that the cost-savings related to SLNB will be observed in the long term and therefore they will be detected when more extensive follow up data become available.

General comments –

The price year was not explicitly stated (therefore, in the conversion exercises to UK£ it was assumed that it was 1998). As the authors highlighted, cumulative charges were used which did not include physician services, especially those of community physicians that care for long term treatment caused by adverse consequences. Therefore, bias against SLNB is likely to be present in the study.

Gemignani, M.L., et al., Impact of sentinel lymph node mapping on relative charges in patients with early-stage breast cancer. *Annals of Surgical Oncology*, 2000. 7(8): p. 575-580.

Design:

Type of study:

Cost study

Cost estimation:

A prospective cohort study with matched control group was used for the cost estimation. Three categories of costs included:

- Operating room (i.e. anesthesia, anesthesia medications and post-anesthesia care unit charges)
- Pathologic diagnosis (i.e. frozen section, gross and microscopic analyses, and immunohistochemical (IHC) staining).
- Hospital stay (room and board for patients admitted).

Total hospital charges included these three categories plus additional costs incurred (e.g. medication, supplies, laboratory tests, roentgenographic localisations and lymphatic mapping).

Total professional charges were obtained separately.

Country: USA, **setting:** Hospital

Inclusion criteria

T1 tumours, breast conservation therapy and absence of clinical suspicion of lymph node metastasis.

Exclusion criteria

Not stated

Population

Intervention group: 50 consecutive patients undergoing SLNB from July 1, 1997 to June 30, 1998.

Control group: 50 patients undergoing ALND during same period, matched by age, tumour size and lymph node status, staged during the same period.

*Note than in the results section the authors reported the results of a retrospective study on

SLNB including 432 patients, but these were not considered for the cost analysis.

Interventions

SLNB versus ALND

Intraoperative frozen-section analysis was performed for SLNB. If metastases was detected in nodes, patients underwent ALND. Further serial sectioning and IHC staining was conducted after the procedure and for those with detected metastasis, ALND was offered later.

Follow up – Period related to the staging process

Results

OUTCOME OF INTEREST	SLNB (n = 50)	ALND (n = 50)	P-value
Costs (\$):			
Operating room	2509	3258	< 0.05
Hospital stay	820	1608	< 0.05
Pathologic examination	1747	969	< 0.05
Intraoperative frozen-section	528	158	< 0.05
Total hospital	6230	6331	
Total hospital costs (UK£ 2006*)	4537	4611	ns

*Currency and price year assumed to have been Canadian\$ for 1997 in order to conduct cost adjustments.

There is some additional information reported in terms of health care resource utilisation (e.g. length of hospital stay, operating room time, etc.).

Authors' conclusions –

SLNB did not result in significantly higher hospital-related charges compared to those of ALND.

General comments –

The price year was not explicitly reported (although it may have corresponded to the period in which surgeries were performed, i.e. latter part of 1997). Currency not reported but it is likely to be Canadian\$. As the authors reported, one limitation was the use of charges rather than costs, which may not be a true reflection of the costs of the intervention/opportunity costs. In the discussion, the authors reported that intuitively, SLNB would offer financial advantages over ALND in patients with EBC since the procedure can be done in an outpatient basis and without general anaesthesia in most of the patients. However, if frozen-section is performed, the associated costs increase considerably. In addition, those patients with negative nodes from frozen-section but positive nodes from further analysis will need to receive further surgery (i.e. ALND). As the authors reported, “an intraoperative frozen-section analysis may help to reduce overall charges because it affords greater opportunity for identification of positive nodes at the time of the initial procedure, thereby decreasing the need for second surgical procedures.”

Perrier, L., et al., Cost comparison of two surgical strategies in the treatment of breast cancer: Sentinel lymph node biopsy versus axillary lymph node dissection. International Journal of Technology Assessment in Health Care, 2004. 20(4): p. 449-454.

Design:

Type of study:

Cost study

Cost estimation:

The cost analysis was based on micro-costing from a retrospective cohort study with random selection of patients from the intervention versus the control groups. Health care resource utilisation was obtained from patients' medical files and unit costs were obtained from the cost accounting department of the authors' institution.

Price year: 2001

Country: France, **setting:** Hospital

Inclusion criteria Patients treated for BC between 1998 and 2001 at the authors' institution.

Exclusion criteria Missing data or concomitant no cancerous pathological conditions requiring extensive hospital stay.

Population number of patients = 50 in the SLNB (with 2 finally excluded) versus 50 in the

ALND (with 7 excluded)

Interventions SLNB versus ALND

Outcomes Total direct medical costs of the staging procedures

Follow up During the staging of patients

Results

OUTCOME OF INTEREST	SLNB (n = 43)			ALND (n = 48)		
	Mean	%	SD	Mean	%	SD
Total direct medical costs without including ALND costs required after SLNB (€ 2001)	1444	81	401	2007	100	283
Total direct medical costs without including ALND costs required after SLNB (£ 2006)	1230	81	342	1710	100	241
Total direct medical costs (%) including ALND costs required after SLNB (€ 2001)	1777	100	645	2007	100	283
Total direct medical costs (%) including ALND costs required after SLNB (£ 2006)	1514	100	549	1710	100	241

Differences were statistically significant when total median costs were compared ($p = 0.0076$).

Authors' conclusions –

SLNB appeared to be less expensive than ALND, and this difference may be even greater if indirect/societal costs were to be accounted for in the analysis.

General comments –

As the authors mentioned, comparisons of their results with those from other studies are difficult. However, Chirikos et al found as well lower costs for SLNB, while Gemignani found that the costs of SLNB were not significantly higher than those of ALND.

3.4 What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis?

Short Summary

From RCT evidence there were no significant differences in overall survival between groups given axillary dissection or axillary sampling with regional node radiotherapy for lymph node positive patients (Chetty *et al.* 2000, Forrest *et al.* 1995); similarly there was no significant difference in overall survival between the groups receiving SLNB and axillary dissection and SLNB or axillary dissection only in SLNB positive patients (Veronesi *et al.* 2003). Finally there were no differences between these groups for locoregional recurrences or axillary recurrences (Chetty *et al.* 2000, Forrest *et al.* 1995, Veronesi *et al.* 2003). There were conflicting views from observational studies on whether patients with micrometastases can be spared axillary surgery from observational studies. The majority of patients with macrometastases in observational studies were given axillary clearance, unless there were clinical reasons not to, or refusal (Chagpar *et al.* 2006; EORTC Intergroup Study 2007; Ganaraj *et al.* 2003; Giard *et al.* 2004; Gipponi *et al.* 2006; Guenther *et al.* 2003; Katz *et al.* 2006; Langer *et al.* 2005; Lyman *et al.* 2005; Naik *et al.* 2004; Park *et al.* 2007; Pinkney *et al.* 2007; Viale *et al.* 2001). A retrospective case series by Samoilova *et al.* (2007) reported that the variable that most reliably separated N1a from N2-3 patients was the size of the tumour deposits in the sentinel lymph node. All patients with sentinel lymph node tumour deposits ≤ 5 mm had three or fewer positive nodes; 95% were sentinel lymph node positive only, and 91% had single-node involvement. The presence of lymphovascular invasion in the primary tumour was statistically significantly different between N1a and N2-3 patients and the presence of extracapsular extension of tumour in the sentinel lymph node was also statistically significantly different between N1a and N2-3 patients. The role of radiotherapy in reducing regional recurrence was unclear.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with invasive breast cancer with histologically-positive axillary nodes demonstrated by a surgical procedure i.e. SLNB or 4 node sampling	Completion axillary clearance	RT or no axillary treatment or change in systemic treatment	<ul style="list-style-type: none"> • Disease Free Survival (DFS) • Axillary recurrence rate • Overall Survival (OS)

The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence Summary

Studies did not directly address the question outlined in the PICO table. Results of a RCT (AMAROS) that is relevant are awaited. This study compares axillary radiotherapy with axillary lymph node dissection in patients with proven axillary lymph node metastases determined by sentinel node biopsy. The NRS tended to focus on tumour characteristics and histology of the metastases without always providing data on follow-up after treatment. The RCTs provided data on recurrences, but not a great deal of detail about the histology of metastases.

Three RCTs were identified comparing axillary clearance/dissection with either axillary sampling and RT if node positive (Chetty *et al* 2000, Forrest *et al* 1995), or with axillary dissection only in patients with positive SNLB (Veronesi *et al* 2003). All three RCTs had a patient population of around 500 participants.

A larger number of non-randomized studies (NRS) were identified. However the majority of these had a very small proportion of patients with positive axillary lymph node metastases (range n = 15-48), many of these studies were descriptive, reported the incidence of metastases in non-SLNs, and most did not report any further interventions or follow-up. Patients found to have macrometastases usually had completion axillary dissection unless there were clinical reasons for not undertaking surgery, or they refused. The histological findings were sometimes modeled in univariate and multivariate analyses to quantify predictive factors for non-SLN metastases, some of these studies were underpowered for multivariate analysis. The conclusions of the smaller studies tended to favour the omission of completion axillary dissection for patients with micrometastases. The ten NRS included in the evidence table were comprised of 2 studies that were predictive using a scoring system (Pinkney *et al* 2007) or nomogram (Park *et al* 2007); the remaining 8 studies were either prospective or retrospective and largely descriptive. Not all studies classified metastases as micrometastases or macrometastases, some (n=4) provided later follow-up data of regional recurrences.

One guideline and one expert review were also included.

Evidence from RCTs

In RCTs pathological tumour sizes were reported in the tables of characteristics. The proportion of node positive patients in RCTs was between 28-43%. For node positive patients metastases were not always sub-classified by size i.e. micrometastases or macrometastases. (Chetty *et al* 2000, Forrest *et al* 1995).

The RCT comparing Axillary sampling + RT vs. AXND (Chetty *et al* 2000) reported no differences between groups for the outcomes Overall Survival (Kaplan-Meier, log rank test $p=0.2$); time to axillary recurrence ($p=0.94$) or time to breast recurrence ($p=0.97$). The authors suggest a selective policy for the management of the axilla.

The earlier RCT (Forrest *et al* 1995) of Axillary node sampling (4 node sampling) + RT to nodes of patients with positive metastases vs axillary node clearance after total mastectomy found no difference in survival between the 2 groups at 11 years. There were more locoregional recurrences in the axillary clearance group than the axillary sampling group (29% vs 19%), however a statistical analysis was not reported. The authors suggested surgical clearance of the axilla is preferred to sampling + RT because of reduced morbidity. However this trial was conducted in the early 1980s.

In a trial comparing sentinel-node biopsy and total axillary dissection (the axillary-dissection group) versus sentinel-node biopsy followed by axillary dissection only if the sentinel node contained metastases (the sentinel-node group) (Veronesi *et al* 2003). No local recurrences were reported in the axilla after a median follow-up of 46 months. Other locoregional recurrences occurred in the supraclavicular fossa, ipsilateral and contralateral breasts. Event rates were small and no statistical analysis was performed between groups. There was no statistically significant difference between groups in the rate of overall survival over 60 months ($p=0.15$).

Table 3.3.1 Survival, recurrence and sites of relapse from RCTs

Study	Overall survival	Recurrence	Sites of relapse
Chetty 2000 N=466 Quality 1+	At 5 years Deaths = 53 Ax CI 82.6% Ax sample + RT 88.6% p=0.2	No differences between the 2 groups in time to axillary recurrence (p=0.94) or time to breast recurrence (p=0.97)	Ax CI Ax sample Axilla 8 7 Supracl 4 2 Ax+sc 0 1
Forrest 1995 N=406 Quality 1+	At 11 years Deaths n=147 Ax CI 76 Ax sample + RT 71 Hazard Ratio 1.11 (95% CI 0.80-1.53) – not significant.	HR 1.35 (95% CI 0.83-2.19) – not significant (reference axillary clearance)	Ax CI Ax sample Axilla 3(4%) 6 (7%) Supracl 9 (11%) 8 (9%)
Veronesi 2003 N=516 Quality 1+	Over 60 months Deaths = 8 AXD 6 SNB 2 Overall survival not significantly different between groups (p=0.15).	25 events associated with breast cancer: AXD n=15 SNB n=10 P=0.26	AXD SNB Axilla 2 0 Supracl 0 0

Evidence from non-randomized studies

Scoring systems

A study (Pinkney *et al* 2007) validating a clinico-pathological score for patient selection for minimally invasive axillary surgery, suggested it may be possible to avoid a second axillary procedure in a large majority of patients. The sensitivity was 90% and specificity 64%, however the sample was small (n=99).

A similar larger retrospective study that used a nomogram for patient selection (Park *et al* 2007) and followed the trend in treatment options suggested that ALND could be omitted for a low-risk subset of SLN-positive patients.

Other non-randomized studies

The findings of the remaining NRS are reported in the associated table. Node metastases are classified and recurrences are reported where available. The findings can be grouped into those studies that recommend omission of axillary dissection when only micrometastases are found in the SN, those that recommend axillary dissection for all patients with positive SN, and those where a particular subgroup may avoid dissection.

Studies suggesting that axillary dissection could be avoided in patients with micrometastases in sentinel nodes were:

Naik *et al* 2004, Gipponi *et al* 2006, Langer *et al* 2005.

Naik *et al* (2004) suggested that there may be a subgroup of patients where axillary dissection is not required.

The study by Ganaraj *et al* (2003) suggests patients with micrometastases and ductal carcinoma may be spared axillary dissection, but those with lobular carcinoma still require axillary dissection.

Viale *et al* (2001) suggests that patients with micrometastases of less than 1mm may avoid axillary dissection, but trial data is required.

The study by Guenther *et al* (2003) recommends trials for evaluation of axillary dissection in patients with positive SNBs.

Studies that recommended axillary dissection for node positive metastases were:

Giard *et al* (2004) concluded that it is necessary to perform axillary clearance when the SNB contains micrometastatic disease, whatever the size or detection method of the metastasis.

Katz *et al* (2006) recommends that completion axillary dissection be performed for any subgroup of patients with +SLNs.

A retrospective case series by Samoilova *et al* (2007) predicted that the variable that most reliably separated N1a from N2-3 patients was the size of the tumour deposits in the sentinel node ($P < .001$). All patients with sentinel node tumour deposits ≤ 5 mm had three or fewer positive nodes; 95% were sentinel node-positive only, and 91% had single-node involvement. The presence of lymphovascular invasion in the primary tumour was statistically significantly different between N1a and N2-3 patients ($P < 0.025$) and the

presence of extracapsular extension of tumour in the sentinel node was also statistically significantly different between N1a and N2-3 patients ($P < 0.01$)

Table 3.3.2 Node metastases and involved nodes

Study (N of participants)	Intervention	Classification of metastases	Node involvement	Recurrence
RCTs				
Chetty 2000 Ax clearance n=232 Ax sample n=234 Quality 1+	Axillary clearance vs axillary sampling + RT if node positive	Not reported	pNode positive: Ax CI n=78 (34%) Ax sample n=66 (28%) Axillary nodes: Ax CI median 15 (4-36) Ax sample median 5 (2-12)	
Forrest 1995 Ax Clearance n=208 Ax sampling n=209 Quality 1+	Axillary clearance vs axillary sampling + RT if node positive	Not reported	pNode positive: Ax CI n=80 (39%) Ax sample n=88 (43%) Axillary nodes: Ax CI mean = 20 Median 20 (5-46) Ax sample mean = 6 Median 4 (0-19)	
Veronesi 2003 AXD n=257 SNB n=259 Quality 1+	Total axillary dissection after positive SNB (AXD) vs AXD only in SNB +ve patients (SNB) All had breast RT	AXD 29/257 had micrometastases (<2mm) (11.3%) SNB 31/259 had micrometastases (11.9%)	pNode positive: AXD n=91 (35.4%) SNB n=92 (35.5% 95%CI 29.7-41.7)	

NRS				
<p>Ganaraj 2003</p> <p>N=305</p> <p>Quality 3</p>	<p>305 SLNB</p> <p>84 (28%) with metastatic disease</p> <p>All patients offered completion AXD</p>	<p>41/84 (49%) micrometastases</p> <p>43/84 (51%) macrometastases</p>	<p>84 patients had positive SNLB</p> <p>14 patients with macrometastases had additional nodes.</p> <p>2 patients with micrometastases had additional nodes</p>	<p>No axillary recurrences at 30 months in the 17 patients who refused axillary dissection.</p>
<p>Giard 2004</p> <p>N=116</p> <p>Quality 3</p>	<p>525 detected SNs</p> <p>Patients with a metastasis were offered axillary clearance.</p> <p>Patients with a negative SNB had no lymphadenectomy.</p>	<p>87/525 (16.6%) positive SN had macrometastases</p> <p>55/525 (10.5%) positive SN had micrometastases.</p>	<p>Mean number SN removed in patients with micrometastases = 1.9 (range 1-4)</p> <p>15% (6/40) of patients with micrometastatic SN had a positive Axillary Clearance</p> <p>SNs were not found in 17 cases and 8 of these axillary clearances were positive.</p>	
<p>Gipponi 2006</p> <p>N=116</p> <p>Quality 3</p>	<p>Axillary lymph node dissection for early stage breast cancer (T1-2,N0,M0).</p>	<p>Size of SN micrometastases</p> <p>≤1 mm n=26</p> <p>1.01-2mm n=90</p>	<p>Mean number SN examined /patient = 2 (range, 1–6: SD 1.2)</p> <p>Mean number non-SN examined = 12.6 (range, 6–29: SD 5.0).</p> <p>No of tumour positive SN</p> <p>1 n=110</p> <p>>1 n=6</p> <p>16/116 (13.7%)</p>	

			<p>with SN micrometastases had tumour involvement of the nonSN. (6 had nonSN micrometastases 10 had nonSN macrometastases)</p> <p>All 15 patients with Grade 1 tumours and SN micrometastases had negative non-SNs. All 19 patients with tumours <10mm had negative non-SNs.</p>	
<p>Guenther (2003)</p> <p>N=46</p> <p>Quality 3</p>	<p>BCS or total mastectomy, then breast irradiation if positive SN detected. No RT to regional nodes.</p> <p>No ALND.</p>	<p>7/46 (15%) had macrometastases (>2 mm)</p> <p>16/46 (35%) had micrometastases (<2 mm)</p> <p>23/46 (50%) had clustered or cellular metastases</p>	<p>Mean 2.6 SNs (median, 2; range, 1-7)</p> <p>39/46 patients (85%) single positive SN</p> <p>7/46 patients (15%) 2 positive SNs</p>	<p>No axillary recurrences during mean follow-up of 32 months (range 4-61)</p>
<p>Langer (2005)</p> <p>N=236</p> <p>N=27 with micrometastases</p> <p>Quality 3</p>	<p>SNB then patients with SLN macrometastases had level I and II ALND. Patients with SLN micrometastases and tumour-free SLN did not have ALND.</p>	<p>33% (74/224) SLN macrometastases</p> <p>12% (27/224) micrometastases (>0.2 mm to <or=2 mm)</p>	<p>SLN alone (n=150):</p> <p>Mean SLN/pt= 2.1 (1-9)</p> <p>SLN+ALND (n=74):</p> <p>Mean SLN/pt= 2.1 (1-8)</p> <p>Mean non-SLN/pt=17 (2-32)</p>	<p>No axillary recurrences in patients with SLN micrometastases at 42 months.</p> <p>Axillary recurrence in subset with negative SLN 0.8% (1/122)</p> <p>Recurrence in patients with SLN micrometastases 0% (0/27).</p>

				<p>Recurrence in patients with SLN macrometastases 1.4% (1/73).</p> <p>10 local recurrences occurred in the breast, and 2 in the axilla.</p>
<p>Katz 2006</p> <p>N=246 with +SLN and AXD</p> <p>Quality 3</p>	<p>SNB then completion axillary dissection for +SLNs</p>	<p>Micrometastases 71/367 (19%) +SLN procedures. Macrometastases 292/367 (80%) +SLN procedures.</p>	<p>Involved SLNs per patient:</p> <p>1 SLN 26% (63/246)</p> <p>2 SLN 11% (27/246)</p> <p>=>3 SLN 3% (7/246)</p> <p>Involved non-SLNs per patient:</p> <p>1 SLN 9% (21/246)</p> <p>2 SLN 4% (11/246)</p> <p>=>3 SLN 1% (2/246)</p>	
<p>Naik 2004</p> <p>N=4008</p> <p>N=1342 +SNLB</p> <p>Quality 3</p>	<p>SNLB positive patients +/- ALND</p>	<p>Not reported</p>	<p>1132/1342 had +SLN and ALND</p> <p>210/1342 had +SLN and no ALND</p> <p>Median of 2 SLN / patient</p> <p>Range 1-18 for ALND</p> <p>Range 1-8 no ALND</p>	<p>For +SNB at 31 months:</p> <p>4/7 axillary recurrences in ALND group.</p> <p>3/7 axillary recurrences in no ALND group.</p>
<p>Viale 2001</p> <p>N=634</p> <p>N=109 micrometastases</p>	<p>SLNB followed by ALND if nodes were metastatic.</p>	<p>113/164 SLNs had micrometastases.</p> <p>34/113 (30.1%)</p>	<p>109 patients had 164 SLNs removed:</p> <p>Mean = 1.5/patient</p>	

<p>es</p> <p>Quality 3</p>		<p>had multiple micrometastases.</p> <p>Additional non-SLN metastases were found in 24/110 (21.8%) dissections.</p>	<p>(range 1-6).</p> <p>2388 axillary non-SLNs were obtained: Mean 22 lymph nodes \pm 7 per patient</p>	
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Evidence Tables

Randomized controlled trials

EORTC Intergroup Study. After mapping of the axilla: radiotherapy or surgery? AMAROS 13079. 2007. Report No.: EORTC 10981-22023.

Design: RCT EORTC trial
Ongoing from 2001
Country: Europe, setting: Multicentre

Aim: To prove equivalent local/regional control for patients with proven axillary lymph node metastasis by sentinel node biopsy with reduced morbidity if treated with axillary radiotherapy instead of axillary lymph node dissection. A second objective is to investigate whether adequate axillary control can be obtained by not subjecting patients with a negative sentinel lymph node to axillary lymph node dissection.

Inclusion criteria :

- Histologically or cytologically proven invasive breast cancer
- Tumour larger than 5mm and smaller than 30 mm at largest diameter
- Clinically negative axillary lymph nodes
- No previous treatment of the axilla

Exclusion criteria

Population number of patients = 3485

Interventions

After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) is an international, multicentre, phase III study comparing a complete axillary lymph node dissection with radiotherapy to the axilla in sentinel biopsy positive patients. Sentinel node negative patients are also followed for the end-points of the study. The involved patients have an operable invasive breast cancer of over 5 mm and less than 3 centimeters, without clinically suspect regional lymph nodes. Patients will have FNA or core biopsy proven unifocal invasive breast cancer and should be fit to undergo either treatments. Patients are stratified by institution and type of breast surgery and randomized between complete axillary lymph node dissection and radiotherapy of the axilla. Sentinel node biopsies are performed by a combined technique using preoperative lymphoscintigraphy by intra- or peritumoural injection of a radioactive tracer, immediate preoperative injection of a dye. Followed by SN-retrieval by both discoloration and intra-operative use of a detection probe.

Randomization takes place before the sentinel node procedure. The patient knows before surgery whether she will have a complete axillary dissection or radiotherapy if the sentinel node(s) is (are) tumour positive on frozen section or definitive histology.

Outcomes

Axillary recurrence

Overall survival

Disease free survival

Follow up**Results**

Ongoing

General comments -

Chetty U, Jack W, Prescott RJ, Tyler C, Rodger A. Management of the axilla in operable breast cancer treated by breast conservation: A randomized clinical trial. Br J Surg 2000;87(2):163-9.

Design: RCT (1987-1995)

Level 1+

Country: Scotland, setting: Not clear whether single or multicentre

Aim: To compare the efficacy of different surgical approaches (axillary node sample or node clearance) in patients with operable breast cancer treated by breast conservation, and to assess morbidity associated with these procedures and radiotherapy (RT).

Inclusion criteria

Age < 70 years

Unilateral invasive breast cancer

Clinical size 4cm or less

No evidence of metastatic disease

Exclusion criteria

Clinically multicentric tumour

Locally inoperable (T4)

Axillary nodes fixed (N2)

History of invasive carcinoma at any site (exception skin basal cell carcinoma)

Population number of patients = 466

Median age 54 years

Premenopausal n=170 (36%)

Perimenopausal n=12 (3%)

Post menopausal n=283 (61%)

Pathological tumour size:

≤ 1cm n=59 (13%)

> 1 ≤ 2cm n=209 (45%)

> 2 ≤ 3cm n=104 (22%)

> 3 cm n=103 (22%)

Node negative n=319 (68%)

Node positive n=144 (31%)

Interventions

Randomization by permuted blocks of eight to axillary clearance (n=232) or axillary node sample (n=234).

Arm 1) Axillary node sampling technique was to obtain at least 4 palpable axillary lymph nodes.

Arm 2) A level III axillary clearance was performed.

Postoperative RT to the breast with paired tangential fields was delivered to all patients (45Gy in 20 fractions over 4 weeks), and a boost to the tumour bed.

Patients receiving axillary clearance did not receive RT to the axilla.
 Patients receiving axillary sampling that revealed involved nodes received RT to the axilla.
 Patients receiving axillary sampling with no involved nodes did not receive RT to the axilla.
 (Between 1987-1990 the policy was to treat all patients with axillary RT after axillary sampling, consequently 39 patients with negative nodes received axillary RT).

The regional lymph nodes were treated by direct anterior field to the axilla and supraclavicular fossa, and a posterior axillary boost. The dose was 45Gy in 20 fractions over 4 weeks.

Outcomes

Overall survival
 DFS
 Locoregional recurrence
 Morbidity

Follow up Median 4.1 years

Results

Intention-to-treat analysis was conducted for assessment of recurrence and survival.
 Of 466 randomized, 4 patients had benign disease and 8 a non-invasive cancer.
 29 patients did not receive their allocated option.

Survival

No statistically significant differences in Overall Survival (Kaplan-Meier, log rank test $p=0.2$) or disease-free survival (Kaplan-Meier, log rank test $p=0.68$).

Estimated 5 year survival rates were:

Axillary sample 88.6% (SE2.5)
 Axillary clearance 82.1% (SE3.1)

44 deaths occurred from breast cancer
 9 deaths were from other causes

Recurrence

There were no differences between the 2 groups in time to axillary recurrence ($p=0.94$) or time to breast recurrence ($p=0.97$).

The sites and number of relapses are shown in the table below.

Site of relapse	Axillary clearance (n=232)	Axillary sample +RT (n=234)
-----------------	----------------------------	-----------------------------

Local:		
Breast	14	15
Regional:		
Axilla	8	7
Supraclavicular fossa	4	2
Axilla + supraclavicular fossa	0	1
Distant	29	29

Author conclusions

A selective policy for the management of the axilla is associated with no increase in axillary recurrence or mortality rate compared with routine axillary node clearance. Patients who are node negative after axillary sample can avoid radiotherapy or axillary clearance.

General comments -

Forrest AP, Everington D, McDonald CC, Steele RJ, Chetty U, Stewart, et al. The Edinburgh randomised trial of axillary sampling or clearance after mastectomy. Br J Surg 1995;82(11):1504-8.

Design: RCT (1980-1983)

Level 1+

Country: Scotland, setting: Single Centre

Aim: The aim of the study was to determine whether a standard 'four-node' axillary sample, followed by careful dissection of removed tissue, could accurately indicate the extent of local treatment required.

Inclusion criteria

Patients fit for surgery and radiotherapy, with clinically operable invasive breast cancer (T1, T2, operable T3, N0, N1, M0).

Exclusion criteria

Patients unlikely to participate in continuous follow-up, those with *in-situ* cancer including Paget's disease of the nipple, and those with multiple, ipsilateral, or contralateral breast cancer.

Population number of patients = 417

209 randomized to treatment by axillary node sampling (50 patients in this group had fewer than 4 nodes sampled)

208 randomized to axillary node clearance

Pathological tumour size:

< 2cm n=181 (45%)

> 2-5cm n=163 (40%)

> 5cm n=9 (2%)

Not known n=53 (13%)

Interventions

Patients were randomized either to a total mastectomy and lower axillary node sampling or to total mastectomy and complete axillary node clearance. The first 282 patients were randomized before operation; the last 135 cases the option was drawn after mastectomy and node sampling, this was extended to full axillary dissection if selected.

Methods for pathological examination of nodes were not described but predate recent techniques.

Radical postoperative 6-MeV radiotherapy was given to 82 of 86 patients with proven metastatic involvement of sampled nodes and to one where no node was identified. RT was delivered to the chest wall, internal mammary node chain, and supraclavicular fossa. RT dose and fractionation were changed during the course of the trial. No patient in the axillary clearance group received radiotherapy.

Outcomes

Survival

Locoregional relapse

Follow up

11 years (range 2-13)

Results

The mean number of nodes identified in the axillary sampling group was 6 (median 4, range 0-19) and in the clearance group 20 (median 20, range 5-46).

The incidence of positive nodes in patients undergoing sampling was no different from that in the full axillary clearance group (43.3%, n=88 and 39.4%, n=80 respectively).

Survival

There were 147 (35%) deaths.

71 deaths in the RT/node sampling group (breast cancer deaths n=57)

78 deaths in the axillary clearance group (breast cancer deaths n=54)

Kaplan-Meier Hazard Ratio 1.11 (95% CI 0.80-1.53) – not significant.

Locoregional relapse

The hazard ratio for axillary node sampling was 1.35 (95% CI 0.83-2.19) – not significant (reference axillary clearance)

Sites of locoregional relapse are shown in the table below.

There was an increased incidence of chest wall relapse in node positive patients treated by axillary clearance (No RT), but this was not statistically significant (17/80 cleared *versus* 11/88 sampled; Chi² 1.72 > 0.1, P < 0.25).

Site of relapse	Axillary sampling			Axillary clearance		
	Node negative n=115	Node positive (+RT) n=88	Total n=203	Node negative n=123	Node positive n=80	Total n=203
Chest wall	8 (7.0%)	11 (12%)	19 (9.4%)	9 (7.3%)	17 (21%)	26 (12.8%)
Axilla	5 (4.3%)	6 (7%)	11 (5.4%)	3 (2.4%)	3 (4%)	6 (3.0%)
Supraclavicular	4 (3.5%)	8 (9%)	12 (5.9%)	6 (4.9%)	9 (11%)	15 (7.4%)
Any locoregional recurrence	12 (10.4%)	17 (19%)	29 (14.3%)	14 (12.2%)	23 (29%)	38 (18.7%)

Author conclusions

There was only a minor difference in axillary relapse, favouring axillary clearance (3.0% versus 5.4%). In patients with operable breast cancer, mastectomy with axillary node sampling gives equal control to mastectomy with axillary node

clearance but, as morbidity is greater, surgical clearance of the axilla is the preferred option.

General comments -

Veronesi U, Paganelli G, Viale G, et al. A Randomized Comparison of Sentinel-Node Biopsy with Routine Axillary Dissection in Breast Cancer N Engl J Med, Volume 349(6).August 7, 2003.546-553.

Design: RCT (1998-1999)

Level 1+

Country: Italy, setting: Single setting

Inclusion criteria

Patients with primary invasive breast cancer, no history of another cancer, and a tumour \leq 2cm in diameter.

Exclusion criteria

Patients with a multicentric cancer or had previously undergone excisional biopsy.

Population number of patients = 649 enrolled, 532 randomized, 516 evaluable.

SNB and total axillary dissection n=257

SNB and axillary dissection if node +ve n= 259

Age range 40-75 years.

Tumour size:

< 1cm n=130 (25%)

1.1-1.5cm n=243 (47%)

> 1.5cm n=143 (28%)

Interventions

All patients had breast conserving surgery (BCS) and were then randomized (on detection of a sentinel node by the gamma probe) to either SNB and total axillary dissection or SNB and axillary dissection only in patients with metastases in the sentinel node.

SNB was performed using radioactive colloid and lymphoscintigraphy for injection and a gamma probe for detection.

Sentinel nodes were examined by frozen section, staining was performed with haemotoxylin and eosin, cytokeratin was used when results were ambiguous.

All patients received breast irradiation and a boost to the surgical scar.

Outcomes

Sensitivity and specificity of SNB

Survival

Locoregional recurrence

Distant metastases

Follow up Median 46 months

Results

Sensitivity of SNB = 91.2%

Specificity of SNB = 100%
Negative predictive value 95.4% (95% CI 91.1-98)

A total of 429 sentinel nodes were removed from 257 patients having axillary dissection (mean 1.7 nodes / patient).

A total of 424 sentinel nodes were removed from 259 patients having SNB (mean 1.6 nodes / patient).

Mean number of 24 non-SLN were removed from each group.

92/259 (35.5% 95%CI 29.7-41.7) of sentinel node group had a positive sentinel node and underwent axillary dissection.

91/257 (35.4%) of the axillary dissection group had axillary metastases. 83/91 (96.9%) of these had a positive SNB (83/257; 32.3% 95% CI 26.6-38.4).

60/175 patients with a positive sentinel node had micrometastases only (\leq 2mm).

10/60 (17%) of these patients had another positive axillary node.

Axillary dissection group n=29 with micrometastases. In 24 of these patients all other axillary nodes were negative, 5 patients had one other positive node.

Sentinel node group n= 31 with micrometastases. In 26 of these patients all other nodes were negative, in 5 patients one other node was positive.

Survival

6 deaths in axillary dissection group and 2 in the sentinel node group. There was no statistically significant difference between groups in the rate of overall survival over 60 months ($p=0.15$).

Recurrence

Number of events:

21 in axillary dissection group and 13 in the sentinel node group ($p=0.13$).

25 events were associated with breast cancer: 15 in axillary dissection group, 10 in sentinel node group.

Cumulative incidence of breast cancer events (recurrence in ipsilateral breast, tumour in contralateral breast, distant metastases) were not statistically significantly different between groups ($p=0.26$).

These findings are shown in the table below:

Event	Axillary dissection group n=257	Sentinel node group n=259
Axillary metastases	2	0
Supraclavicular	0	0

metastases		
Recurrence in ipsilateral breast	1	1
Cancer in contralateral breast	2	3
Distant metastases	10	6
Other primary tumour	6	3
Total	21	13
Death from breast cancer	2	1
Death from other causes	4	1
General comments -		

Observational Studies (eg. Prospective Cohort or Retrospective Cohort or Case Series):

Scoring systems

Pinkney TD, Nightingale P, Carmichael AR. A prospective study of use of a clinicopathological score to select patients for the type of axillary surgery. Eur J Surg Oncol 2007;33(2):153-6.

Design: NRS consecutive series
 Level 3
 Country:UK, setting: Single hospital

Aim: To prospectively assess a previously described and independently validated clinicopathological score for counselling and selecting patients for sentinel node biopsy or axillary clearance.

Inclusion criteria Patients presenting with breast cancer

Exclusion criteria

Population number of patients = 99

Interventions

Based on a previously validated clinicopathological score, patients with a score of 10 or below were classed as less likely to have positive lymph nodes and hence were offered for minimally invasive axillary surgery and patients with a score of 11 or above were regarded to have high risk of nodal involvement and were counselled for axillary clearance.

Score	0	1	2	3	4
Age years		>60	40-60	<40	
Palpable		No	Yes		
Grade		1		2-3	
Size mm		0.1-10	11-19	20-40	>40
Lymphovascular invasion	No				
Quadrant		Inner	Outer		

31 patients were classified as low score (10 or less)
 43 patients were classified as high score (11 or more)

Outcomes

Predictive values

ROC

Sensitivity

Follow up

Results

Exclusions n=25

Lowest score was 6, highest score 16.

True positive n=27

True negative n=28

False positive n=16

False negative n=3

3 /31 (10%) patients in the low score group had axillary metastasis and needed further axillary treatment (Negative predictive value = 90%).

27/43 (63%) underwent axillary clearance for a high score and had positive axillary nodes (positive predictive value = 63%)

From this data the sensitivity and specificity of the scoring system with a cut-off value of ≥ 11 as the indicator for axillary dissection are:

Sensitivity = $27/30 = 90\%$

Specificity = $28/44 = 64\%$

An ROC curve found the Area Under the Curve (AUC) to be 0.83 (95% CI 0.74-0.93). This was better than tumour size only (AUC 0.72) or size and grade of tumour (AUC 0.71).

Author Conclusions: Until preoperative axillary staging becomes widely available, by using the clinico-pathological score for patient's selection for minimally invasive axillary surgery, it may be possible to avoid a second axillary procedure in a large majority of patients.

General comments -

Park J, Fey JV, Naik AM, Borgen PI, Van Zee KJ, Cody III HS. A declining rate of completion axillary dissection in sentinel lymph node-positive breast cancer patients is associated with the use of a multivariate nomogram. *Ann Surg* 2007;245(3):462-8.

Design: NRS (Consecutive retrospective) (1997-2004)
Level 3

Country: USA, setting: Single Cancer Centre

Aim: To compare sentinel lymph node (SLN)-positive breast cancer patients who had completion axillary dissection (ALND) with those who did not, with particular attention to clinicopathologic features, nomogram scores, rates of axillary local recurrence (LR), and changes in treatment pattern over time.

Inclusion criteria

SLN positive patients on the MSKCC database.

Exclusion criteria

Planned “backup” ALND

Failed mapping

Nonmalignant lesions, nonmammary cancers, pure ductal carcinoma in situ, inflammatory cancer, bilateral cancers

Prophylactic mastectomy, nonaxillary SLN, and male breast cancer

Population number of patients = 1673 SLN positive

1673 (85%) had SLN +ALND

287 (15%) had SLN no ALND

Interventions

SLN biopsy included a radioisotope and blue dye combination.

Intraoperative and final pathological examination of frozen sections

(intraoperative) and by immunohistochemical (IHC) anticytokeratin staining (FS negative).

Outcomes

Axillary local recurrence (LR)

Follow up Median 23 months (6-87) SLN+/ no ALND

Median 30 months (6-93) SLN+/ ALND

Results

Patients in the SLN+/no ALND group were significantly older, more likely to have breast conservation, and had more favourable tumour types. Tumour size was smaller, low grade lesions were more frequent, and both LVI and multicentricity were less frequent.

The distribution of nodes removed and number of positive nodes are shown below:

	SLN+ / no ALND n=287 (%)	SLN+/ALND n=1673 (%)
SLN excised		
1	48 (17)	395 (24)
2	77 (27)	438 (26)
3	47 (16)	341 (20)
>3	115 (40)	499 (30)
Non-SLN excised		
0	149 (52)	3 (0.2)
1-3	97 (34)	22 (1.3)
4-9	35 (12)	213 (12.7)
≥10	6 (2)	1435 (85.8)
Total nodes excised		
1-3	122 (43)	4 (0.2)
4-9	121 (42)	68 (4.1)
≥10	44 (15)	1601 (95.7)
Positive SLN		
1	258 (89.9)	1211 (72)
2	23 (8)	336 (20)
3	4 (1.4)	82 (5)
>3	2 (0.7)	44 (3)
Positive non-SLN		
0	279 (97)	1029 (62)
1-3	8 (3)	410 (25)
4-9	0 (0)	142 (8)
≥10	0 (0)	92 (5)
Total positive nodes		
1-3	283 (99)	1308 (78)

4-9	4 (1)	253 (15)
≥10	0 (0)	112 (7)

SLN = sentinel lymph node
ALND = axillary lymph node dissection
NonSLN = nonsentinel lymph node

The proportion of SLN excised was similar between groups, however the extent of involved nodes was greater in the SLN+/ALND group.

Twelve patients developed axillary local recurrence (LR), 6 in the SLN+/ALND group and 6 in the SLN+/no ALND group. The rate was marginally higher in the SLN+/no ALND group (2% vs. 0.4%, P = 0.004) at a median 23 to 30 months follow-up. Half of all axillary LR in SLN+/no ALND patients were coincident with other local or distant sites. The pattern of local relapse are shown in the table below:

Intervention	Axillary LR as first event	Axillary LR coincident with breast recurrence	Axillary LR coincident with distant recurrence	Axillary LR overall
SLN+/no ALND N= 287	1% (3)	0.7% (2)	0.3% (1)	2% (6)
SLN+/ALND N=1673	0.2% (3)	0.2% (3)	0%	0.4% (6)
P	<0.044	NS	NS	0.004

There was no consistent pattern of clinicopathologic features in the 12 patients developing axillary LR. Lymphovascular invasion was present in all 6 patients who had SLN+/ALND. Among the SLN+/no ALND group, 15% of patients with complete follow-up (41 of 269) received additional radiotherapy to the axilla and/or supraclavicular nodes. None of the 6 patients with axillary local recurrence in this group received axillary and/or supraclavicular radiotherapy.

Author conclusions: SLN+/no ALND breast cancer patients, a selected group with relatively favourable disease characteristics, had a 9% predicted likelihood of residual axillary disease by nomogram but an observed axillary LR of 2%. A gradual and significant decline over time in the rate of completion ALND is associated with, but not entirely explained by, the institution of a predictive nomogram. It is reasonable to omit ALND for a low-risk subset of SLN-positive patients.

General comments –

This study overlaps with an earlier study by Naik (2004) which is also an analysis of the MSKCC database.

Prospective NRS

Giard S, Baranzelli MC, Robert D, Chauvet MP, Robin YM, Cabaret V, et al. Surgical implications of sentinel node with micrometastatic disease in invasive breast cancer. Eur J Surg Oncol 2004 Nov;30(9):924-9.

Design: NRS prospective (2001-2003)

Level 3

Country: France setting:

Aim: To assess the rate of positive axillary clearance (AC) when the sentinel node biopsy (SNB) contains micrometastatic disease in invasive breast cancer and to evaluate factors that could predict positivity.

Inclusion criteria

Patients with a unifocal invasive breast cancer (histological diagnosis by previous percutaneous biopsies), T0- T1 (<20 mm on ultrasound measurement) N0 M0 with no previous treatment.

Exclusion criteria

Population number of patients = 542 SLN procedures

Interventions

A combined technique of patent blue dye and radio-colloid with a peritumoral injection for palpable lesions (217/542, 40%) and a sub-areolar injection for non-palpable lesions.

Patients with a N0 detected SN or a positive SNB at intraoperative examination had immediate complementary AC.

Patients with a negative SNB had no lymphadenectomy.

Patients with a metastasis in the final histological report had an axillary clearance.

Outcomes

Characteristics of micrometastatic disease

Characteristics of complementary axillary clearance

(Definitions: micrometastasis UICC, size 2mm or less

Isolated cells UICC, single tumour cells or small clusters 0.2mm or less)

Follow up

Results

525 sentinel nodes (SN) were found, 142 contained metastases.

87 positive SN were macrometastatic.

55 of the positive SN contained micrometastatic disease only (44 true micrometastases, 6 had isolated cells).

40/55 patients with micrometastases underwent completion AC.

6/40 (15%) patients with micrometastatic SN had a positive AC (5 had micrometastasis

between 0.2 and 2 mm (5/6), one had isolated cells in the SN (1/6). Four of the AC had 1 involved node, and 2 ACs had 2 involved nodes.

SNs were not found in 17 cases and 8 of these axillary clearances were positive.

A univariate analysis of tumour and patient factors [age (< or > 50 years), histological tumour size (< or > 5mm), histological grade, estradiol receptor (ER), histological tumour type, size and method of micrometastasis detection] did not significantly predict the status of the AC.

The authors also showed that the frequency of micrometastases increased with pathological tumour size as shown in the table from the paper below:

Pathological Tumour (mm)	No detected SN	%SN+	%SN+ macrometastatic	%SN+ micrometastatic	SN micro/SN+
0-0.99	141	9.9	2.8	7.1	71.4
10-14.9	179	22.3	15.1	7.3	32.5
15-19.9	112	31.2	21.4	9.8	31.4
20-24.9	62	54.8	30.6	24.2	44.1
25-29.9	31	61.3	41.9	19.4	31.6

Author conclusions: As long as the results of ongoing prospective randomised studies are unknown, it remains necessary to perform AC when the SNB contains micrometastatic disease, whatever the size or the detection method of the metastasis.

General comments –

Gipponi M, Canavese G, Lionetto R, Catturich A, Vecchio C, Sapino A, et al. The role of axillary lymph node dissection in breast cancer patients with sentinel lymph node micrometastases. *Eur J Surg Oncol* 2006 Mar;32(2):143-7.

Design: NRS prospective (1998-2004)

Level 3

Country: Italy, setting: Two oncology centres

Aim: To identify by means of clinical and histopathological features a subset of breast cancer patients with sentinel lymph-node (sN) micrometastases and metastatic disease confined only to the sN in order to spare them an unnecessary axillary lymph node dissection (ALND).

Inclusion criteria

Patients with early-stage (T1–2 N0 M0), invasive breast cancer who underwent sN biopsy and ALND, with histologically detected micrometastases (0.2mm-2.0mm).

Solitary nodule < 3cm (echography)

Clinically N0

Exclusion criteria

Previous breast or axillary operations

Multifocal or locally advanced breast cancer

Pregnancy

Population number of patients = 116

Mean age 61 years (24-84)

Primary tumour size:

≤10 mm n=19

11-20 mm n=66

>20 mm n=31

Size of SN micrometastases

≤1 mm n=26

1.01-2mm n=90

No of tumour positive SN

1 n=110

>1 n=6

Interventions

SNB procedure involved breast lymphoscintigraphy 16-18 hours before surgery using radioactive colloid and detection with a gamma probe.

Pathological staging was by the UICC TNM classification.

SNB samples were examined by frozen section and stained with haematoxylin-eosin, and if negative stained with keratin antibodies.

Outcomes

Tumour involvement of the non-SN in patients with SN micrometastases.

Follow up

Results

Median primary tumour size 16mm

Mean primary tumour size 17mm

Mean number of SN examined per patient = 2 (range, 1–6: SD, 1.2)

Mean number of non-SN examined = 12.6 (range, 6–29: SD, 5.0).

16/116 (13.7%; 95% CI 8-22%) with SN micrometastases had tumour involvement of the non-SN.

6 had non-SN micrometastases

10 had non-SN macrometastases

Mean tumour size in patients with non-SN involvement was 21.3 mm (range, 12–38 mm).

All 15 patients with Grade 1 tumours and SN micrometastases had negative non-SNs.

All 19 patients with tumours <10mm had negative non-SNs.

On multivariate logistic regression analysis primary tumour size ($P=0.011$), lymphovascular invasion ($P=0.001$), and size of SN micrometastases were the only variables remaining in the model (the latter was not significant).

An odds ratio for metastasis in a non-SN was 8 times higher for patients with a lymphovascular invasion, 6 times higher for patients with a primary tumour diameter over 16 mm, and 5 times higher for patients with a micrometastasis diameter of greater than 1 mm. (OR test values not reported).

Author conclusions

In patients with SN micrometastases, primary tumour size and lymphovascular invasion significantly predict non-SN status; notably, no patient with T1a-T1b and/or Grade 1 tumours had non-SN metastases so that they could be spared an unnecessary ALND.

General comments –

This is an incidence study, the effects of further treatments were not reported. Although described as a prospective study, the records were reviewed retrospectively.

Guenther JM, Hansen NM, DiFronzo LA, Giuliano AE, Collins JC, Grube BL, et al. Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes.[see comment]. Arch Surg 2003 Jan;138(1):52-6.

Design: NRS prospective (1996-2001) Level 3

Country: USA, setting: 2 hospital breast centres

Aim: To assess the value of axillary lymph node dissection (ALND) in patients with positive sentinel node metastases.

Inclusion criteria

Women with positive SN metastases who refused ALND or were recommended to omit ALND due to serious comorbid conditions.

Exclusion criteria

Not reported

Population number of patients = 46

Mean patient age was 61.6 years (age range, 36-92 years).

Mean tumour size was 1.65 cm (range, 0.4-5.5 cm).

Interventions

Lymphatic mapping was performed using isosulfan blue dye, no radioisotopes were used. All blue stained nodes were removed, and the remainder of the axilla inspected and palpated to exclude suspicious non-SNs.

Breast surgery included segmentectomy or total mastectomy.

Patients with positive SNs received adjuvant therapy and breast irradiation.

Axillary, internal mammary and supraclavicular fields were not used with one exception (received supraclavicular RT).

Outcomes

Axillary recurrence

Follow up Mean 32-month follow-up, (range 4-61)

Results

35 (76%) of 46 tumours were ductal carcinomas

39 (87%) of 45 were estrogen receptor-positive

A mean of 2.6 SNs were identified (median, 2; range, 1-7)

39/46 patients (85%) had a single positive SN

7/46 patients (15%) had 2 positive SNs

7/46 (15%) had macrometastases (>2 mm)

16/46 (35%) had micrometastases (<2 mm)

23/46 (50%) had clustered or cellular metastases (IHC staining)

There were no axillary recurrences during the follow-up period.

One patient (ER progesterone -ve, T1c tumour and 2 SN metastases) developed distant metastases during follow-up.

Author conclusions:

Patients with SN metastases who did not have ALND had a low incidence of regional failure. To confirm this observation, we suggest that patients with SN metastases are ideal candidates for trials evaluating the necessity of ALND.

Langer I, Marti WR, Guller U, Moch H, Harder F, Oertli D, et al. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: prospective analysis of 150 patients after SLN biopsy. *Ann Surg* 2005 Jan;241(1):152-8.

Design: NRS Prospective (1998-2002)

Level 3

Country: Switzerland, setting: single centre

Aim: To evaluate midterm follow-up data, focusing on axillary recurrences and outcome of breast cancer patients with negative SLN and SLN micrometastases undergoing SLN biopsy only.

Inclusion criteria

Palpable breast cancer

Tumour size \leq 3cm

Absence of clinically palpable axillary nodes

Exclusion criteria

None reported

Population number of patients = 234 patients (236 SLN procedures)

224 mappings

SLN alone n=150

SLN and ALND n=74

T stage	SLN alone	SLN and ALND	
T1a	8 (5.3%)	1 (1.3%)	p<0.0001
T1b	24 (16%)	2 (2.7%)	
T1c	76 (50.7%)	24 (32.4%)	
T2	39 (26%)	40 (54.1%)	
T3	0 (0%)	3 (4.1%)	
T4	3 (2%)	4 (5.4%)	

Interventions

SNB procedure involved breast lymphoscintigraphy using radioactive colloid and blue dye, then detection with a gamma probe. All hot and/or blue lymph nodes were excised and labeled separately as SLNs.

Frozen sections were examined intraoperatively and stained with haematoxylin and eosin.

Negative SLNs were assessed using cytokeratin antibodies.

Patients with SLN macrometastases immediately underwent level I and II ALND. Conversely, no ALND was performed in patients with SLN micrometastases and tumour-free SLN.

Definitions:

Micrometastases (AJCC classification) diameter $>0.2 \leq 2$ mm.

Submicrometastases ≤ 0.2 mm were considered node negative.

Outcomes

Deaths

Recurrence

Follow up Median 42 months (12-64)

Results

Mean age was 59.9 (± 11.7) years in the SLN alone group (n=150), and 63.5 (± 12.0) years in the SLN and ALND group (n=74) (p=0.008).

Mean tumour size was 16.5 (± 11.2 mm) for the SLN alone group and 26.9 (± 11.7) mm for the SLN and ALND group (p<0.0001).

Number of SLN/ patient:

	SLN alone (n=150)	SLN and ALND (n=74)
Mean	2.07 \pm 1.4	2.14 \pm 1.4
Range	(1-9)	(1-8)

Number of non-SLN/ patient:

Mean	17 \pm 5.8
Range	(2-32)

SLN macrometastases were found in 33% (74/224) and micrometastases (>0.2 mm to ≤ 2 mm) in 12% (27/224) of patients.

99% (222/224) of evaluable patients were reassessed.

There were 11 deaths, 5 of these were due to metastatic disease.

One patient with a negative SLN developed axillary recurrence (0.7%, 1/122)

All 27 patients with SLN micrometastases were disease-free at the last follow-up control.

10 local recurrences occurred in the breast, and 2 in the axilla.

Characteristics of the treatment and tumour of the one recurrence in the ALND group were:

Age 60 years, postmenopausal, mastectomy, SLN biopsy, and formal ALND for a pT2 invasive, poorly differentiated lobular carcinoma, estrogen and progesterone-receptor positive, with a tumour size of 25 mm. The SLN contained a macrometastasis, and another 14 out of 23 axillary lymph nodes were involved.

Postoperative adjuvant therapy consisted of a combination of tamoxifen and chemotherapy. No radiotherapy was applied.

The second axillary recurrence was in a 47-year-old premenopausal woman who had a tumorectomy and SLN biopsy only for a pT2 invasive, moderately differentiated lobular carcinoma, estrogen- and progesterone-receptor positive, with a tumour size of 41 mm and a tumour-free SLN.

Postoperative radiotherapy to the breast and tamoxifen plus chemotherapy

were administered. The axillary lymph node metastases, as well as the remaining level I and II lymph nodes, were then removed.

None of the patients with SLN micrometastases developed axillary recurrences.

Axillary recurrence rate in the subset with negative SLN was 0.8% (1/122), in patients with SLN micrometastases 0% (0/27), and in patients with SLN macrometastases 1.4% (1/73).

Distant metastases were detected in 10 of 222 patients (4.5%). Seven of those had SLN macrometastases. Three SLN-negative patients developed distant metastases.

OUTCOME OF INTEREST	SLN alone (n=150)	SLN+ALND (n=74)	RESULT
Metastatic disease	2 (1.3%)	9 (12.1%)	P=0.001
Deaths			
Tumour related	1 (0.7%)	4 (5.4%)	P=1.0
Non-tumour related	2 (1.4%)	4 (5.4%)	
Local recurrence			
Breast	6	4	
Axilla	1 (-ve SLNB)	1	

Author conclusions: Axillary recurrences in patients with negative SLN or SLN micrometastases did not occur more frequently after SLN biopsy alone compared with results from the recent literature regarding breast cancer patients undergoing formal ALND. Based on a median follow-up of 42 months-one of the longest so far in the literature-the present investigation does not provide evidence that the presence of SLN micrometastases leads to axillary recurrence or distant disease and supports the theory that formal ALND may be omitted in these patients.

Retrospective NRS

Naik AM, Fey J, Gemignani M, Heerdt A, Montgomery L, Petrek J, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg* 2004 Sep; 240(3):462-8.

Design: NRS Retrospective (1996-2003)

Level 3

Country: USA, setting: Single cancer centre

Aim: To assess the experience of SLN biopsy, with particular emphasis on the incidence and pattern of axillary LR.

Inclusion criteria

Patients undergoing SLN biopsy who were entered into the Memorial Sloan-Kettering Cancer Centre (MSKCC) SLN database. At least one year of follow-up.

Exclusion criteria

- (1) failed SLN mapping
- (2) benign disease (primarily cases of prophylactic mastectomy)
- (3) bilateral breast cancer
- (4) intraductal carcinoma (DCIS)
- (5) inflammatory cancer
- (6) primary breast tumors of non-mammary origin
- (7) incomplete data

Population number of patients = 4008

Mean age across subgroups 53-59 years.

Breast conservation n=2843 (71%)

Mastectomy n=1166 (29%)

Tumour size:

T1ab n=1552 (39%)

T1c n=1657 (41%)

T2 n=700 (17%)

T3 n=47 (1%)

Tx n=52 (1%)

Patients were categorized into 4 groups:

SLN-negative with axillary lymph node dissection (ALND, n = 326)

SLN-negative without ALND (n = 2340)

SLN-positive with ALND (n = 1132)

SLN-positive without ALND (n = 210)

Interventions

SLN mapping with radioisotope and isosulfan blue dye.

Intraoperative and final pathological examination of frozen sections

(intraoperative) and by immunohistochemical (IHC) anticytokeratin staining (FS negative).

ALND defined as removal of at least 10 lymph nodes.

In the SLN-positive without ALND (n = 210) subgroup 149 patients had breast conserving treatment, and 53 (36%) of these also had radiotherapy.

23/53 (43%) had RT to the breast only

30/53 (57%) also received tangential fields to the axilla.

Outcomes

Local recurrences (LR) were categorized as:

(1) axillary LR as the first site of treatment failure

(2) axillary LR coincident with breast LR

(3) axillary LR coincident with distant disease.

Follow up median follow-up of 31 months (range 1-75)

Results

SLN procedure failed in 2.7% of cases.

Number of SLN and non-SLN removed were comparable between the ALND and no-ALND groups.

The distribution of nodes excised is shown in the table below:

	SLN-		SLN+	
	ALND n=326	No ALND n=2340	ALND n=1132	No ALND n=210
No SLN excised	3.0	2.0	2.0	2.0
Median	4.0	2.6	3.1	2.9
Mean	1-23	1-9	1-18	1-8
Range				
No non-SLN excised				
Median	11.0	0.0	17.0	1.0
Mean	12.9	1.0	18.1	1.9
Range	0-57	0-8	0-63	0-8
No total SLN excised				
Median	14.0	3.0	20.0	5.0
Mean	17.0	3.6	21.2	4.8
Range	10-58	1-9	10-65	1-9

Axillary LR occurred in 10/4008 (0.25%) patients overall.

In 3 cases (0.07%) the axillary LR was the first site of treatment failure.

In 4 cases (0.1%) LR was coincident with breast LR.

In 3 cases (0.07%) LR was coincident with distant metastases.

7/1342 (0.5%) axillary recurrences in +SNB patients.

4/7 recurrences in ALND group.

3/7 recurrences in no ALND group.

The authors reported that axillary LR was more frequent among the unconventionally treated SLN-positive/no ALND patients than in the other 3 conventionally treated cohorts (SLN negative/ALND, SLN negative/no ALND, and SLN positive/ALND) [1.4% (n=3) versus 0.18% (n=7), P = 0.013].

None of the subgroup receiving RT (n=53) either to the breast or to the axilla and breast developed an axillary recurrence.

The pattern of axillary recurrence by category is shown in the table:

Procedure	At first event	Coincident with breast recurrence	Coincident with distant recurrence	Total
SNLB-/ALND n=326	0	0	0	0
SNLB-/no ALND n=2340	1 (0.04%)	1 (0.04%)	1 (0.04%)	3 (0.12%)
SNLB+/ALND n=1132	1 (0.09%)	2 (0.18%)	1 (0.09%)	4 (0.35%)
SNLB+/no ALND n=210	1 (0.5%)	1 (0.5%)	1 (0.5%)	3 (1.4%)

A comparison of axillary recurrence rates by type of treatment is shown in the table below:

(conventional treatment:
SLN- with or without ALND
SLN+ with ALND
Unconventional treatment:
SLN+ without ALND)

Axillary local recurrence	Conventional treatment (n=3798)	Unconventional treatment (n=210)	P value
At first event	2	1	NS
Coincident with breast recurrence	3	1	NS
Coincident with distant recurrence	2	1	NS
Total axillary recurrence	7 (0.18%)	3 (1.4%)	0.013

Author conclusions:

Axillary LR after SLN biopsy, with or without ALND, is a rare event, and this

low relapse rate supports wider use of SLN biopsy for breast cancer staging. There is a low-risk subset of SLN-positive patients in whom completion ALND may not be required.

General comments –

Data from SLN negative patients was included for comparison with SLN + patients.

Ganaraj A, Kuhn JA, Jones RC, Grant MD, Andrews VR, Knox SM, et al. Predictors for nonsentinel node involvement in breast cancer patients with micrometastases in the sentinel lymph node. *Baylor University Medical Center Proceedings* 2003 Jan;2003 Jan; 16(1):3-6

Design: NRS retrospective (1997-1999)

Level 3

Country: USA, setting: Single hospital centre

Aim: To correlate size of nodal metastasis and tumour histology as predictors of involvement of non-SLNs based on serial sectioning and IHC of all non-SLNs.

Inclusion criteria

Not reported

Exclusion criteria

Not reported

Population number of patients = 84 of 305 (28%) patients having SLNB had metastases

Median age 53 years (range, 33-83)

Interventions

SLN biopsy then completion axillary dissection

17 patients with micrometastases refused axillary dissection

Outcomes

Follow up 30 months

Results

84/305 positive SLN metastases.

50% of positive patients had T1c tumour.

17 had infiltrating lobular carcinoma

67 had infiltrating ductal carcinoma

Micrometastases

Micrometastases identified in 41/84 (49%)

12 had infiltrating lobular carcinoma - 7 had completion axillary dissection 2 (29%) had additional positive nodes.

29 had infiltrating ductal carcinoma – 17 had completion axillary dissection none had additional positive nodes.

17 patients refused axillary dissection.

Macrometastases

Macrometastases identified in 43/84 (51%)

5 had infiltrating lobular carcinoma – 4 had completion axillary dissection 3 (75%) had additional positive nodes.

38 had infiltrating ductal carcinoma – 35 had completion axillary dissection 11 (31%) had additional positive nodes.

	Infiltrating ductal carcinoma		Infiltrating lobular carcinoma	
	Macrometastases	Micrometastases	Macrometastases	Micrometastases
N of patients	38	29	5	12
N of AXD	35	17	4	7
N additional +ve nodes on H&E staining	11 (31%)	0	3 (75%)	2 (29%)

No axillary recurrences among the 17 with micrometastases who refused axillary dissection.

Author conclusions

These data suggest that patients with micrometastasis in the SLN from infiltrating lobular carcinoma have a significant risk of harbouring additional nodal disease and should undergo completion axillary dissection. However, those with micrometastatic disease from infiltrating ductal carcinoma have a very low incidence of additional metastasis and may not need completion axillary dissection.

Viale G, Maiorano E, Mazzarol G, et al. Histologic detection and Clinical Implications of Micrometastases in Axillary Sentinal Lymph Nodes for Patients with Breast Carcinoma. *Cancer* 2001, 92 (6), 1378-84.

Design: NRS Retrospective (1997-1999) Level 3

Country: Italy, setting: Single centre

Aim: To determine the risk of axillary non-SLNs metastases in patients with micrometastatic SLNs (an additional objective was to assess the detection rate of SLN micrometastases in relation to the sectioning interval and the number of sections examined).

Inclusion criteria

Patients with clinical T1 and small T2N0 breast carcinoma who underwent SLN biopsy.

Exclusion criteria

Population number of patients = 684

366 had immediate ALND

318 were part of a trial (see Veronesi 2003) and were randomized to immediate ALND or to axillary dissection only if the SLN was metastatic.

Interventions

SLNB procedure was described in an earlier publication (Viale 1999).

Sections (adjacent pairs) were stained with H&E or IHC.

Patients with metastatic SLNs had ALND.

Outcomes

Frequency of additional axillary metastases in non-SLNs

Follow up

Results

250 (36.5%) patients had SLN metastases.

Micrometastases

109/250 (43.6%) had micrometastases (included 1 male patient):

Pathological type	Tumour size (cm)	N (%)
pT1a	< 0.5 cm	3 (2.7%)
pT1b	0.6-1.0cm	21 (19.1)
pT1c	1.1-1.5cm	47 (42.7)
pT1c	1.6-2.0	22 (20)
pT2	>2	17 (15.5)

109 patients had 164 SLNs removed (mean 1.5/patient; range 1-6, median 1)
113/164 SLNs had micrometastases (1 patient had 3 micrometastatic SLNs, 1 had 2 micrometastatic SLNs)

34/113 (30.1%) had multiple micrometastases.

12 of 77 dissections (15.6%) in patients with SLN micrometastases ≤ 1 mm had additional metastases in non-SLNs.

12 of 33 dissections (36.4%) in patients with SLN micrometastases > 1 mm had additional metastases in non-SLNs ($P=0.02$).

2388 axillary non-SLNs were obtained:

Mean 22 lymph nodes ± 7 per patient

Median 21 lymph nodes, range 3-49.

Additional non-SLN metastases were found in 24/110 (21.8%) dissections after intraoperative detection of micrometastases (mean 2 metastases; median 1 metastasis; range 1-16 metastases).

6/24 had only micrometastases in the non-SLNs

18/24 had additional metastases > 2 mm in non-SLNs

Macrometastases

141/250 patients had macrometastases (> 2 mm) in SLNs

63/141 (44.7%) had non-SLN metastases.

Author conclusions

Outside of clinical trials, patients with T1 and small T2 breast carcinoma and micrometastatic SLNs should undergo complete ALND for adequate staging. However, patients with SLN micrometastases up to 1 mm in greatest dimension have a significantly lower risk of additional axillary metastases, raising the question of whether ALND may be avoided in this subgroup of patients.

General comments -

Studies from related topic 11

Katz, Niemierko, Gage, Evans, Shaffer, Fleury & Smith . Can axillary dissection be avoided in patients with sentinel lymph node metastasis? J.Surg.Oncol. 93[7], 550-558. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3

Country: USA, setting: Tertiary care

Aim: To identify potential prognostic factors for the involvement of non-SLNs in patients with SLN metastases, and identify a subgroup who may avoid completion axillary dissection.

Inclusion criteria

Patients treated with SLNB between 1998 and 2003.

110 patients had DCIS, out of a larger series of 1133 patients.

307 patients underwent mastectomy and 833 breast conserving surgery. In 8 patients the type of definitive surgery was unknown.

367 patients had disease-positive SNs.

Exclusion criteria

Retrospective study: none reported.

Population

number of patients = 246 with +SLN (367 +SLN procedures), age range 30 to 96 years, median age = 57 years.

Interventions

Retrospective analysis of 1148 SLNB procedures in 1133 patients treated at a single centre and recorded on a pathology database.

All patients underwent SLNB and were found to have positive SNs. 246 patients underwent ALND.

Histology technique:

1. SNs: Frozen section intraoperatively; H&E analysis of 2 levels at 60 micron spacing; IHC performed on all SNs negative on H&E and for all invasive carcinomas.

2. Non-SNs: H&E, 1 level.

Size classification for SN metastases:

<=0.2mm (i+)

0.21-2.0mm (IHC)

<=2.0mm (H&E)
 2.1-4.0mm (H&E)
 4.1-10.0 (H&E)
 >10.0 (H&E)
 Unknown

Outcomes

Node involvement in +SLN and non-SLNs
 Type of metastases.

Follow up

No follow-up reported, study assesses predictive factors for SN and non SN axillary nodal involvement.

Results

367 patients had disease-positive SNs of these 246 (67%) underwent ALND.
 121 patients had involved SNs and did not undergo axillary clearance.
 98/246 (40%) had involved non-SLNs.

Size of the largest SN metastasis ($p < 0.001$) as follows:

Size of largest SN metastasis	n		%
<=0.2mm (i+)	7	1	14%
0.21-2.0mm (IHC)	10	0	0%
<=2.0mm (H&E)	48	11	21%
2.1-4.0mm (H&E)	26	7	30%
4.1-10.0 (H&E)	74	35	55%
>10.0 (H&E)	67	43	59%
Unknown	21	2	25%

Rates of metastases:

Micrometastases

71/367 (19%) +SLN procedures.

Macrometastases

292/367 (80%) +SLN procedures.

Involved SLNs per patient:

1 SLN 26% (63/246)

2 SLN 11% (27/246)

=>3 SLN 3% (7/246)

Involved non-SLNs per patient:

1 SLN 9% (21/246)

2 SLN 4% (11/246)

=>3 SLN 1% (2/246)

Number of involved and uninvolved SLNs in patients who had + SLN and axillary dissection (n=246):

Number of SLNs involved (p=0.05)		
	Non-SLN positivity	%
1	64/180	36
2	27/55	49
=>3	7/11	63
Number of uninvolved SLNs (p<0.001)		
0	64/121	53
1	21/61	34
2	11/33	33
=>3	2/31	6

When tumour size was classified into 2 groups (tumours less than 2cm or greater than 2cm) then patients with >2cm tumours had higher rates of non-SLN involvement than those with tumours <2cm (48% vs. 34%, p=0.02).

Another subgroup with SLN metastases <2.0mm, primary tumour <2.0cm and no LVSI, 14% (4/29) had additional involved non-SLNs on completion axillary dissection.

No subgroup was identified that did not have a significant rate of non-SLN involvement on completion axillary dissection, exceptions were those with a large number of negative SLNs (> or =3) and small size of the largest SLN metastasis (<10 mm).

Author conclusions:

The data does not support eliminating completion axillary dissection for any subgroup of patients with +SLNs.

General comments

Patients with disease-positive SNs underwent ALND or not, at the discretion of the treating surgeon in consultation with the patient.

Expert reviews

Chagpar AB, McMasters KM. Treatment of sentinel node-positive breast cancer. [Review] [59 refs]. Expert Review of Anticancer Therapy 2006 Aug;6(8):1233-9.

This review addresses the controversies regarding the management of sentinel node-positive breast cancer patients. One of the key conclusions relating to the finding of a positive sentinel node biopsy, was that axillary dissection is still recommended. Patients not choosing to undergo completion axillary dissection when a positive sentinel node is detected, should be informed of the potential increased risk of regional nodal recurrence.

Guidelines

The most recent guideline relating to sentinel lymph node biopsy and axillary lymph node dissection was published by ASCO.

Lyman GH, Giuliano AE, Somerfield MR, son III AB, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23(30):7703-20.

Design: Guideline

Country: USA

Aim: To develop a guideline for the use of sentinel node biopsy (SNB) in early stage breast cancer.

Inclusion criteria

Exclusion criteria

Population

Interventions

An American Society of Clinical Oncology (ASCO) Expert Panel conducted a systematic review of the literature available through February 2004 on the use of SNB in early-stage breast cancer. The panel developed a guideline for clinicians and patients regarding the appropriate use of a sentinel lymph node identification and sampling procedure (SNB). The guideline was reviewed by selected experts in the field and the ASCO Health Services Committee and was approved by the ASCO Board of Directors.

Outcomes

Follow up -

Results

The literature review identified one published prospective randomized controlled trial in which SNB was compared with axillary lymph node dissection (ALND), four limited meta-analyses, and 69 published single-institution and multicentre trials in which the test performance of SNB was

evaluated with respect to the results of ALND (completion axillary dissection). There were no data on the effect of SLN biopsy on long-term survival of patients with breast cancer. However, a review of the evidence demonstrated that, when performed by experienced clinicians, SNB appeared to be a safe and acceptably accurate method for identifying early-stage breast cancer without involvement of the axillary lymph nodes.

Conclusions:

SNB is an appropriate initial alternative to routine staging ALND for patients with early-stage breast cancer with clinically negative axillary nodes. Completion ALND remains standard treatment for patients with axillary metastases identified on SNB. Appropriately identified patients with negative results of SNB, when done under the direction of an experienced surgeon, need not have completion ALND. Isolated cancer cells detected by pathologic examination of the SLN with use of specialized techniques are currently of unknown clinical significance. Although such specialized techniques are often used, they are not a required part of SLN evaluation for breast cancer at this time. Data suggest that SNB is associated with less morbidity than ALND, but the comparative effects of these two approaches on tumour recurrence or patient survival are unknown.

3.5 What is the prognostic significance of small metastatic deposits in sentinel nodes?

Short Summary

Five observational studies report the proportion of patients who undergo axillary lymph node dissection (ALND) after the finding of metastatic sentinel lymph node is made by SLNB, out of all patients with metastatic sentinel lymph nodes. The range of values is 63.2%-95.2% with the highest rate reported by a small, prospective study (de Widt-Levert *et al.* 2003) and the remainder of values from larger, but retrospective, studies.

Eight observational studies indicate a trend whereby larger size of the metastasis in the sentinel lymph node is associated with higher rates of non sentinel lymph node metastases. The mean proportion of patients with metastatic non sentinel lymph nodes is 10% for sentinel lymph node isolated tumour cells (ITCs), 17.7% for sentinel lymph node micrometastases and 53.2% for sentinel lymph node macrometastases (de Widt-Levert *et al.* 2003; Goyal *et al.* 1990; Bolster *et al.* 2007; Calhoun *et al.* 2005; Houvenaeghel *et al.* 2006; Katz *et al.* 2006a; van Rijk *et al.* 2006; Viale *et al.* 2005). From two systematic reviews (Cserni *et al.* 2004; Degnim *et al.* 2003) the pooled estimate for the rate metastatic non sentinel lymph nodes in patients with sentinel lymph node metastases of size 2mm or less was 20.2% (95% CI 15.5%-24.9%) when the sentinel lymph node metastases are detected by haematoxylin and eosin (H&E) staining, and 9.4% (95% CI 6.2%-12.6%) when the sentinel lymph node metastases are detected by immunohistochemistry (IHC) techniques.

Evidence from observational studies suggests that size of the sentinel lymph node metastasis was frequently a statistically significant independent predictive factor along with several other tumour/treatment related variables (Goyal *et al.* 2004; Bolster *et al.* 2007; Degnim *et al.* 2005; Houvenaeghel *et al.* 2006; Katz *et al.* 2006a; Viale *et al.* 2005).

From four studies reporting on the size of metastasis in non sentinel lymph nodes in patients with metastatic sentinel lymph nodes who then undergo ALND (Bolster *et al.* 2007; Calhoun *et al.* 2005; van Rijk *et al.* 2006; Viale *et al.* 2005), (see Tables 5-7 of full evidence review for this topic on the accompanying CD-ROM) the data indicates that patients with sentinel lymph node ITCs (<0.2mm in size) and those with sentinel lymph node micrometastases (of size 0.2-2mm in size) may be found to have larger non-sentinel lymph node metastases when ALND is performed, and at potentially high rates, although due to small numbers, estimates of rates are unreliable.

Of the included studies only one (Calhoun *et al.* 2005) provides data for recurrence and survival. All patients were alive at a mean follow-up of 80.5 months (6 years, 8 months).

PICO

Population	Intervention	Comparison	Outcome
Patients who receive SLNB as staging surgery	Close pathological examination of sentinel nodes	Meaningful comparison is the detection rate (% of cases) and prognostic value of: Isolated tumor cells versus: micrometastases versus: macrometastases	Macrometastases: Rate of occurrence of further positive nodes (ie 2 nd , 3 rd or 4 th nodes etc) and size of nodal deposits Rates of axillary dissection based upon attribution of positive sentinel node status Axillary recurrence rate Overall survival, disease-free survival Cost Effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There is moderate evidence on the importance of size of the largest sentinel node (sentinel lymph node) metastasis, including two systematic reviews and a number of observational studies. The studies have good applicability in that each considers subgroups based on the size of the largest metastasis in the sentinel lymph node.

All studies address the use of histology capable of detecting small sentinel lymph node metastases (e.g. serial sectioning, IHC) although the precise technique is a source of inconsistency

The included studies provide no reliable data on rates of recurrence or survival by subgroup for size of sentinel lymph node metastasis with survival data presented in only one observational study.

There is considerable heterogeneity across the studies in terms of histological assessment of sentinel lymph nodes and non-sentinel lymph nodes

All but one study report consistently that increasing size of sentinel lymph node metastases is associated with a greater likelihood of metastatic non-sentinel lymph nodes.

Table 1: Histology techniques used for assessment of SNs and non-SNs

Study	Design	Histology technique	
		Sentinel nodes	Non-sentinel nodes
(Cserni <i>et al.</i> 2004)	Systematic review & meta-analysis	Reported by method of detection: either standard H&E or IHC, or detected by IHC alone	H&E
(Degnim <i>et al.</i> 2003)	Systematic review & meta-analysis	Not reported: implied H&E and IHC	Standard H & E staining - 5 studies; H & E staining with additional sections and IHC - 3 studies as follows: i) 2 levels with a 250-micron interval - 1 study ii) 2 levels with a 40-micron interval - 1 study, iii) 3-8 levels in the subgroup of patients with primary tumors measuring < 2 cm and micrometastasis in the SN - 1 study Histology with and without IHC - 1 study Not specified - 3 studies
(de Widt-Levert <i>et al.</i> 2003)	Prospective case series	Interoperative imprint cytology (giemsa & papanicolaou) Definitive technique: H&E; at least 3 levels at 500 micron interval; also IHC using CAM 5.2 (Becton & Dickenson, 1:20)	H&E; 2 levels
(Goyal <i>et al.</i> 2004)	Prospective case series	Bisection if < 5 mm or sliced at 3 mm intervals if > 5 mm. Single sections stained with H&E. No intraoperative examination.	Bisection if < 5 mm or sliced at 3 mm intervals if > 5 mm. Single sections stained with H&E. No intraoperative

Study	Design	Histology technique	
		Sentinel nodes	Non-sentinel nodes
			examination.
(Bolster <i>et al.</i> 2007)	Retrospective case series	>=3 levels; >= 150 micron intervals, by H&E analysis. If no metastasis detected by this method: IHC analysis.	1-2 levels; H&E
(Calhoun <i>et al.</i> 2005)	Retrospective case series	Cytokeratin IHC if negative by H&E	H&E
(Degnim <i>et al.</i> 2005)	Retrospective case series	'method of detection' classified as by IHC only, routine/serial or frozen.	Single H&E section
(Houvenaeghel <i>et al.</i> 2006)	Retrospective case series	Intraoperative assessment in 53% of cases by imprint cytology, scrapings or both; serial sections with H&E analysis (54% of cases) and IHC analysis in 73% of cases	Not reported
(Katz <i>et al.</i> 2006a)	Retrospective case series	Frozen section interoperatively; H&E analysis of 2 levels at 60 micron spacing; IHC performed on all SNs negative on H&E and for all invasive carcinomas	H&E, 1 level
(Katz <i>et al.</i> 2006b)	Retrospective case series	Frozen section interoperatively; H&E analysis of 2 levels at 60 micron spacing; IHC performed on all SNs negative on H&E and for all invasive carcinomas	H&E, 1 level
(van Rijk <i>et al.</i> 2006)	Retrospective case series	Bisection or section in 2 mm slices. Paraffin blocks cut at 3 levels with minimally 150 micron intervals. IHC assessment in the case of a tumor-negative sentinel node by H&E.	3 nodes evaluated at 1 level and stained with H&E; IHC not routinely performed.
(Viale <i>et al.</i> 2005)	Retrospective case series	15 pairs of adjacent sections, 5 microns thick, cut at 50 micron intervals from both lymph node halves, i.e. 60 sections per node. For remaining tissue: sections at 100 micron intervals. H&E analysis of one section of each pair and cytokeratin analysis by MNF116 monoclonal antibody for the other section.	3-6 H&E-stained sections per node, at 100- to 500 micron intervals.

Rate of performance of axillary lymph node dissection

Five observational studies report the proportion of patients who undergo axillary lymph node dissection (ALND)¹⁰ after the finding of metastatic SN is made by SLNB, out of all patients with metastatic SNs (in the remainder of studies, 100% of patients underwent ALND by design). The range of values is 63.2%-95.2%. Unfortunately there are no data from these studies by size of the SN metastasis (Table 2). The highest rate reported is by a small, prospective study (de Widt-Levert *et al.* 2003) and the remainder of values are from larger, but retrospective, studies.

Table 2: Rates of performance of ALND

Study	Population (stage)	n cases (+ve SN)	n (ALND)	% (ALND/+ve SN)
(de Widt-Levert <i>et al.</i> 2003)	Clinical/radiological T1N0	21	20	95.2%
(Bolster <i>et al.</i> 2007)	T size <=5cm	203	186	91.6%
(Calhoun <i>et al.</i> 2005)	SN ITCs only; stage N0(i+)	78	61	78.2%
(Katz <i>et al.</i> 2006a)	Approx. 10% of parent series had DCIS	367	246	71.0%
(van Rijk <i>et al.</i> 2006)	SN micrometastases/ITCs	253	160	63.2%

Rate of occurrence of further positive nodes

Rate of positive non-SNs by subgroup for size of SN metastasis

The included observational studies indicate a trend whereby larger size of the metastasis in the SN is associated with higher rates of non-SN metastases (Table 3). Across eight studies that contribute data, the mean proportion of patients with metastatic non-SNs is 10% for SN ITCs (size <0.2mm), 17.7% for SN micrometastases (size 0.2-2.0mm) and 53.2% for SN macrometastases (size >2mm) (de Widt-Levert *et al.* 2003; Goyal *et al.* 1990; Bolster *et al.* 2007; Calhoun *et al.* 2005; Houvenaeghel *et al.* 2006; Katz *et al.* 2006a; van Rijk *et al.* 2006; Viale *et al.* 2005).

Table 3: Proportion of patients with metastatic non-SNs by SN metastasis size as reported in eight primary studies

¹⁰ During the period of definitive treatment; excluding that performed for subsequent axillary recurrence

Study	Sample size	Proportion of patients with metastatic non-SNs by SN metastasis size					
		ITCs	Micrometastases		Macrometastases		
		<0.2mm	0.2-2mm	All <=2mm grouped	All >2mm grouped	2-10mm	>10mm
(de Widt-Levert <i>et al.</i> 2003)	21	0	25	6.3	75		
(Goyal <i>et al.</i> 2004)	64			7		45	100
(Bolster <i>et al.</i> 2007)	203	12.9	26.4	19.6	36.5		
(Calhoun <i>et al.</i> 2005)	61	4.9					
(Houvenaeghel <i>et al.</i> 2006)	488	16	14.3	15			
(Katz <i>et al.</i> 2006a)	367	14	0	18.5	50.9	42	59
(van Rijk <i>et al.</i> 2006)	160	7.4	18.9	15			
(Viale <i>et al.</i> 2005)	1228	14.7	21.4		50.3		
Mean		10	17.7	13.6	53.2		
Median		12.9	20.1	15	50.6		
lowest		0	0	6.3	36.5		
highest		16	26.4	19.6	75		

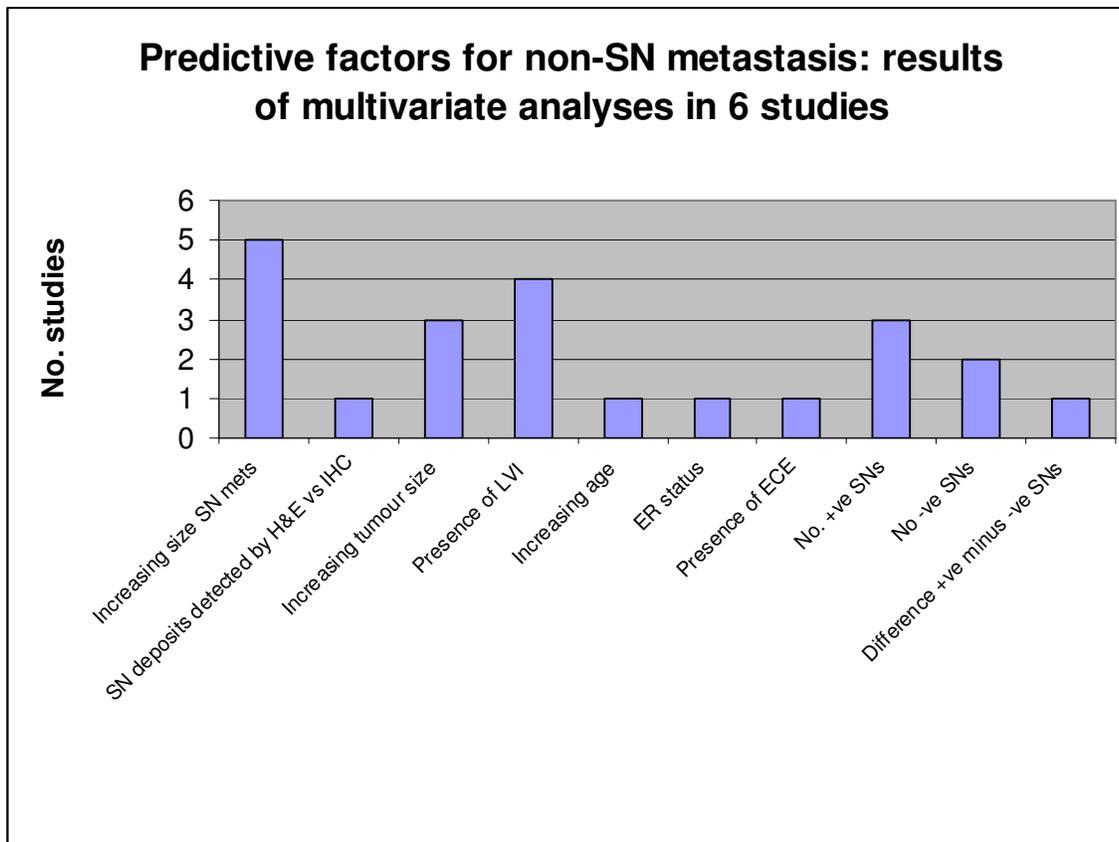
Two systematic reviews (Cserni *et al.* 2004; Degnim *et al.* 2003) which preceded these studies summarised previous primary data for the rate of metastatic non-SNs in patients with SN metastases of size 2mm or less (including both micrometastases of size 0.2-2mm and isolated tumour cells (ITCs) of size <0.2mm). The pooled estimate of this proportion reported by Cserni and co-workers was 20.2% (95% CI 15.5%-24.9%) when the SN metastases are detected by haematoxylin and eosin (H&E) staining, and 9.4% (95% CI 6.2%-12.6%) when the SN metastases are detected by immunohistochemistry (IHC) techniques. Degnim and co-workers reported a mean value of 18% (range 13%-22%) for this proportion, without subgrouping by the histological method that detected the SN metastases. In contrast the corresponding rate when the SN is macrometastatic (deposits >2mm in size) had a mean value across studies of 58% (range 45% to 79%) (Degnim *et al.* 2003). The pooled estimates

should be interpreted with caution due to a high level of heterogeneity across the primary studies (Cserni *et al.* 2004; Degnim *et al.* 2003).

SN metastasis size as a predictive factor for non-SN metastasis

Observational studies have performed multivariate analyses to identify predictive factors for non-SN metastases (Goyal *et al.* 2004; Bolster *et al.* 2007; Degnim *et al.* 2005; Houvenaeghel *et al.* 2006; Katz *et al.* 2006a; Viale *et al.* 2005). In these studies size of the SN metastasis was frequently a statistically significant independent predictive factor along with several other tumour/treatment related variables (Figure 1).

Figure 1



Abbreviations:

- SN: sentinel node
- H&E: haematoxylin and eosin staining
- IHC: immunohistochemistry analysis
- LVI: primary tumour lympho-vascular invasion
- ER: oestrogen receptor
- ECE: sentinel node extra-capsular extension

Notes:

1. No. of -ve SNs was the only variable with a negative (protective) association with non-SN metastases.
2. SN deposits detected by H&E vs. IHC may be related to size of the SN metastasis, with IHC likely to detect smaller deposits.

Strength of size of SN metastasis as a predictive factor for non-SN metastasis

Four studies provide odds ratios to indicate the strength of association between SN metastasis size and the rate of metastatic non-SNs (Table 4).

Table 4: Odds ratios for metastatic non-SNs according to size of SN metastasis

Study	Analysis	SN deposit size variable	OR	95% CI
(Bolster <i>et al.</i> 2007)	Multivariate	pN0(i+)(sn) <= 0.2 mm	1.0	
		pN1mi(sn) 0.2 mm – 2 mm	3.1	0.99-9.8
		pN1+(sn) > 2mm	4.0	1.4-11.5
(Degnim <i>et al.</i> 2003)	Meta-analysis (Mantel-Haenszel method for common odds ratios)	>2mm vs. <=2mm	6.2	4.5-8.5
(Degnim <i>et al.</i> 2005)	Univariate	per 1.0 mm increase in size	1.16	1.12-1.21
(Viale <i>et al.</i> 2005)	Multivariate	<= 1mm	1.0	
		1-2 mm	2.24	1.35-3.73
		>2 mm	4.57	3.27-6.38

Size of non-SN metastases

Four studies reported on the size of metastasis in non SNs in patients with metastatic SNs who then undergo ALND (Bolster *et al.* 2007; Calhoun *et al.* 2005; van Rijk *et al.* 2006; Viale *et al.* 2005), (Tables 5-7). The data indicate that patients with SN ITCs (<0.2mm in size) and those with SN micrometastases (of size 0.2-2mm in size) may be found to have larger non-SN metastases when ALND is performed, and at potentially high rates, although due to small numbers, estimates of rates are unreliable. In one study (van Rijk *et al.* 2006), of a total of 18 patients upstaged by ALND, 7 (all with micrometastasis in the SN) were offered systemic treatment that would not have been offered without the information from ALND. In the remaining 11 patients, systemic therapy was indicated by other patient/disease factors.

Table 5. Size of metastases in non-SNs: patients with SN ITCs; size ≤ 0.2 mm; stage by SLNB: pN0(i+)(sn)

Study	n cases	No. with positive non-SNs (% of cases)	Size of non-SN metastatic deposits (ALND)			% of +ve SNs with larger metastases in non-SNs
			≤ 0.2 mm	0.2 mm – 2mm	> 2mm	
(Bolster <i>et al.</i> 2007)	54	7 (12.9%)	0	2	5	(5+2)/7=100%
(Calhoun <i>et al.</i> 2005)	61	3 (4.9%)		2	1	(2+1)/3=100%
(van Rijk <i>et al.</i> 2006)	54	4 (7.4%)	2	0	2	(2+0)/4=50%
(Viale <i>et al.</i> 2005)	116	17 (14.7%)	1	3	13	(13+3)/17=94%

Table 6. Size of metastases in non-SNs: Patients with SN micrometastases; size 0.2-2 mm; stage by SLNB pN1mi(sn)

Study	n cases	No. with positive non-SNs (% of cases)	Size of non-SN metastatic deposits (ALND)			% of +ve SNs with larger metastases in non-SNs
			≤ 0.2 mm	0.2 mm – 2mm	> 2mm	
(Bolster <i>et al.</i> 2007)	53	14 (26.4%)	4	4	6	6/14=43%
(van Rijk <i>et al.</i> 2006)	106	20 (18.9%)	0	4	16	16/20=80%
(Viale <i>et al.</i> 2005)	318	68 (21.4%)	6	20	42	42/68=62%

Table 7. Size of metastases in non-SNs: Patients with SN macrometastases; size >2 mm; stage by SLNB pN1(sn) and above

Study	n cases	No. with positive non-SNs (% of cases)	Size of non-SN metastatic deposits (ALND)		
			<= 0.2 mm	0.2 mm – 2mm	> 2mm
(Bolster <i>et al.</i> 2007)	96	35 (36.5%)	0	5	30
(Viale <i>et al.</i> 2005)	794	399 (50.3%)	12	27	360

NB: Uppermost stage considered here is pN1 and above, based on node deposit >2mm in size.

Multiple positive axillary nodes

One observational study (Katz *et al.* 2006b) examined the occurrence of four or more metastatic axillary nodes in patients with SN metastases. Overall, 19% of patients had four or more metastatic axillary nodes, with distribution by size of SN metastasis as follows (Table 8):

Table 8: Proportion of patients with >= 4 involved axillary nodes by size of SN metastasis, reported by Katz et al. 2006

Size of largest SN metastasis	no. cases	no. with >=4 involved nodes	%
<=0.2mm	56	0	0%
2.1-4.0mm	26	1	4%
4.1-10.0 mm	74	17	23%
>10.0 mm	68	24	35%
Unknown	4	1	25%

On multivariate analysis the following variables were statistically significant predictors of four or more metastatic nodes (Katz *et al.* 2006b) (Table 9):

Table 9: Predictors of four or more metastatic axillary nodes, reported by Katz et al. 2006

Variable	OR	95% CI	p value
LVI	3.2	1.4-7.6	0.008
No. +ve SNs	2.6	1.4-4.9	0.003
Size of SN deposit	1.1	1.0-1.2	<0.001
Histology (ductal vs. lobular)	0.2	0.1-0.6	0.002

Recurrence and survival

Of the included studies only one (Calhoun *et al.* 2005) provides data for recurrence and survival, which is based on a small series and which has only moderate follow-up. Of 78 patients with ITCs only in the SN, 61 patients underwent ALND. All patients were alive at a mean follow-up of 80.5 months (6 years, 8 months). In this time there were no axillary recurrences, including the 17 patients in whom ALND was omitted. There were two cases of

distant metastases, both in patients who underwent ALND: one who had positive non-SN status, and one whose status was negative (Calhoun *et al.* 2005).

UPDATE EVIDENCE

Using the SEER database, a retrospective study assessed whether micrometastatic disease (N1mi) alone can predict a poorer prognosis for patients with early breast cancer (Chen *et al.* 2007). Specifically the study investigated whether the survival of patients with solely micrometastatic disease (N1mi) would be intermediate to patients with 1-3 tumour-positive lymph nodes (N1) and those with no positive lymph nodes (N0) (Chen *et al.* 2007).

Results

- N1mi diagnoses increased from 2.3% to 7% among the 209,720 study patients ($p < 0.001$).
- Overall, N1mi patients had a statistically worse survival than N0 patients and better than N1 patients.
- In a T-stage stratified univariate analysis, N1mi patients had a poorer prognosis when compared to N0 patients. However, this was only significant for patients with T2 lesions (univariate analysis, $p < 0.001$)
- There was statistical better survival in N1mi patients compared to N1 patients with T1-T3 lesions.
- 5 and 10 year survival was intermediate for N1mi patients when compared to N0 and N1 patients.
- On multivariate analysis, N1mi remained a significant prognostic indicator across all patients ($p < 0.0001$).
- HR (hazard ratio)= 1.35 (compared to N0 disease)
- HR = 0.82 (compared to N1 disease)

Other negative prognostic factors included male gender, oestrogen-receptor negativity, progesterone-receptor negativity, lobular histology, higher grade, older age, higher T-stage, and diagnosis in an earlier time period.

Author's Conclusion: Nodal micrometastasis of breast cancer carries a prognosis intermediate to N0 and N1 disease, even after adjusting for tumour and patient related factors. Adjuvant therapy trials should consider using N1mi as a stratification factor when determining nodal status. Prospective studies will confirm results with less bias involved.

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Evidence Tables

Systematic review of combined study designs

Cserni, Gregori, Merletti, Sapino, Mano, Ponti, Sandrucci, Baltas & Bussolati . Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer.[see comment]. Br.J.Surg. 91[10], 1245-1252. 2004.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2-
Country: Various, setting: Tertiary care

Inclusion criteria

25 articles reporting the incidence of non-SN metastases in association with small metastases in the SN.

Patient population represented is patients with SN micrometastases (size 0.2-2mm) or ITCs (size <0.2mm).

Exclusion criteria

Conference proceedings and unpublished papers.

Population

number of patients = 789.

Interventions

Aim: to estimate non-SN tumour involvement associated with small metastases in the SN.

Patients underwent SLNB (all patients had low burden SN metastasis; see 'inclusion criteria). The majority of patients underwent axillary dissection.

Histology technique: Results are reported according to the histology technique used to detect the SN metastases: either any method (standard H&E or IHC), or detected by IHC alone. Non sentinel node assessment was always by standard H&E technique.

Outcomes

Pooled proportion of non-SN involvement of any type, including metastases larger than 2 mm, micrometastases and ITCs (non-SN+) in patients with SN involvement by micrometastasis or ITCs (microSN+), referred to as non-SN+/microSN+. This outcome was presented in two ways:

a) Proportion of non-sentinel node (SN) involvement identified by standard

histology (non-SN+) in patients with SN involvement by micrometastases (regardless of the method of detection) (microSN+).

b) Proportion of non-sentinel node (SN) involvement identified by standard histology (non-SN+) in patients with SN involvement by micrometastases detected by immunohistochemistry (microSN+ (IHC)).

Subgroup analysis was performed after classifying papers according to five criteria:

1. Performance of axillary dissection;
2. Level of the axillary dissection;
3. Number of levels of histological examination;
4. Frequency of levels assessed by IHC;
5. Study quality ('high' or 'low').

Follow up

Not reported.

Results

Pooled proportions of non-SN+/microSN+ detected either by standard haematoxylin and eosin staining or by immunohistochemistry (25 studies)

	Pooled proportion	95% confidence interval	P (homogeneity)
Non-SN+/microSN+(H&E)	0.202	0.155, 0.249	<0.001
Non-SN+/microSN+ (IHC)	0.094	0.062, 0.126	0.430

Subgroup analysis of pooled proportions

	No. of studies	Non-SN+/microSN+	No. of studies	Non-SN+/microSN+ (IHC)
Back-up dissection				
Yes	17	0.170 (0.142, 0.198)	10	0.105 (0.049, 0.161)
No	1	0.025 (0, 0.103)	2	0.130 (0, 0.426)
Level of axillary dissection				
I-III (complete)	5	0.214 (0.121, 0.308)	5	0.153 (0.012, 0.223)
I-II	7	0.157 (0.078, 0.235)	2	0.050 (0, 0.35)
No. of sections				
≥4	10	0.250 (0.186, 0.313)	4	0.125 (0, 0.292)

<4	6	0.156 (0.087, 0.225)	4	0.111 (0, 0.288)
Levels (IHC)				
Not all levels	7	0.193 (0.123, 0.262)	3	0.102 (0, 0.52)
All levels	7	0.229 (0.143, 0.315)	6	0.117 (0.043, 0.194)
Quality				
High	11	0.152 (0.106, 0.199)	6	0.100 (0.001, 0.198)
Low	9	0.244 (0.183, 0.305)	6	0.135 (0.039, 0.232)

General comments

A Medline search using the term 'breast and sentinel' was performed on title and abstract for papers published between January 1998 and June 2003. All papers written in English, German or French were considered.

Each paper was assessed as of 'high' or 'low' quality by nine reviewers (three epidemiologists, three surgeons and three pathologists) who used a common quality assessment form. Technical and statistical details, validation, performance of axillary dissection and detailed histopathology formed the main aspects of the quality assessment.

Study heterogeneity was assessed prior to meta-analysis. For one of two pooled results (Non-SN+/microSN+(H&E)) the test revealed significant heterogeneity between studies ($p < 0.001$). This was also evident from individual study data (not shown) and also Forrest plots (for both results), so the results should be interpreted with caution.

The finding in the subgroup analysis that a higher rate of non-SN involvement occurs where axillary dissection is performed (for Non-SN+/microSN+; since the 95% confidence intervals do not overlap) is not surprising - and may arise because only 1 study omitted axillary clearance, or because axillary recurrence may take a long time to become apparent, or because the decision to perform axillary dissection considered also other tumour and patient factors.

Degnim, Griffith, Sabel, Hayes, Cimmino, Diehl, Lucas, Snyder, Chang & Newman . Clinicopathologic features of metastasis in nonsentinel lymph nodes of breast carcinoma patients. Cancer 98[11], 2307-2315. 2003.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2 -

Country: Various, setting: Tertiary care

Inclusion criteria

Primary studies that reported the association between patient/disease characteristics and the likelihood of positive non-SNs were selected by the following criteria:

- 1) the study identified the population of patients with a positive SN and who underwent completion axillary clearance;
- 2) original data were reported on the number of SN-positive patients who had positive non-SNs stratified by various patient/tumour characteristics;
- 3) statistical analysis for these characteristics was not based on groups that included patients with negative SNs;
- 4) the study population included patients with both micrometastatic and macrometastatic disease in the SNs.

Exclusion criteria

Defined by inclusion criteria.

Population

number of patients = 1535.

Interventions

Aim: to assess the strength of association between primary tumour/sentinel node characteristics and likelihood of further disease-positive non sentinel nodes.

Patients underwent SLNB followed by axillary clearance due to the finding of disease-positive SNs.

Histology technique for non-SNs:

Standard H & E staining - 5 studies;

H & E staining with additional sections and IHC - 3 studies as follows:

- i) 2 levels with a 250-micron interval - 1 study
- ii) 2 levels with a 40-micron interval - 1 study,
- iii) 3-8 levels in the subgroup of patients with primary tumors measuring < 2 cm and micrometastasis in the SN - 1 study

Histology with and without IHC - 1 study

Not specified - 3 studies

Outcomes

Common odds ratios across studies for odds of positive non-SNs, by each factor studied

Crude rates of positive non-SNs

Factors found to be predictive of positive non-SNs, by multivariate analysis in primary studies

Follow up

Not reported

Results

Crude rates of positive non-SNs

There was a positive association between the size of the metastasis in the SN and the proportion of patients with positive non-SNs. In patients with micrometastatic (≤ 2 mm) SN disease, approximately 13–22% had additional metastasis by H & E staining in non-SNs, in contrast to 45–79% of patients with macrometastatic (>2 mm) disease.

Table: Proportion of patients with positive non-SNs (determined by H&E) by subgroup for size of SN deposit (8 studies, 1 of which included non-SN deposits detected by IHC):

SN deposit size	% positive non-SN		
	mean	lowest	highest
≤ 2 mm	18	13	22
> 2 mm	58	45	79

In those studies that classified the SN metastasis size as detected by IHC only, ≤ 2 mm excluding IHC-detected disease, or > 2 mm, there was a trend toward further discrimination among patients with micrometastatic disease.

Table: Proportion of patients with positive non-SNs (determined by H&E) by subgroup for characteristic of SN deposit i.e. detected by IHC only, ≤ 2 mm excluding IHC-detected, or > 2 mm (4 studies):

SN deposit size	% positive non-SN		
	mean	lowest	highest
IHC only	13	8	20
≤ 2 mm excluding IHC	24	18	33
> 2 mm	61	49	79

Factors found to be statistically significantly predictive of positive non-SNs, by multivariate analysis performed in primary studies:

Larger tumour size (6 studies)

SN metastases size >2mm (5 studies)
 Extracapsular extension of SN metastases (2 studies)
 Tumour LVI (2 studies)
 >1 positive SN (1 study)

Mantel-Haenszel meta-analysis of common odds ratios across studies for odds of positive non-SNs, by each factor studied

Factor	OR	95% CI
Size of metastases: >2mm vs. ≤2mm	6.2	4.5-8.5
SN extranodal extension: present vs. absent	4.8	3.2-7.4
Tumour size: >2cm vs. ≤2cm	2.6	2.1-3.3
No. positive SNs: ≥2 vs. 1	2.5	1.8-3.4
LVI: present vs. absent	2.2	1.6-3.1
Lobular vs. ductal histology	1.9	1.0-3.7
ER status: negative vs. positive	1.8	1.1-3.0
HER-2 status: positive vs. negative	1.8	0.9-3.7
No. SNs removed: 1-2 vs. ≥3	1.6	1.1-2.3
Tumour grade: III vs. I-II	1.5	1.1-2.0
Palpable tumour: yes vs. no	1.4	0.7-2.9
PR status: negative vs. positive	1.4	0.9-2.3
Age group: <50 years vs. ≥50 years	0.9	0.6-1.3

General comments

Literature search: performed on MEDLINE database using the following keywords: nonsentinel node, non-sentinel node, nonsentinel lymph node, non-sentinel lymph node, sentinel lymph node biopsy; combined with: breast neoplasms and characteristics, sentinel lymph node biopsy; combined with: breast neoplasms and predictors, and breast neoplasms; combined with: axillary dissection and metastasis.

Data extraction was checked by an external consultant.

Study-specific odds ratios were calculated from the abstracted data, and the common odds ratios across studies were estimated using the Mantel-Haenszel method. For the meta-analysis, data regarding non-SNs found to be positive by H & E evaluation were used whenever available, but data from studies in which IHC was performed on non-SNs were included.

The 11 studies included in the meta-analysis were published between 1999 and 2003.

NB - All of the included studies were also included in the meta-analysis by Cserni et al. (2004), but this paper provides a different analysis of some of the same data.

The study sample sizes (patients with a positive SN who underwent completion ALND) ranged from 60-389 patients. Patient age, the number of SNs obtained, and the number of non-SNs obtained appeared similar across studies. There was variation across studies in disease stage distribution; the proportions of patients with tumors ≤ 2 cm and with SN micrometastasis ranged from 30-78% and 25-57%, respectively. The authors report that the variation in histology technique (see 'interventions') is likely to be the most important source of heterogeneity between studies.

Prospective case series

de Widt-Levert, Tjan-Heijnen, Bult, Ruers & Wobbes . Stage migration in breast cancer: surgical decisions concerning isolated tumour cells and micro-metastases in the sentinel lymph node. Eur.J.Surg.Oncol. 29[3], 216-220. 2003.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: Holland, setting: Tertiary care

Inclusion criteria

Patients with clinical & radiological T1N0 breast cancer treated consecutively in the year 2000-2001.

Of 38 patients who underwent SLNB, the SN was localised in 34, of whom 21 had histologically proved SN metastases.

Exclusion criteria

See inclusion criteria.

Population

number of patients = 21.

Interventions

Aim: to investigate the clinical significance of isolated tumour cells and micrometastases in the SN.

Histology techniques:

SNs:

Interoperative imprint cytology (giemsa & papanicolaou)

Definitive technique: H&E; at least 3 levels at 500 micron interval; also IHC using CAM 5.2 (Becton & Dickenson, 1:20).

Non-SNs:

H&E only; 2 levels.

Outcomes

Crude rate of disease-positive non-SNs in patients with positive SNs.

Follow up

Not reported - study reports on the time of definitive surgical treatment.

Results

The rate of non-SN metastases in 21 patients with metastatic SNs was as follows (numbers = patients):

Size of SN deposit	No.	Rate of axillary clearance	Rate of positive non-SNs
Macrometastases (>2mm)	4	4/4	3/4
Micrometastases (<= 2mm)	4	4/4	1/4
ITCs	13*	12/13*	0/12

*NB 1 patient did not undergo axillary clearance at the time of definitive treatment and experienced a later axillary recurrence, and underwent delayed axillary clearance.

Matched controls (n=75):

The rate of positive axillary nodes attributed by standard H&E histology was 52/75 = 69%.

General comments

Prospective cases series with comparison to historical control group, treated before the era of SLNB.

Small subgroups based on only 21 patients that meet the population specified for this question lead to unreliable crude rates.

Staging scheme applied to the SLNB study group was that of UICC International Union Against Cancer (Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Communication of the UICC International Union against cancer: classification of isolated tumour cells and micrometastases. Cancer 1999; 86: 2668-73), as follows:

pN0: No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITC).

pN0(i-): No regional lymph node metastasis histologically, negative morphologic findings for ITC.

pN0(i1): No regional lymph node metastasis histologically, positive morphologic findings for ITC.

pN0(mol-): No regional lymph node metastasis histologically, negative nonmorphologic findings for ITC.

pN0(mol1): No regional lymph node metastasis histologically, positive nonmorphologic findings for ITC.

Goyal, Douglas-Jones, Newcombe, Mansel & Almanac . Predictors of non-sentinel lymph node metastasis in breast cancer patients. European journal of cancer (Oxford, England.: 40[11], 1731-1737. 1990.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: UK, setting: Tertiary care

Inclusion criteria

64 patients treated at a single centre with SLNB plus axillary clearance between Feb 1998 - Dec 2001. All patients had disease-positive SNs and were identified from a larger series of 618 patients treated with the same protocol at numerous centres, of whom 201 had positive SNs.

Exclusion criteria

Patients with disease-negative SNs.
Patients who underwent, in addition to SLNB, four node sample instead of axillary clearance.
Pregnant women.
Patients with known multi-centric tumours.
Patients with a history of previous surgery to the same breast or axilla.

Population

number of patients = 64, age range 35 to 89 years, median age = 54 years.

Interventions

Aim: to identify a subgroup of patients with a positive SN who do not need to be exposed to the morbidity and cost associated with completion axillary clearance.

All patients underwent SLNB and axillary clearance during the centre's validation period for SLNB.

Histology technique:

The SNs and non-SNs were bisected if less than 5 mm or sliced at 3 mm intervals if greater than 5 mm and assessed using single sections stained with haematoxylin and eosin (H&E). Intraoperative histological examination was not utilised.

SN deposit size groups:

Micrometastases: <2mm

Macrometastases: >=2mm.

Outcomes

Association between clinicopathological factors and the finding of disease-positive non-SNs. (Univariate analysis: Chi square test for binary and

unordered categorical variables; Mann-Whitney test for ordinal/continuous variables. Factors found to be statistically significant in univariate analyses were entered into a stepwise logistic regression (multivariate analysis)).

Factors examined were age; tumour size; tumour grade; No. SNs removed; No. positive SNs; No. negative SNs, tumour pathological subtype; multifocality; size of SN metastasis; extracapsular extension; LVI; % replacement of SN by tumour.

Follow up

Not relevant; study is of peri-operative period.

Results

1. Data from the centre reporting size of largest SN metastasis:

On univariate analysis, increasing size of the SN metastasis, percentage replacement of SN by tumour and extracapsular extension around the SN, all were significantly associated with non-SN involvement ($P < 0.001$, $P < 0.001$, $P = 0.01$, respectively). The rate of non-SN involvement was 7% in the presence of SN micrometastasis (<2 mm), compared with 60% when the SN had a macrometastasis (>2 mm). All patients with metastasis of >10 mm had additional positive nodes in the axilla.

Crude rate of positive non-SNs by size of SN deposit:

<2 mm: 7%

2-10mm: 45%

>10 mm: 100%; $p < 0.001$.

82% of patients with extracapsular extension around the SN had non-SN involvement, while only 40% of patients without extracapsular extension around the SN had non-SN metastasis.

On multivariate analysis, size of the SN metastasis was the only statistically significant factor, predictive of non-SN involvement: ($P < 0.001$); multiple logistic regression equation:

Logit (proportion with positive non-SNs) = $0.257 \times$ size of largest metastasis (mm) - 1.732.

2. Data from all centres (no variable for size of largest SN metastasis)

Increasing tumour size, tumour grade and number of positive SNs were all associated with an increased likelihood of NSLN metastasis on univariate analysis ($P = 0.002$, $P = 0.040$, $P = 0.019$, respectively). The total number of sentinel nodes removed and number of negative sentinel nodes were significant negative predictors ($P = 0.014$, $P < 0.001$, respectively).

Only the difference in the number of positive and negative SNs removed remained predictive of non-SN involvement on multivariate analysis ($P <$

0:001); multiple logistic regression equation:

Logit (proportion with positive non-SNs) = 0.614 x positive SNs - 0.864 x negative SNs - 0.36.

General comments

Study presents data from the non-randomised validation phase of the ALMANAC RCT. Only one centre assessed the size of metastatic deposit in the SN (n=64) whereas results from the larger series (n=201) are also cited.

Authors report that using only single-centre data may be underpowered to detect potentially important predictive variables by multivariate analysis.

Retrospective case series

Bolster, Peer, Bult, Thunnissen, Schapers, Meijer, Strobbe, van Berlo, Klinkenbijn, Beex, Wobbes & Tjan-Heijnen . Risk factors for non-sentinel lymph node metastases in patients with breast cancer. The outcome of a multi-institutional study. Ann.Surg.Oncol. 14[1], 181-189. 2007.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: The Netherlands, setting: Tertiary care

Inclusion criteria

203 patients with a positive SN, identified from a larger series of 541 patients treated with SLNB over an 18 month period within the years 2002 - 2003 in 4 centres. Patients had tumours of ≤ 5 cm in size.

Exclusion criteria

Pre-surgical proof of axillary metastases;
Multifocal tumours;
Previous axillary surgery/RT;
Neo-adjuvant systemic therapy;
Patients in whom the SN was not detectable.

Population

number of patients = 203.

Interventions

Aim: to measure the rate of positive non-SNs in patients, by size of SN metastasis, and to assess predictive factors for positive non-SNs.

Patients underwent SLNB. A completion ALND was indicated in the presence of ITCs, micrometastases or macrometastases.

Histology technique:

1. SNs: ≥ 3 levels; ≥ 150 micron intervals, by H&E analysis. If no metastasis detected by this method: IHC analysis.
2. ALND: 1-2 levels; H&E analysis

SN metastasis size classification - based on TNM (2002):

pN0(i+): solitary tumour cells or clusters of size ≤ 0.2 mm

pN1mi: micrometastases of size 0.2 mm - 2 mm

pN1+ Macrometastases: > 2 mm in size

pNtotal: refers to final stage attributed after inclusion of non-SNs.

For SN findings the term 'sn' was added to the terms, and for ALND findings, 'n'.

Outcomes

Rate of performance of ALND

Rate of positive non-SNs and size of these deposits

Factors associated with positive non-SNs. Factors explored were age, size of SN deposit, tumour size, grade, ER-PR status, presence/absence of LVI.

Follow up

Not applicable

Results

203 patients had positive SNs. Of these, 186 underwent ALND (91.6%).

Rate of further non-SNs: 56/186 = 30.1%

SN deposit size	n cases	No. with positive non-SNs (% of cases)	Size of non-SN metastasis		
			pN0(i+)(n) <= 0.2 mm	pN1mi(n) 0.2 mm – 2 mm	pN1+(n) > 2mm
pN0(i+)(sn) <= 0.2 mm	54	7 (12.9%)	0	2	5
pN1mi(sn) 0.2 mm – 2 mm	53	14 (26.4%)	4	4	6
pN1+(sn) > 2mm	96	35 (36.5%)	0	5	30
	203	56	4	11	41

The difference in the rate of positive non-SNs by size of SN metastatic deposit (ITCs vs. micrometastases vs. macrometastases: 14.6%, 28.6% and 38.0%, respectively) was statistically significant (Chi square; $p < 0.0001$).

Upstaging of patients on the basis of final stage attributed after inclusion of non-SNs:

Of 107 patients with micrometastases or ITCs only in the SN, 13 (12.1%) were upstaged by non-SNs. This broke down as 7/54 = 13.0% for SN ITCs and 6/53 = 11.3% for SN micrometastases.

SN deposit size	n cases(%)	pNtotal: final stage attributed after inclusion of non-SNs		
		pN0(i+)(n) <= 0.2 mm	pN1mi(n) 0.2 mm – 2 mm	pN1+(n) > 2mm

pN0(i+)(sn) <= 0.2 mm	54 (26.6%)	47	2	5
pN1mi(sn) 0.2 mm – 2 mm	53 (26.1%)	-	47	6
pN1+(sn) > 2mm	96 (47.3%)	-	-	96
Total	203 (100%)	47	49	107

Predictive factors for positive non-SNs

On univariate analysis and multivariate analysis, size of SN deposit and size of primary tumour were statistically significantly associated with positive non-SNs.

Multivariate analysis (logistic regression model):

		OR	95% CI	p
	pN0(i+)(sn) <= 0.2 mm	1.0		
SN deposit size	pN1mi(sn) 0.2 mm – 2 mm	3.1	0.99-9.8	
	pN1+(sn) > 2mm	4.0	1.4-11.5	0.03
Primary tumour size	< 3 cm	1.0		
	> 3 cm	3.1	1.2-8.1	0.001
LVI	Absent	1.0		
	Present	2.0	0.9-4.2	0.17

General comments

Re: rate of performance of ALND, of 17 patients with a positive SN in whom ALND was omitted, in 3 patients non-sentinel nodes were also examined and found to be negative for metastasis. Of 338 patients excluded from the analysis, positive non-SNs were removed during SLNB along with the SNs.

Some subtle inconsistencies between paper & data tabulated here exist; re: % of +ve non-SNs by size of SN deposit - may arise from this data extraction and from nomenclature of SN stage and final stage. The discrepancy is difficult to source or to otherwise explain, but is minor: ITCs vs. micrometastases vs. macrometastases: 14.6%, 28.6% and 38.0%,

respectively in text, and 12.9%, 26.4% and 36.5% tabulated here.

Calhoun, Hansen, Turner & Giuliano . Nonsentinel node metastases in breast cancer patients with isolated tumor cells in the sentinel node: implications for completion axillary node dissection. Am.J.Surg. 190[4], 588-591. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Tertiary care

Inclusion criteria

78 patients treated with SLNB between January 1995 and December 1999 who were found to have at least 1 ITC positive SN i.e. stage N0(i+). Patients were identified from a total series of 634 patients.

Patient and tumour characteristics: reported by subgroup, but inconsistently (not cited).

Exclusion criteria

See inclusion criteria.

Population

number of patients = 78.

Interventions

Aim: to assess the rate of positive non-SNs in patients staged as N0(i+) by SLNB.

All patients (78) underwent SLNB. ALND was recommended for patients with positive SLNs, including those with ITCs only.

61 patients underwent ALND; 17 patients did not.

Pathological assessment:

SNs: cytokeratin IHC if negative by H&E.

ALND: (non-SNs): H&E.

All SN specimens were either prospectively or retrospectively (i.e. re-examination) classified as macrometastatic, micrometastatic, or ITC, according to the AJCC staging system (2002).

Outcomes

Rate of positive non-SNs.

Disease-related events.

Follow up

Mean 80.5 months.

Results

Non-SN status in patients who underwent ALND:

Positive on H&E: 3/61 = 4.9%

Negative on H&E: 58/61 = 95.1%

Of 3 cases with positive non-SNs, 2 patients had only micro-metastases in the non-SNs and 1 had macrometastasis (3 mm) in their non-SN.

Recurrence & survival

	Axillary recurrence	Breast recurrence	Distant metastasis	Death
Non-SN + (n=3)	0	0	1	0
Non-SN - (n=58)	0	3	1	0
No ALND (n=17)	0	0	0	0

No patients experienced axillary recurrence (all patients i.e. including 17 patients who did not undergo ALND). Crude rate = 0/78 = 0%.

Disease-free survival (crude rate, by subgroup):

Non-SN +: 2/3 = 67%

Non-SN -: 54/58 = 93%

No ALND: 17/17 = 100% (small numbers make data unreliable)

Overall survival (crude rate; all patients): 78/78 = 100%

General comments

Staging criteria:

Macrometastasis: ≥ 2 mm foci;

Micrometastasis: ≥ 0.2 mm to 2 mm foci; [N1mi];

ITCs: disease detected by IHC analysis: 0- to 0.2 mm foci; [N0(i+)]

No metastases detected by IHC: N0(i-).

'A majority' of the 61 patients with negative non-SNs received adjuvant chemotherapy, and 77.6%, adjuvant hormone therapy. All 3 patients with positive non-SNs received 'adjuvant therapy'. 15/17 women who did not undergo ALND received adjuvant systemic therapy.

Subgroups, particularly for patients with positive non-SNs and those who did not undergo ALND, are small; crude rates for disease-free and overall-survival are unreliable.

Degnim, Reynolds, Pantvaidya, Zakaria, Hoskin, Barnes, Roberts, Lucas, Oh, Koker, Sabel & Newman . Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am.J.Surg. 190[4], 543-550. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Tertiary care

Inclusion criteria

574 patients who underwent SLNB then completion ALND for SN metastases between October 1997 and June 2004 at two centres as follows:

1. University of Michigan (n=109)
2. Mayo Clinic (n=465)

Exclusion criteria

None reported.

Population

number of patients = 574, age range 26 to 88 years, mean age = 57 years.

Interventions

Aim: to assess the validity of a previously published Memorial Sloan Kettering Cancer Center (MSKCC) nomogram (<http://www.mskcc.org/mskcc/html/15938.cfm>) using patient data from this series and assess whether the addition of further variables to the model improves its performance.

Data from both institutions were used to assess the performance of the MSKCC model. A new predictive model was developed from the Mayo dataset of 465 patients by adding the following variables: size of SN metastasis, location of SN metastasis, presence/absence of extracapsular extension, proportion of SN replaced by metastasis and location of metastasis: subcapsular, parenchymal or both subcapsular and parenchymal. This Mayo model was applied to the Michigan dataset for performance analysis (data not cited).

Histology techniques:

1. SNs: not directly reported, but 'method of detection' classified as IHC only, routine/serial or frozen.
2. Non-SNs: Single H&E section

Outcomes

Predictive factors for non-SN metastasis.

Factors examined were: age, pathologic size of primary invasive breast tumour, tumour type, Nottingham tumour grade, presence of lymphovascular invasion, multifocality of primary tumour, estrogen and progesterone receptor status, method of detection of SN metastasis (frozen section analysis, routine/serial hematoxylin-eosin staining, or immunohistochemistry), total number of SNs removed, number of positive and negative SNs, measured size of largest metastasis in the SN, proportion of SN replaced by metastasis, location of metastasis (subcapsular, parenchymal, or combined subcapsular and parenchymal), and the presence or absence of extracapsular extension. Tumour type and grade were combined into 4 categories: ductal carcinoma grade I, ductal carcinoma grade II, ductal carcinoma grade III, and lobular carcinoma.

Follow up

Not applicable

Results

Univariate analysis: Associations between clinicopathologic features and positive non-SNs:

Variable	OR	95% CI	p
Age (per 10 y)	0.96	0.8-1.1	0.56
Tumor size (per 1.0 cm)	1.3	1.2-1.5	<0.0001
Tumor type and grade			
Ductal, tumor grade II versus I	2.1	1.0-4.3	0.04
Ductal, tumor grade III versus I	2.6	1.2-5.6	0.01
Lobular versus ductal, tumor grade I	3.8	1.8-8.2	0.0007
Lymphovascular invasion (yes vs no)	2.0	1.1-3.7	0.03
Multifocality (yes vs no)	1.3	0.8-2.1	0.32
Estrogen receptor status (positive vs negative)	0.9	0.5-1.5	0.61
Method of detection			
IHC versus frozen	0.2	0.08-0.5	0.001
Routine/serial versus frozen	0.3	0.1-0.6	0.0003
Number of positive SNs (per node)	1.6	1.2-2.1	0.001
Number of negative SNs (per node)	0.8	0.7-0.9	0.001
Size of metastasis (per 1.0 mm)	1.16	1.12-1.21	<0.0001
Parenchymal metastasis	3.3	2.1-5.1	<0.0001

Extracapsular extension	4.0	2.7-5.9	<0.0001
Proportion of SLN involved with metastases (per .10 involved)	1.3	1.2-1.4	<0.0001

On multivariate analysis the following variables were statistically significantly predictive of non-SN metastases: age of the patient, size of primary tumor, estrogen receptor status, size of SN metastasis, extracapsular extension, and number of positive and negative SNs.

General comments

In the development of the predictive model, 3 Mayo Clinic patients had no tumour size data, hence the sample size was 462.

Houvenaeghel, Nos, Mignotte, Classe, Giard, Rouanet, Lorca, Jacquemier, Bardou & Groupe des Chirurgiens de la Federation des Centre . Micrometastases in sentinel lymph node in a multicentric study: predictive factors of nonsentinel lymph node involvement--Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer.[see comment]. J.Clin.Oncol. 24[12], 1814-1822. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: France, setting: Tertiary care

Inclusion criteria

700 patients with micrometastatic SNs revealed SLNB, who underwent in addition ALND, treated between January 1998 and December 2003 at 16 centres.

Mean tumour size 19 mm (range 1-170 mm).

Exclusion criteria

None defined; study provides no data for patients with SN deposits >2mm in size.

Population

number of patients = 700, age range 25 to 86 years, mean age = 56 years, median age = 55 years.

Interventions

Aim: to determine:

- (1) the rate of non-SN involvement at ALND in the case of SN micrometastasis,
- (2) predictive factors of non-SN involvement at ALND,
- (3) a subpopulation of patients in whom ALND can be omitted.

All patients had SN micrometastases revealed by SLNB, and underwent in addition, ALND.

Histological technique:

1. SNs: Intraoperative assessment in 53% of cases by imprint cytology, scrapings or both; serial sections with H&E analysis (54% of cases) and IHC analysis in 73% of cases
2. Non-SNs: not reported

SN deposit size criteria:

ITCs: < 0.2 mm (also referred to as 'submicrometastases')

Micrometastases: ≥ 0.2 mm but < 2 mm

Macrometastases: ≥ 2 mm

Outcomes

Rate of positive non-SNs

Predictive factors for positive non-SNs: factors examined were menopausal status, T stage, tumour grade, LVI, tumour histology, size of SN metastasis, method of detection of SN micrometastases (H&E vs. IHC), no. of sections, section interval, localisation of the SN (outer, inner, central), ER status, PR status.

Follow up

Not applicable

Results

Of 700 patients, size of SN deposits was known for 488 patients as follows:

ITCs ≤ 0.2 mm: 187

Micrometastases > 0.2 but ≤ 2 mm: 301

Unknown: 212.

Of 700 patients 94 (13.4%) had disease-positive non-SNs.

Rate of positive non-SNs by size of SN deposit:

ITC ≤ 0.2 mm: $30/187 = 16\%$

Micrometastases > 0.2 mm but ≤ 2 mm: $43/301 = 14.3\%$

Unknown: $21/212 = 9.9\%$ ($p=0.16$)

On univariate analysis the following variables were significantly associated with a higher rate of non-SNs: increasing T stage, presence of LVI, mixed tumour histology, and SN metastases detected by H&E analysis (c.f IHC).

On multivariate analysis the following variables were significantly associated with a higher rate of non-SNs:

T stage ≤ 20 mm vs. > 20 mm: OR 2.54 (95% CI 1.607-4.014); $p<0.0001$

Micrometastases detected by H&E vs. IHC alone: OR 1.734 (95% CI 1.084-2.773); $p=0.027$

Presence of LVI: OR 1.706 (95% CI 1.082-2.690); $p=0.021$

General comments

Since 212 patients had micrometastases of unknown size, this may reduce the study power to detect an association between SN deposit size and positive non-SNs.

Variables analysed as predictive factors reflect the manner in which data was available for collation retrospectively, across 16 centres.

Katz, Niemierko, Gage, Evans, Shaffer, Fleury & Smith . Can axillary dissection be avoided in patients with sentinel lymph node metastasis? J.Surg.Oncol. 93[7], 550-558. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Tertiary care

Inclusion criteria

Patients treated with SLNB between 1998 and 2003.

110 patients had DCIS, out of a larger series of 1133 patients.

307 patients underwent mastectomy and 833 breast conserving surgery. In 8 patients the type of definitive surgery was unknown.

367 patients had disease-positive SNs.

Exclusion criteria

Retrospective study: none reported.

Population

number of patients = 367, age range 30 to 96 years, median age = 57 years.

Interventions

Retrospective analysis of 1148 SLNB procedures in 1133 patients treated at a single centre and recorded on a pathology database.

All patients underwent SLNB and were found to have positive SNs. 246 patients underwent ALND.

Aim: to identify predictive factors for the involvement of non-SNs in patients with a SN metastasis.

Histology technique:

1. SNs: Frozen section intraoperatively; H&E analysis of 2 levels at 60 micron spacing; IHC performed on all SNs negative on H&E and for all invasive carcinomas.

2. Non-SNs: H&E, 1 level.

Size classification for SN metastases:

$\leq 0.2\text{mm}$ (i+)

0.21-2.0mm (IHC)

$\leq 2.0\text{mm}$ (H&E)

2.1-4.0mm (H&E)
4.1-10.0 (H&E)
>10.0 (H&E)
Unknown

Outcomes

Risk factors for the presence of SN metastases.

Risk factors for the presence of further axillary node metastases in patients who undergo axillary clearance for positive SLNB result.

Factors examined were: age, primary surgery/histology, size of the lesion, nuclear grade, LVI, number of SNs involved, number of SNs uninvolved, number of SNs examined, size of the largest SN metastasis, method of SN metastasis detection, extranodal extension, and estrogen and progesterone receptor status

Follow up

No follow-up reported, study assesses predictive factors for SN and non SN axillary nodal involvement.

Results

367 patients had disease-positive SNs of these 246 (67%) underwent ALND. 121 patients had involved SNs and did not undergo axillary clearance.

Prevalence of axillary disease = $367/1148 = 32\%$

Risk factors for involvement of non-SNs

By Pearson Chi square (univariate analysis) the proportion of patients with positive further nodes varied significantly by subgroup for the following variables (as categorical variables):

Presence of lymphovascular invasion ($p=0.001$);

Number of SNs examined (higher rates of further nodal involvement where fewer SNs were examined, $p=0.03$);

Histological method to detect SN metastasis (higher rates of further nodal involvement for H&E, $p=0.03$);

Number of involved SNs (higher rates of further nodal involvement where ≥ 3 SNs involved, $p=0.002$ for H&E histology and $P=0.05$ for any histological technique);

Number of uninvolved SNs (higher rates of further nodal involvement where fewer SNs uninvolved, $p<0.001$);

Size of the largest SN metastasis ($p<0.001$) as follows:

Size of largest SN metastasis	n		%
$\leq 0.2\text{mm}$ (i+)	7	1	14%
0.21-2.0mm (IHC)	10	0	0%

<=2.0mm (H&E)	48	11	21%
2.1-4.0mm (H&E)	26	7	30%
4.1-10.0 (H&E)	74	35	55%
>10.0 (H&E)	67	43	59%
Unknown	21	2	25%

By Pearson Chi square the proportion of patients with involved non-SNs did not vary significantly by subgroup for the following variables (as categorical variables):

Age;

Type of definitive surgery;

Tumour size;

Histology.

On multiple logistic regression analysis the presence of lymphovascular invasion, increasing number of positive SNs, increasing size of the largest SN metastasis and decreasing number of negative SNs were statistically significantly associated with further axillary node involvement (no further details reported).

General comments

It is not reported, but this series of patients appear to have been treated in an operational phase for SLNB i.e. without planned axillary clearance for any patients irrespective of SN status.

Patients with disease-positive SNs underwent ALND or not, at the discretion of the treating surgeon in consultation with the patient.

Katz, Niemierko, Gage, Evans, Shaffer, Smith, Taghian & Magnant . Factors associated with involvement of four or more axillary nodes for sentinel lymph node-positive patients. *Int.J.Radiat.Oncol.Biol.Phys.* 65[1], 40-44. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3

Country: USA, setting: Secondary care

Inclusion criteria

224 patients who underwent SLNB and ALND due to disease-positive SNs. Patients were treated at a single centre between 1998 and 2003.

Exclusion criteria

22 patients who did not undergo ALND in spite of a positive SN (at the discretion of the treating physician).

Population

number of patients = 224, age range 32 to 90 years, median age = 52 years.

Interventions

Retrospective analysis of 1148 SLNB procedures in 1133 patients treated at a single centre and recorded on a pathology database.

All patients underwent SLNB and were found to have positive SNs. 246 patients underwent ALND.

Aim: to identify predictive factors for the involvement of non-SNs in patients with a SN metastasis.

Histology technique:

1. SNs: Frozen section interoperatively; H&E analysis of 2 levels at 60 micron spacing; IHC performed on all SNs negative on H&E and for all invasive carcinomas.

2. Non-SNs: H&E, 1 level.

Size classification for SN metastases:

<=2.0 mm

2.1-4.0 mm

4.1 - 10.0mm

>10.0mm

Outcomes

Rate of occurrence of four or more nodes, by subgroup for SN deposit size.

Risk factors for the presence of four or more involved nodes in patients who undergo axillary clearance for positive SLNB result.

Factors examined were: age, primary surgery, size of the lesion, nuclear grade, LVI, number of SNs involved, number of SNs uninvolved, number of SNs examined, size of the largest SN metastasis, method of SN metastasis detection, extranodal extension, and estrogen and progesterone receptor status.

Follow up

Not applicable

Results

The rate of axillary dissection in patients with positive SNs was 224/246 = 91.1%.

42/224 = 18.8% of patients had four or more positive axillary nodes as follows:

Size of largest SN metastasis	no. cases	no. with ≥ 4 involved nodes	%
$\leq 0.2\text{mm}$	56	0	0%
2.1-4.0mm	26	1	4%
4.1-10.0 mm	74	17	23%
$>10.0\text{ mm}$	68	24	35%
Unknown	4	1	25%

On univariate analysis, increasing tumour size, lobular histology, LVI, increasing no. of involved SNs, fewer uninvolved nodes and size of SN metastasis (as shown above; $p < 0.001$) were all statistically significantly associated with four or more positive nodes.

On multivariate analysis the following variables were statistically significant predictors of four or more metastatic nodes:

Variable	OR	95% CI	p value
LVSI	3.2	1.4-7.6	0.008
No. +ve SNs	2.6	1.4-4.9	0.003
Size of SN deposit	1.1	1.0-1.2	<0.001
Histology (ductal vs. lobular)	0.2	0.1-0.6	0.002

General comments

Paper reports on the same patient series as in a second paper by the same team of authors (also included), but with a different outcome measure.

Paper states 'four or more involved nodes' which taken literally, includes the

SN.

van Rijk, Peterse, Nieweg, Oldenburg, Rutgers & Kroon . Additional axillary metastases and stage migration in breast cancer patients with micrometastases or submicrometastases in sentinel lymph nodes. Cancer 107[3], 467-471. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: The Netherlands, setting: Tertiary care

Inclusion criteria

160 patients who underwent SLNB followed by ALND due to the finding of SN micrometastases/ITCs. Patients were identified from a larger series of 2150 who underwent SLNB, of whom 649 had disease-positive SNs.

Exclusion criteria

349 patients with SN macrometastases (> 2 mm in size);
93 patients with SN micrometastases/ITCs (<= 2mm in size) who did not undergo ALND.

Population

number of patients = 160.

Interventions

Aim: to investigate the incidence of micrometastases and ITCs in the sentinel lymph node, to estimate the risk of additional metastasis in the remaining axillary lymph nodes, and to consider the implications for staging and treatment.

All patients underwent SLNB plus ALND.

Authors performed a retrospective review of SN histology slides.

Histological assessment:

1. Sentinel nodes: bisected or sectioned in 2 mm slices and completely embedded. Paraffin blocks cut at 3 levels with minimally 150 micron intervals. H&E assessment with in case of a tumor-negative sentinel node with H&E staining.

2. Non-sentinel nodes from ALND: 3 nodes evaluated at 1 level and stained with H&E; IHC not routinely performed.

SN deposit size criteria:

ITCs: <= 0.2 mm

Micrometastases: 0.2 mm to <=2 mm

Macrometastases: >2 mm

Stage criteria:

pN0(i+): no regional lymph node metastasis histologically, positive morphological findings;

pN1mi: micrometastases; 0.2 mm <=2 mm;

pN1a, 1-3 involved axillary nodes;

pN2a, 4-9 involved axillary lymph nodes

Outcomes

Rate of performance of ALND;

Prevalence of disease-positive non-SNs revealed by ALND;

Rate of understaging by SLNB, in the light of further staging information by ALND.

Follow up

Not applicable

Results

Of 253 patients with ITC/micrometastatic SN deposits, 160 underwent ALND i.e. rate 160/253 = 63.2%.

Rate of further positive axillary nodes revealed by ALND by size of SN deposit:

Size of SN deposit	No. cases	No. with further positive nodes by ALND (%)	Size of non-SN deposit by ALND		
			Submicro <= 0.2 mm	Micro 0.2 mm to <=2 mm	Macro >2 mm
ITCs: <= 0.2 mm	54	4 (7.4%)	2	0	2
Micrometastases: 0.2 mm to <=2 mm	106	20 (18.9%)	-	4	16

Of 24 patients with further positive non-SNs, 18 were upstaged by ALND. Of these 18, 7 (all with micrometastasis in the SN) were offered systemic treatment that would not have been offered without the information from ALND. In the remaining 11 patients, systemic therapy was indicated by other patient/disease factors.

Stage Migration in Patients With Micrometastases and submicrometastases after ALND

SN stage	n cases	pN0 (i+)	pN0 (i+)	ALND stage	
				pN1a	pN2a
pN0 (i+)	54	2	0	2	0

pN1mi	106	0	4	10	6
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General comments

Histological classification uses the terms 'ITC' and 'submicrometastasis' synonymously.

The rate of performance of ALND is not an outcome specified by the paper, although data permit its use. However in this retrospective study the performance of ALND is not the result of a prospective study protocol.

Viale, Maiorano, Pruneri, Mastropasqua, Valentini, Galimberti, Zurrada, Maisonneuve, Paganelli & Mazzarol . Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy.[see comment]. Ann.Surg. 241[2], 319-325. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Italy, setting: Tertiary care

Inclusion criteria

1228 patients with breast cancer of tumour size ≤ 3 cm who were treated at a single centre within the years 1997-2003 with SLNB and also axillary clearance due to metastatic SNs.

Exclusion criteria

No further details reported.

Population

number of patients = 1228, age range 26 to 82 years, mean age = 53 years.

Interventions

Aim: to assess the actual prevalence of ITC only in the axillary SLN of patients with breast cancer and its predictive implications on the status of the remaining axillary lymph nodes.

The authors performed a pathology review and measured the largest axis of the SN metastasis.

Histology technique:

1. Sentinel nodes:

Fifteen pairs of adjacent 5 micron thick sections cut at 50 micron intervals from both lymph node halves, i.e. 60 sections per node; for remaining tissue: sections at 100 micron intervals. H&E analysis of one section of each pair and cytokeratin analysis by MNF116 monoclonal antibody for the other section.

2. Non-sentinel nodes:

3-6 H&E-stained sections per node, at 100- to 500 micron intervals.

SN deposit size criteria:

ITC: < 0.2 mm

Micrometastases: 0.2-2 mm (also analysed as ≤ 1 mm and 1-2mm)

Macrometastases: > 2 mm

Outcomes

Prevalence of further positive non-SNs

Size of SN metastasis as a predictive factor for positive non-SNs in univariate and multivariate analyses. Co-variables included age, sex, tumour diameter and histology, grade and proliferative fraction, multifocality, ER, PR and HER2-neu receptor status, LVI, no. of positive SNs.

Follow up

Not applicable

Results

Distribution of non-SN metastases by size of SN metastases:

SN metastases size	No. cases	No. with +ve non-SNs (%); p	Non-SN metastases size		
			ITC: <0.2 mm	Micrometastases: 0.2 mm – 2 mm	Macrometastases: >2 mm
ITC: <0.2 mm	116	17 (14.7%)	1	3	13
Micrometastases: 0.2 mm – 2 mm	318	68 (21.4%); p=0.15	6	20	42
Macrometastases: >2 mm	794	399 (50.3%); p<0.0001	12	27	360
Total	1228	484 (39.4%)	19	50	415

Distribution of non-SN metastases by size of SN metastases (data for 318 patients with micrometastases):

SN metastases	SN metastases size	No. cases	No. with +ve non-SNs (%)	p
Micrometastases	0.2-1 mm	212	36 (17.0%)	
	1-2 mm	106	32 (30.2%)	0.009
Total		318		

On univariate analysis, the following variables were found to statistically significantly predict non-SN involvement in patients with positive SNs: SN metastasis size, no. of positive SNs, tumour size, tumour grade and presence of LVI.

On multivariate analysis the following variables were found to statistically significantly predict non-SN involvement in patients with positive SNs: SN metastasis size; no. of positive SNs, tumour size, tumour grade and presence of LVI.

Results of multivariate analysis: factors predictive of non-SN involvement in patients with positive SNs.

Factor	Value	OR	p
SN metastasis size	<= 1 mm	1.00	
	1-2 mm	2.24 (95% CI 1.35-3.73)	0.0019
	> 2 mm	4.57 (95% CI 3.27-6.38)	<0.0001
No. +ve SNs	1	1.00	
	>=2	2.47 (95% CI 1.68-3.62)	<0.0001
LVI	Absent	1.00	
	Present	2.12 (95% CI 1.64-2.75)	<0.0001
Tumour size	<=1 cm	1.00	
	1-2 cm	0.88 (95% CI 0.61-1.26)	0.47
	> 2 cm	1.24 (95% CI 0.82-1.87)	0.32
Tumour grade	I	1.00	
	II-III	1.37 (95% CI 0.96-1.94)	0.08

Using the statistically significantly predictive variable on multivariate analysis, the authors applied a predictive model to the same series of patients as follows:

SN metastases size	LVI	No. +ve SNs	No. cases	% of cases with +ve non-SNs	OR	p
<= 1 mm	Absent	1 SN +ve	217	13.4%	1.00	
		2 SN +ve	7	14.3%		
	Present	1 SN +ve	99	22.2%	1.84 (95% CI 1.00-3.35)	0.0480
		2 SN +ve	5	20.0%		<0.0001
> 1 mm	Absent	1 SN +ve	459	34.9%	3.46 (95% CI 2.25-5.32)	<0.0001
		2 SN +ve	69	66.7%	12.93 (95% CI 6.88-24.3)	<0.0001
	Present	1 SN	308	57.8%	8.85 (95% CI 5.67-	<0.0001

		+ve			13.8)	
		2 SN +ve	64	73.4%	17.87 (95% CI 9.10- 35.1)	<0.0001

General comments

The predictive model is based on the predictive variables from multivariate analysis and is applied to the same patient series. For this reason it is not surprising that cumulative negative disease factors are associated with increasing odds of positive non-sentinel nodes. Some odds ratios are missing, possibly for subgroups with few patients.

Chen, S. L., Hoehne, F. M. & Giuliano, A. E. (2007) The prognostic significance of micrometastases in breast cancer: A SEER population-based analysis. *Annals of Surgical Oncology*, 14: 3378-3384.

Design: Retrospective Study
Country: US

Aim: To assess whether micrometastatic disease (N1mi) alone can predict a poorer prognosis for patients with early breast cancer.

This study investigated whether the survival of patients with solely micrometastatic disease (N1mi) would be intermediate to patients with 1-3 tumour-positive lymph nodes (N1) and those with no positive lymph nodes (N0).

Inclusion criteria

The surveillance, epidemiology and end results (SEER) database for all patients between 1992 and 2003 with invasive ductal or lobular breast cancer without distant metastases and ≤ 3 axillary nodes with macroscopic disease.

- Patients had a diagnosis of histologically confirmed infiltrating ductal or infiltrating lobular breast cancers.
- Study population contained either no regional lymphatic spread (N0), or patients with nodal spread limited to micrometastases, no larger than 2 mm (N1 mi) and patients with macrometastases in no more than 3 nodes (N1).

Exclusion criteria

Patients with an unknown number of tumour- involved nodes, insufficient staging information and evidence of distant mets.

Population

N= 209,720 patients

Interventions

- All patients were restaged with AJCC 6th ed. criteria for T-stage and N-stage.
- Patients were stratified by nodal involvement and compared using the Kaplan-Meier method.

Outcomes

Cox proportional hazards regression was used to compare survival after adjusting for patient and tumour characteristics.

Results

- N1mi diagnoses increased from 2.3% to 7% among the 209,720 study patients ($p < 0.001$).
- Overall, N1mi patients had a statistically worse survival than N0 patients and better than N1 patients.
- In a T-stage stratified univariate analysis, N1mi patients had a poorer prognosis when compared to N0 patients. However, this was only significant for patients with T2 lesions (univariate analysis, $p < 0.001$)
- There was statistical better survival in N1mi patients compared to N1 patients with T1-T3 lesions.
- 5 and 10 year survival was intermediate for N1mi patients when compared to N0 and N1

patients.

- On multivariate analysis, N1mi remained a significant prognostic indicator across all patients ($p < 0.0001$).
- HR (hazard ratio)= 1.35 (compared to N0 disease)
- HR = 0.82 (compared to N1 disease)
- Other negative prognostic factors included male gender, oestrogen-receptor negativity, progesterone-receptor negativity, lobular histology, higher grade, older age, higher T-stage, and diagnosis in an earlier time period.

General comments

Author's Conclusion: Nodal micrometastasis of breast cancer carries a prognosis intermediate to N0 and N1 disease, even after adjusting for tumour and patient related factors. Adjuvant therapy trials should consider using N1mi as a stratification factor when determining nodal status. Prospective studies will confirm results with less bias involved.

3.6 When is it appropriate to perform immediate breast reconstructive surgery?

Short Summary

A moderate volume of observational studies exists for breast reconstruction following mastectomy for breast cancer. There are few direct comparisons of immediate reconstruction versus delayed reconstruction.

With respect to psychological outcomes one systematic review of observational studies suggests that better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction (Fischbacher *et al.* 2002). Subsequently published observational studies suggest that psychological outcomes are generally good following immediate reconstruction (Drucker-Zertuche and Robles-Vidal 2007; Gendy *et al.* 2003).

There is high heterogeneity with regard to assessment of cosmetic outcome between the studies. No evidence was identified from one systematic review of observational studies and subsequent observational studies to suggest superiority of immediate versus delayed reconstruction in terms of cosmetic result. The majority of the observational studies report high rates of acceptable cosmetic results between 80% and 96% (Anderson *et al.* 2004; Drucker-Zertuche and Robles-Vidal 2007; Gendy *et al.* 2003; Cordeiro *et al.* 2004; Vandeweyer *et al.* 2003) whereas in one study the reported rate is only 20% (Knottenbelt *et al.* 2004).

Two systematic reviews of observational studies suggest that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction (Fischbacher *et al.* 2002; Javaid *et al.* 2006). A third less rigorous review found similar rates of capsular contraction between immediate and delayed reconstruction with implants, but with a trend for unfavourable results with immediate autologous tissue reconstruction (Taylor *et al.* 2005). Apart from radiotherapy, studies that examined potential risk factors for complications following reconstruction did not consistently identify any other factors (Anderson *et al.* 2004; Woerdeman *et al.* 2006).

No reliable evidence was identified on whether immediate breast reconstruction following mastectomy delays the start of adjuvant chemotherapy or radiotherapy. Whilst a minority of observational studies included in an expert review (Taylor and Kumar 2005) indicated that such delays occur after immediate reconstruction, the review's authors concluded that the evidence was inconclusive. Subsequently published observational studies have demonstrated little difference in the interval from surgery to adjuvant therapy in patients treated with immediate reconstruction compared to those for whom reconstruction is delayed, or those who do not receive reconstruction (Gouy *et al.* 2005; Taylor & Kumar 2005; Wilson *et al.* 2004; Rey *et al.* 2005).

No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction. One systematic review citing observational studies reported no difference in recurrence and survival following mastectomy with immediate reconstruction compared to mastectomy with no reconstruction. One expert review (Taylor *et al.* 2005), summarised the rate of local

recurrence with a median value of 5%, drawn from observational studies of patients treated with mastectomy and immediate reconstruction. The rate of distant metastasis in 16 studies of similarly treated patients had a median value 10.5%.

Evidence from observational studies suggests that in general, patients are satisfied with their reconstructed breasts following either immediate reconstruction, or delayed reconstruction. However some patients are not satisfied with their reconstructions and the impact of this is not further explored by the identified studies (Tykka *et al.* 2002; Ascherman *et al.* 2006; Cordeiro *et al.* 2004; Vandeweyer *et al.* 2003). Very little direct evidence for women’s preference for immediate versus delayed breast reconstruction was identified.

PICO

Population	Intervention	Comparison	Outcome
Patients with breast cancer who undergo total breast reconstruction following mastectomy.	Immediate total breast reconstruction	Delayed total breast reconstruction (e.g. >6 months after definitive surgery)	<ul style="list-style-type: none"> • Patient preferences • Effect on type of procedure offered • Cosmetic outcome – including longterm • Psychological outcome • Complication rates (short and long term) • Local recurrence rates • Delay in oncological treatment

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

A moderate volume of evidence from observational studies of breast reconstruction following mastectomy for breast cancer exists including two systematic reviews and an expert review of observational studies.

There are few direct comparisons of immediate reconstruction versus delayed reconstruction with the majority of recent studies appearing to focus on immediate reconstruction.

The studies vary in their inclusion of patient series who were treated with autologous tissue reconstruction (commonly TRAM or latissimus dorsi flap reconstructions) or prosthetic implants (permanent or possibly using a temporary expander) or with a combination of autologous tissue and implant. The studies vary also with regard to adjuvant therapies; radiotherapy and chemotherapy may affect some outcomes.

The majority of data originate from observational studies, many of them representing small patient series or samples with high heterogeneity across studies. As such the findings in this report should be interpreted cautiously.

Evidence suggests that better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction.

There is no high quality evidence on cosmetic outcome following immediate versus delayed reconstruction.

Poor quality evidence suggest that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction

There is no evidence differences in overall survival or recurrence in immediate versus delayed surgery.

Evidence from a single retrospective study from the UK suggests that the use of immediate reconstruction increased over the period 1997-1999, and also reconstruction with autologous tissue.

Psychological outcomes

One systematic review of observational studies suggests that better psychological outcomes arise in patients treated with immediate reconstruction compared to delayed reconstruction (Fischbacher *et al.* 2002). A randomised trial included in the same systematic review found that patients treated with immediate reconstruction had similar psychological outcomes over the first post-operative year compared to patients who could expect reconstruction at a later date.

One prospective case series study (Drucker-Zertuche and Robles-Vidal 2007) measured patients' satisfaction with their reconstructions, perception of body image and quality of life following immediate reconstruction (autologous, expander/implant or in combination). Patient perception of body image was reported as 'very good' or 'good' in 84% of cases. 90% of patients reported that their sexual life was unchanged following surgery and 94% that their social life was unchanged following surgery.

A prospective case series study (Gendy *et al.* 2003) measured quality of life in patients treated with immediate latissimus dorsi myocutaneous flap reconstruction, 21% of whom received adjuvant RT. Quality of life was assessed using 4 different quantitative scales. Results were as follows:

Anxiety as measured with the Hospital anxiety and depression scale (HADS) was as follows:

Normal (score 0-7): 65%

Mild (score 8-10): 21%

Moderate (score 11-14): 14%

Severe (score 15-21): 0%

HADS anxiety score had mean 5 (range 0-14) NB (score range 0-21; low score represents low anxiety)

Depression as measured with the Hospital anxiety and depression scale (HADS) was as follows:

Normal (score 0-7): 93%
Mild (score 8-10): 5%
Moderate (score 11-14): 2%
Severe (score 15-21): 0%

HADS depression score had mean 1 (range 0-10) NB (score range 0-21; low score represents low depression)

Mean Rosenberg self-esteem scale (RSE) was 24 (range 10-29) NB score range 10-40; low score indicates high self esteem

Mean Hopwood body image scale (HBIS) was 5 (range 0-21) NB score range 0-30; low score represents less disturbance of body image

Concern regarding residual cancer had a mean score of 45 (visual analogue scale; possible range 1-100).

Cosmesis

There is no high quality evidence on cosmetic outcome following immediate versus delayed reconstruction, so findings should be interpreted with caution. There is high heterogeneity with regard to assessment of cosmetic outcome between the studies. No evidence was identified from one systematic review of observational studies and subsequent observational studies to suggest superiority of immediate versus delayed reconstruction in terms of cosmetic result.

One systematic review of observational studies suggests that study results for cosmesis following immediate versus delayed reconstruction are inconclusive (Fischbacher *et al.* 2002).

One retrospective comparative study (Anderson *et al.* 2004) found in univariate analysis that the sequencing of breast reconstruction (immediate or delayed until after adjuvant radiotherapy) was not a statistically significant risk factor for adverse cosmetic outcome. Cosmetic result was assessed as 'excellent/good' in 85% of the whole series (immediate plus delayed reconstruction) and as 'fair/poor' in 15% of the whole series.

One retrospective comparative study (Spear *et al.* 2005) found no statistically significant difference between patients who underwent TRAM after RT and those who underwent TRAM before RT with regard to scores for aesthetic result, symmetry or hyperpigmentation. In this study cosmesis was assessed by 16 blinded, independent individuals. Patients who received no RT had generally better cosmetic outcomes than patients in either RT-treated subgroup

One prospective case series (Drucker-Zertuche and Robles-Vidal 2007) assessed aesthetic outcome using 8 separate ordinal scales (shape with brassiere, shape without brassiere, contralateral match, inframammary fold, mobility, consistency, overall result, projection) in patients treated with immediate reconstruction. There was no difference in overall aesthetic result between the three types of reconstruction (TRAM flap versus expander/implant versus Latissimus dorsi flap + implant); $p = \text{NS}$. For individual scales, mobility and consistency in the reconstructed breast was closer to that of the contralateral breast in patients who received TRAM reconstruction ($p=0.015$) but for all other aesthetic scales, there were no statistically significant differences between reconstruction groups. The surgeon evaluated the aesthetic result as 'excellent' or 'good' (rather than 'fair' or 'poor') in 91% of cases.

In one prospective case series (Gendy *et al.* 2003) patients underwent skin sparing mastectomy with immediate latissimus dorsi myocutaneous flap reconstruction; 21% of whom received adjuvant RT. Cosmesis was assessed by patients, a blinded multi-disciplinary panel of 5 assessors and by breast retraction assessment (BRA). Overall a good cosmetic result was achieved. A marked degree of retraction by BRA was observed in 14% of patients. Patients rated their cosmetic result with a mean score of 72 out of a highest possible 100, but with wide range in score (3-100).

One retrospective case series (Ascherman *et al.* 2006) studied cosmesis following immediate reconstruction with tissue expander/implant. Mean symmetry score was statistically significantly higher in patients who received no RT compared to those who received RT.

One retrospective case series (Cordeiro *et al.* 2004) studied patients treated with immediate tissue expander/implant reconstruction and found the Proportion of patients with 'good' or 'excellent' aesthetic result to be 80% where RT was subsequently given compared with 88% where no radiotherapy was subsequently given ($p=0.006$).

One retrospective case series (Knottenbelt *et al.* 2004) examined cosmetic result in patients who underwent immediate reconstruction with subpectoral tissue expander. Cosmesis was assessed by the plastic surgeon and surgical oncologist as 'excellent' or 'good' in 20% of patients.

One retrospective case series (Vandeweyer *et al.* 2003) examined complications in patients treated with immediate expander reconstruction, with comparison groups for patients treated with, and without adjuvant chemotherapy. There were no statistically significant differences between groups in the rate of implant displacement, implant deflation, breast symmetry (assessed as optimal or satisfactory in approximately 96% of cases in each group), breast volume compared to the preoperative assessment and location of intramammary fold compared to the preoperative assessment.

Complications

There is no high quality evidence on complications following immediate versus delayed reconstruction, so findings should be interpreted with caution.

One systematic review of observational studies suggests that immediate reconstruction may be associated with a higher rate of complications compared to delayed reconstruction (Fischbacher *et al.* 2002). An expert review (Taylor *et al.* 2005) found that capsular contraction occurred at a median rate of 33% (range 2%-73%) in patients treated with immediate expander/implant reconstruction followed by radiotherapy. The median rate of capsular contraction in patients treated with radiotherapy then delayed expander/implant reconstruction was 35% (range 26%-60%). In patients who received autologous tissue reconstruction the rate of flap tissue necrosis/loss had a median value of 44% (range 0%-59%) where reconstruction was immediate and followed later by radiotherapy, and a median value of 15% (range 5%-34%) where reconstruction was delayed until after radiotherapy (Taylor *et al.* 2005). A subsequent systematic review (Javaid *et al.* 2006) found that complications (necrosis, delayed wound healing, fibrosis, capsular contracture) were more frequent in patients treated with immediate reconstruction followed by radiotherapy than in

patients in whom reconstruction was delayed, and also compared to control groups (no radiotherapy).

One retrospective comparative study (Anderson *et al.* 2004) found in univariate analysis that the sequencing of breast reconstruction (immediate or delayed until after adjuvant radiotherapy) was not a statistically significant risk factor for complications. Other factors explored as potential risk factors for complications were smoking history, type of reconstruction, type of bolus used, use of RT boost, sequencing of reconstruction and use of systemic therapy. Of all the factors examined in the univariate analysis, only bolus type was predictive of complications.

One retrospective comparative study (Gouy *et al.* 2005) found that the need for further corrective cosmetic surgery arising from complications within two years of surgery was equal at 50% in patients who received immediate reconstruction and those who received delayed reconstruction. Capsular contracture of Baker grade II-IV occurred in 64% of patients who underwent immediate reconstruction with an implant. In the whole study 96% of patients received radiotherapy.

One retrospective comparative study (Mortenson *et al.* 2004) found the crude rate of complications in a subgroup of patients treated with mastectomy plus immediate reconstruction to be 22%. The mean follow-up in the entire study was 33 months.

One retrospective comparative study (Spear *et al.* 2005) found no statistically significant difference in the crude rate of short-term complications between patients treated with immediate (before radiotherapy) TRAM flap reconstruction (50%) and those in whom TRAM flap reconstruction was delayed until after radiotherapy (57%; $p=NS$). Mean contracture score was higher (representing less contracture) in patients who underwent TRAM after RT (3.81) than in patients who underwent TRAM before RT (2.86), $p=0.009$.

One prospective case series (Benediktsson and Perbeck 2006) found the crude rate of capsular contracture (Baker grade III-IV) in patients treated with immediate reconstruction with a subcutaneously located prosthesis to be 21%. The rate was 42% in the subgroup of patients who subsequently received radiotherapy compared to 15% in the subgroup of patients who did not receive radiotherapy ($p=0.012$).

One prospective case series (Drucker-Zertuche and Robles-Vidal 2007) found the crude rate of complications (predominantly short-term) in patients treated with immediate reconstruction to be 26%. This included two cases of symptomatic capsular contracture. The majority of complications (81%) occurred in patients who subsequently received radiotherapy.

One retrospective case series (Ascherman *et al.* 2006) studied complications following immediate reconstruction with tissue expander/implant. The crude rate of major complications leading to implant loss was 9%, and of minor complications not leading to implant loss, 17%. Radiotherapy was associated with major complications (19% where radiotherapy was given compared to 4% where no radiotherapy was given; $p<0.025$) but not with minor complications (22% where radiotherapy was given compared to 13% where no radiotherapy was given; $p = NS$).

One retrospective case series (Cordeiro *et al.* 2004) studied patients treated with immediate tissue expander/implant reconstruction and found the rate of implant removal due to complications to be 7%, and the rate of capsular contracture (Baker grade II-IV) to be 53%. Radiotherapy was associated with implant removal (11% where radiotherapy was given compared to 6% where no radiotherapy was given; $p < 0.0001$) and with capsular contracture (67% where radiotherapy was given compared to 40% where no radiotherapy was given; $p = 0.006$).

One retrospective case series (Henriksen *et al.* 2005) of predominantly delayed implant reconstructions performed with prostheses found the overall crude rate of any adverse event to be 31%, with the incident rate per 1000 patient months being 23%. These data were from initial reconstructions, rather than second procedures (i.e. either planned, or arising from complications).

One retrospective case series (Rey *et al.* 2005) provided data for early and late complications in the first postoperative year in subgroups of patients who underwent immediate reconstruction and either conventional chemotherapy ($n=67$), or high dose chemotherapy ($n=23$). In the larger series of 105 patients, 72% received adjuvant radiotherapy. The crude rate of early complications in patients treated with reconstruction was 2%, and late complications, 22%. Crude rates of capsular contracture were 22% (high dose chemotherapy) and 16% (conventional chemotherapy); $p=0.51$.

One retrospective case series (Vandeweyer *et al.* 2003) examined complications in patients treated with immediate expander reconstruction, with and without adjuvant chemotherapy. The crude rate of short term complications in all patients was 13%. Total complications occurred in 25% of patients in the chemotherapy group and in 8% of patients in the control group; $p = 0.04$. Complications warranting implant removal occurred in 11% of the chemotherapy group and 2% of the control group; $p = 0.0084$. There was no statistically significant difference between groups in the distribution of capsular contracture grade ($p=1$; Fisher's exact test); 70% of patients in the chemotherapy group and 63% of patients in the no chemotherapy group had capsular contracture of grade I.

One retrospective case series (Woerdeman *et al.* 2006) found the crude rate of complications in patients treated with immediate expander/implant reconstruction to be 33%. The crude rate of severe complications leading to implant loss was 14%. In univariate analysis only age and unilateral surgery were statistically significant risk factors for short-term complications. The only statistically significant risk factors for serious complication resulting in loss of implant were being treated by a resident plastic surgeon and a history prior to mastectomy of breast conserving surgery and RT.

One prospective case series (Sandelin *et al.* 2004) found the crude rate of complications occurring within 30 days of surgery following immediate reconstruction to be 11%.

Delay to adjuvant therapy

No reliable evidence was identified on whether immediate breast reconstruction following mastectomy delays the start of adjuvant chemotherapy or radiotherapy. Whilst a minority of observational studies included in an expert review (Taylor & Kumar 2005) indicated that such

delays occur after immediate reconstruction, the review's authors concluded that the evidence was inconclusive.

One expert review (Taylor and Kumar 2005) found that in nine observational studies there was no difference in the time to onset of chemotherapy between patients who underwent mastectomy and immediate reconstruction versus mastectomy alone. However in the same review two observational studies were suggestive of a delay in starting chemotherapy arising from post-operative complications following immediate reconstruction (Taylor and Kumar 2005). A higher quality systematic review (Fischbacher 2002) found that the evidence on whether immediate reconstruction delays chemotherapy is inconclusive.

One retrospective comparative study (Gouy *et al.* 2005) found no statistically significant difference in the mean interval from surgery to starting adjuvant chemotherapy between patients who received immediate reconstruction (26 days) and those who received delayed reconstruction (23 days); $p=0.11$. There was also no statistically significant difference in the interval to radiotherapy (87 and 81 days respectively; $p=0.22$). There was also no difference in mean interval between surgery and onset of adjuvant treatment according to the type of immediate reconstruction performed:

One retrospective comparative study (Taylor & Kumar 2005) examined whether immediate breast reconstruction had an impact on chemotherapy in terms of dose given, need for supportive treatment and delays in commencing/continuing chemotherapy. The mean time from surgery to chemotherapy initiation was similar between groups as follows:

Mastectomy: 38 days

Immediate reconstruction: 36 days

The most commonly recorded cause of a delay in starting chemotherapy of > 40 days was incomplete wound healing, which occurred in 41% in patients treated with TRAM reconstruction and 4% of patients treated with mastectomy without reconstruction. The proportion of patients treated with full intended dose of chemotherapy was also similar between groups, as follows:

Mastectomy: 97%

Immediate reconstruction: 95%

One retrospective comparative study (Wilson *et al.* 2004) assessed whether immediate breast reconstruction following mastectomy leads to a delay in the delivery of chemotherapy. The median time from surgery to the start of chemotherapy was similar between groups: 29 (range 17-55) days in the immediate reconstruction group and 28 (range 16-52) days in the mastectomy alone group.

A retrospective case series (Rey *et al.* 2005) studied whether high dose chemotherapy is delayed by immediate breast reconstruction. There was no statistically significant difference in the interval from surgery to the start of high dose chemotherapy between patients treated with immediate reconstruction (54 days) and those treated with mastectomy without reconstruction, (60 days); $p= 0.13$.

Recurrence/survival

No reliable evidence was identified to suggest that recurrence or survival differs in patients treated with immediate reconstruction compared to those who receive delayed reconstruction.

In one systematic review (Fischbacher *et al.* 2002) and one expert review (Taylor *et al.* 2005), observational studies reported no difference in recurrence and survival following mastectomy with immediate reconstruction compared to mastectomy with no reconstruction. In the systematic review (Fischbacher *et al.* 2002) one study reported a lower risk of recurrence in women who had immediate reconstruction, but did not adjust for baseline risk. The authors concluded that the evidence was insufficient (Fischbacher *et al.* 2002). One expert review (Taylor *et al.* 2005), summarised the rate of local recurrence in 19 studies of patients treated with mastectomy and immediate reconstruction with a median value of 5% (range 0-15%). The rate of distant metastasis in 16 studies of likewise-treated patients had median value 10.5% (range 2-39%).

Seven subsequently published observational studies report data on recurrence and survival following, in the majority of cases, immediate reconstruction or delayed reconstruction, or both (Table).

Updated 2018

Table: recurrence and survival outcomes reported in observational studies (published subsequent to reviews by (Fischbacher *et al.* 2002) and (Taylor *et al.* 2005)

Study & reconstruction timing	Reconstruction type	Follow-up	Recurrence outcome	Survival outcome
(Gouy <i>et al.</i> 2005) Immediate vs. delayed	Mixed: Implant, Expander, TRAM, Latissimus dorsi	5-year and 10-year outcomes reported	5-year estimated local recurrence-free survival: Immediate reconstruction: 89% Mastectomy alone: 90% Delayed reconstruction: 93%; p=NS	10-year estimated distant disease-free survival: Immediate reconstruction: 48% Mastectomy alone: 43% Delayed reconstruction: 64%; p=0.04
(Drucker-Zertuche & Robles-Vidal 2007) Immediate	Mixed: TRAM flap, TEIR, Latissimus dorsi flap + implant	Mean 48 months (range 10-92 months)	Crude rates: Distant: 3/105=2.9% Loco-regional + distant: 1/105=1.0%	None
(Sandelin <i>et al.</i> 2004) Immediate	Mixed: Permanent prosthesis, expander, bilateral free TRAM, free TRAM, pedicled free TRAM	Minimum 5 years	Local recurrence: Crude rate: 13/203 = 6.4%	Deaths due to breast cancer: Crude rate: 31/203 = 15%
Henriksen, 2005 7713 /id} Delayed	Mixed: implant, or implant + autologous tissue	Initial implantation: mean 23 months, range 3-56 months; Subsequent implantation: mean 24 months, range 4-52 months.	Local recurrence: 1. Initial implantation: Crude rate: 1.7% Incidence rate per 1000 person-months: 1.1 2. Subsequent implantation: Crude rate 0.3% Incidence rate per 1000 person-months: 0.2	None
(Knottenbelt <i>et</i>	Mixed: Subpectoral	Minimum 60	Local recurrence	Disease-free

Study & reconstruction timing	Reconstruction type	Follow-up	Recurrence outcome	Survival outcome
<i>al.</i> 2004) Immediate	tissue expander, TRAM flap, or permanent implant	months	(crude rate out of all treated breasts at risk): 1/58 = 1.7% Distant metastasis (crude rate out of all treated breasts at risk): 13/58 = 22.4% (includes 1 patient with local recurrence also)	survival at 5 years: 93% Deaths with metastatic disease: 9/58 = 15.5%
(Mustonen <i>et al.</i> 2005) Immediate	Mixed, by group: 1. Wide local excision and latissimus dorsi miniflap; 2. Skin sparing mastectomy and TRAM or latissimus dorsi flap; 3. Subcutaneous mastectomy and TRAM or latissimus dorsi flap	Mean 3.6 years.	Recurrences by mastectomy-treated groups: Skin sparing mastectomy and TRAM or latissimus dorsi flap (n=22): Local: 2 Regional: 0 Distant: 3 Subcutaneous mastectomy and TRAM or latissimus dorsi flap (n=34): Local: 3 Regional: 1 Distant: 0 Difference across groups: p=NS	Estimated 5-year overall survival (all patients): 88% Estimated 5-year disease-free survival (all patients): 80%
(Woerdeman <i>et al.</i> 2006) Immediate	Mixed: permanent implant or tissue expander	Prophylactic mastectomy subgroup: mean 70 months, range 52-91 months.	Prophylactic mastectomy: zero events Curative intent subgroup: local-regional	Prophylactic mastectomy: zero events Curative intent subgroup: Distant

Study & reconstruction timing	Reconstruction type	Follow-up	Recurrence outcome	Survival outcome
		Curative intent subgroup: mean 73 months, range 53-171 months	recurrence, crude rate: 2/85=2.4%	metastasis, crude rate: 5/85=5.9% Estimated actuarial 5-year overall survival rate in patients treated with curative intent: 96%

Updated 2018

Effect on type of procedure offered

Evidence from a single retrospective study from the UK suggests that the use of immediate reconstruction increased over the period 1997-1999, and also reconstruction with autologous tissue. The proportion of patients who receive immediate autologous tissue reconstruction in whom the need for radiotherapy is anticipated changed little over time in this study: from 88% to 100%. However the data may not reflect practice today, nor variation that occurs across centres in the UK.

One retrospective case series (Hussien *et al.* 2004) studied patients treated in the UK who underwent immediate breast reconstruction with either tissue expander or autologous tissue between two time periods; January 1997 to March 1998 and March 1998 to June 1999. The study found that there was an increase in the use of immediate reconstruction, in the later period studied. Also the proportion of patients who underwent immediate reconstruction with autologous tissue alone increased in the second period relative to the first period (49% and 29% respectively, $p=0.0004$). The requirement for RT by treatment period was as follows:

Jan 97-Mar 98: 10 (24%)

Apr 98-Jun 99: 23 (29%)

In the first period autologous immediate reconstruction was performed in all 5 patients for whom RT was expected; 5 patients who unexpectedly received RT had undergone immediate implant reconstruction. In the second period 15/17 patients for whom RT was expected underwent immediate autologous reconstruction; 6 patients who unexpectedly received RT had undergone immediate implant reconstruction.

Patient satisfaction

Evidence from observational studies suggests that in general, patients are satisfied with their reconstructed breasts following either immediate reconstruction, or delayed reconstruction. However some patients are not satisfied with their reconstructions and the impact of this is not further explored by the identified studies (Tykka *et al.* 2002; Ascherman *et al.* 2006; Cordeiro *et al.* 2004; Vandeweyer *et al.* 2003).

A prospective case series study (Tykka *et al.* 2002) evaluated patient satisfaction following delayed breast reconstruction with autologous tissue. Patient satisfaction with general outcome of the operation at 6 months post-operatively was as follows:

Very good: 45%

Quite good: 48%

Quite poor: 5%

Very poor: 0%

The cosmetic outcome at 6 months against patients' preoperative expectations was as follows:

Much better than expected: 17%

Better than expected: 42%

As expected: 27%

Poorer than expected: 8%

Much poorer than expected: 3%

The patient-reported extent to which surgical scarring was a disturbance at 6 months post-operatively was as follows:

Very much: 0%

To some extent: 10%
Slightly disturbed: 60%
Not at all: 27%

The most commonly cited benefits of the delayed reconstruction were 'a new breast of one's own', 'no need for external prosthesis' and 'feeling whole'. The most commonly reported drawback of the reconstructions were 'difficult operation' and 'abdominal operation' (Tykka *et al.* 2002).

One retrospective case series (Ascherman *et al.* 2006) measured patients satisfaction following immediate tissue expander/implant reconstruction using a three-point scale: 1=dissatisfied, 2=partially satisfied, 3=fully satisfied. Mean score was 2.4 in patients who in addition received RT compared with 2.7 for patients who received no RT (p=NS).

One retrospective case series (Cordeiro *et al.* 2004) found that following immediate reconstruction tissue expander/implant, the proportion of patients who were satisfied with their reconstructions was 67% who received in addition radiotherapy versus 88% in patients who received no radiotherapy; p=0.004

One retrospective case series study (Vandeweyer *et al.* 2003) found that following immediate expander reconstruction, there was no statistically significant difference in the proportion of patients who were fully satisfied with the cosmetic result between patients who received adjuvant chemotherapy (83%) compared with patients who did not receive chemotherapy (88%; p=NS).

Patient preference

Very little direct evidence for women's preference for immediate versus delayed breast reconstruction was identified. One study with limited applicability is reported below, but it is likely to be of little value in the light of indirect evidence with better applicability e.g. audits of uptake of immediate reconstruction or delayed reconstruction over time.

One prospective comparative study (Belouli *et al.* 2005) assessed the spontaneous (i.e. no prior education on breast cancer) preference of healthy women, half of whom were nurses, for either immediate or delayed breast reconstruction. The sample included no patients with breast cancer. Overall 66% of participants voted for breast reconstruction. Of these 21% voted for immediate reconstruction, 27% for delayed reconstruction and 52% gave no preference. The most common reason for preferring immediate reconstruction was a wish to undergo only one surgical procedure (56%) followed by a wish to avoid mutilation and altered body image (44%). The most common reasons expressed against immediate reconstruction was a fear that it may mask local recurrence (62%) and secondly, a need to come to terms with cancer illness (35%).

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Evidence Tables

Systematic review of combined study designs

Fischbacher . Immediate versus delayed breast reconstruction. STEER. 2[17]. 2002.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2-

Country: Various, setting: Secondary care

Inclusion criteria

Controlled studies that compared immediate versus delayed reconstruction; or studies comparing immediate reconstruction with no reconstruction provided one of the following outcomes were reported:

- i) Psychological outcomes;
- ii) Delays to start of chemotherapy;
- iii) Recurrence and survival.

Exclusion criteria

Uncontrolled studies;

Comparisons of cosmetic effects following immediate reconstruction versus no reconstruction;

Comparisons of surgical complications following immediate reconstruction versus no reconstruction;

Population

-

Interventions

Aim: to summarise evidence on benefits and harms of immediate reconstruction compared with delayed reconstruction.

All studies included patients who underwent either prosthetic or autologous breast reconstruction following mastectomy for breast cancer.

Outcomes

Psychological measures;

Patient satisfaction;

Cosmesis;

Surgical complications;

Delay to chemotherapy;

Recurrence and survival.

Follow up

Details inconsistently reported.

Results

IMMEDIATE VERSUS DELAYED RECONSTRUCTION

Psychological outcomes

Three cohort studies found that immediate reconstruction reduced emotional distress and interference with sexual function and improved self esteem and body image compared with delayed reconstruction.

Patient satisfaction

One cohort study reported similar levels of patient satisfaction in immediate reconstruction and delayed reconstruction groups after controlling for confounding factors.

Cosmetic effects

Two cohort studies reported that satisfactory cosmetic results were slightly more common in women who had immediate reconstruction than women who had delayed reconstruction. However, the confidence intervals for the differences were wide, included the null hypothesis value of no difference and did not rule out a possible effect in favour of delayed reconstruction.

Operative complications

Three cohort studies found that complication rates were similar for immediate and delayed reconstruction. However, the confidence intervals included the null hypothesis value of no difference and were consistent with possibly large advantages for either procedure. The fourth, a larger prospective cohort study, which accounted for confounding factors, found that complications were more common with immediate reconstruction.

IMMEDIATE VERSUS NO RECONSTRUCTION

Psychological outcomes

The randomised controlled trial found that immediate reconstruction reduced psychiatric morbidity at three months compared with no reconstruction (but with expectation of reconstruction at a later date): Absolute risk for score ≥ 12 on General Health Questionnaire at 3 months 7% with immediate reconstruction versus 36% with no reconstruction (Absolute risk reduction 29%, 95% CI 7% to 48%). However, this difference was not statistically significant after adjustment for baseline differences in psychological morbidity. The unadjusted difference was much smaller at 12 months: Absolute risk for score ≥ 12 on General Health Questionnaire at 12 months 4% with immediate reconstruction versus 10% with no reconstruction (Absolute risk reduction 7%, 95% CI -9% to 23%). There was no evidence for an increased likelihood of psychiatric illness diagnosed by psychiatrist: Absolute risk at 3 months: 7% with immediate reconstruction versus 19% with no reconstruction (Absolute risk reduction 13%, 95% CI -5% to 30%); at 12 months 0% with immediate reconstruction versus 3% with no reconstruction (difference 3%, 95% CI -8% to 17%)

Delay to chemotherapy

Three cohort studies examined delay in chemotherapy resulting from immediate reconstruction versus no reconstruction. The first study reported a longer delay to the start of chemotherapy with immediate reconstruction than with no reconstruction [median interval to postoperative chemotherapy 35 days (range 5 to 91 days) with immediate reconstruction v 21 days (range 8 to 145 days) with no reconstruction ($p = 0.05$)]. The second study reported the opposite [mean interval to postoperative chemotherapy 41 days (range 14 to 131 days) with immediate reconstruction v 53 days (range 1 to 215 days) with no reconstruction ($p = 0.04$, Mann-Whitney test)]. The third reported no difference [median interval to postoperative chemotherapy 44 days (range 18 to 82 days) with immediate reconstruction v 45 days (range 11 to 81 days) with no reconstruction]. Time to chemotherapy differed substantially among studies, suggesting that factors other than reconstructive procedure may have contributed to the delay.

Cancer recurrence and survival

Four cohort studies reported that recurrence and survival were similar for immediate and no reconstruction. One study reported a lower risk of recurrence in women who had immediate reconstruction, but did not adjust for baseline risk. None of the studies provided confidence intervals for the difference.

AUTHORS' CONCLUSIONS

One randomised controlled trial was identified. The other studies were cohort studies with comparison groups that differed by other characteristics. Studies of this design are intrinsically susceptible to confounding and are therefore inconclusive.

Psychological outcomes

There is limited evidence from cohort studies and one randomised controlled trial that immediate reconstruction improves psychological outcomes compared with delayed reconstruction.

Patient satisfaction

One large cohort study found limited evidence that patient satisfaction was similar after immediate and delayed reconstruction.

Cosmetic effects

There is insufficient evidence about cosmetic effects of immediate versus delayed reconstruction.

Operative complications

One cohort study that attempted to control for confounding provided weak evidence that complications may be more common with immediate reconstruction.

Delay to chemotherapy

There is inconclusive evidence about effects of immediate versus delayed reconstruction on delay to start of chemotherapy.

Cancer recurrence and survival

There is insufficient evidence about effects on recurrence and survival of immediate versus delayed reconstruction.

General comments

18 primary studies of either prosthesis/expander reconstruction or autologous reconstruction were included, dating to 2002 and representing an estimated minimum of 3000 patients:

Systematic reviews (1)

RCT (1)

Observational studies (referred to as 'cohorts'; most likely to be case series) (16)

Although the time period of the literature studied by this review and that of Javaid et al. (2006) is similar, no primary study appears in both reviews. The review by Javais et al. (2006) was restricted to autologous reconstruction. In contrast to Javais et al. (2006) this review has little emphasis on the relationship between timing of reconstruction and radiotherapy.

Literature search:

Search date: July 2002. Primary sources: Medline 1966 to date; Embase 1980 to date; Cochrane Library Issue 2, 2002; Clinical Evidence Issue 7; Centre for Reviews and Dissemination, University of York, UK (comprising Database of Abstracts of Reviews of Effectiveness, UK Health Technology Assessment Database, NHS economic evaluation database, UK).

Assessment of study quality is evident and presented narratively. The observational studies are referred to as unreliable and subject to confounding: women treated with immediate reconstruction tended to be younger and differed with regard to tumour stage, adjuvant therapy, smoking and psychological state at the time of the operation. Many studies did not examine these confounding factors. Only four studies controlled for baseline differences between groups compared. One study matched on prognostic factors and one presented results stratified by tumour stage. In no study were outcomes assessed by individuals who were blind to treatment group.

Javaid, Song, Leinster, Dickson & James . Radiation effects on the cosmetic outcomes of immediate and delayed autologous breast reconstruction: an argument about timing. [Review] [21 refs]. Journal of Plastic., Reconstructive.& Aesthetic Surgery: JPRAS. 59[1], 16-26. 2006.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2-

Country: Various, setting: Secondary care

Inclusion criteria

Primary studies as follows:

>20 subjects;

Of patients who received autologous reconstruction following any type of mastectomy and who received radiotherapy either before or after their reconstruction;

Report cosmetic outcomes;

Included patients with failed previous breast conserving surgery plus RT.

Exclusion criteria

Studies of patients treated with breast conserving surgery without RT;

Studies of patients who received only prosthetic reconstruction.

Population

number of patients = 980.

Interventions

Aim: to review evidence on the optimal timing of RT in relation to autologous reconstruction i.e. to answer the question, 'Should autologous reconstruction be delayed if there is a probability of RT in the post-operative period?'

Patients underwent mastectomy and either:

i) immediate autologous reconstruction followed by RT;

ii) delayed autologous reconstruction after RT.

The type of autologous reconstruction most commonly performed was the TRAM flap.

Outcomes

1. Cosmesis (appearance, volume and symmetry);
2. Immediate complications (e.g. wound complications, infection, fat necrosis, partial or total flap loss);
3. Delayed complications (e.g. fibrosis, contracture).

Follow up

Range of reported means/medians: 18 months-4 years

Results

STUDY CHARACTERISTICS

10 studies met the inclusion criteria (with a total of 980 participants), of which only one was prospective. 9/10 studies were retrospective reviews of medical notes and pre/post-operative photographs. No studies performed power calculations or provided confidence intervals of results. Only 5 studies described objective methods for assessment of cosmesis and only one of these studies used a blind, independent assessment to minimise bias.

RESULTS

Data on the timing, cosmetic outcome and complication rates for autologous breast reconstruction in patients who previously or subsequently undergo breast or chest wall RT are limited.

Two studies in this review which recommend delaying the breast reconstruction until after RT provide strong statistical support in favour of their conclusion:

1) Tran et al. (2003): Late complications in immediate reconstruction group 87.5% vs. 8.6% in delayed reconstruction group; $p < 0.0001$.

2) Rogers et al. (2002):

Fat necrosis: 'RT after reconstruction' group: 23% vs. 0% control group (no RT); $p = 0.006$

Fibrosis: 'RT after reconstruction' group: 56% vs. control group (no RT): 0%; $p < 0.0001$

Flap contracture: 'RT after reconstruction' group: 16% vs. control group (no RT): 0%; $p = 0.023$

Three other studies in which RT was given before delayed reconstruction found no statistically significant adverse cosmetic effect although there was a trend for a higher rate of complications where RT preceded reconstruction.

Studies that favoured immediate reconstruction as the cosmetically acceptable option with RT performed afterwards lacked an inter-group comparison and statistical support for their recommendations.

Studies that directly compared immediate reconstruction (with RT later) versus delayed reconstruction (with RT before) suggest that fibrosis and contracture leading to adverse cosmetic outcome is more common if RT is used after reconstruction.

Adverse effects of radiotherapy:

The main adverse effects reported were fat necrosis, delayed wound healing, fibrosis resulting in contracture, loss of volume and distortion of the breast.

Early surgical complications did not appear to vary according to whether preoperative or post-operative RT was given, with the exception of fat necrosis in some studies. However two studies reported a trend towards higher rate of early complications associated with delayed breast

reconstruction compared with immediate reconstruction.

Authors conclude that the available data suggest a case for delayed rather than immediate TRAM reconstruction in patients who need post-operative RT. Where the need for RT is not known before surgery, patients should be counselled about the risks of post-operative RT to the cosmetic result.

General comments

Studies included date up to 2002.

Authors report that the adverse effects of RT following reconstruction with breast prostheses/expanders are well established and are therefore not part of this review.

'Immediate' reconstruction refers to before RT.

Literature search summarised as follows:

Medline, EMBASE, CINAHL, Psych INFO, Cochrane Specialist Register of trials with terms 'breast reconstruction' and 'radiation/radiotherapy'. Within the identified abstracts a search was performed for 'immediate' and 'delayed' reconstruction, 'radiotherapy', 'radiation therapy' and 'autologous reconstruction'.

Study quality appraisal evident, presented narratively. Results tabulated and discussed narratively.

The authors acknowledge that in general the included studies are few, underpowered and retrospective, lacking objective assessment of cosmetic outcomes. There is high heterogeneity with regard to study design, RT dose and results. For these reasons interpret findings with caution.

Review

Taylor, Horgan & Dodwell . Oncological aspects of breast reconstruction. [Review] [84 refs]. Breast 14[2], 118-130. 2005.

Design

Design: Review (therapy), evidence level: 4

Country: Various, setting: Secondary care

Inclusion criteria

Primary studies of breast reconstruction following mastectomy to treat patients with breast cancer where:

- i) the majority of patients were treated after 1980;
- ii) median/mean follow up period >1 year in the case of assessment of recurrence.

Exclusion criteria

None stated.

Population

-

Interventions

Aim: to review evidence on the impact of breast reconstruction on disease-related outcomes and its interaction with oncological interventions.

Patients were treated according to primary studies; there was much variation but interventions commonly included mastectomy, chemotherapy or radiotherapy and reconstruction (implant and/or autologous; either before or after adjuvant therapy).

Outcomes

Recurrence risk;

Delay in the start of adjuvant therapy;

Interactions between radiotherapy and reconstruction.

Follow up

Mean 57 months; median 49 months (based on a sub-group of 19 primary studies that reported recurrence rates).

In general short follow-up is a feature of the primary studies.

Results

RECURRENCE

Two observational studies provided direct comparisons of mastectomy and immediate reconstruction compared to mastectomy alone and found, at a follow up of 3 years or more, no difference in recurrence-free survival between the treatment groups.

Further 'single group' observational studies:

Local recurrence after mastectomy and immediate breast reconstruction (19 studies; 2305 patients in total; median follow-up 49 months[range 26-156 months]):

Mean: 5.4%

Median: 5%

Range: 0-15%

Distant recurrence (or, in one study, deaths from disseminated disease) after mastectomy and immediate breast reconstruction (16 studies; 1759 patients in total; median follow-up 49 months[range 26-156 months]):

Mean: 12.5%

Median: 10.5%

Range: 2-39%

Author reports that given the limitations of these studies (see 'comments', their data suggest that there is no obvious increased risk of local/distant recurrence after reconstruction.

DELAY IN STARTING ADJUVANT THERAPY

(15 studies; 587 patients in total; reconstruction type: various implant/expander or autologous)

One observational study recorded delays of greater than 1 month in two patients of 23 requiring chemotherapy amongst 46 patients treated with immediate reconstruction. A second study reported that seven out of 28 patients who had immediate TRAM flap reconstruction experienced delayed chemotherapy due to postoperative complications.

Nine other studies that compared time to onset of chemotherapy after immediate reconstruction with control group treated by mastectomy alone revealed no significant difference; chemotherapy commenced on average 41-53 days after operation.

Rate of early postoperative wound complications after immediate reconstruction: 8%-49% (5 studies).

Three observational studies found that in patients who had immediate reconstruction chemotherapy dose was maintained at similar rates to that of patients who underwent mastectomy alone.

RADIOTHERAPY AND RECONSTRUCTION

1. RT immediately after mastectomy plus immediate reconstruction with implant or expander (11 small studies; 173 patients in total; median follow-up 31 months [range 19-43 months]):

Rate of capsular contraction:

Mean: 38%

Median: 33%

Range: 2.2%-73% Note: subgroups are so small that they do not permit reliable interpretation.

Cosmesis: (% 'good'/'excellent'): 3 studies report 60%, 7% and 54%, respectively, but subgroups are so small that they do not permit reliable interpretation. In one further study RT was associated with a lower cosmesis score; in one study the mean cosmesis score was 2.99 (scale 1-4); in one study 50% of patients were satisfied with the cosmetic result.

2. Chest wall RT after reconstruction with autologous tissue (predominantly TRAM; 4 studies; 111 patients in total; median follow-up: 28 months [range 19-53 months]):

Rate of flap tissue loss/necrosis:

Mean: 37%

Median: 44%

Range: 0%-59%

Cosmesis: (% 'good'/'excellent'): 2 studies report 90% and 17%, respectively, but subgroups are so small that they do not permit reliable interpretation. In one further study 7/10 patients had a worse cosmetic result after RT.

3. Delayed reconstruction with implant, performed after RT (6 small studies; 116 patients in total; median follow-up 31 months [range 28-46 months]):

Rate of capsular contraction:

Mean: 39%

Median: 35%

Range: 26%-60% Note: subgroups are so small that they do not permit reliable interpretation.

Cosmesis: (% 'good'/'excellent'): 1 study reports 31% and in another study 45% of patients had an 'acceptable' cosmetic result, but subgroups are so small that they do not permit reliable interpretation. In one further study the mean cosmesis score was 2.9 (scale 1-4); in 1 study 50% of patients were satisfied with their cosmetic result.

4. Delayed autologous tissue reconstruction, performed after RT (6 studies; 399 patients in total; median follow-up 29 months [range 24-60 months]):

Rate of flap tissue loss/necrosis:

Mean: 17%

Median: 15%

Range: 5%-34%

Cosmesis: (% 'good'/'excellent'): 1 study reports 64%. In one further study the mean cosmesis score was 2.7 (scale 1-4).

General comments

84 studies were included; identified through a MEDLINE search. Inclusion

criteria are very general and no explicit assessment is made of study quality; hence the grading as level 4 evidence.

Authors report that patients treated with immediate reconstruction tend to be younger patients with poorer prognostic factors, making adjuvant therapy more likely. Also the need for adjuvant therapy is often not realised until after definitive surgery (including after immediate reconstruction).

The authors describe the nature of the included studies, which have the following drawbacks: small size, mostly single institution, retrospective, uncontrolled, short follow-up, high heterogeneity with regard to interventions.

The data on cosmesis are of particularly poor quality: inconsistently reported, methods of assessment unknown, based on very small patient groups, and the direction of the cosmesis scale (1-4) is not reported.

For the above reasons the quality of the evidence is poor and the findings should be interpreted cautiously.

Updated 2018

Prospective comparative study

Belouli, Wyss, Vetter, Meyer & Beer . Immediate or delayed breast reconstruction after mastectomy: What do women really want. European Journal of Plastic.Surgery 28[5], 331-336. 2005.

Design

Design: Prospective comparative study (therapy), evidence level: 3
Country: Switzerland, setting: Community

Inclusion criteria

200 sampled healthy women, 100 of whom were non-surgical nurses.

Exclusion criteria

Age < 20 years;
Age > 70 years

Population

number of patients = 200, age range 20 to 69 years.

Interventions

Aim: to assess the preference of healthy women for either immediate or delayed breast reconstruction, and in the case of declining reconstruction, examining reasons why.

Two groups were prospectively defined:

Group 1: Randomly chosen healthy women (n=100)

Group 2: Non-surgical hospital nurses (n=100)

No information was provided about breast reconstruction. Women were interviewed to obtain their spontaneous preference for or against breast reconstruction and the timing: immediate or delayed, and the type: autologous, implant or both.

Outcomes

Preferences expressed re: reconstruction;

Self esteem (Visual analogue scale; range 1-5; 5 representing highest self esteem);

Significance of the breast from an aesthetic viewpoint (Visual analogue scale; range 1-5; 5 representing highest aesthetic significance).

Follow up

Not relevant

Results

Overall 66% of participants voted for breast reconstruction (group 1: 61%; group 2: 71%).

Overall, a preference for reconstructive surgery correlated with younger age (Spearman $r=0.56$, $p<0.01$), higher education (Spearman $r=0.25$, $p<0.01$), higher self esteem (Spearman $r=0.34$, $p<0.01$) and high aesthetic importance of the breast (Spearman $r=0.62$, $p<0.01$).

Overall 21% of participants voted for immediate reconstruction, 27% delayed reconstruction and 52% gave no preference.

The most common reason for preference for immediate reconstruction was a wish to undergo only one surgical procedure (56%) followed by a wish to avoid mutilation and altered body image (44%).

The most common reasons expressed against immediate reconstruction was a fear that it may mask local recurrence (62%) and secondly, a need to come to terms with cancer illness (35%).

For the type of reconstruction, 40% of participants who voted for reconstruction preferred the use of autologous tissue, 14% the use of implants and 23% a combined technique of both methods; 23% could not reach a decision spontaneously.

A preference for autologous tissue reconstruction was due to aversion of foreign bodies (especially silicone) in 87% of participants. Reasons provided for preferring implant reconstruction were confidence of better results (63%), less scarring (21%) and less complex surgery (5%).

General comments

The nurses (group 1) were younger on average (mean age 35 years) than the sample of women (mean age 43 years); $p<0.01$, Mann-Whitney test.

100 % of the nurses (group 1) were classified as 'highly educated' compared to 30% of the sample of women (p NS).

The study provides no details of how participants were sampled, nor any adequate details of why healthy women including 100 nurses were sampled: probably a convenience sample, with unknown applicability to this question.

Only general information is provided re: the interviews: it is not possible to tell whether some responses were open-ended or categorical.

Responses are reportedly spontaneous, with a statement that no information was given. There is probably a differential between the two groups with regard to prior knowledge of breast cancer and surgery. Also spontaneous results may be less valid than if some information had been given e.g. preference between different types of reconstruction. There is high likelihood that context

is lost since no patients with breast cancer were sampled.

Updated 2018

Retrospective comparative study

Anderson, Hanlon, Fowble, McNeeley & Freedman . Low complication rates are achievable after postmastectomy breast reconstruction and radiation therapy. *Int.J.Radiat.Oncol.Biol.Phys.* 59[4], 1080-1087. 2004.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

85 patients who were treated for breast cancer with modified radical mastectomy, breast reconstruction (immediate or delayed; tissue expander/implant or autologous) and radiotherapy (either before or after reconstruction).

Exclusion criteria

None reported

Population

number of patients = 85, age range 29 to 70 years, median age = 45 years.

Interventions

Aim: to report the complication rate and cosmetic result in patients who receive mastectomy and breast reconstruction and RT, and to identify factors that may be predictive of adverse outcome. Study was performed by a retrospective chart review.

All patients underwent modified radical mastectomy and breast reconstruction with either tissue expander/implant (50 patients) or TRAM flap (35 patients).

70 patients received immediate reconstruction followed by RT (median interval from surgery to RT: 7 months):

TEI: n=44

TRAM: n= 26

15 patients received RT then delayed reconstruction (median interval from RT to reconstruction: 13 months):

TEI: n=6

TRAM: n=9

RT dose: 50-50.4 Gy (plus a 10 Gy scar boost in 4 patients). RT was given with a bolus every-other day, to increase the dose to the surface tissue: a custom wax bolus was used in 44 patients (52%) and a standard bolus was used in 41 patients (48%).

Adjuvant medical therapy:
78 patients (92%) received chemotherapy;
55 patients (65%) received tamoxifen.

Outcomes

Complications:

Actuarial incidence of complications dated from either the time of initiation of RT (immediate reconstruction) or from the time of reconstruction (delayed reconstruction), using Kaplan-Meier method; log-rank test.

Major complications: requiring corrective surgery or loss of the reconstruction.

Minor complications: infection, chest wall fibrosis, fat necrosis, contracture.

Cosmesis:

Originally classified using a four category Harvard scale: 'Excellent' (same as opposite breast), 'good' (minimal but identifiable effects of RT visible), 'fair' (significant effects of RT seen on treated breast), and 'poor' (severe tissue sequelae secondary to RT). In this study cosmesis was binary:

'excellent/good' or 'fair/poor'. Differences were examined using Fisher's exact test.

Potentially predictive factors for adverse outcome:

Factors explored were smoking history, type of reconstruction, type of bolus used, use of RT boost, sequencing of reconstruction and use of systemic therapy (using univariate analysis; log-rank test).

Follow up

Median 28 months (range 1-153 months)

Results

Complications:

3-year actuarial rate of complications by reconstruction type:

TEI: 19%

TRAM: 27%; $p=0.16$, log-rank test.

3-year actuarial rate of major complications by reconstruction type:

TEI: 5%

TRAM: 0%; $p=0.21$, log-rank test.

3-year actuarial rate of minor complications by reconstruction type:

TEI: 14%

TRAM: 27%; $p=0.04$, log-rank test.

Predictive factors for complications:

Of all the factors examined in the univariate analysis, only bolus type was predictive of complications. Rate of complications by bolus type:

Custom: 9%

Standard: 24%; $p=0.05$, log-rank test.

Cosmesis:

'Excellent/good': 85%

'Fair/poor': 15%

None of the factors examined were predictive of cosmetic outcome.

Sequencing of RT/reconstruction was neither predictive of complications nor cosmetic outcome.

General comments

The aim of the custom wax bolus was to minimise air gaps over the skin, hence increasing homogeneity of dose.

'Delayed' reconstruction (i.e. after RT) is a small sub-group (n=15), of which 9 patients (60%) underwent TRAM reconstruction c.f. immediate reconstruction, where 26/70=37% of patients underwent TRAM reconstruction. Therefore the influence of sequencing of reconstruction and RT may be confounded by reconstruction type. The univariate analyses would not account for any confounding factors.

Updated 2018

Gouy, Rouzier, Missana, Atallah, Youssef & Barreau-Pouhaer . Immediate reconstruction after neoadjuvant chemotherapy: effect on adjuvant treatment starting and survival. Ann.Surg.Oncol. 12[2], 161-166. 2005.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: France, setting: Secondary care

Inclusion criteria

Patients treated within the years 1985-1995 for invasive breast cancer of tumour stage T2-T4a-c.
The indication for mastectomy was tumour size ≥ 3 cm and bifocal tumours.

Mean age:

Mastectomy: 51 years

Immediate reconstruction: 44 years

Delayed reconstruction: 46 years

Recorded disease characteristics:

Tumour stage:

T2: 123

T3: 101

T4: 37

Clinical lymph node stage:

N0: 103

N1/N2: 148

Grade:

I: 11

II: 157

III: 65

Exclusion criteria

Patients who underwent lumpectomy.

Population

number of patients = 261.

Interventions

Aim: To compare the delay between surgery and adjuvant therapy and also local control and survival, in patients treated with neoadjuvant chemotherapy and mastectomy, with or without reconstruction.

Three treatment groups were defined:

1. Mastectomy (n=181): underwent mastectomy without reconstruction

2. Immediate reconstruction (n=48): underwent mastectomy plus immediate reconstruction as follows:

Implant: 29

Expander: 3

TRAM: 7

Latissimus: 9

3. Delayed reconstruction (n=32) underwent mastectomy plus delayed reconstruction as follows:

Implant: 6

Expander: 1

TRAM: 15

Latissimus: 10

All patients received neoadjuvant anthracycline-based chemotherapy in either three (90 patients) or four (171 patients) cycles, using four regimens.

250 patients received adjuvant RT: 45 Gy.

Tamoxifen was given to all post-menopausal patients and pre-menopausal patients with ER+ tumours.

Outcomes

Interval from reconstruction to commencement of adjuvant therapy;

Local recurrence-free survival and distant disease-free survival;

Need for further cosmetic surgery;

Capsular contracture (assessed using Spear and Baker's classification).

Follow up

Paper reports 5-year and 10-year recurrence outcomes.

Results

Mean interval between surgery and onset of adjuvant treatment (days):

Chemotherapy

Immediate reconstruction: 26

Mastectomy (includes delayed reconstruction): 23; p=0.11

RT

Immediate reconstruction: 87

Mastectomy (includes delayed reconstruction): 81; p=0.22

There was also no difference in mean interval between surgery and onset of adjuvant treatment (days) according to the type of immediate reconstruction

performed:

Chemotherapy

Implant/expander: 25

Autologous: 28; $p=0.23$

RT

Implant/expander: 88

Autologous: 82; $p=0.58$

5-year estimated local recurrence-free survival:

Immediate reconstruction: 89%

Mastectomy: 90%

Delayed reconstruction: 93%; $p=NS$

10-year estimated distant disease-free survival:

Immediate reconstruction: 48%

Mastectomy: 43%

Delayed reconstruction: 64%; $p=0.04$

Need for further cosmetic surgery (implant removal, flap amelioration) within two years of reconstruction:

Immediate reconstruction: 50%

Delayed reconstruction: 50%

64% of patients who underwent immediate reconstruction with an implant (with or without an autologous flap) developed a capsular contracture (Baker II-IV).

General comments

37/181 = 20% of patients had stage T4 disease (i.e. population outside guideline scope).

The three groups were similar in terms of T stage, nodal status, histology, grade, ER status and chemotherapy regimen (statistically tested), although patients undergoing reconstruction were younger (mean 44 and 46 years; immediate and delayed reconstruction, respectively), than those who did not undergo reconstruction (mean 51 years; $p<0.04$). Patients who received immediate reconstruction were more likely to have four, rather than three courses of neoadjuvant chemotherapy ($p<0.04$), whereas clinical response was similar across groups. The immediate reconstruction group tended to receive implant reconstruction (60%) whereas the delayed reconstruction group tended to receive Latissimus dorsi flap reconstruction (p value flap versus implant: <0.001).

No definition is provided of 'delayed' reconstruction, which presumably means after adjuvant therapy.

Authors report that the apparent survival advantage in the delayed reconstruction group is likely to be due to the fact that patients with early metastatic events were not offered a delayed reconstruction.

Updated 2018

Mortenson, Schneider, Khatri, Stevenson, Whetzel, Sommerhaug, Goodnight & Bold . Immediate breast reconstruction after mastectomy increases wound complications: however, initiation of adjuvant chemotherapy is not delayed. Arch.Surg. 139[9], 988-991. 2004.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

128 women who underwent mastectomy for breast cancer between January 1995 and December 2002

Exclusion criteria

Patients whose reconstructions involved a skin graft;
Patients receiving chemotherapy for a non-breast cancer at the time of their mastectomy.

Population

number of patients = 128.

Interventions

Aim: to compare wound complications between patients treated with mastectomy versus patients treated with mastectomy plus immediate reconstruction, and to assess whether complications interfered with adjuvant chemotherapy.

Two groups were defined retrospectively:

Mastectomy (n=66)

Mastectomy and immediate breast reconstruction (n=62) with either tissue expander/implant (38/62 = 61%) or autologous tissue (latissimus dorsi or TRAM); including prophylactic antibiotics and closed suction drains. Where used, tissue expansion commenced in the third post-operative week and was completed over 6-8 weeks. This process was interrupted to administer unexpected RT, but was rarely interrupted to administer adjuvant chemotherapy.

Outcomes

Minor complications: defined as any complication requiring antibiotics or debridement.

Major complications: those requiring re-operation, re-admission or delay in chemotherapy (from the scheduled date of commencement and owing to a surgical complication).

Follow up

Mean 33 months (SD 20.8 months).

Results

All complications by group n (mastectomies):

Mastectomy: 6/72 = 8.3%

Reconstruction: 17/76 = 22.3%; $p=0.02$, Fisher's exact test.

Major complications by group:

Mastectomy: 4/66 = 6%

Reconstruction: 11/62 = 18%

Minor complications by group:

Mastectomy: 2/66 = 3%

Reconstruction: 6/62 = 10%

Mean interval to initiation of chemotherapy (months):

Mastectomy (n=39): 1.54

Reconstruction (n=42): 1.70; $p=0.43$, Student's t test

Complications by treatment group in the subgroup of patients who underwent chemotherapy (n=81):

Mastectomy (n=39): 5%

Reconstruction (n=42): 24%; $p=0.02$ Fisher's exact test

Complications by receipt of chemotherapy:

Chemotherapy: 12/81 = 15%

No chemotherapy: 9/47 = 19%; $p=0.52$ Fisher's exact test

Complications arising during administration of chemotherapy by treatment group:

Mastectomy (72 unreconstructed mastectomies): 2 (3%)

Reconstruction (76 reconstructed mastectomies): 2 (3%); $p=0.96$, Fisher's exact test

General comments

There are 20 more mastectomies than patients; reported as prophylactic mastectomies; presumably in the contralateral breast: some outcomes are reported for 148 mastectomies rather than 128 patients.

The reconstruction group was significantly younger (mean 48 years) than the mastectomy group (mean 59 years); $p<0.001$, Student's t test. Disease stage was equally distributed between groups except for stage III disease, which was more common in the mastectomy group (35%) than the reconstruction group (10%), $p<0.001$, Fisher's exact test. Women in the reconstruction group

were more likely to have received prophylactic mastectomy (23%) than those in the mastectomy group (10%); $p=0.04$, Fisher's exact test.

Updated 2018

Spear, Ducic, Low & Cuoco . The effect of radiation on pedicled TRAM flap breast reconstruction: outcomes and implications. [Review] [12 refs]. Plastic.& Reconstructive.Surgery 115[1], 84-95. 2005.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

150 patients who underwent 171 TRAM reconstructions within the years 1988 - 1999.

Distribution of active smokers:

1. TRAM only: 18%
2. TRAM after RT: 13%
3. TRAM before RT: 9%

There was no statistically significant difference in smoking history across groups.

Distribution of patients classes as overweight/obese (based on BMI):

1. TRAM only: 47%
2. TRAM after RT: 50%
3. TRAM before RT: 62%

There was no statistically significant difference in BMI group across groups.

25% of procedures were bilateral, with no statistically significant difference in laterality across groups.

Exclusion criteria

None stated.

Population

number of patients = 150, mean age = 47 years.

Interventions

Aim: to compare adverse effects after TRAM flap breast reconstruction. Three groups of patients were defined retrospectively:

1. TRAM only (78 patients; 91 reconstructions)
2. TRAM after RT (38 patients; 42 reconstructions)
3. TRAM before RT(34 patients; 38 reconstructions)

Distribution of vascular delay procedures:

1. TRAM only: 6.6%
2. TRAM after RT: 11.9%; cf TRAM only, $p=0.0003$
3. TRAM before RT: 10.5%; cf TRAM only, $p=0.0003$

Outcomes

Complications:

Infection

Haematoma (requiring surgery/drainage)

Seroma (requiring surgery/drainage)

Delayed wound healing (requiring surgical intervention)

Fat necrosis

Partial flap necrosis (not requiring surgery)

Total flap necrosis (requiring surgery)

Cosmesis (Assessed by 16 blinded, independent individuals and rated for each factor as 1=poor, 2=fair, 3=good and 4=excellent) with three factors:

i) Aesthetic outcome

ii) Symmetry

iii) Contracture

Also: presence/absence of hyperpigmentation

Follow up

Not reported: outcomes are evaluable in the short term.

Results

Cosmesis

	Aesthetic result (mean)	Symmetry (mean)	Hyperpigmentation (%)	Contracture (mean)
TRAM alone	3.77	3.72	0/24=0%	3.81
TRAM after RT	3.27	3.27	2/11=18.1%	3.81
TRAM before RT	2.76	2.78	10/23=43.4%	2.86
Statistics				
TRAM vs. TRAM after RT	P=0.021	P=0.03	P=0.09	P=0.03
TRAM vs. TRAM after RT	P=0.0001	P=0.0001	P=0.0002	P=0.0001
TRAM after RT vs. TRAM before RT	P=0.09	P=0.12	P=0.25	P=0.009

There was no statistically significant difference between patients who underwent TRAM after RT and those who underwent TRAM before RT with regard to aesthetic result, symmetry or hyperpigmentation. Mean contracture score was higher in patients who underwent TRAM after RT (3.81) than in

patients who underwent TRAM before RT (2.86), $p=0.009$.

Patients who received no RT had generally better cosmetic outcomes than patients in either RT-treated subgroup.

Complications

Overall rate of complications (% of no. TRAM flaps):

All patients: $88/171=51.5\%$

TRAM only: $45/91 = 49.5\%$

TRAM after RT: $24/42 = 57.1\%$

TRAM before RT: $19/38 = 50\%$

There were no statistically significant differences between groups for any of the complications variables.

General comments

Provides information on immediate and delayed reconstruction, based on timing prior to/post RT; author's description of 'delay' appears unrelated; concerning preparatory vascular surgery.

Good description of patient subgroups and assessment of outcomes.

Updated 2018

Taylor & Kumar . The effect of immediate breast reconstruction on adjuvant chemotherapy. Breast 14[1], 18-21. 2005.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

Patients treated for breast cancer by mastectomy, with or without immediate breast reconstruction, and who received chemotherapy, within the years March 1999 and December 2002, identified by the regional tumour registry.

Mean age:

Mastectomy: 52 years

Reconstruction: 43 years

Proportion of patients with disease-positive lymph nodes:

Mastectomy: 78%

Reconstruction: 75%

Proportion of patients with locally advanced disease:

Mastectomy: 47%

Reconstruction: 55%

Mean Nottingham Prognostic Index:

Mastectomy: 5.33

Reconstruction: 4.70

Exclusion criteria

None stated.

Population

number of patients = 93.

Interventions

Aim: to examine whether immediate breast reconstruction had an impact on chemotherapy in terms of dose given, need for supportive treatment and delays in commencing/continuing chemotherapy.

Two groups were defined retrospectively:

1. Reconstruction group (n=44): underwent mastectomy, immediate reconstruction and chemotherapy.

2. Mastectomy group (n=49): underwent mastectomy and chemotherapy.

Reconstruction type:

TRAM: 22 (50%)

Latissimus dorsi: 15 (34%)

Implant/expander: 7 (16%).

Outcomes

Interval from surgery to commencement of chemotherapy;

Delay during chemotherapy;

Dose of chemotherapy given;

Need for medical support during chemotherapy.

Follow up

Not reported: study assesses short-term sequelae following mastectomy, reconstruction and during chemotherapy.

Results

Mean time from surgery to chemotherapy initiation (days):

Mastectomy: 38

Reconstruction (total): 36

TRAM: 43

Latissimus dorsi: 32

Implant/expander: 33

The most commonly recorded cause of a delay in starting chemotherapy of > 40 days was incomplete wound healing, which occurred in 41% in patients treated with TRAM and 4% of patients treated with mastectomy without reconstruction.

Proportion of patients treated with full intended dose of chemotherapy:

Mastectomy: 97%

Reconstruction (total): 95%

TRAM: 93%

Latissimus dorsi: 98%

Implant/expander: 98%

Approximately 10% of patients in each group needed support during chemotherapy with either antibiotics or GCSF.

General comments

Retrospective study of immediate reconstruction based on routinely collected audit data. No statistical analysis provided.

Wilson, Brown, Weiller-Mithoff, George & Doughty . Immediate breast reconstruction does not lead to a delay in the delivery of adjuvant chemotherapy. Eur.J.Surg.Oncol. 30[6], 624-627. 2004.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

285 patients treated for breast cancer whose treatment included chemotherapy.

Exclusion criteria

Patients who did not receive chemotherapy.

Population

number of patients = 285.

Interventions

Aim: to assess whether immediate breast reconstruction following mastectomy leads to a delay in the delivery of chemotherapy.

Three groups were retrospectively defined:

1. Immediate breast reconstruction group (n=95): underwent skin sparing mastectomy and immediate breast reconstruction and chemotherapy.

Reconstruction was as follows:

Becker implant: 22%

Latissimus dorsi: 51%

Latissimus dorsi + implant: 14%

Free tissue transfer: 13%

2. Mastectomy group (n=95): underwent non-reconstructive mastectomy and chemotherapy.

3. Breast conserving surgery group (n=95): underwent breast conserving surgery and chemotherapy.

Outcomes

Time from surgery to the start of chemotherapy

Follow up

Not reported; extent appears adequate.

Results

Median time (range) to the start of chemotherapy (days) by group:

Immediate reconstruction: 29 (17-55)

Mastectomy: 28 (16-52)

Breast conserving surgery: 26 (20-42)

Median time (range) to the start of chemotherapy (days) by reconstruction type:

Becker implant: 25 (16-31)

Latissimus dorsi: 27.5 (19-41)

Latissimus dorsi + implant: 24 (17-55)

Free tissue transfer: 38 (26-52)

General comments

Study provides data for immediate reconstruction.

Short paper with few details on patient characteristics.

Study does not state directly that patients who received reconstruction underwent mastectomy.

Method of selection of the two non reconstructed groups of patients is not described, except that all patients were treated over the same period.

Cited results for reconstruction are based upon smaller subgroups.

Updated 2018

Prospective case series

Benediktsson & Perbeck . Capsular contracture around saline-filled and textured subcutaneously-placed implants in irradiated and non-irradiated breast cancer patients: five years of monitoring of a prospective trial. Journal of Plastic., Reconstructive.& Aesthetic Surgery: JPRAS. 59[1], 27-34. 2006.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: Sweden, setting: Secondary care

Inclusion criteria

145 patients with with large (>3cm) or multifocal primary unilateral breast cancer tumours and with a healthy contralateral breast; operated within the years 1991-1994.

Exclusion criteria

Patients who received secondary RT due to local recurrence in the 5-year follow-up period (n=12);
Patients who died or who were too ill for review (n=12);
Patients whose implants were removed due to failure without contracture (n=14).
This left 107 patients for evaluation.

Population

number of patients = 107, age range 32 to 75 years, mean age = 54 years.

Interventions

Aim: to measure the incidence and outcome of capsular contracture in irradiated and non-irradiated breasts after subcutaneous mastectomy and immediate reconstruction with a subcutaneously-located saline-filled prosthesis.

Patients underwent subcutaneous mastectomy and immediate reconstruction with a subcutaneously located prosthesis.

24 patients received RT after reconstruction (dose: 46 Gy in 2 Gy fractions, 5 days a week), and an unspecified number of pre-menopausal patients received chemotherapy.

Prophylactic antibiotics were given, and surgical drains placed at the operation site.

Outcomes

Extent of capsular contraction assessed by:

1. Applanation tonometry: ratio of breast compressibility at the time of follow-

up relative to the time of surgery; a ratio <0.5 was considered to be indicative of contracture.

2. Modified Baker/Palmer classification based on clinical examination:

B1A-B1B - Good cosmetic result;

B2- Satisfactory;

B3 - B4 - Capsular contraction.

Follow up

Mean 56 months; median 60 months, range 24-60 months.

Results

Rate of capsular contracture (B3-B4):

All patients: $22/107=20.6\%$

By RT subgroup:

RT: $10/24 = 41.7\%$

No RT: $12/83 = 14.5\%$; $p=0.012$

16/22 patients with capsular contracture required re-operation; the remaining 6 patients did not receive further reconstructive surgery either due to choice, or due to advanced disease.

There was good correlation between the two methods of assessment of capsular contracture with mean (standard deviation) applanation tonometry ratio for each Baker/Palmer group as follows:

B1A: 0.798 (0.223)

B1B: 0.635 (0.254)

B2: 0.531 (0.199)

B3: 0.451 (0.070)

B4: 0.250 (0.000)

General comments

Provides data on immediate reconstruction.

Some of the exclusion criteria detract from an evaluation of the efficacy of implant reconstruction.

Drucker-Zertuche & Robles-Vidal . A 7 year experience with immediate breast reconstruction after skin sparing mastectomy for cancer. Eur.J.Surg.Oncol. 33[2], 140-146. 2007.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: Mexico, setting: Secondary care

Inclusion criteria

105 patients treated for breast cancer within the years 1997-2004, with mastectomy plus immediate reconstruction (autologous, expander/implant or in combination), performed by a single surgeon.

Disease stage:

Stage 0: n=16

Stage I: n=39

Stage IIA: n=28

Stage IIB: n=14

Stage IIIA: n=6

Stage IIIB: n=1

Histology:

Invasive ductal: n=72

Invasive lobular: n=7

DCIS: n=10

Tubular: n=1

81/105 = 77% of patients were pre-menopausal.

Exclusion criteria

None stated.

Population

, age range 22 to 58 years, mean age = 40 years.

Interventions

Aim: to assess the oncologic safety of mastectomy and immediate reconstruction in patients treated for breast cancer.

Primary surgery:

Total mastectomy (n=26)

Total mastectomy plus sentinel node biopsy (n=19)

Modified radical mastectomy (n=60)

Immediate reconstruction:

TRAM flap (n=70)

TEIR (n=29)

Latissimus dorsi flap + implant (n=6)

50 patients received in addition, contralateral breast adjustment.

Adjuvant therapy:

Neoadjuvant chemotherapy: n=30

Concomitant chemotherapy + RT: n=14

Chemotherapy: n=67

RT: n=20

Patients participated in a 30 minute interview to ascertain their satisfaction with their reconstructions, perception of body image and quality of life. In addition cosmetic outcome was assessed by an independent plastic surgeon who did not perform any of the reconstructions.

Outcomes

Local recurrence (defined as biopsy-proven cancer in skin flaps, transposed tissues or chest wall)

Regional recurrence (defined as ipsilateral axillary or supraclavicular nodes)

Distant recurrence (any other site than the above)

Aesthetic outcome (assessed on 8 separate ordinal scales: shape with brassiere, shape without brassiere, contralateral match, inframammary fold, mobility, consistency, overall result, projection)

Complications

Patient satisfaction

Follow up

The interviews were performed for all patients at ≥ 6 months following the reconstruction.

Mean follow-up 48 months (range 10-92 months)

Results

Complication rate:

All patients: $27/105 = 25.7\%$; as follows:

Minor complications:

Necrosis of wound margin: n=9;

Fluid collection n= not specified;

Major hematoma: n=6;

Minor fat necrosis: n=7;

Symptomatic capsular contracture: n=2

Major complications:

Total flap necrosis: n=1

Implant exposure: n=2

Abdominal complications:

Abdominal hernia: n=2

22/27 complications were in patients who had received RT, and of these 13/22 were in patients who received expander or implant reconstructions.

Recurrence:

Distant (n=3)

Loco-regional + distant (n=1)

Aesthetic outcome:

There was no difference in overall results between the three types of reconstruction (p=0.324; no further details reported).

Mobility and consistency of reconstructed breast was closer to that of the contralateral breast in patients who received TRAM reconstruction (p=0.015; no further details provided).

For all other aesthetic scales examined, there were no statistically significant differences between reconstruction groups.

Surgeon evaluation:

Excellent: n=39

Good: n=57

Fair: n=6

Poor: n=3

Patient satisfaction:

Extremely satisfactory: n=35

Satisfactory: n=53

Less than satisfactory: n=11

Disappointing: n=6

Patient perception of body image:

Very good: n=31

Good: n=57

Moderately good: n=12

Poor: n=5

Patient reporting of sexual life:

Unchanged: n=95

Deteriorated: n=9

Improved: n=1

Patient reporting of social life:

Unchanged: n=99

Deteriorated: n=0

Improved: n=6

General comments

Provides data re: immediate reconstruction.

Study reports details of treatment carefully but provides few details of analysis of results. For many outcomes where a baseline assessment would have been beneficial, it is lacking.

Limited applicability: question does not specify a comparison of outcome by type of reconstruction performed.

Updated 2018

Gendy, Able & Rainsbury . Impact of skin-sparing mastectomy with immediate reconstruction and breast-sparing reconstruction with miniflaps on the outcomes of oncoplastic breast surgery. Br.J.Surg. 90[4], 433-439. 2003.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

Contactable, disease-free patients who underwent either of two procedures (see interventions) within the years 1991-1999. Indications for skin sparing mastectomy with immediate latissimus dorsi myocutaneous flap reconstruction were widespread DCIS, local recurrence following previous breast conserving surgery, prophylaxis and patient preference.

Recorded disease characteristics:
Tumour diameter median 20mm, range 9-90mm.

Tumour grade:

I: 11

II: 21

III: 8

Histology:

Invasive ductal: 31

Invasive lobular: 8

Mixed invasive ductal plus invasive lobular: 1

DCIS: 18

Axillary nodal stage:

N0: 38

N1: 17

Not sampled: 3

Exclusion criteria

Patients who declined to participate.

Population

number of patients = 57, age range 31 to 62 years, mean age = 48 years.

Interventions

Aim: to compare local control, cosmesis, functional disturbance and psychological morbidity in patients with breast cancer treated with two strategies as follows:

1. Skin sparing mastectomy with immediate latissimus dorsi myocutaneous

flap reconstruction (n=57); 12 of whom received adjuvant RT: 50 Gy, 25 fractions over 12 weeks.

2. Partial mastectomy with immediate or delayed latissimus dorsi miniflap reconstruction of the resection defect (n=49); NB no data cited.

Outcomes

1. Cosmesis, assessed by:

- i) Patient-scored visual analogue scale (range 0-100; 100 representing optimal result);
- ii) Photographic assessment by a multi-disciplinary panel of 5 assessors, blinded to procedure: Mean score of the panel members (range 1-5; 1 representing gross unacceptable deformity; 5 representing no deformity)
- iii) Breast retraction assessment (BRA): based upon measurements to assess symmetry between ipsilateral and contralateral breasts; lower score represents less contraction and better symmetry; score >3.5 represents unsatisfactory outcome.

2. Physical disability, assessed by:

- i) Patient-subjective-assessment of physical symptoms in the treated breast, donor site and shoulder, including pain, sensory changes, muscle contraction, restriction in activities;
- ii) Observer-assessed-objective assessment of sensitivity to pain, temperature, touch and vibration of the ipsilateral breast, using the contralateral breast as control.

3. Quality of life, assessed by two psychologists, not involved in patient care, using 3 scales:

- i) Hospital anxiety and depression scale (HADS);
- ii) Rosenberg self-esteem scale (RSE);
- iii) Hopwood body image scale (HBIS).

Follow up

Mean 34 (range 6-65) months.

Results

Skin sparing mastectomy with immediate latissimus dorsi myocutaneous flap reconstruction:

Complication rate: $8/57 = 14\%$

Skin envelope necrosis (6/8 complications)

Further surgery was required in $45/57 = 79\%$ of patients

Local recurrence rate: $1/57 = 1.7\%$ (occured in a patient who did not receive RT).

Cosmesis:

Overall a good cosmetic result was achieved. Median (range) values as follows:

BRA: 2 (0-5.3) NB a marked degree of retraction (BRA > 3.5) was observed in 8 patients.

Panel assessment: 2.9 (1-4.4) NB on this scale a score of 3 represents moderate deformity/difference between breasts.

Patient satisfaction (cosmesis): 72 (3-100)

Patient satisfaction (freedom of dress): 76 (1-100).

Physical disability:

Objective assessment:

Breasts with normal nipple-areola sensation: 2%

Quadrants with normal sensation: median 1 (range 0-4)

Surface area with intact sensation: 35% (range 5-100%)

Subjective assessment:

Breast and nipple-areolar complex feels normal: VAS median 28 (range 0-82)

Breast self-examination 'easy': VAS median 48 (range 1-100)

Shoulder disability restricts some activities: 73%

Anxiety and depression (HADS):

Anxiety level:

Normal (score 0-7): 65%

Mild (score 8-10): 21%

Moderate (score 11-14): 14%

Severe (score 15-21): 0%

Depression level:

Normal (score 0-7): 93%

Mild (score 8-10): 5%

Moderate (score 11-14): 2%

Severe (score 15-21): 0%

Psychological morbidity: mean (range) scores:

Anxiety HADS: 5 (0-14) NB (score range 0-21; low score represents low anxiety)

Depression HADS: 1 (0-10) NB (score range 0-21; low score represents low depression)

Self esteem (RSE): 24 (10-29) NB score range 10-40; low score indicates high self esteem

Body image (HBIS): 5 (0-21) NB score range 0-30; low score represents less disturbance of body image

Concern re: residual cancer: 45 (1-100) NB VAS

General comments

The study compared outcomes following skin sparing mastectomy with immediate latissimus dorsi myocutaneous flap reconstruction versus partial mastectomy with immediate or delayed latissimus dorsi miniflap reconstruction of the resection defect. Our research question does not apply to the latter procedure; no data are cited.

Three of the 57 women had bilateral procedures.

The finding that only 2% of operated breasts had normal nipple-areola sensation is unsurprising since these tissues are excised in skin sparing mastectomy.

Accepting that the main study comparison is not cited, the study benefits from rigorous description of its measurement techniques and its prospective nature. Some value is lost in citing 'single arm' data, but some limited comparison may be possible with other studies.

Updated 2018

Sandelin, Wickman & Billgren . Oncological outcome after immediate breast reconstruction for invasive breast cancer: A long-term study. Breast 13[3], 210-218. 2004.

Design

Design: Prospective case series (therapy), evidence level: 3
Country: Sweden, setting: Secondary care

Inclusion criteria

203 patients with invasive breast cancer who underwent immediate breast reconstruction.

Tumour stage:

T1: 121

T2: 73

T3: 9

Proportion of patients with involved lymph nodes: 30%

Exclusion criteria

Patients with locally advanced breast cancer or inflammatory breast cancer did not usually undergo immediate reconstruction.

Population

, age range 23 to 70 years, median age = 48 years.

Interventions

Aim: to report disease-related events in a series of patients who received immediate breast reconstruction.

188 patients underwent mastectomy and immediate reconstruction for primary breast cancer.

14 women had surgery (possibly breast conserving surgery) plus immediate reconstruction for recurrent breast cancer.

Reconstruction was performed as follows:

Permanent prosthesis: 22 (11%)

Expander: 168 (83%)

Bilateral free TRAM: 1 (0.5%)

Free TRAM: 3 (1.5%)

Pedicled free TRAM: 9 (4%)

137/203 = 67% of patients underwent contralateral plastic surgery.

21/203 = 10% of patients received neoadjuvant chemotherapy.

60/203 = 30% of patients received chemotherapy.

69/203 = 34% of patients received RT; 46-50 Gy.

108/203 = 53% of patients received hormone therapy.

Outcomes

Postoperative complications

Deaths due to breast cancer

Local recurrence

Follow up

Minimum 5 years

Results

Postoperative complications occurring within 30 days of surgery:

Crude rate: 23/203 = 11%; as follows:

Bleeding requiring re-operation: 5

Implant loss: 3

Flap necrosis: 3

Fat necrosis: 2

Infection: 5

Misc: 5

Deaths due to breast cancer:

Crude rate: 31/203 = 15%

Local recurrence:

Crude rate: 13/203 = 6.4%

General comments

Study provides data on immediate reconstruction.

188/203 = 93% of women underwent mastectomy and immediate reconstruction; the remainder may have received breast conserving surgery i.e. outside the scope of this question.

Tykkä, sko-Seljavaara & Hietanen . Patient satisfaction with delayed breast reconstruction: a prospective study. Ann.Plast.Surg. 49[3], 258-263. 2002.

Design

Design: Prospective case series (), evidence level: 3
Country: Finland, setting: Secondary care

Inclusion criteria

Patients treated with delayed, autologous tissue breast reconstruction following previous mastectomy between August 1999 and December 1999.

Marital status:

Married/long term relationship: 55 (73%)

Single: 10 (13%)

Divorced: 7 (7%)

Widowed: 3 (4%)

Reconstruction was performed a mean of 3.9 years after mastectomy (range 1.2-16.6 years)

Exclusion criteria

None specified

Population

number of patients = 75, age range 30 to 65 years, mean age = 50 years.

Interventions

Aim: to evaluate patient satisfaction with delayed breast reconstruction with autologous tissue and to examine related factors.

80 patients operated on over a 5-month period were invited to complete questionnaires prior to delayed reconstructive surgery.

Participants were also given questionnaires at 3-month and 6-month post-operative hospital visits.

The questionnaires collected data on socio-demographic variables, general health and the specific outcomes (see below).

Reconstructions performed were as follows:

TRAM: 67 (89%)

Latissimus dorsi 8 (11%)

Outcomes

Patient satisfaction

Proportion of patients reporting pain and problematic scarring

Patient-reported benefits and drawbacks of reconstructive surgery.

Follow up

Patients were assessed prior to reconstructive surgery, and at 3 months and 6 months post-operatively.

Results

Response rate to questionnaires:

Pre-operative: 75/80 = 94%

3 month post-operative: 60/75 = 80%

6 month post-operative: 60/75 = 80%

Patient satisfaction (rating) with general outcome of the operation at 3 months post-operatively:

Very good: 28 (47%)

Quite good: 26 (44%)

Quite poor: 1 (2%)

Very poor: 0 (0%)

Patient satisfaction (rating) with general outcome of the operation at 6 months post-operatively:

Very good: 27 (45%)

Quite good: 29 (48%)

Quite poor: 3 (5%)

Very poor: 0 (0%)

There was no difference in patient satisfaction according to type of reconstruction, waiting time, co-morbidity or any demographic factor.

Outcome at 3 months against patients' preoperative expectations:

Much better than expected: 9 (15%)

Better than expected: 21 (35%)

As expected: 23 (38%)

Poorer than expected: 4 (7%)

Much poorer than expected: 1 (2%)

Outcome at 6 months against patients' preoperative expectations:

Much better than expected: 10 (17%)

Better than expected: 25 (42%)

As expected: 16 (27%)

Poorer than expected: 5 (8%)

Much poorer than expected: 2 (3%)

Proportion of patients reporting pain (shoulder, neck and back):

Pre-operatively: 41 (55%)

3 months post-operatively: 19 (32%); $p=0.011$

6 months post-operatively: 20 (33%); $p=0.00097$

Patient-reported extent to which surgical scarring was a disturbance at 6 months post-operatively:

Very much: 0 (0%)

To some extent: 6 (10%)

Slightly disturbed: 36 (60%)

Not at all: 16 (27%)

This variable was negatively correlated with satisfaction at 3 months post-operatively ($p=0.032$) but not statistically significantly so at 6 months ($p=0.065$)

Patient responses to questions about the most important benefits of their reconstruction (no. responses):

A new breast of one's own: 31

No need for external prosthesis: 24

Feeling whole: 18

Easier to find clothes: 10

Flat stomach: 7

Improved self esteem: 4

Easier to exercise: 3

One can forget the cancer: 1

Patient responses to questions about the most important drawbacks of their reconstruction (no. responses):

Difficult operation: 17

Abdominal operation: 11

Pain: 11

Long recovery time: 9

Fears, uncertainty: 7

Asymmetrical breasts: 7

Scars: 1

General comments

Provides data on delayed reconstruction.

Some multivariate analysis was performed, but not cited as the authors do not appear to have fully reported which variables were included in the model.

Retrospective case series

Ascherman, Hanasono, Newman & Hughes . Implant reconstruction in breast cancer patients treated with radiation therapy. *Plastic.& Reconstructive.Surgery* 117[2], 359-365. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

104 women who underwent mastectomy and TEI reconstruction within the years 1996-2003.

Exclusion criteria

Patients who received mantle RT due to Hodgkins disease

Population

number of patients = 104.

Interventions

Aim: to examine the outcome of breast reconstruction using modern tissue expanders and implants in patients who undergo RT before completion of their reconstructions.

Two patient groups were defined (all patients underwent TEI reconstruction):

1. RT group (n=27)

Patients who underwent mastectomy plus immediate reconstruction plus RT. NB in this group RT either preceded mastectomy due to previous failed lumpectomy (n=8), or took place after mastectomy due to high risk tumours/close margins (n=19).

2. Control group (n=77)

Patients who underwent mastectomy plus immediate reconstruction without RT.

Only 3 reconstructions were described as 'delayed'; all of which were for patients in the control group (range of delay 13 months to 22 years).

Outcomes

i) Complications resulting in removal or replacement of implant (6 parameters: infection, extrusion, port malfunction, capsular contracture, pain, rippling);

ii) Complications not resulting in removal or replacement of the implant (5 parameters: pulmonary embolism, seroma, skin necrosis, cellulitis, pain);

iii) Symmetry (3 point scale: 1=unsatisfactory, 2=satisfactory, 3=optimal);

iv) Patient satisfaction (3 point scale: 1=dissatisfied, 2=partially satisfied, 3=fully satisfied)

Follow up

Not reported.

Results

i) Complications resulting in removal or replacement:

RT group: 5 (18.5%)

Control group: 4 (4.2%); $p < 0.025$, Chi square

Within the above, 'extrusion' was the only individual variable that was statistically significantly different between groups:

RT group: 4 (14.8%)

Control group: 0 (0%); $p < 0.001$, Chi square

ii) Complications not resulting in removal or replacement of the implant:

RT group: 6 (22.2%)

Control group: 12 (12.5%); p NS, Chi square

Within the above, no individual variable was statistically significantly different between groups.

iii) Symmetry (mean score)

RT group: 2.1

Control group: 2.6; $p < 0.01$, Mann-Whitney U test

iv) Patient satisfaction (mean score)

RT group: 2.4

Control group: 2.7; p NS, Mann-Whitney U test

Association between smoking, diabetes and chemotherapy with complications (univariate analysis); complication rate shown:

Smokers: 2/14=14%

Non-smokers: 24/90=26%; p NS, Chi square test

Diabetic: 2/6=33%

Non-diabetic: 24/98=24%; p NS, Chi square test

Chemotherapy: 18/55=33%

No chemotherapy: 8/49=16%; $p < 0.01$, Chi square test

There was no statistically significant difference in the rate of complications, symmetry or patient satisfaction according to timing of RT (before mastectomy vs. after implant/expander insertion but before implant exchange/port removal); no data provided.

General comments

Study evaluates predominantly immediate reconstruction (97.6%).

In 19 patients reconstruction was bilateral, thus some analyses are for a total of 123 reconstructed breasts, making results imprecise for outcomes where non-independence of the two breasts applies.

Patients in the RT group were more likely to receive chemotherapy than those in the control group (85% and 43% respectively; $p < 0.001$, Chi square test) and were more likely to receive 'Mentor' devices (as opposed to 'McGhan' devices) than the control group (26% and 9% respectively; $p < 0.025$, Chi square test).

The RT group is likely to consist of poorer-prognosis patients owing to the need for RT and in most cases, chemotherapy. Chemotherapy had a demonstrated association with complications.

Analyses were univariate

Updated 2018

Cordeiro, Pusic, Disa, McCormick & VanZee . Irradiation after immediate tissue expander/implant breast reconstruction: outcomes, complications, aesthetic results, and satisfaction among 156 patients. *Plastic.& Reconstructive.Surgery* 113[3], 877-881. 2004.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

Patients treated between 1995 and 2001 with mastectomy, immediate TEIR and subsequent RT.

Exclusion criteria

Patients who previously received RT

Population

number of patients = 623, mean age = 48 years.

Interventions

Aim: to evaluate surgical complications, aesthetic results and patient satisfaction in patients who received mastectomy with immediate tissue expander/implant reconstruction (TEIR).

Two groups were retrospectively defined:

1. TEIR + RT group (n=81): were treated as follows:

- i) Mastectomy plus immediate TEIR;
- ii) Tissue expansion during adjuvant chemotherapy, commencing 10-14 days from surgery;
- iii) Exchange of expander for permanent implant at approximately 4 weeks after completion of chemotherapy;
- iv) Chest wall RT beginning 4 weeks after exchange.

2. TEIR alone group (n=542): patients were treated as above but with no RT.

RT included 50 Gy in 25-28 fractions to the chest wall, implant and supraclavicular fossa, plus a 5mm bolus over the chest wall

Outcomes

Complications (including capsular contracture, assessed on a Spear/Baker scale of 1-4; 1 representing no contracture and 2-4 representing increasing degrees of contracture);

Aesthetic result: assessed as poor, fair, good or excellent;

Patient satisfaction.

Follow up

TEIR + RT group: mean 33 months;
TEIR alone group: mean 34 months.

Results

Rate of removal of implants:

TEIR + RT group: 9/81 = 11%

TEIR alone group: 33/542 = 6%; $p < 0.0001$, Fisher's exact test.

Reasons for implant removal included infection, implant exposure, implant leakage, recurrent cancer and capsular contracture.

Rate of any capsular contracture (grade 2-4):

TEIR + RT group: 46/68 = 67.6%

TEIR alone group: 30/75 = 40%; $p = 0.006$, Fisher's exact test.

Proportion of patients with 'good' or 'excellent' aesthetic result:

TEIR + RT group: 53/66 = 80.3%

TEIR alone group: 66/75 = 88.0%; $p = 0.0006$, Mann-Whitney test.

Proportion of patients who were satisfied with their reconstructions:

TEIR + RT group: 67%

TEIR alone group: 88%; $p = 0.004$, Fisher's exact test.

General comments

Most outcomes are reported for a subgroup of patients in the RT group with > 1 year of follow-up and a randomly selected subgroup of patients who received no RT:

TEIR + RT group: $n = 68$

TEIR alone group: $n = 75$

Contracture and aesthetic result were assessed by an independent observer and the operating surgeon.

Henriksen, Fryzek, Holmich, McLaughlin, Krag, Karlsen, Kjoller, Olsen & Friis . Reconstructive breast implantation after mastectomy for breast cancer: clinical outcomes in a nationwide prospective cohort study. Arch.Surg. 140[12], 1152-1159. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Denmark, setting: Secondary care

Inclusion criteria

A retrospective review of a large, routinely compiled patient database identified 574 patients treated with mastectomy for breast cancer, followed by breast reconstruction.

Either initial implantation or subsequent implantation procedures were included with data presented as follows:

Initial implantation: 484 implants in 407 patients

Subsequent implantation: 417 implants in 302 patients.

49% of subsequent implantations were planned second stage events; the remainder occurring due to patient request e.g. different size (20%) or due to clinical complications (64%).

Mean age (initial implantation): 50 years, range 21-78 years;

Mean age (subsequent implantation): 51 years, range 24-78 years.

Tumour dissemination:

Local: 65.1%

Regional: 26.9%

Distant: 1.2%

Unspecified: 6.8%

Histology:

Invasive ductal: 66.9%

DCIS: 6.8%

Lobular, invasive: 13.7%

LCIS: 0.2%

Others: 12.4%

Exclusion criteria

Patients who underwent solely autologous reconstruction.

Population

number of patients = 574.

Interventions

Aim: to report on the clinical course following post-mastectomy breast reconstruction in 574 patients with breast cancer.

Patients underwent mastectomy and reconstruction as follows:

Immediate: 7%

Delayed; with implant: 88%

Delayed; with implant + autologous tissue (3%)

Delayed; with other procedure e.g. liposuction (2%)

Outcomes

Total adverse events occurring within 2 years of the reconstruction (and of the individually listed adverse events, those cited are wound infection, capsular contracture [Baker grade], skin necrosis, local recurrence).

Proportion of the above events that prompted further surgery.

Follow up

Initial implantation: mean 23 months, range 3-56 months;

Subsequent implantation: mean 24 months, range 4-52 months.

Results

Wound infection

Initial implantation:

No (%): 29 (7.1)

Incidence rate per 1000 person-months: 4.8

Proportion requiring surgery: 44.8%

Subsequent implantation:

No (%): 13 (4.3)

Incidence rate per 1000 person-months: 2.9

Proportion requiring surgery: 23.1%

Capsular contracture; Baker Grade II:

Initial implantation:

No (%): 35 (8.6)

Incidence rate per 1000 person-months: 5.7

Proportion requiring surgery: 80%

Subsequent implantation:

No (%): 15 (5)

Incidence rate per 1000 person-months: 3.2

Proportion requiring surgery: 60%

Severe capsular contracture; Baker grade III-IV:

Initial implantation:

No (%): 17 (4.2)

Incidence rate per 1000 person-months: 2.7

Proportion requiring surgery: 94.1%

Subsequent implantation:

No (%): 20 (6.6)

Incidence rate per 1000 person-months: 4.3

Proportion requiring surgery: 80%

Skin necrosis:

Initial implantation:

No (%): 5 (1.2)

Incidence rate per 1000 person-months: 0.8

Proportion requiring surgery: 20%

Subsequent implantation:

No (%): 3 (1)

Incidence rate per 1000 person-months: 0.6

Proportion requiring surgery: 33.3%

Local recurrence:

Initial implantation:

No (%): 7 (1.7)

Incidence rate per 1000 person-months: 1.1

Proportion requiring surgery: 28.6%

Subsequent implantation:

No (%): 1 (0.3)

Incidence rate per 1000 person-months: 0.2

Proportion requiring surgery: 100%

Any adverse event:

Initial implantation:

No (%): 125 (30.7)

Incidence rate per 1000 person-months: 22.5

Proportion requiring surgery: 21.1%

Subsequent implantation:

No (%): 108 (35.8)

Incidence rate per 1000 person-months: 29.7

Proportion requiring surgery: 20.5%

General comments

Data in this paper appear to be compiled from different samples/sources, the majority of the data (88%) refer to delayed reconstruction, with implant.

All cited data refer to n (patients).

Hussien, Salah, Malyon & Wieler-Mithoff . The effect of radiotherapy on the use of immediate breast reconstruction. Eur.J.Surg.Oncol. 30[5], 490-494. 2004.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: UK, setting: Secondary care

Inclusion criteria

121 patients treated with mastectomy and immediate breast reconstruction between January 1997 and June 1999.

Exclusion criteria

None stated.

Population

number of patients = 121.

Interventions

Aim: to evaluate the effect of RT on the choice of immediate breast reconstruction technique in view of the increased number of breast cancer patients receiving adjuvant RT.

Two groups were retrospectively defined according to the period of treatment, the contemporary indications for RT being as follows:

1. January 1997 to March 1998 (n=42): inadequate excision margins, >4 involved lymph nodes, T3-T4 tumour;
2. March 1998 to June 1999 (n=79): criteria widened to include medial tumours, Grade III tumours of stage T1-T2 and presence of lympho-vascular invasion

Case notes were reviewed and all patients were sent a questionnaire.

Outcomes

Patterns of use of different types of immediate reconstruction;

Relationship between use of RT and type of immediate reconstruction performed.

Follow up

Not relevant.

Results

Questionnaire response rate was 100%.

Group 2 was significantly larger than group 1 (79 versus 42 patients respectively; $p=0.008$), representing an increase in the use of immediate reconstruction, in the later period studied.

Type of immediate reconstruction performed: n (patients); Jan 97 to Mar 98:

Tissue expander: 18

Latissimus dorsi + implant: 12

Latissimus dorsi: 2

Free flap (DIEP): 10

Type of immediate reconstruction performed: n (patients); Apr 98 to Jun 99:

Tissue expander: 24

Latissimus dorsi + implant: 16

Latissimus dorsi: 26

Free flap (DIEP): 13

The increase in the proportion of patients who underwent immediate reconstruction with autologous tissue alone increased in the second period relative to the first period (49% and 29% respectively, $p=0.0004$)

Requirement for RT by treatment period:

Jan 97-Mar 98: 10 (24%)

Apr 98-Jun 99: 23 (29%)

Of patients receiving RT, proportion for whom RT was expected at time of reconstruction by treatment period:

Jan 97-Mar 98: $5/10 = 50\%$

Apr 98-Jun 99: $17/23 = 74\%$

In the first period autologous immediate reconstruction was performed in all 5 patients for whom RT was expected; 5 patients who unexpectedly received RT had undergone immediate implant reconstruction.

In the second period 15/17 patients for whom RT was expected underwent immediate autologous reconstruction; 6 patients who unexpectedly received RT had undergone immediate implant reconstruction.

General comments

Provides data on immediate reconstruction only.

Criteria for expecting RT are probably based upon triple assessment information.

The role of the patient questionnaire is not described; presumably to augment data from case notes; possible recall bias.

Knottenbelt, Spauwen & Wobbes . The oncological implications of immediate breast reconstruction. Eur.J.Surg.Oncol. 30[8], 829-833. 2004.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: The Netherlands, setting: Secondary care

Inclusion criteria

54 patients who underwent immediate reconstruction of the breast following mastectomy for breast cancer, who were treated between Jan 1993 and Dec 1996:

Premenopausal: 39
Postmenopausal: 13
Not known: 2

Stage:
pT1-T2, N0: 32 (35 breasts)
pT1-T2, N1: 14 (15 breasts)
pT3-T4, N0: 2
pT3-T4, N1: 6

Four patients had bilateral breast cancer, making a total of 58 reconstructions.

Exclusion criteria

None stated.

Population

number of patients = 54, age range 32 to 70 years, mean age = 46 years.

Interventions

Aim: to assess whether the presence of a breast prosthesis interferes with the detection and management of recurrent disease, and whether recurrence and survival differ from that seen in patients treated with mastectomy alone.

All patients underwent modified radical mastectomy with immediate reconstruction as follows:

Subpectoral tissue expander (55 reconstructions)
TRAM flap (1 reconstruction)
Permanent implant (2 reconstructions)

Adjuvant therapy:

RT to the axilla and/or chest wall (n=15)

Systemic chemotherapy (n=14)

Chemotherapy + RT (n=8)

Post menopausal women with positive lymph nodes received tamoxifen (n not

specified).

Outcomes

Cosmesis (assessed by the plastic surgeon and surgical oncologist as excellent, good, fair or poor).

Disease-related events.

Follow up

Minimum 60 months.

Results

Cosmesis:

Excellent/good: 11 patients

4 patients developed severe contractures or encapsulation requiring corrective surgery (no further data).

Local recurrence (crude rate out of all treated breasts at risk):

1/58 = 1.7%

Distant metastasis (crude rate out of all treated breasts at risk):

13/58 = 22.4% (includes 1 patient with local recurrence also)

Deaths with metastatic disease:

9/58 = 15.5%

Disease-free survival at 5 years: 93%

General comments

Cosmesis is not a primary study outcome; a description of assessment is provided but only partial results.

No methods are reported to derive the figure for disease-free survival at 5 years of 93%; may be an actuarial estimate.

Mustonen, Kataja, Berg, Pietilainen & Papp . Recurrences after immediate reconstruction in breast cancer. Scandinavian Journal of Surgery: SJS 94[1], 21-24. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Finland, setting: Secondary care

Inclusion criteria

Patients treated with immediate breast reconstruction within the years 1998-2001.

Mean ages in groups 1, 2 and 3 were 52, 47 and 47 years, respectively.

Exclusion criteria

None stated.

Population

number of patients = 79.

Interventions

Aim: to measure local-regional and distant recurrence of breast cancer in patients treated with immediate breast reconstruction as follows:

1. Wide local excision and latissimus dorsi miniflap (n=23);
2. Skin sparing mastectomy and TRAM or latissimus dorsi flap (n=22);
3. Subcutaneous mastectomy and TRAM or latissimus dorsi flap (n=34);

Patients in the first group (breast conserving surgery) received RT; 50 Gy.

Patients with disease-positive lymph nodes or tumours >20mm in size received chemotherapy; patients with ER+ or PR+ tumours received hormone therapy.

Outcomes

Local, regional and distant recurrence;

Disease-free and overall survival, estimated by Kaplan-Meier method.

Follow up

Mean 3.6 years.

Results

Estimated 5-year overall survival (all patients): 88%

Estimated 5-year disease-free survival (all patients): 80%

Recurrences by mastectomy-treated groups:

Skin sparing mastectomy and TRAM or latissimus dorsi flap (n=22):

Local: 2

Regional: 0

Distant: 3

Subcutaneous mastectomy and TRAM or latissimus dorsi flap (n=34):

Local: 3

Regional: 1

Distant: 0

There was no statistically significant difference in recurrence at any site between the treatment groups.

General comments

Study provides data on immediate reconstruction.

The group treated with wide local excision and latissimus dorsi miniflap (n=23) do not meet the criteria for this question, therefore applicability of this study is 71%.

Updated 2018

Rey, Martinelli, Petit, Youssef, De, Rietjens, Garusi & Giraldo . Immediate breast reconstruction and high-dose chemotherapy. Ann.Plast.Surg. 55[3], 250-254. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Switzerland, setting: Secondary care

Inclusion criteria

105 patients treated with mastectomy between 1999 and 2002.

Mean age (years):

Group 1: 44

Group 2: 46

Group 3: 50

Exclusion criteria

Patients who received autologous tissue reconstruction.

Population

number of patients = 105.

Interventions

Aim: to evaluate whether high dose chemotherapy is delayed by immediate breast reconstruction.

All patients underwent total mastectomy plus axillary clearance. Three groups were defined retrospectively according to additional treatment as follows:

1. Immediate reconstruction plus high dose chemotherapy (n=23);
2. High dose chemotherapy without reconstruction (n=15);
3. Immediate reconstruction with conventional dose chemotherapy (n=67).

Reconstruction type was as follows:

Prosthesis: 80%

Expander: 20%

Reconstruction was performed always before chemotherapy, but in the case of expanders, these were exchanged for permanent implants after the conclusion of chemotherapy.

64% of patients receiving reconstruction had in addition, plastic surgery to the contralateral breast.

72% of patients received RT.

Outcomes

Complications:

Local infection;

Capsular contracture (Baker 3 or 4);

Necrosis, warranting surgical removal;

Delay from surgery to high dose chemotherapy.

NB complications were recorded as 'early' if occurring before chemotherapy and 'late' if occurring after commencement of chemotherapy.

Follow up

Group 1: mean 12 months

Group 2: mean 13 months

Group 3: mean 13 months

Results

Early Complications:

	Group		
	Reconstruction + high dose chemo	Reconstruction + conventional chemo	High dose chemo; no reconstruction
Local infection	0	2 (2.9%)	0
Local necrosis	0	0	0
Interval: surgery to high dose chemotherapy (days)	54		60

There was no statistically significant difference in the interval from surgery to the start of high dose chemotherapy between group 1 (immediate reconstruction, 54 days) and group 2 (mastectomy, 60 days); $p= 0.13$.

Late complications:

	Group		
	Reconstruction + high dose chemo	Reconstruction + conventional chemo	High dose chemo; no reconstruction
Capsular contracture	5 (22%)	11 (16%)	
Local infection	3 (13%)	0	0
Local necrosis	1 (4.3%)	0	0

The local infection rate was statistically significantly higher for patients who

received high dose chemotherapy after reconstruction (13%) than patients who received conventional dose chemotherapy after reconstruction (0%), $p = 0.014$. There was no statistically significant difference in capsular contracture rates between these two groups (22% versus 16%; $p=0.51$).

General comments

Study provides data for immediate reconstruction.

The three treatment groups were visibly similar in terms of length of hospital stay, follow-up, TNM stage and receipt of RT. The only difference was in the use of neoadjuvant chemotherapy, which was 60% in patients who received high dose chemotherapy without reconstruction, 13% in patients who received immediate reconstruction plus high dose chemotherapy and 10% in patients who received immediate reconstruction and conventional chemotherapy. The reconstruction technique was similar in both reconstructed groups (differences not tested statistically).

The need for chemotherapy at all, or at which dose, was never known at the time of commencing definitive surgery.

Re: observed rates of capsular contracture: the majority had received RT: 4/5 patients with contracture in group 1 and 10/11 patients with contracture in group 2. However, there was no statistically significant difference in the rate of capsular contraction when subgroup analysis was performed between patients given RT and those not given RT for:

Group 1 (immediate reconstruction plus high dose chemotherapy); $p = 1$;

Group 2 (high dose chemotherapy without reconstruction); $p=0.5$.

Vandeweyer, Deraemaeker, Nogaret & Hertens . Immediate breast reconstruction with implants and adjuvant chemotherapy: a good option? Acta Chir Belg. 103[1], 98-101. 2003.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Belgium, setting: Secondary care

Inclusion criteria

91 patients treated for breast cancer with mastectomy plus immediate expander reconstruction between January 1990 and December 1997.

In 11 Of 91 patients (12.1%) mastectomy was performed due to disease recurrence

Mean age (range)

Chemotherapy group: 44 (29-66) years

Control group: 51 (29-77) years

Histology

Chemotherapy group:

Invasive ductal: 85.7%

DCIS: 0%

Invasive lobular: 14.3%

LCIS: 0%

No chemotherapy group:

Invasive ductal: 53%

DCIS: 36.4%

Invasive lobular: 7.6%

LCIS: 3%

Exclusion criteria

Patients who underwent reconstruction with only autologous tissue.

Population

number of patients = 91.

Interventions

Aim: to examine complications and disease related events in patients treated for breast cancer with mastectomy and immediate reconstruction; and the effect of adjuvant therapy.

All patients underwent mastectomy (modified radical or simple) with immediate reconstruction, and with plastic surgery to the contralateral breast.

The expander implants were expanded on the 3rd, 6th and 9th post-operative days.

Two groups were defined retrospectively:

1. Chemotherapy group (n=27): patients received adjuvant chemotherapy (total 28 implants);

2. Control group (n=66): patients did not receive adjuvant chemotherapy

No patients received RT.

Outcomes

Complications (short term: prior to administration of chemotherapy e.g. haematoma, cutaneous necrosis, infection; total, and those warranting implant removal);

Cosmetic outcome;

Patient satisfaction;

Follow up

Mean 44 months (range 13-93 months); equal between groups.

Results

Complications (crude rate; short-term; prior to administration of chemotherapy):

All patients: 12/91 = 13%

Total:

Chemotherapy group: 7/28 = 25%

Control group: 5/66 = 7.6%; p = 0.04, Fisher's exact test.

Complications warranting implant removal:

Chemotherapy group: 3/28 = 10.7%

Control group: 1/66 = 1.5%; p = 0.0084, Fisher's exact test.

Cosmetic outcome:

Capsular contracture (assessed as grade I-IV):

There was no statistically significant difference between groups in the distribution of capsular contracture grade (p=1; Fisher's exact test); 70% of patients in the chemotherapy group and 63% of patients in the no chemotherapy group had capsular contracture of grade I.

There were no statistically significant differences between groups in the rate of implant displacement, implant deflation, breast symmetry (assessed as optimal or satisfactory in approximately 96% of cases in each group), breast volume of preoperative assessment, location of intramammary fold of preoperative assessment.

Patient satisfaction:

There was no statistically significant difference in patient satisfaction between groups ($p=1$; Fisher's exact test); in the chemotherapy group 83% of patients were fully satisfied, compared with 88% of patients who did not receive chemotherapy.

General comments

Study provides data on immediate breast reconstruction.

Treatment groups originate from indications based upon TNM stage. Patients in the chemotherapy group appear to have more advanced stage than those in the no chemotherapy group; respective proportions with pN1 disease 82% and 4.5% , but with a bias since not all patients in the no chemotherapy group underwent axillary staging surgery.

Scale for capsular contracture not described - Grade 1 may represent little or no contracture.

Other factors possibly explain the observed differences in short term (occurring before administration of chemotherapy) complication rates between groups e.g. definitive surgery.

Updated 2018

Woerdeman, Hage, Smeulders, Rutgers & van der Horst . Skin-sparing mastectomy and immediate breast reconstruction by use of implants: an assessment of risk factors for complications and cancer control in 120 patients. *Plastic.& Reconstructive.Surgery* 118[2], 321-330. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: The Netherlands, setting: Secondary care

Inclusion criteria

120 patients who underwent skin-sparing mastectomy and immediate implant reconstruction (total 174 reconstructions) between July 1996 and June 2000.

54 (45%) patients underwent bilateral mastectomy and reconstruction

33/120 = 28% of patients were smokers.

16/120 = 13% of patients had an adverse general health factor (listed as rheumatoid arthritis, plumonary disease, previous oncologic (non breast cancer) treatment, diabetes mellitus, cardiovascular disease, alcohol abuse, multiple sclerosis, cowden disease).

10/120=8% of patients (10 breasts) had been treated previously with breast conserving surgery and RT

Exclusion criteria

None reported

Population

number of patients = 120.

Interventions

Aim: to examine patient-related and breast-related risk factors for complications following skin sparing mastectomy with immediate implant reconstruction.

Immediate reconstruction was performed with either a permanent implant (18 breasts) or a tissue expander (156 breasts), with expansion commenced two weeks after surgery and repeated fortnightly, with insertion of a final implant at a mean of 8 months (range 1-22 months) from surgery.

All patients were treated with prophylactic antibiotics during the peri-opertaive period.

Adjuvant therapy (n patients):
RT: 5

Chemotherapy: 3

Hormone therapy: 9

Combined: 5

Adjuvant therapy was never commenced within the first 6 post-operative weeks, nor delayed due to the immediate reconstruction.

Outcomes

Recurrence

Survival

De novo breast cancer in patients who received prophylactic mastectomy

Short term post-operative complications (seroma, haematoma, infection, wound dehiscence, ischaemia - occurring within 6 weeks of surgery), also classed as 'severe' if the implant was lost and otherwise, 'mild'.

Potential risk factors modelled in univariate/multivariate analysis for complications:

1. 'Patient-related' factors

Age, general health risk factors (rheumatoid arthritis, pulmonary disease, previous oncologic [non breast cancer] treatment, diabetes mellitus, cardiovascular disease, alcohol abuse, multiple sclerosis, cowden disease), smoking, body mass index and unilateral vs. bilateral surgery.

2. 'Breast-related' factors

Experience of the general surgeon and plastic surgeon (staff vs. resident), indication (curative vs. prophylactic), implant type (implant vs. expander), duration of antibiotic use, axillary surgery and previous RT.

Follow up

Minimum 4 years;

Subgroup of patients treated with prophylactic mastectomy: mean 70 months, range 52-91 months.

Subgroup of patients treated with curative intent: mean 73 months, range 53-171 months.

Results

Complications

Crude rates:

All complications: 40/120 = 33% (patients)

Mild complications: 23/120 = 19% (patients)

Severe complications: 17/120 = 14% (patients)

Patient related factors:

In univariate analysis only age and unilateral surgery were statistically significant risk factors for short-term complications. :

Univariate analysis: patient-related risk factors for short term complications

Factor	OR	95% CI	p
Age (>44 years)	2.23	1.01-4.88	0.05
BMI (>25kg/m ²)	0.74	0.32-1.69	0.48
Smoking	2.22	0.97-5.12	0.06
General health factors	2.25	0.78-6.53	0.14
Unilateral surgery	2.57	1.15-5.88	0.02

In multivariate analysis there was no statistically significant interaction between age and laterality of surgery.

Breast-related factors:

In univariate analysis no characteristic statistically significantly predicted short term complications.

Univariate analysis: breast-related risk factors for short term complications

Factor	OR	95% CI	p
Prophylactic surgery	1.23	0.62-3.41	0.56
Resident general surgeon	1.25	0.61-2.55	0.55
Resident plastic surgeon	2.21	0.90-5.44	0.09
Definitive prosthesis	1.73	0.63-4.75	0.29
Single dose antibiotics	0.74	0.38-1.44	0.38
Axillary dissection	2.01	0.98-4.12	0.06
Separate incision for axillary dissection	2.35	0.75-7.40	0.14
Previous breast conserving surgery + RT	2.73	0.75-9.87	0.13

Risk factors for loss of implant:

Patient-related factors:

Univariate analysis: patient-related risk factors for severe complications leading to loss of implant

Factor	OR	95% CI	p
Age (>44 years)	2.27	0.78-6.60	0.13
BMI (>25kg/m ²)	0.75	0.23-2.48	0.64
Smoking	0.82	0.25-2.74	0.75
General health factors	0.85	0.18-4.11	0.84
Unilateral surgery	3.00	0.93-10.0	0.06

Breast related factors:

Univariate analysis: breast-related risk factors for severe complications leading to loss of implant

Factor	OR	95% CI	p
Prophylactic surgery	0.63	0.24-1.64	0.34
Resident general surgeon	1.13	0.40-3.15	0.82
Resident plastic surgeon	5.07	1.75-14.7	0.003
Definitive prosthesis	1.02	0.22-4.83	0.98
Single dose antibiotics	0.85	0.33-2.20	0.73
Axillary dissection	0.99	0.34-2.93	0.99
Separate incision for axillary dissection	1.54	0.32-7.54	0.59
Previous breast conserving surgery + RT	6.62	1.68-26.1	0.007

The only statistically significant risk factors for serious complication resulting in loss of implant were being treated by a resident plastic surgeon and a history prior to mastectomy of breast conserving surgery and RT.

Influence of short term surgical complications on subsequent implant loss (univariate analysis):

Univariate analysis: short term surgical complications as risk factors for severe complications leading to loss of implant

Factor	OR	95% CI	p
Infection	257	42.9-1520	<0.001
Skin problem	9.76	2.86-33.3	<0.001
Haematoma	9.00	1.19-68.1	0.03
Seroma	4.28	1.42-12.9	0.01

Recurrence and deaths due to breast cancer:

No recurrence or deaths due to breast cancer occurred in any of the 35 patients treated with prophylactic mastectomy.

In the 85 patients treated with curative intent, 2 patients experienced a local-regional recurrence and 5 patients a distant metastasis. Five of these patients died; the estimated actuarial 5-year overall survival rate in patients treated with curative intent: 96%.

General comments

Whilst some multivariate analyses were performed, little reporting is made of them in the paper. Most of the findings on risk factors come from univariate analyses that do not account for the combined effects of different factors. In addition two separate groups of factors were considered ('patient-related' and

'breast-related'), which the authors point out, are theoretical and cannot be considered conjointly.

Many results are reported for numbers of treated breasts; this means that data points from patients treated bilaterally are not independent.

The finding that short term complications were strongly predictive of complications leading to implant loss is not surprising; short-term complications and long term complications as events may be measuring the same thing.

Data from the subgroup of 35 patients (29% of the series) treated with prophylactic mastectomy have limited applicability to this question.

Updated 2018

Chapter 4 – Post-operative and adjuvant therapy planning

4.1 Does progesterone receptor status add further, useful information to that of oestrogen receptor status in patients with invasive breast cancer?

Short summary

Four retrospective studies addressed the relative contribution of progesterone receptor (PR) status to the choice and outcomes of endocrine therapy. Ponzzone *et al.* (2006) examined the effects of various endocrine therapies. Two moderate quality cohort studies compared tamoxifen with a non-intervention control (Dowsett *et al.*, 2006 and Stendahl *et al.*, 2006) and a third study re-examined tissue from a trial which had compared tamoxifen with anastrozole versus both in combination (Dowsett *et al.*, 2008). All groups used immunohistochemistry to visualise the presence of hormone receptors but the criteria used to assign negative and positive status was not consistent.

Positive hormone receptor status (either estrogen or progesterone) was associated with significantly longer relapse-free survival compared with negative receptor expression. Weak evidence suggested that the ER+ve/PR-ve sub-group experienced a significant relapse-free survival benefit with tamoxifen therapy compared with controls whilst those with ER-ve status had a poorer relapse-free survival (Dowsett *et al.*, 2006).

Low levels of either ER or PR correlated with a shorter time to recurrence but hormone status did not predict the superiority of anastrozole over tamoxifen that had been found in a large multi-centre RCT (Dowsett *et al.*, 2008).

Tamoxifen therapy was significantly better than control treatment with respect to RFS when either ER or PR were labelled in > 75% of cells at which point PR was also independently associated with favourable overall survival (Stendahl *et al.*, 2006).

Compared with the other three sub-groups, ER-positive/PR-negative status was initially associated with superior prognosis with respect to disease-free survival but after 8 years this advantage was lost and the prognosis was reversed (Ponzzone *et al.* (2006).

There was no strong evidence to support PR being predictive of a response to endocrine therapy despite being independently prognostic for relapse-free survival and/or overall survival. The benefits of PR status appeared to change with time and with the degree of cellular expression. There were no prospective studies comparing the response to a specific endocrine therapy of ER/PR sub-groups and no evidence with regard to treatment decisions based on hormone receptor status.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with invasive breast cancer	PR testing by Immunohistochemistry (IHC)	ER testing alone by IHC	<ul style="list-style-type: none">• Change in treatment decision e.g. to give endocrine therapy• Choice of systemic treatments e.g. endocrine therapy, chemotherapy• Response to hormone treatment for ER+/PR+ versus ER+/PR- groups

The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence summary

With the direction that papers should be included for appraisal only if endocrine status had been determined by immunohistochemistry, three studies were identified for this topic: one large (n=972) retrospective case series and two moderate quality retrospective cohort studies (total n=1,313). The assignment to positive or negative endocrine status i.e. cut-off point, was not consistent in the three papers. There were no prospective studies comparing the response to a specific endocrine therapy of ER/PR sub-groups and no evidence with regard to treatment decisions.

Dowsett *et al.* (2006) reported the results from a retrospective study of histological material from two large RCTs (NATO and CRC), both of which had compared the use of tamoxifen (TAM) versus no adjuvant treatment for 2 years in post-menopausal women with early breast cancer (pre-menopausal women were acceptable in one trial providing they were node +ve). Archived histological samples from these trials were processed by immunohistochemistry for endocrine status and assessed by operators blinded to the original treatment allocation. Relapse-free survival (RFS) was analysed with respect to endocrine receptor sub-group (ER and PR) status. Assignment of endocrine status involved both signal intensity and the number of labelled cells – this method may be non-standard (for comparison purposes the percentage of ER +ve/PR +ve samples was ~53% of the total).

Comparing positive with negative status, both ER and PR were individually strongly associated with prognosis. By multivariate analysis of RFS, only data for ER -ve status correlated with a lack of significant benefit for tamoxifen compared with the 'no adjuvant therapy' option. When data were analysed for the four ER/PR combinations, ER +ve/PR -ve produced the only relative risk that was significantly in favour of tamoxifen (although the P value was not given).

Stendahl *et al.* (2006) presented a similar retrospective study using archived histological samples from a previous RCT which had compared TAM with a control for 2 years in pre-menopausal women (or post-menopausal if <50 years) with stage II invasive breast cancer. Tumour tissue was re-sampled, prepared for micro-array and labelled for ER and PR status. Quantification of the labelling allowed sub-grouping on the basis of the percentage of cells stained i.e. 0-10%, 11-50%, 51-74% and >75%. The outcomes of interest were RFS and overall survival (OS) and data were presented as separate Kaplan Meier plots for ER and PR and for each of the % expression sub-groups.

It was clear for ER data that the plotted RFS curves for TAM and control treated subjects diverged, starting from the point where ER concentration >10% (regarded in some studies as defining ER +ve) and increasing thereafter. However, the P value presented with each plot did not reach significance until ER >75%. The authors disregarded the P values in reporting this outcome, emphasising the divergence from ER >10% onwards and expressed their opinion that ER was a poor prognostic factor for the response to TAM compared with controls.

The RFS curves for PR showed a different pattern, but with a similar statistical outcome. The survival curves of TAM and control did not diverge visibly until PR expression >75% such that high levels of PR expression might predict an advantage of TAM therapy when compared with control treatment. This PR +ve sub-group comprised 37% of the total study population. These results were similar for PR regardless of ER status and multivariate analyses confirmed a strong reduction in risk of relapse for women with tumours expressing a high level of PR (RR = 48 (95%CI: 0.26-0.88) P = 0.018) and for prolonged OS (RR = 0.52 (95%CI: 0.28-0.99) P = 0.048). The authors concluded that women with PR expression in >75% cells responded favourably to TAM with respect to RFS and OS, regardless of ER status, and that fractionation studies would be preferable to using dichotomous outcomes in the prediction of those patients who would most benefit from TAM therapy.

Ponzone *et al.* (2006) presented data from a large retrospective study of patients who had received endocrine therapy and for whom sufficient clinical and pathological data were available with adequate follow-up. ER and PR status had been determined by immunohistochemistry and the threshold for positive status was 1% labelled cells. The main outcome of interest was disease-free survival (DFS) in relation to endocrine status. The endocrine therapy with which study

participants had been treated varied greatly and included TAM, aromatase inhibitors and GnRH agonists. Many women had also received chemotherapy. Data were not analysed by treatment type.

Multivariate analysis indicated that PR –ve status was a highly significant prognostic factor for DFS in response to therapy for women with tumours of ER +ve status (HR = 2.3 (95%CI: 1.3-3.4) P = 0.002) and this was confirmed by multivariate analysis. However, after 8 years the survival curves for PR +ve and PR –ve showed a cross-over effect meaning that after this time had elapsed PR –ve status was no longer advantageous and instead conferred a poorer prognosis. Women with ER –ve status were not included in these data analyses. This paper presented only very weak evidence in favour of determining PR status in ER +ve tumours in order to identify sub-groups which might gain greater benefit from (unspecified) endocrine therapy.

Updated evidence summary

One study updated the evidence on the relative contribution of progesterone receptor (PR) to the choice and outcomes of endocrine therapy. The authors of a retrospective case series (Dowsett *et al.*, 2008) processed archived tissue from the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial to determine endocrine status. The results were correlated with trial outcomes to identify potential prognostic factors in the response to therapy. Low levels of either endocrine receptor, ER or PR, matched to a shorter time to recurrence, results that were similar regardless of treatment assignment. Whilst the ATAC trial had demonstrated a superior efficacy for ATA compared with TAM this advantage was not reflected by endocrine status in the post-trial study.

References

Dowsett, M., Houghton, J., Iden, C., Salter, J., Farndon, J., A'Hern, R., Sainsbury, R. & Baum, M. (2006) Benefit from adjuvant tamoxifen therapy in primary breast cancer patients according oestrogen receptor, progesterone receptor, EGF receptor and HER2 status. *Ann Oncol*, **17**: 818-826.

Dowsett M., Allred C., Knox J., Quinn E., Salter J., Wale C., Cuzick J., Houghton J., Williams N., Mallon E., Bishop H., Ellis I., Larsimont D., Sasano H., Carder P., Cussac AL., Knox F., Speirs V., Forbes J and Buzdar A (2008) Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. *J Clin Oncol* **26**: 1059-1065

Ponzone, R., Montemurro, F., Maggiorotto, F., Robba, C., Gregori, D., Jacomuzzi, M., Kubatzki, F., Marengo, D., Dominguez, A., Biglia, N. & Sismondi, P. (2006) Clinical outcome of adjuvant endocrine treatment according to PR and HER-2 status in early breast cancer. *Ann Oncol*, **17**: 1631-1636.

Stendahl, M., Ryden, L., Nordenskjold, B., Jonsson, P. E., Landberg, G. & Jirstrom, K. (2006) High progesterone receptor expression correlates to the effect of adjuvant tamoxifen in premenopausal breast cancer patients. *Clin Cancer Res*, **12**: 4614-4618

Updated 2018

Evidence Tables

Ponzzone <i>et al.</i> (2006)
Design: Retrospective case series (prognosis). Evidence level: 3 Country: Italy
Inclusion criteria: Patients who had received endocrine therapy and for whom clinical & pathological data were available Adequate follow-up Written informed consent
Exclusion criteria: N/A
Population: Number of patients = 972, median age = 60.5 years, range: 20-90
Interventions: Interventions: All patients had received endocrine therapy: Tamoxifen for 5 years = 74.6% Tamoxifen + GnRH analogs (2 years) (pre-menopausal) = 13% Aromatase inhibitors for 5 years if TAM contra-indicated (post-menopausal) = 12.3% Chemotherapy (if node +ve or high risk) then endocrine therapy = 39.3% NB. Chemotherapy: CMF, FEC/FAC or anthracyclines with taxanes.
Outcomes: To verify the influence of PR and Her2 status on ER +ve breast cancer and determine the association of endocrine status with the response to adjuvant endocrine therapy. Primary outcome: Disease-free survival (from date of surgery to progression) (DFS).
Follow up: Median follow-up = 35 months (range: 1-205 months)
Results: Distribution of endocrine status determined by IHC: ER +ve: Median % = 70.5; Mean % = 67.2 PR +ve: Median % = 50; Mean % = 41.3 ER +ve/ PR +ve = 76% ER +ve/ PR -ve = 18% ER -ve/ PR +ve = 3.5% ER -ve/ PR -ve = 2.4% Distribution of Her2 status: Median % Her2 +ve = 0 Mean % = 11.9

Her2 +ve status occurred in ER +ve/ PR -ve tumours = 39%
Her2 +ve status occurred in ER +ve/ PR +ve tumours = 17.7% P=0.000

DFS (univariate analysis of predictive factors) in women with ER +ve status:
PR status: 0% (-ve) vs $\geq 1\%$ (+ve) cellular expression: HR = 2.3 (95%CI: 1.3-3.4) P = 0.002
HER2 status $\geq 40\%$ (+ve) vs $< 40\%$ (-ve) cellular expression: HR = 1.9 (95%CI: 1.0-3.5) P = 0.03

DFS (multivariate Cox analysis of prognostic factors):
PR status: lack of expression: HR = 2.3 (95%CI: 1.3-4.0) P = 0.003 (favouring PR -ve status)
Her2 status: overexpression: HR = 2.0 (95%CI: 1.0-3.9) P = 0.05 ('borderline')
Prognostic significance of Her2 only for ER +ve/ PR -ve tumours: HR = 2.4 (95%CI: 1.1-5.3) P = 0.04

General comments:

This paper describes a large retrospective study of data collected from 972 women, consecutively treated for primary breast cancer and who had been given endocrine therapy between January 1988 and January 2005 at a single Italian centre.

ER and PR status were determined by IHC (no methodology details given) and if $\geq 1\%$ cells were positively stained the sample was classed as endocrine +ve. Similarly, Her2 overexpression was assessed by IHC using CB11 or Hercept. Overexpression cut-off was 40% of cells. Finding relationships between endocrine and Her2 status in the response to endocrine therapy was the primary outcome of interest and was conducted using data from women with ER +ve status only (~74%).

A significant effect of PR -ve status as an initial protective factor for early relapse was shown but a cross-over effect occurred at 96 months which meant that, after that time, PR -ve status indicated a poorer prognosis compared with PR +ve. Her2 status continued to be associated with a poor prognosis throughout as the data did not show a significant cross-over effect at any time.

The data analysis takes no account of the, admittedly small, number of ER -ve patients (~6%).

The authors concluded that knowledge of PR status could help to identify which sub-set of women with ER +ve tumours might derive the most benefit from endocrine therapy.

This is a reasonable quality but, nonetheless, retrospective analysis without a comparative control group. The results provide only limited evidence.

Dowsett *et al.* (2006)

Design: Retrospective cohort study (prognosis). Evidence level: 2+

Country: UK

Inclusion criteria:

Nolvadex Adjuvant Trials Organisation (NATO): women \leq 75 years, following total mastectomy and ALN clearance or sampling \pm RT, pre-menopausal women acceptable if node +ve.

Cancer Research Campaign (CRC): women \leq 75 years, following total mastectomy and ALN clearance or sampling \pm RT (local excision post-1983).

Exclusion criteria:

None stated

Population:

Number of patients = 813, age range: 24-83 years

Interventions:

Samples were obtained from two trials:

1] NATO (n = 1285): Tamoxifen (TAM) 10mg x2 per day vs no adjuvant treatment for 2 years

2] CRC: (n = 2230): TAM 10mg x2 per day vs no adjuvant treatment vs cyclophosphamide vs TAM + cyclophosphamide (last 2 groups not included in this study) for 2 years.

Outcomes:

Outcome of post-trial study was relapse-free survival (RFS) with respect to endocrine status.

Follow up:

Median follow-up NATO = 20 years

Median follow-up CRC = 16 years

Results:

Distribution of endocrine status:

ER +ve = 76%

PR +ve = 64% (NB. does not agree with the 55.7% below)

ER +ve/ PR +ve = 52.5%

ER +ve/ PR -ve = 23.4%

ER -ve/ PR +ve = 3.2%

ER -ve/ PR -ve = 20.9%

RFS (univariate analysis of prognostic impact):

ER +ve (n = 617) vs ER -ve: HR = 0.79 (95%CI: 0.65-0.96) P = 0.015

PR +ve (n = 453) vs PR -ve: HR = 0.81 (95%CI: 0.69-0.96) P = 0.014

RFS (multivariate analysis – relative risk of relapse TAM vs control):

ER +ve (n = 324 vs 293): RR = 0.77 (95%CI: 0.63-0.93) P = 0.006

ER -ve (n = 102 vs 94): RR = 0.73 (95%CI: 0.52-1.02) NSD

PR +ve (n = 233 vs 220): RR = 0.78 (95%CI: 0.63-0.98) P = 0.033

PR -ve (n = 193 vs 193): RR = 0.74 (95%CI: 0.58-0.96) P = 0.021

ER +ve/ PR +ve: RR = 0.81 (95%CI: 0.65-1.02) NSD

ER +ve/ PR -ve: RR = 0.70 (95%CI: 0.49-0.99) no P value given

ER -ve/ PR +ve: RR = 0.46 (95%CI: 0.11-1.19) NSD

ER -ve/ PR -ve: RR = 0.79 (95%CI: 0.55-1.14) NSD

ER +ve and/or PR +ve: RR = 0.75 (95%CI: 0.62-0.90) no P value.

General comments:

This paper described a study in which archived histological samples from 2 large RCTs were processed for IHC to label biomarkers including ER and PR. Endocrine status was assessed by persons blinded to treatment allocation.

ER and PR were visualised using 1D5 and 1A6 antisera respectively. Antigen retrieval was also used to optimise signal (0.01M citrate buffer at 60°C). In some cases, rather than preparing sections from archived tissue blocks, pre-mounted slides were used (these may have been up to 20 years old). Negative and positive controls and double operator quality control were employed. Receptor status was graded using both staining intensity and number of cells. For the data analysis, ER sections which were either weakly or strongly stained were considered +ve. It is not clear how this method of quantification accords with that employed by other studies.

Data were analysed by ER and PR response separately and together. By univariate analysis, ER and PR status were clearly strong prognostic indicators but, by multivariate analysis, there was no statistical difference in ER +ve, ER -ve, PR +ve or ER -ve individually in the response to tamoxifen treatment compared with no adjuvant therapy (all confidence intervals overlapped, although the RR value for ER -ve was actually non-significant as the confidence interval included '1'). When ER and PR status were combined only the ER +ve/ PR -ve sub-group was associated with a significant advantage to tamoxifen (RR = 0.70 95%CI: 0.49-0.99, no P value given) but, taken together the four sub-groups were not significantly different from one another.

The authors claimed the possibility of a substantial benefit for tamoxifen in women in the ER -ve/ PR +ve group but they base this assertion on a point estimate for RR where the confidence interval of this figure clearly crosses the line of no effect and hence is of no significance. Nonetheless the authors concluded that, in the event of proven ER -ve status, a PR test might be warranted. This sub-group comprises a low percentage of the population of women with breast cancer.

The reporting of these results appears to be somewhat biased within the paper since the authors often refer to 'trends' and 'suggestions' of difference which the statistics do not support. However, the results were well reported and therefore open to a fair interpretation by the reader.

Stendahl <i>et al.</i> (2006)
Design: Retrospective cohort study. Evidence level: 2+ Country: Sweden
Inclusion criteria: Participants in a RCT of tamoxifen (TAM) vs control (2 years) who were: Pre-menopausal women or, if post-menopausal, <50 years With stage II invasive breast cancer
Exclusion criteria: N/A
Population: Number of patients = 500
Interventions: 0.6mm core tumour samples were taken from archived histological samples using H&E stained sections as guidance. Samples were immunostained for ER and PR using tissue micro-array with 6F11 and clone 16 antisera for quantification of ER and PR respectively. Positive nuclei were sub-grouped into fractions (0-10%, 11-50%, 51-74%, >75% and unknown).
Outcomes: From the original RCT: Overall survival (OS) and recurrence-free survival (RFS). Recurrence excluded contralateral breast cancer.
Follow up: Median follow-up = 13.9 years
Results: Distribution of labelled sub-groups, if counting >10% cells labelled as '+ve' (n=500 patients): ER -ve/ PR +ve = 130 (26% of patients) ER -ve/ PR -ve = 13 (2.6% of patients) ER +ve/ PR +ve = 274 (54.8% of patients) ER +ve/ PR -ve = 30 (6% of patients) ER unknown/ PR -ve = 3 (0.6% of patients) ER unknown/ PR +ve = 7 (1.4% of patients) ER -ve/ PR unknown = 8 (1.6% of patients) ER +ve/ PR unknown = 20 (4% of patients) Endocrine status unknown = 15 (3% of patients) NB. PR +ve expression of >75% cells (i.e. highly expressed) occurred in 168 (37%) of patients. Authors stated that the benefit of TAM vs no treatment became 'apparent' from the point at which ER were expressed in >10% cells and that this benefit increased as ER expression increased hence ER +ve status was predictive for a benefit with TAM compared with controls. However, no relative risk (RR) evaluation was presented and the

P value of the difference between curves on the Kaplan Meier graph for RFS showed significance only when ER >75% of cells (P=0.03) even though the gap between the 'TAM' and 'no treatment' curves diverged more as ER positivity increased.

Authors stated that the benefit of TAM vs no treatment when gauged by PR expression in tumour material, regardless of ER status, was not apparent until PR was labelled in >75% cells at which point RR for RFS = 0.41 (95%CI: 0.24-0.69) P = 0.001 and RR for OS = 0.46 (95%CI: 0.26-0.83).

Further analysis revealed similar results for PR >75% regardless of ER status and a multivariate analysis of outcomes when PR >75% gave a RR for RFS = 0.48 (95%CI: 0.26-0.88) P = 0.018 and for OS = 0.52 (95%CI: 0.28-0.99) P = 0.048

General comments:

This paper presents the results from a post-RCT study in which archived histological samples were processed for ER and PR sub-group status using tissue micro-array. Survival outcomes in response to two years tamoxifen therapy vs no treatment were then analysed by endocrine sub-group. Note that staining intensity did not form part of the endocrine status assessment.

Fractionation of the ER/PR labelling allowed predictive sub-groups to be identified for example, where previously PR >10% may not have demonstrated independent prognostic strength in determining survival outcomes, PR >75% was clearly advantageous to both RFS and OS, regardless of the ER status.

The authors stated that, whatever the cut-off value for ER status, survival outcomes were not improved by TAM compared with no treatment unless PR was highly expressed but in tumours highly expressing PR, ER status alone did not predict outcome. The purpose of their study was to show that fractionation of endocrine receptor status could provide more useful information in making treatment decisions than dichotomised outcomes only.

Whilst the study was of good intention there was a lack of statistics to support some evidence statements and appeared to be contradiction in the reporting of the significance, or otherwise, of ER status. There were no details of patient demographics.

Dowsett *et al.* (2008)

Design: Retrospective case series (prognosis). Evidence level: 3

Country: Multi-national

Inclusion criteria:

Postmenopausal women with histologically proven operable invasive breast cancer
Completion of primary treatment.

Assignment to either the anastrozole (ANA) or tamoxifen (TAM) arms of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial

Exclusion criteria:

Assignment to the combined arm of ANA + TAM in the ATAC trial

Know to have had endocrine –ve tissue

Population:

Number of patients = 9366 (original trial) of which tissue from 1856 women was successfully stained and combined with patient outcomes data. Median age = 63 years.

Interventions:

Original ATAC trial consisted of three treatment arms: ANA at 1 mg vs TAM at 20 mg vs combined treatment with ANA + TAM. The combined arm was closed after a median follow-up of 33 months having shown no greater efficacy than TAM alone.

Archived tissue was collected from two centres but processed in only one for endocrine receptor (ER and PR) status and Her2 status using standard immunocytochemistry.

Outcomes:

To identify molecular characteristics of tumours that might indicate a benefit of ANA vs TAM. Correlating endocrine status to time to relapse (TTR).

Follow up:

Median follow-up of original study = 68 months.

Results:

1782 patients were ER +ve and/or PR +ve (78.5% were PR +ve).

TTR for ANA vs TAM in original ATAC group (n=5216): HR = 0.74 (95%CI: 0.64-0.87) (P = 0.0002) for endocrine +ve tumours

TTR for ANA vs TAM in post-study group (n=1856): HR = 0.69 (95%CI: 0.53-0.91) (P = 0.008) for endocrine +ve tumours.

Recurrence was slightly lower for both treatment arms in the post-study group than in the original ATAC group.

Relationship between ER status and TTR for ANA and TAM patients:

TAM: P = 0.078 (NSD)

ANA: P = 0.0009

Relationship between PR status and TTR for ANA and TAM patients:

TAM: P = 0.0012

ANA: P < 0.0001

After 5 years of treatment with ANA, 2.6%, 5.1%, 8.3% and 13.2% of survivors were found in the highest, second highest, third highest and lowest PR +ve quartiles respectively (P < 0.0001).

By central analysis:

TTR for ANA vs TAM in post-study group: HR = 0.72 (95%CI: 0.52-1.01) for ER +ve/PR +ve tumours

TTR for ANA vs TAM in post-study group: HR = 0.68 (95%CI: 0.40-1.17) for ER +ve/PR –ve tumours (NSD).

Univariate analyses:

ANA arm (n=857):

ER status: HR = 0.83 (95%CI: 0.73-0.95) (P = 0.004)

PR status: HR = 0.89 (95%CI: 0.84-0.94) (P < 0.0001)

TAM arm (n=829):

ER status: HR = 0.90 (95%CI: 0.81-1.00) (P = 0.057) (NSD)

PR status: HR = 0.92 (95%CI: 0.87-0.97) (P = 0.001)

Multivariate analyses:

ANA arm:

ER status: HR = 0.89 (95%CI: 0.79-1.01) (P = 0.07) (NSD)

PR status: HR = 0.92 (95%CI: 0.87-0.99) (P = 0.016)

TAM arm:

ER status: HR = 0.94 (95%CI: 0.84-1.04) (P = 0.2) (NSD)

PR status: HR = 0.93 (95%CI: 0.88-0.99) (P = 0.014)

General comments:

This paper presents the findings from a retrospective exercise using tissue from a large multi-centre trial comparing ANA with TAM therapy for women with early stage breast cancer. Archived specimens were centrally processed for endocrine (and Her2) status, the results of which were compared with patient outcome data to identify possible prognostic factors.

Assessment of endocrine status from stained sections was performed by personnel blind to any other factor. ER was quantified using an H-score (percentage of cells weakly stained plus 2x the number of cells moderately stained plus x3 the number of cells strongly stained where a positive score was >1). PR was scored simply as percentage of cells stained where > 10% was regarded as positive.

The populations in the original ATAC trial and in this smaller post-trial group were similar in most respects except that in this study more women had node negative tumours and fewer women had received adjuvant chemotherapy.

Univariate analysis showed that both ER and PR status were strong prognostic factors for TTR where low receptor expression was associated with shorter TTR. These analyses were not affected by treatment choice between ANA and TAM. Multivariate analyses, which included nodal status, tumour size and grade, produced P values for ER status of 0.023 (ANA) and 0.32 (TAM) and for PR status of 0.09 (ANA) and 0.032 (TAM).

The authors comment on the apparently contradictory result from the main ATAC trial in which a greater relative benefit of ANA vs TAM was conferred on patients with ER +ve/PR -ve status compared with ER +ve/PR +ve whereas this study shows no significant difference between these groups. They suggest firstly that the ATAC analysis was unplanned but that also the present analysis comprised smaller sub-groups. Hence the results remain contradictory. It would not be possible to determine if the relationship

between endocrine status and TTR occurs naturally or is influenced by therapy.

Several authors disclosed potential conflicts of interest.

Updated 2018

4.2 What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer?

Adjuvant! On-line: review of evidence concerning its validity, and other considerations relating to its use in the NHS

A report by Jonathan Gribbin & Robyn Dewis

Introduction

The Guideline Development Group (GDG) for early and locally advanced breast cancer proposed a piece of work to assess the validity of Adjuvant! On-line as a tool to assist with clinical decisions, about adjuvant therapy, in patients with early invasive breast cancer. This document summarises the methodology used to assess this, and the key findings including a description of the Adjuvant! product, the methods used to develop it, and commercial issues associated with recommending its use.

Adjuvant! can be accessed at www.adjuvantonline.com¹. It is a tool for assessing the risks of an individual patient developing recurrent disease and/or dying within 10 years, when receiving specific treatment (on the basis of well validated factors such as age, menopausal status, oestrogen receptor (ER) status, number of involved axillary nodes etc.). Doctor and patient can use the tool together to decide on the most appropriate adjuvant treatment regimen (chemotherapy, hormone therapy, or none). Adjuvant! is a decision aid and does not direct towards a specific treatment regimen.

This appraisal has been proposed as an alternative to a question that had been framed in the PICO question 'What are the indications for adjuvant chemotherapy in patients with early invasive breast cancer?'. The GDG agreed that this PICO question covered huge topic areas and would need to be addressed using a very long list of search terms which the group were unable to specify satisfactorily.

Noting that Adjuvant! is already in use in the UK and is designed to incorporate the Oxford Overview meta-analyses, an alternative, pragmatic approach was proposed, namely of undertaking an appraisal of evidence about the validity of Adjuvant!. Two SpR/SpTs providing support to the GDG were asked to undertake this appraisal by reviewing what is known about the tool. The following represents their understanding of the research question, and the approach they took in addressing it.

Research question

The primary purpose of the appraisal was to summarise and critique what is known about Adjuvant!, and its validity as a tool for supporting clinical decisions about adjuvant chemotherapy, in UK patients, with early invasive breast cancer. Where it exists, evidence regarding its usefulness is also included.

This is a narrative report incorporating a formally referenced review of the published literature, together with other information provided by Adjuvant!. It addresses:

- A description of Adjuvant!: its intended purpose and use

- Current usage in the NHS
- Methodology underpinning Adjuvant!, including how it was developed and how it is updated.
- Any caveats/issues/known shortcomings highlighted to Adjuvant! users
- An appraisal of published evidence about Adjuvant!'s validity
- An appraisal of any published evidence regarding its usefulness
- General assumptions/issues/uncertainties in applying this tool based on USA data to NHS patients
- Commercial considerations – implications for Adjuvant!'s validity and/or practical use
- Licensing considerations – implications for unrestricted access to Adjuvant!
- Any other practical considerations relating to Adjuvant!'s use in the NHS.

Specific questions raised by GDG members that were included within scope

1. To what extent does the SEER database on which the tool is based consider adverse reactions?
2. What is the applicability of the USA data in the SEER database to UK patients in the NHS?
3. What commercial relationships underpin the design and maintenance of the system?
4. Are there any current/future licensing considerations for NHS users?
5. What are the key practical considerations relating to its use?

Excluded from scope

The decision about which chemotherapy or hormone therapy regimen to recommend are separate questions, which fall outside the scope of this appraisal. This appraisal focuses on the validity of the Adjuvant! tool itself.

This approach highlights issues relating to major assumptions inherent in the methodology which are apparent from a consideration of Adjuvant!'s methodology and the published literature. However, it does not provide a systematic, exhaustive breakdown of all the individual factors, algorithms and statistical models on which the Adjuvant! model may be based (except where these are appraised in the published literature). Similarly, this relatively short piece of work is not intended to be a critical appraisal of the Oxford Overviews (whose meta-analyses are fundamental to Adjuvant!).

Search strategy

Sources

The Ovid search engine was used to interrogate MEDLINE database (1950 to October 2007) and EMBASE. A subsequent search was also made against SIGLE for relevant grey literature.

Search parameters

A pilot search experimented with a number of synonyms for Adjuvant!. The final definitive search was executed using the following search criteria and the above source.

Table 1 Parameters and logic used in the automated search

Search	Criteria applied	Date run	Result
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1	Breast neoplasm\$ or breast cancer\$ And (decision making or computer assisted or computer\$ or decision support or decision support systems or software or decision support techniques) And (adjuvant\$)	15/10/07	615 papers
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Further screening & supplementary information

The results of the automated search were manually screened, by reading the abstracts, in order to identify relevant articles and to exclude all other papers that were not reporting research into Adjuvant! or similar decision support tools.

Adjuvant Inc. was invited to respond directly to specific questions that the literature does not address. These responses are incorporated in the findings.

Search results

Executing the automated search strategy resulted in the identification of 615 papers satisfying the search parameters. Manual screening of abstracts resulted in the exclusion of all but 9 of these papers²⁻¹⁰. Excluded papers included studies of specific treatments, risk communication and other methods of displaying outcomes e.g. prognostic tables.

Findings

Adjuvant! Online tool

The purpose of Adjuvant!¹ is to assist health professionals and patients with early stage breast cancer discuss the risks and benefits of adjuvant therapy after surgery. It does this by presenting estimates of the risk of cancer-related mortality or relapse, which can be used in consultations. It is intended to be operated and interpreted by oncologists and suitably qualified health professionals. It is not intended to replace clinical judgement and is not designed to be used by patients.

Conceptual design

The concept behind Adjuvant! is that the quality of decision-making about adjuvant therapy is enhanced in consultations where clinicians can communicate to patients the net benefit of various adjuvant therapies³. Therefore Adjuvant! is designed to:

- 1) Estimate the 'baseline' risk of mortality or relapse for patients without adjuvant therapy
- 2) Estimate the proportion of negative events that given therapies are known to prevent
- 3) Apply this effect to the baseline risk so that direct comparisons can be made of the estimated risks of mortality or relapse between treatments and with no treatment.

User functionality

The current version of Adjuvant! is version 8. User functionality comprises facilities to:

- 1) Enter patient information including age, co-morbidities plus tumour information including size, oestrogen receptor status and number of involved nodes. This is

- used to estimate risk at 10 years of breast cancer related death or relapse without additional therapy.
- 2) Display information about the efficacy of different therapy options, with the option of overriding the estimated efficacies.
 - 3) Derive estimates of risk at 10 years of breast cancer related death or relapse for the treatments selected by the user.
 - 4) Print results, access on-line help and links to sources of evidence.

Underlying this user functionality there are tables and algorithms, which aim to encapsulate evidence of effectiveness according to the Oxford Overviews. These are maintained by Adjuvant! Inc. User access to these is limited to that described above.

User access to Adjuvant! is controlled via a logon screen requiring a username and password. Registration for a username and password is open to users willing to sign a license agreement. In doing so they agree that they are a suitably qualified medical professional. There is no additional authentication of this at registration.

Technological implementation

Users access Adjuvant via a desktop browser with an Internet connection to www.adjuvantonline.com. User functionality is implemented in a Java-based program which is only present for the duration of the user's session. Some functionality also requires Adobe Acrobat and/or a printer. The server functionality runs under a Unix operating system. No patient identifiers are entered into Adjuvant!, thereby avoiding any risk or concern relating to patient confidentiality.

Further evaluation of the physical implementation is beyond the scope of this study.

There are also versions of Adjuvant designed to run on Palmtop or PocketPC. These are also beyond the scope of this study.

Control and licensing

Adjuvant! is owned by a US-based company called Adjuvant Inc. Adjuvant Inc. and all IP rights in the Adjuvant! tool are owned by Dr Ravdin, who has created and developed the tool over a period of more than 10 years. Dr Ravdin's stated motivation is academic; the venture has not been for the purpose of realising financial profit¹¹.

Over the years, funding has been secured from government, industry and research foundations. None of these sources of funding exercise editorial purview over the content of releases. Adjuvant! carries no advertising and there are no other sources of revenue.

Licenses to use Adjuvant! are free of charge. Dr Ravdin states they will remain free of charge indefinitely; there is no plan to charge a license fee either now or in the long term¹¹.

Maintenance and development

Maintenance of functionality in the current version of the tool is undertaken by Adjuvant! Inc., which secures part-time or occasional assistance from a small group of relevant specialists.

Help files are updated to reflect the current literature. The user functionality and underlying methodology is updated less frequently; recent versions of the tool have incorporated only minor changes.

The direction and timing of these developments is determined by Dr Ravdin, according to the publication of new evidence, requests from users, and the availability of personnel to implement the changes. In the past, new versions have been released around the time of major research meetings, e.g. ASCO, San Antonio Breast Cancer Symposium.

Currently efforts are focussed on developing the next major release of Adjuvant!, which will incorporate recent trial evidence relating to human epithelial growth factor receptor (HER2) and trastuzumab. Beyond this, there is no formally documented plan describing the development path for the product.

Users are not required to undertake any maintenance.

Current usage in the NHS

Dr Ravdin reports that there were 2,978 registered active users in the UK as at July 2007 (which represents about 7% of the total registered user base of more than 42,000). This is based on information supplied at registration which is not authenticated.

Estimates of frequency of usage are derived from the number of Adjuvant! sessions that ran in a given period of time. In the first six months of 2007 the Adjuvant! platform delivered 110,800 user sessions. Based on the crude assumption that frequency of usage is the same across all users, this represents an estimated 8,000 user sessions in the same period for users registered in the UK. It is not possible to determine how many of these sessions supported actual consultations with NHS patients.

A survey of usage amongst oncologists in the UK is planned but will not report before July 2008 at the earliest¹².

Underlying Methodology - derivation of baseline risk estimate

Population

The data used for the baseline risk estimate was derived from the SEER database (Surveillance, Epidemiology and End Results Program in the USA)¹³. Adjuvant! was based upon database 9 which covered 14% of the US population¹⁴. Detailed information was not available on the breakdown for the SEER 9 population but studies have assessed its similarity to the US population:

1. The SEER population is similar to the US population in terms of age and sex distribution. The US population has larger percentage of the population in the under 55 age groups and fewer in the over 55 age groups, when compared to the population of England and Wales¹⁵.
2. The SEER population over represents certain ethnic groups, e.g. Native American/Hawaiian and some South East Asian groups compared to the US population. This is related to the States that are included in the database e.g. Alaska and Hawaii¹³.
3. The ethnic mix of the US population differs from that of England and Wales. Only broad categories can be considered due to differences in categorising ethnicity, but broadly speaking in the US there are lower percentages of white and mixed races, with higher percentages of Black and Other Races¹³.
4. Socioeconomic data in the SEER database is of poor quality.

5. Date and cause of death are recorded. Date of death is considered robust, however cause of death is of poor quality¹⁴.

As survival is analysed in terms of age group the differences in the age of the population is unlikely to affect the generaliseability of the data. The difference in ethnicity, however, is likely to affect this. The incidence of breast cancer is highest in the white population, but mortality is highest in the black population. A program based on this data, that does not take ethnicity into account, will tend to overestimate survival in the black population and underestimate in the white. It is difficult to assess what effect this would have on other ethnic groups or to know if survival differs in these ethnic groups in the United Kingdom.

Selection

Ravdin et al³ selected a population from the SEER database for the development of Adjuvant!. Women who met the following criteria were included in the calculations of baseline risk:

1. Had invasive, unilateral and non-inflammatory breast cancer
2. Had received definitive surgery and axillary staging with at least 6 lymph nodes
3. Had data on tumour size, number of nodes sampled and the number of positive nodes.

Women were specifically excluded from the calculations of baseline risk for the following reasons:

1. Those aged under 35 years.
This group of young women were observed to have a worse prognosis than the other age groups. (A correction applied to allow for this group of women is described below.)
2. Those aged over 59 years. This group of women was believed to be healthier and have better access to health care. Analysis of this group revealed that women with breast cancer appeared to have better survival than the general US population of the same age.

Survival

The SEER data were then used to calculate survival. This was observed survival for 5 years that was then extrapolated to 10 years, as the data were insufficient to cover this period. Relative survival was used, which makes an adjustment for age specific death rates from other causes. This survival estimate is based upon the tumour size, the number of positive nodes and the oestrogen receptor status of the tumour. There are some assumptions made in calculating survival for Adjuvant!.

1. Impact of ER status. There were data issues around ER status that led to estimates inconsistent with what would be expected from the literature. For this reason a relative risk of 1.3 was applied to predict survival in ER positive and negative individuals (based on evidence from long-term studies of node negative patients).
2. The effect of stage of tumour and adjuvant therapy received. An assumption was made that a percentage of the population would have received adjuvant therapy. In order to find the 'base line risk', the survival without the use of adjuvant therapy, it was assumed that at stage one the adjuvant therapy would have improved outcomes by 15% and at all other stages by 30%.
3. Constant Hazard. Survival calculations assume that the risk of death/recurrence remain constant throughout the study period considered.

Relapse

The SEER database does not hold information on relapse of disease. An assumption is made that, on average, individuals survive for three years after relapse of breast cancer in order to calculate the risk of relapse.

Other issues with UK US comparisons

Other differences between the US and UK population were also considered. There is a lack of universal access to health care in the US, which may affect the survival of certain groups within the US. However, individuals' data were only entered into the study when they had received initial surgery and staging and so should not affect applicability to the UK population. There are also differences in attitudes towards healthcare between the two countries, e.g. the UK population tend to choose less radical surgery than the US population¹⁶. Although this may lead to differences in decisions made when using the tool it does not affect its validity for the UK.

Estimating negative outcomes averted

Adjuvant! applies an estimation of negative outcomes averted to the baseline survival to give an estimation of survival following one or more adjuvant therapies³. Estimation of negative outcomes averted is quantified in terms of the proportion risk reduction (PRR), i.e. the proportion of the baseline risk, which is reduced by each therapy.

PRR for specific therapies are derived from the Overviews. They are incorporated into Adjuvant! to derive estimates of breast cancer-specific mortality. To avoid the possibility of gross error in estimating the breast cancer specific mortality of over 70 year olds (in which group most mortality is probably non-breast cancer-specific), Adjuvant! applies the PRR for 50-69 years for women 70 years or older. When the operator is using the tool to model outcomes for patients over 70 years of age, Adjuvant! warns the user about the possible effect of this simplifying assumption.

To model the relative value of various chemotherapy regimen Adjuvant! groups treatments into three distinct "generations", based on their perceived efficacy and toxicity. Prompts appear on screen at relevant points in the user session with details of the basis on which this grouping has been done. The prompts also outline the key inferences that Adjuvant! makes to estimate relative efficacy (e.g. of a third generation regimen compared to none) and points the user to further information contained in the Help files.

Applying calculation to previous baseline

The Oxford Overviews report the results of clinical trials. Few trials for cancer therapy consider the effect of one treatment against placebo/no treatment. The majority report the risk reduction of using one treatment over another. According to Ravdin³, the Overviews suggest that treatment effects are independent of other treatment used. Adjuvant! uses this assumption, through the following formula, to calculate the proportionate risk reduction achieved by the use of a specific adjuvant therapy:

$$\text{PRR combined therapy} = 1 - [(1 - \text{PRR therapy 1}) \times (1 - \text{PRR therapy 2})]$$

Validation

Since Ravdin et al's 2001 paper describing the tool and its methodology, there have been two further published studies that assess the validity of the Adjuvant! tool. The tool is currently being compared against two further European registers¹¹.

Prospective population-based validation

Olivotto et al⁸ set out to independently validate Adjuvant! by comparing the observed 10 year outcome of each of 4083 patients with stage 1 and 2 breast cancer on a British Columbian register with the outcome predicted by Adjuvant!.

Taking the cohort as a whole, they found a high degree of agreement between the predicted and observed overall survival and breast cancer specific survival. They also analysed the differences between observed and predicted outcomes for specific subgroups which in most cases were within 2% or not significantly different (at $P > 0.05$).

For patients younger than 35 years of age or with lymphatic or vascular invasion (LVI) Adjuvant! over-estimated the survival. After the operators applied their judgement to adjust for LVI using the prognostic factor impact calculator tool within Adjuvant! (PFIC), the 10 year predictions were no longer significantly different.

The strength of this study is that it provides validation of Adjuvant! predictions using an external reference population. The strength of evidence it provides in this assessment is limited by the following factors:

- The study was undertaken on version 5 of Adjuvant!
- It is implicit that the operators were very familiar with the tool, and may have included its author. It is not clear whether an "average" operator would achieve the same level of agreement when making adjustments using the prognostic factor impact calculator (PFIC).

In summary, the study provides independent validation of an earlier version Adjuvant!. For women aged 30 to 59 years of age whose adverse prognostic factors are automatically accounted for within the tool, Adjuvant! provides reliable predictions of the benefits of adjuvant therapy. The reliability of predictions for other groups depends in part on the knowledge and judgement of the operator in making adjustments using the PFIC.

It should be noted that more recent versions of Adjuvant! incorporate an adjustment to "correct" the overestimation of survival for young ER positive patients¹¹.

Clinician-based validation

Loprinzi et al⁴ describe the development of an algorithm to calculate 10-year outcomes for breast cancer patients. As part of this, they asked 11 US oncologists for their estimates of 10-year disease-free survival. The mean of these estimates were compared to predictions generated by Adjuvant!. The degree of correlation was not measured formally; the graphical representation of the correlation suggests a reasonable degree of agreement.

These published data provides weak evidence for the validity of Adjuvant!. However, the fact that the predictions of oncologists vary supports the rationale that there is a need for a tool, which provides evidence-based predictions in an understandable format.

Impact and usefulness

The purpose of Adjuvant! is to provide predictions of risk that support dialogue between clinician and patient about the most appropriate adjuvant therapies for that patient. There is little published literature evaluating the impact of Adjuvant! on these interactions, nor on the degree to which clinicians correctly handle the tool or what meaning patients ascribe to the predictions. A USA study⁷ of the effects on treatment choices of Adjuvant! compared to a well presented information pamphlets did not find statistically significant differences between the groups. After adjusting for disease-related and socio-demographic confounders, they found that those who used Adjuvant! were less likely to choose adjuvant treatment (OR 0.32 95%CI 0.12-0.84). This is broadly consistent with the findings of an apparently related study⁹.

A study of 102 treatment management decisions in a Hong Kong oncology centre¹⁰ found that clinicians changed their decision in 13 instances after taking into consideration the predictions made by Adjuvant!. Based on analysis of this decision-making, Adjuvant!'s impact was attributed to: the distinction it makes between the marginal benefits of intervention compared to prognosis per se, the deeper consideration of therapeutic goals and costs for individuals which it enables, a comparison of the relative benefits of different treatments, the quantification of iatrogenic risks. The study found that treatment decisions continued to be strongly influenced by factors *omitted* from the version of Adjuvant used in the study (e.g. lymphovascular invasion and HER2 expression). Clinicians in this study tended to ignore the adjustments to risk recommended by the programme on the basis of low tumour grade when these adjustments were perceived to conflict with other indicators such as node-positivity. Clinicians' attitudes to the utility of Adjuvant were varied but the study authors formed the impression that, in the context of case discussions, the tool enabled groups to achieve consensus more quickly.

There is a body of literature concerning the impact of *other* decision tools on a range of patient-clinician interactions. For example, a systematic review¹⁷ of 17 RCTs did not show a consistent impact on patient knowledge and satisfaction. More recently, there has been at least one trial to evaluate the effect of a decision support tool on the knowledge and satisfaction of breast cancer patients in particular¹⁸. A full review of this literature is beyond the scope of this assessment.

Summary/Conclusions

The predictions made by Adjuvant! are based on a published methodology, which has been updated periodically as evidence of treatment effectiveness and data on risk factors becomes available.

Help files and published descriptions of the tool make clear some of the assumptions and limitations that underpin the methodology. The impact of these individual assumptions is difficult to assess, and beyond the scope of this paper. Adjuvant! deals with key uncertainties by alerting the user to them at relevant points.

Survival estimates are derived from a US population. Quantifying the impact on survival of socio-economic background and of ethnic differences between the US and UK populations is difficult.

The strongest evidence of Adjuvant's validity for the UK is derived from comparisons between its predictions and observed outcomes using a Canadian population. This study found its predictions to be reliable for most groups. Since that study, an adjustment has been applied to 'correct' the predictions made for a subset of younger patients.

Further validation is under way using European populations. Dr Ravdin would welcome similar validation against a UK population.

Weaker evidence for its validity includes comparisons of its predictions with the predictions of clinicians. The development path for Adjuvant! appears to be consistent with a product which intends to remain evidence-based.

Dr Ravdin's stated intention is that license to use Adjuvant! will remain free of charge. This together with its web-based design means that the cost to users of using Adjuvant! should remain very low.

There are only two trials assessing the impact of Adjuvant! in doctor-patient interactions. These indicate that in a USA setting patients considering adjuvant treatment were less likely to select adjuvant treatment if their consultation involved use of Adjuvant! instead of an information pamphlet. A third study of 102 clinician decisions about patient management found that using Adjuvant! resulted in a change of decision in 13 cases, and that clinicians' views of the tool's utility were varied.

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4.3 What is the optimal time interval from completion of definitive surgery to commencement of adjuvant therapy?

Short Summary

There is a moderate volume of evidence to address the sequencing of adjuvant therapies, including several randomised trials. Non-randomised, retrospective studies of the interval between surgery and adjuvant therapy were also available.

Sequencing Of Adjuvant Therapies

Concurrent adjuvant chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy: There is high quality evidence from randomised controlled trials (RCTs) (Hickey *et al.* 2006; Calais *et al.* 2005; Toledano *et al.* 2007) that suggest there is no advantage arising from concurrent adjuvant chemotherapy/radiotherapy versus sequential chemotherapy followed by radiotherapy in terms of local recurrence, distant metastases and overall survival. RCT evidence on acute toxicity for this comparison is not consistent, since there is no difference with regard to some toxic effects, whereas other toxic effects are more common following either concurrent therapy, or sequential therapy. RCT evidence suggests that late toxic effects are more common following concurrent therapy than sequential therapy and that in the subgroup of lymph node-positive patients local recurrence-free survival is higher following concurrent therapy than sequential therapy.

Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy: Further RCT evidence (Hickey *et al.* 2006; Huang *et al.* 2003) suggests there is no advantage arising from radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy in terms of distant metastases and overall survival. RCT evidence is suggestive of a higher rate of neutropenic sepsis in patients who receive radiotherapy before chemotherapy but with no difference for other toxicity outcomes. One meta-analysis of data from observational studies suggests that loco-regional recurrence is higher where chemotherapy precedes radiotherapy, compared to radiotherapy then chemotherapy.

Early versus late chemotherapy: RCT evidence from the International Breast Cancer Study Group (1997) suggests there is no difference in 5-year disease-free survival or overall survival arising from early chemotherapy given over the first three months following surgery versus delayed chemotherapy given between 9 and 15 months following surgery.

Interval Between Surgery And Start Of Adjuvant Therapy

Interval from surgery to radiotherapy: There is considerable high quality evidence that addresses this clinical issue (Huang *et al.* 2003; Whelan *et al.* 2003; Hershman *et al.* 2006a). Evidence from a meta-analysis of data from

observational studies suggests that locoregional recurrence is more likely if radiotherapy is delayed more than 8 weeks following surgery. Other observational studies do not consistently indicate that a longer interval to start of radiotherapy is associated with greater likelihood of locoregional recurrence, but these studies consider different lengths of interval. Evidence from a meta-analysis of data from observational studies suggests there is no difference in the rate of distant metastases arising from an interval to radiotherapy of 8 weeks or more, compared to an interval of less than 8 weeks. Authors of a Canadian guideline based upon a systematic review conclude that evidence does not support definition of an optimal interval between surgery and radiotherapy (Whelan *et al.* 2003).. One retrospective cohort study (Hershman *et al.* 2006a) suggests that in elderly patients who receive radiotherapy and no chemotherapy, higher mortality is observed where radiotherapy is given 3 months or more following surgery, compared to within 3 months of surgery. In the same study numerous demographic and tumour-related variables were also associated with mortality outcomes, making interpretation difficult.

Other observational studies found that disease free and overall survival were not adversely affected by increasing delay to the start of radiotherapy in the first three months after surgery (Benchalal *et al.* 2005; Jobsen *et al.* 2006; Mikeljevic *et al.* 2004). A large UK cohort study of 7800 women found that overall survival was adversely affected only in those whose radiotherapy was delayed for at least 5 to 6 months after surgery (Mikeljevic *et al.* 2004).

Interval from surgery to chemotherapy: One retrospective cohort study (Hershman *et al.* 2006b) suggests that in elderly patients who receive chemotherapy with no radiotherapy prior to chemotherapy, higher mortality is observed where chemotherapy is given 3 months or more following surgery, compared to within 3 months of surgery. In the same study numerous demographic and tumour-related variables were also associated with mortality outcomes, making interpretation difficult.

Other cohort studies found increasing delay to the start of adjuvant chemotherapy in the first 3 months after surgery was not associated with poorer disease free or overall survival (Cold *et al.* 2005; Colleoni *et al.* 2000; Lohrisch *et al.* 2006; Sanchez *et al.* 2007; Shannon *et al.* 2003). Colleoni *et al.* (2000) reported that disease free survival was adversely affected by delays of three or more weeks in the sub-group of women with ER-negative disease. Another study reported that disease free and overall survival were adversely affected only when the start of chemotherapy was delayed until at least three to six months after surgery (Lohrisch *et al.* 2006).

PICO

Patient Population	Intervention	Comparison	Outcome
Patients who have received definitive surgery (including simultaneous reconstructive surgery) and who receive adjuvant therapy	Early adjuvant therapy: <ul style="list-style-type: none"> • Chemotherapy • Radiotherapy • Hormone therapy 	Late (delayed) adjuvant therapy: <ul style="list-style-type: none"> • Chemotherapy • Radiotherapy • Hormone therapy 	Local recurrence Disease-free survival Overall survival Patient acceptability Psychological morbidity

Evidence Summary

There is a moderate volume of evidence to address the sequencing of adjuvant therapies, including several randomised trials. Non-randomised, retrospective studies of the interval between surgery and adjuvant therapy are also available.

Published randomised trials compare different *sequences* of adjuvant therapies following surgery, three of which have been summarised in a high quality Cochrane systematic review (Hickey *et al.* 2006). Although not stated originally in the PICO formatted research question, the GDG communicated that outcome data following different sequencing strategies are of interest and for this reason, are reported here.

Only non-randomised studies exist of the effect of the *interval* between definitive surgery and start of adjuvant treatment on important outcomes (e.g. recurrence, survival). However numerous large, retrospective studies addressed this issue so an arbitrary inclusion threshold of studies with at least 1000 patients was used.

The RCT findings are consistent. The findings of the cited observational studies are inconsistent and should be interpreted with caution. In particular where meta-analyses have been performed using data from observational studies (i.e. Huang *et al.* 2003) there is the risk that confounding and bias in the primary studies contribute to a precise, but spurious pooled estimate. Authors of a Canadian clinical guideline supported by a systematic review (without meta-analysis) report that for some outcomes the evidence is inadequate to support treatment decisions (Whelan *et al.* 2003).

The SECRA trial is in progress, comparing a sequential schedule of chemotherapy followed by radiotherapy with a synchronous schedule of radiotherapy administered during the chemotherapy regimen, but no data from this trial are available yet.

Since the Cochrane Review of randomised studies by Hickey *et al.* 2006 (Hickey *et al.* 2006) evaluates the effect of sequencing of adjuvant RT relative to adjuvant CT, further primary non-randomised studies of sequencing were excluded.

However data from some such studies was included in two systematic reviews that are cited here (Huang et al. 2003; Whelan et al. 2003)

SEQUENCING OF ADJUVANT THERAPIES

1. Concurrent adjuvant chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy

In a meta-analysis of data from two RCTs (Arcangeli 2006; Calais 2004), the Cochrane review (Hickey *et al.* 2006) found no statistically significant difference between concurrent chemotherapy/radiotherapy versus chemotherapy followed by radiotherapy in terms of ipsilateral local recurrence [OR (concurrent:sequential) 1.30; 95% CI 0.45 to 3.77; $p=0.63$] and distant metastases [OR (concurrent:sequential) 1.43 95% CI 0.86 to 2.37, $p=0.16$]. Only one included trial (Arcangeli 2006) reported overall survival, which did not statistically significantly differ at 5 years follow-up, being 94.7% in the concurrent arm and 93.9% in the sequential arm.

In the Cochrane systematic review (Hickey *et al.* 2006) one included RCT (Arcangeli 2006) reported that acute toxicity was “mild” in both randomised arms. The other trial (Calais 2004) found no statistically significant difference between randomised arms for fever (OR 1.27, 95% CI 0.79 to 2.03, $p=NS$), cardiac complications (OR 1.73, 95% CI 0.50 to 5.96, $p=NS$), neutrophil toxicity (OR 0.89, 95% CI 0.63 to 1.27, $p=NS$) or platelet toxicity (OR 0.89, 95% CI 0.39 to 2.06, $p=NS$). However, oesophageal toxicity (OR 1.44, 95% CI 1.03 to 2.02, $p=0.03$), haematological toxicity (OR 1.43, 95% CI 1.01 to 2.03, $p=0.04$) and skin toxicity (OR 1.46, 95% CI 1.00-2.14), $p=0.05$) were significantly lower with sequential therapy. Nausea and vomiting was significantly less common with concurrent therapy (OR 0.70, 95% CI 0.50 to 0.98, $p=0.04$). In both trials and in both randomised arms, all women received 80% or more of the prescribed chemotherapy (judged by Hickey *et al.* 2006 to be a sensible arbitrary threshold). All patients in both randomised groups in the Arcangeli 2006 trial received 100% of their planned radiotherapy, and there was no significant difference in the total dose delivered in both groups of the RCT by Calais 2004 (Hickey *et al.* 2006).

An abstract paper updated the data from the Calais 2004 trial with longer follow-up (Calais *et al.* 2005). At a median 6.7 years follow-up there remained no differences between the two arms in rates of overall survival, disease-free survival or loco-regional control. In the subgroup of node-positive patients the survival rate without local and regional failure was significantly higher in the concurrent therapy arm ($p<0.035$). The incidence of late toxic effects (subcutaneous fibrosis, telengectasia, skin pigmentation, and breast atrophy) was higher in the concurrent arm than in the sequential arm.

Subsequent to the Cochrane Review (Hickey *et al.* 2006) another RCT compared concurrent chemotherapy/radiotherapy with sequential chemotherapy followed by

radiotherapy (Toledano *et al.* 2007). There were no statistically significant differences between the sequential therapy group and the concurrent therapy group in 5-year rates of disease-free survival (80% and 80% respectively; $p=0.83$, Log-rank test), recurrence-free survival (92% and 95% respectively; $p=0.76$, Log-rank test) and overall survival (90% and 91% respectively; $p=0.76$, Log-rank test). There was also no difference in local recurrence-free survival in the node-negative subgroup of patients between the sequential therapy group (93%) and the concurrent therapy group (93%; $p=0.81$, Log-rank test). However in the node-positive subgroup local recurrence-free survival was statistically significantly worse in the sequential therapy group (91%) compared to the concurrent therapy group (97%; $p=0.02$, Log-rank test; HR 0.61, 95% CI 0.38-0.93).

This trial reported acute toxicities. Oesophagitis was more frequent in the concurrent arm than the sequential arm (115 v 89 respectively; $p = .04$). Nausea/vomiting was significantly higher in the sequential treatment arm than the concurrent treatment arm (235 v 248 respectively; $p = .008$), whereas anaemia was significantly more frequent in the concurrent arm than the sequential treatment arm (111 v 81 respectively; $p = .02$) (Toledano *et al.* 2007).

This trial also reported late toxicities attributed to radiotherapy in a non-intention-to-treat analysis of a sample of randomised patients (Toledano *et al.* 2006). At a median follow-up of 6.7 years Subcutaneous fibrosis, telangectasia, skin pigmentation, and breast atrophy occurred at higher rates in the concurrent arm than in the sequential arm. Twenty patients experienced Grade 2 or higher subcutaneous fibrosis in concurrent arm versus 5 patients in the sequential arm ($p = 0.003$). Twenty-five patients and 7 patients showed Grade 2 or higher telangectasia in the concurrent arm and the sequential arm, respectively ($p = 0.001$). Forty-four patients and 20 patients showed Grade 2 or higher breast atrophy in the concurrent arm and the sequential arm, respectively ($p = 0.0006$). Thirty patients experienced Grade 3 or higher skin pigmentation in the concurrent arm versus 15 patients in the sequential arm ($p = 0.02$). No statistical difference was observed between the 2 arms concerning Grade 2 or higher breast oedema, arm lymphoedema or Grade 2 or higher pain (Toledano *et al.* 2006).

A Canadian clinical guideline underpinned by a systematic review of mixed study designs (predominantly from non-randomised studies) addressed strategies for breast radiotherapy after breast-conserving surgery for early breast cancer (Whelan *et al.* 2003). The authors identified no evidence to confirm that concurrent adjuvant chemotherapy and radiotherapy results in a better outcome, whilst evidence suggested that concurrent treatment results in an increased chance of toxic effects.

2. Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy

Data from one RCT (Bellon 2005) cited in the Cochrane systematic review (Hickey *et al.* 2006) found no statistically significant difference arising from radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy in terms of distant metastases [HR (RT first:CT first) 0.82, 95% CI 0.49 to 1.36, p=0.44] and overall survival [HR (RT first:CT first) 0.85, 95% CI 0.51 to 1.40, p=0.52].

In the Cochrane systematic review (Hickey *et al.* 2006) one included RCT (Bellon 2005) found that radiotherapy before chemotherapy was associated with statistically significantly more neutropenic sepsis than chemotherapy before radiotherapy [OR (RT first: CT first) 2.96, 95% CI 1.26 to 6.98, p=0.02]. There was no significant difference in outcome between randomised arms for skin toxicity [OR (RT first: CT first) 1.48, 95% CI 0.68 to 3.26, p=NS], subcutaneous toxicity [OR (RT first: CT first) 2.05, 95% CI 0.50 to 8.40, p=NS], pneumonitis [OR (RT first: CT first) 11.47, 95% CI 0.63 to 209.7, p=NS], lymphoedema [OR (RT first: CT first) 0.11, 95% CI 0.01 to 2.02, p=NS] and brachial plexopathy [OR (RT first: CT first) 3.02, 95% CI 0.12 to 74.98, p=NS]. Owing to the small number of events, many of the results had wide confidence intervals.

A systematic review of mostly observational studies (Huang *et al.* 2003) performed a meta-analysis using data from 11 studies (one RCT) comparing adjuvant chemotherapy followed by radiotherapy versus adjuvant radiotherapy followed by chemotherapy. Loco-regional recurrence at 5 years follow-up had OR (CT first: RT first) 2.28 (95% CI, 1.45 to 3.57), corresponding to a statistically significant increase in the 5-year LRR from 6.0% in the RT first group to 16.0% in the chemotherapy-first group.

3. Early versus late chemotherapy

An RCT with 2x2 factorial design (International Breast Cancer Study Group 1997) permits comparison of early CMF chemotherapy (i.e. months 1, 2 and 3 following surgery) versus delayed CMF chemotherapy (i.e. months 9, 12 and 15 following surgery). All patients received tamoxifen and patients who received breast conserving surgery received radiotherapy; given after early chemotherapy or before late chemotherapy, with randomisation stratified according to whether radiotherapy was given. 5-year disease-free survival was 64% in the early chemotherapy group and 59% in the delayed chemotherapy group. 5-year overall survival was equal at 74% in both groups. Differences in survival were not statistically significant across the four analysis groups, which also included patients treated with adjuvant tamoxifen alone, and patients treated with both early and late chemotherapy. The rate of toxicity of grade 3 or worse was 9.7% in the early chemotherapy group and 7.6% in the delayed chemotherapy group.

INTERVAL BETWEEN SURGERY AND COMMENCEMENT OF ADJUVANT THERAPY

Interval from surgery to radiotherapy

A systematic review of mostly observational studies examined the relationship between the interval from surgery to starting radiotherapy and local control (Huang *et al.* 2003). In a meta-analysis of data from eight studies locoregional recurrence was more frequent when radiotherapy was delayed: OR (interval>8 weeks:interval ≤8 weeks) 1.62 (95% CI, 1.21 to 2.16); corresponding to an increase in the 5-year rate of loco-regional recurrence from 5.8% in those patients treated within 8 weeks to 9.1% in those patients treated between 9 and 16 weeks after surgery.

Two further studies cited by Huang *et al.* 2003 used different definitions of delay and were not included in the meta-analysis. One study showed a statistically significantly higher risk of local recurrence for patients who waited for RT for more than 80 days after lumpectomy ($P < .05$) whereas the other study reported no significant difference in any recurrence between patients treated with postoperative RT within 4 weeks after surgery and those treated more than 4 weeks after surgery ($P = 0.44$) (Huang *et al.* 2003).

The systematic review by Huang *et al.* 2003 also performed a meta-analysis for the odds of distant metastases comparing women receiving postoperative RT more than 8 weeks after surgery and those women treated within 8 weeks after surgery. There was no statistically significant difference: OR (interval>8 weeks:interval ≤8 weeks) 1.22 (95% CI, 0.94 to 1.59). Two further included studies were not included in the meta-analyses, but both found no association between delay and the rate of distant metastasis (Huang *et al.* 2003).

A Canadian clinical guideline underpinned by a systematic review of mixed study designs addressed strategies for breast radiotherapy after breast-conserving surgery for early breast cancer (Whelan *et al.* 2003). The authors concluded that the evidence reviewed was inadequate to define an optimal interval between breast-conserving surgery and the start of radiotherapy.

A retrospective cohort study examined the effect upon survival of the interval between surgery and radiotherapy in 13,907 patients of age 65 years or older who received radiotherapy within one year of diagnosis and who did not receive chemotherapy (Hershman *et al.* 2006a). Overall survival and breast cancer-specific survival were similar in patients who received RT within 1 month, 2 months, or 3 months after surgery (no data shown). In a multivariate analysis, overall mortality rates were higher among women who delayed RT 3 months or more after surgery relative to women who received RT within 3 months of surgery (HR 1.61; 95% CI, 1.42–1.82), as were cancer-specific mortality rates (HR 2.14; 95% CI, 1.79–2.57). This analysis adjusted for the effect upon survival of numerous demographic and tumour-related variables. However numerous variables were also found to be statistically significantly associated in isolation with survival outcomes: patient age, disease stage, hormone receptor status,

tumour grade, comorbidity score, marital status, type of hospital and socioeconomic status (Hershman *et al.* 2006a).

Other observational studies found that disease free and overall survival were not adversely affected by increasing delay to the start of radiotherapy in the first three months after surgery (Benchalal *et al.* 2005; Jobsen *et al.* 2006; Mikeljevic *et al.* 2004). Survival analyses were adjusted for known prognostic factors. A large UK cohort study of 7800 women found that overall survival was adversely affected only in those whose radiotherapy was delayed for at least five to six months after surgery (Mikeljevic *et al.* 2004). In the cohort analysed by Jobsen *et al.* (2006), delayed radiotherapy was associated with a reduction in the risk of cancer death, although radiotherapy delay appeared to be confounded with year of treatment in their cohort.

Interval from surgery to adjuvant chemotherapy

Similar to the study described above by Hershman *et al.* 2006, the same team of authors examined the effect upon survival of the interval between surgery and chemotherapy in a retrospectively studied cohort of 5003 women of age 65 years and older, who received chemotherapy within 1 year of their diagnosis of breast cancer, but who did not receive radiotherapy prior to chemotherapy (Hershman *et al.* 2006b). Breast cancer specific survival was similar in patients who received chemotherapy within 1 month, 2 months, or within 3 months following surgery. Overall survival also did not differ among patients who started treatment in any of these time intervals (full data not shown). In a multivariate analysis, the breast cancer specific mortality rate was higher among women who delayed chemotherapy 3 months or more following surgery (HR >3 months :<1 month 1.69, 95% CI 1.31–2.19), as was the overall mortality rate (HR >3 months :<1 month 1.46, 95% CI 1.21–1.75). This analysis adjusted for the effect upon survival of numerous demographic and tumour-related variables. However several variables were also found to be statistically significantly associated in isolation with survival outcomes, including advanced age, African American race, residence in a non-metropolitan location, estrogen receptor negative tumors, poorly differentiated tumors, increased number of comorbidities, being unmarried, and undergoing radiotherapy ($p < 0.05$ in all cases).

Other cohort studies found increasing delay to the start of adjuvant chemotherapy in the first three months after surgery was not associated with poorer disease free or overall survival (Cold *et al.* 2005; Colleoni *et al.* 2000; Lohrisch *et al.* 2006; Sanchez *et al.* 2007; Shannon *et al.* 2003). Three of the studies used comparable stratification of chemotherapy delay (Cold *et al.* 2005; Colleoni *et al.* 2000; Shannon *et al.* 2002). Colleoni *et al.* (2000) reported that disease free survival was adversely affected by delays of three or more weeks in the sub-group of women with ER-negative disease. Another study reported that disease free and overall survival were adversely affected only when the start of chemotherapy was delayed until at least three to six months after surgery

(Lohrisch *et al.* 2006). However the start of chemotherapy was delayed for three to six months in only four percent of the cohort.

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Evidence Tables

Hickey, Francis & Lehman . Sequencing of chemotherapy and radiation therapy for early breast cancer. Cochrane Database of Systematic Reviews 2006 Issue 4. Chichester (UK), John Wiley & Sons, Ltd.
Design
Systematic review of RCTs. Country of origin: various Evidence grade: 1+
Inclusion criteria
Aim: To determine the effects of different sequencing of radiotherapy and chemotherapy for women with early stage breast cancer who have been treated surgically. Types of studies Randomised trials evaluating different ways of sequencing radiotherapy and chemotherapy were eligible. The comparison between different sequences had to be unconfounded (i.e. the randomised groups differed only in relation to the sequencing of the two treatments). Trials incorporating the use of other adjuvant treatments, such as monoclonal antibodies or hormonal therapy, were eligible if these other treatments were applied in both groups in the randomised trial. Published and unpublished studies were eligible.
Exclusion criteria
Women who had previously received adjuvant therapy for breast cancer were not eligible.
Population
N=1097 Types of participants Women with surgically treated, histologically confirmed early stage breast cancer who required both adjuvant chemotherapy and radiotherapy were included. Early breast cancer included tumours classified as UICC stage T1-3N0-1M0. Surgery could comprise mastectomy, lumpectomy, wide local excision or quadrantectomy, with or without axillary dissection, axillary sampling or sentinel node biopsy.
Interventions
The following comparisons were eligible: 1) Adjuvant radiotherapy followed by adjuvant chemotherapy versus adjuvant chemotherapy followed by adjuvant radiotherapy; 2) Adjuvant chemotherapy followed by adjuvant radiotherapy versus a 'sandwich technique' (when one or more courses of chemotherapy are followed by radiotherapy, which is followed by further chemotherapy); 3) Adjuvant chemotherapy followed by adjuvant radiotherapy versus concurrent adjuvant

chemotherapy and radiotherapy.

Chemotherapy regimens included those delivered at standard doses (i.e. not high dose), and could include drugs such as cyclophosphamide, 5-fluorouracil, anthracyclines, taxanes and other agents.

Radiotherapy had to be delivered to the breast or chest wall, including or not including the supraclavicular fossa and axilla. Standard fractionation (1.8 to 3.0 Gy per fraction) had to be used, delivering a total of 40 to 61 Gy at the reference point. It could include a boost (using electrons, interstitial therapy or external beam) or new techniques.

Outcomes

Primary outcomes

- Local recurrence in the ipsilateral breast
- Cause-specific mortality

Secondary outcomes

- Overall survival
- Distant metastases (in isolation or at the same time as local recurrence)
- Relapse-free survival
- Subsequent mastectomy
- Harms, including acute and late effects of radiotherapy, chemotherapy-related toxicity
- Ability to deliver the prescribed dose of chemotherapy; ability to deliver the prescribed dose of radiotherapy
- Costs
- Quality of life
- Patient preference

The authors set an arbitrary threshold of 80% when assessing the ability to deliver the prescribed dose of chemotherapy or radiotherapy, as acceptable.

Local recurrence included recurrence in the ipsilateral breast, the skin and parenchyma.

Follow up

Median values for three included RCTs:
Arcangeli 2006: 65 months
Bellon 2005: 135 months (range 17-196 months)
Calais 2004: 36 months

Results

1. Concurrent treatment versus chemotherapy followed by radiotherapy

Two trials; n=853; (Arcangeli 2006;Calais 2004)

NB: OR < 1 indicates a beneficial effect of concurrent treatment compared with sequential treatment

Local recurrence (ipsilateral):

OR concurrent therapy vs. chemotherapy followed by radiotherapy 1.30 (95% CI 0.45 to 3.77, p=0.63).

Overall survival:

Arcangeli 2006 reported the overall survival in concurrent and sequential groups at 5 years as being 94.7% and 93.9% respectively, with a non-significant hazard ratio (HR).

Distant metastases:

OR 1.43 (95% CI 0.86 to 2.37, p=0.16).

Harms and toxicity:

The Arcangeli 2006 report includes the comment that acute toxicity was “mild in both groups, with infrequent moist desquamation in limited areas”.

The other trial (Calais 2004); n=647; reported harms and toxicity in detail. No significant difference was found between the treatment groups for fever (OR 1.27, 95% CI 0.79 to 2.03, p=NS), cardiac complications (OR 1.73, 95% CI 0.50 to 5.96, p= NS), neutrophil toxicity (OR 0.89, 95% CI 0.63 to 1.27, p= NS) or platelet toxicity (OR 0.89, 95% CI 0.39 to 2.06, p=NS). However, oesophageal toxicity (OR 1.44, 95% CI 1.03 to 2.02, p=0.03), haematological toxicity (OR 1.43, 95% CI 1.01 to 2.03, p = 0.04) and skin toxicity (OR 1.46, 95% CI 1.00-2.14), p=0.05) were significantly lower with sequential therapy. Nausea and vomiting was significantly less common with concurrent therapy (OR 0.70, 95% CI 0.50 to 0.98, p= 0.04).

Ability to deliver the prescribed chemotherapy dose (compliance):

The arbitrary threshold of the delivery of at least 80% of the prescribed chemotherapy was achieved for all women in both trials.

Ability to deliver the prescribed radiotherapy dose (compliance):

All patients in both randomised groups in the Arcangeli 2006 trial received 100% of their planned radiotherapy, and there was no significant difference in the total dose delivered in both groups of Calais 2004.

2. Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy

One trial, n=244, (Bellon 2005).

NB: an OR or HR of less than 1.0 favours the group allocated to receive radiotherapy first.

Overall survival:

HR 0.85 (95% CI 0.51 to 1.40, p=0.52)

Distant Metastases:

HR 0.82 (CI 0.49 to 1.36, p=0.44)

Harms and toxicity:

Radiotherapy before chemotherapy was associated with significantly more neutropenic sepsis (OR 2.96, CI 1.26 to 6.98, p=0.02). There was no significant difference in outcome between randomised arms for skin toxicity (OR 1.48, 95% CI 0.68 to 3.26, p=NS), subcutaneous toxicity (OR 2.05, 95% CI 0.50 to 8.40, p=NS), pneumonitis (OR 11.47, 95% CI 0.63 to 209.7, p=NS), lymphoedema (OR 0.11, 95% CI 0.01 to 2.02, p=NS) and brachial plexopathy (OR 3.02, 95% CI 0.12 to 74.98, p=NS). Owing to the small number of events, many of the effects had wide CIs.

Authors' conclusions

Evidence from three well conducted randomised trials indicates that local control and survival is similar for concurrent chemotherapy and radiotherapy, radiotherapy followed by chemotherapy, and chemotherapy followed by radiotherapy for women with early breast cancer when the radiotherapy is commenced within seven months after surgery.

General comments

Literature search methods

Cochrane Breast Cancer Group Specialized Register (10 March 2005) and CENTRAL (Issue 4 2005), MEDLINE (1996 to 2005), CINAHL, Current Contents (1998 to June 2005) and Science Citation Index. Search strategy for searching MEDLINE detailed.

Study selection

Three authors selected studies independently on the basis of title/abstract and resolved differences by discussion. Studies were selected with their results masked.

Data extraction

Two authors extracted data and resolved differences by discussion.

Quality assessment

Study quality assessment was performed considering allocation concealment (graded as B – unclear) in all three trials; intention to-treat analysis and extent of follow-up (arbitrary threshold of 80% of patients accounted for). Blinding was not feasible and so was not considered to be relevant.

Heterogeneity of results

No significant heterogeneity was detected for any outcomes analysed.

Other factors

Data were not available for many outcomes; the included trials are anticipated to publish further results. Specifically, the authors note that the review cannot answer questions on the basis of the evidence that is currently available regarding:

1. Harms, costs, patient preferences and quality of life;
2. The impact of newer chemotherapy regimens and biological agents;
3. The impact of new modes of radiotherapy;
4. Concurrent administration of modern chemotherapy and radiotherapy.

The authors advise that caution be employed in interpreting these results due to:

1. The low event rate for some endpoints such as local recurrence; low statistical power;
2. Inclusion of patients with positive margins in the RCT by Bellon 2005
3. Inadequate follow-up for survival outcomes.

Huang, Barbera, Brouwers, Browman & Mackillop . Does delay in starting treatment affect the outcomes of radiotherapy: a systematic review (DARE structured abstract). Journal of Clinical Oncology 21, 555-563. 2003.
Design
Systematic review of mixed study design Country of origin: USA Evidence grade: 2-
Inclusion criteria
All studies in any language that examined the relationship between delay in RT and the outcomes of treatment. Specifically, studies in which: <ul style="list-style-type: none"> • All patients were treated with RT; • The delay in initiating RT was defined and described; • Relevant outcomes were reported quantitatively.
Exclusion criteria
Two studies that commented on the relationship between delay and outcomes without presenting any analytic results were excluded.
Population
N=9896 Patients with breast cancer treated with RT after definitive surgery.
Interventions
Radiotherapy
Outcomes
Local control; Distant metastasis; Survival NB: few studies reported distant metastasis or survival Results were meta-analysed to produce pooled odds ratios (OR) of outcome in the delayed group versus the nondelayed group. Heterogeneity of results was assessed, and when present, exploratory analyses were performed to examine the effects of age, disease stage, residual tumour, length of follow-up and study quality.
Follow up
Meta-analysis performed on the basis of 5-year follow-up where available
Results

21 studies of patients with breast cancer were included (n=9876).
10 studies examined the effect of RT delay (n=7401; after lumpectomy in nine studies and lumpectomy or mastectomy in one study).
12 studies examined sequencing of RT relative to other therapies (n=2495).

1. Relationship between interval to starting RT and local control in breast cancer

Loco-regional recurrence:

Eight (of ten, see above) studies compared local control between patients who were treated more than 8 weeks after surgery and those treated within 8 weeks of surgery. In each of these studies, delay in starting postoperative RT was associated with an increase in LRR at 5 years (although not always statistically significantly so, since some of the 95% CIs for the reported ORs for LRR included the null hypothesis value of 1). The pooled random-effects OR from the meta-analysis was 1.62 (95% CI, 1.21 to 2.16), corresponding to an increase in the 5-year LRR from 5.8% in those patients treated within 8 weeks to 9.1% in those patients treated between 9 and 16 weeks after surgery. There was no significant heterogeneity among the eight studies ($p=0.66$).

The relationship between delay and the risk of local recurrence remained significant when one low-quality study was excluded (OR 1.60, 95% CI, 1.20 to 2.14).

The remaining two studies used different definitions of delay and could not be included in the meta-analysis. One study showed a significantly higher risk of local recurrence for patients who waited for RT for more than 80 days after lumpectomy ($P < .05$).

The other study reported no significant difference in any recurrence between patients treated with postoperative RT within 4 weeks after surgery and those treated more than 4 weeks after surgery ($P =0.44$).

Other outcomes:

The association between delay in RT and the rate of distant metastasis was reported in five studies. Three compared the rate of distant metastasis between women receiving postoperative RT more than 8 weeks after surgery and those women treated within 8 weeks after surgery. On the basis of analyses of these three studies, the pooled random-effects OR was 1.22 (95% CI, 0.94 to 1.59).

The other two studies did not report their results in a way that permitted their inclusion in the meta-analyses, but both reported that there was no statistically significant association between delay and the rate of distant metastasis.

None of these studies reported the relationship between delay and survival.

2. Relationship between sequencing of RT with systemic chemotherapy and local control in breast cancer

Locoregional recurrence:

12 studies provided data (primary surgery as follows: lumpectomy in 10 studies, mastectomy in one study, and not specified in one study).

One report provided insufficient information for inclusion in the combined analysis. It

showed no significant association between delay in RT and local control (P=0.92) or distant failure (P=0.41).

The remaining 11 studies involved 1,927 patients. One study was a RCT and the others were observational cases series. The pooled random-effects OR from the combined analysis of these 11 studies was 2.28 (95% CI, 1.45 to 3.57), corresponding to an increase in the 5-year LRR from 6.0% in the RT first group to 16.0% in the chemotherapy-first group.

When five low-quality studies were excluded from the analysis, the association between delayed RT and increased local failure remained statistically significant (OR 2.38, 95% CI, 1.29 to 4.40). There was no significant heterogeneity between the results of these studies (P=0.70).

Other outcomes:

Several studies of the sequencing of RT and chemotherapy reported rates of distant metastasis, but these were not analysed because the timing of chemotherapy was considered to be a more important determinant of systemic recurrence rates than the timing of RT.

General comments

Well-conducted systematic review, but most data originate from observational studies, therefore the results should be interpreted with caution.

Search Strategy

MEDLINE and CANCELIT from 1975 to June 2001, using the following text words or Medical Subject Headings (MESH) terms: delay, waiting times, waiting lists, neoplasm, clinical outcome, radiation treatment, radiotherapy, sequence, interval, local control, relapse, recurrence rate, metastasis, quality of life, and survival.

The electronic searches were supplemented by manual searches of studies presented in the American Society for Therapeutic Radiology and Oncology conferences and the annual meeting of the Royal College of Physicians and Surgeons of Canada. Additional reports from the reference lists of key articles were identified.

Data extraction

The following data were extracted independently by two reviewers using a proforma: year of publication; demographic characteristics of the patients (age, sex); characteristics of the disease (primary site, stage or size of tumor, histology, grade, nodal status, and estrogen receptor status in breast cancer); type of surgery and status of surgical margins; definition of delay and number of patients at each level of delay; details of RT (dose, fractionation, overall time); details of any systemic therapy and its timing in relation to RT; median follow-up; and outcomes (rates of local recurrence rate [LRR], metastasis, and survival).

Quality Assessment

Most of the relevant studies were retrospective observational studies.

A quality scale was designed to distinguish between observational studies with greater or lesser potential for bias. The nine-point scale was constructed to measure the extent to

which each study provided the information necessary either to ensure that the delayed and control groups were similar or to control for differences between them in our analysis. The following factors were considered:

1. Demographic characteristics (age and sex)
2. Disease-related factors (tumor stage or size, histology or tumor grade, and status of surgical margin)
3. Intervention-related factors (RT dose and fractionation, surgical procedure, and chemotherapy regimen)
4. Completeness of follow-up.

The scale ranges from 0 to 9, with higher scores indicating higher quality. All eligible studies were independently assessed by two investigators. Intraclass correlation coefficient (r_i) was 0.95 (95% confidence interval [CI], 0.91 to 0.97). Any discrepancies were reconciled before data entry. Studies with scores ≥ 5 are referred to below as high-quality studies, and studies with scores < 5 are referred to as low-quality studies.

Analysis

Studies of the sequencing of RT and chemotherapy were analysed separately from pure RT studies. Studies were categorised into two or three groups on the basis of duration of delay. To enable us to include as many studies as possible in the meta-analysis, the data were dichotomised using the cutoff points of 8 weeks. In three studies the definition of delay differed from the norm (Benk et al. 1999; Nixon et al. 1994; Yock 2000). These studies were not included in the meta-analysis, but their data are presented separately.

Whelan, Olivotto, Levine & Health Canada 's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update). CMAJ Canadian Medical Association Journal Available at http://www.cmaj.ca/cgi/data/158/3/DC1/21 . 2003.
Design
Guideline (appraised here as a systematic review of mixed study designs) Country of origin: Canada Evidence grade: 2-
Inclusion criteria
Specific criteria for selection of studies are not reported, although these may be reported in the original guideline of 1997, which this updates.
Exclusion criteria
Not reported.
Population
Patients with breast cancer who receive RT following breast conserving surgery.
Interventions
Aim: To help physicians and their patients arrive at optimal strategies for breast radiation therapy after breast-conserving surgery (BCS) for early breast cancer.
Outcomes
Local control Survival Quality of life Adverse effects Cosmetic results
Follow up
Variably reported; not summarised.
Results
1. Interval between surgery and adjuvant RT. The guideline/systematic review authors concluded that the optimal interval between BCS and the start of irradiation has not been defined on the basis of the following studies: One observational study of 436 patients found that patients who began radiation therapy more than 7 weeks after BCS appeared to be at greater risk of recurrence than patients receiving treatment earlier (14% v. 5%). However, the demonstrated effect of the interval between radiation therapy and surgery was not statistically significant when other relevant

factors were considered in a multivariate analysis (Clarke et al. 1985; level V evidence).

In a study involving 653 patients with node-negative breast cancer who received a dose of 60 Gy or greater to the primary tumour site, when risk factors were controlled, there was no difference in the recurrence rates associated with intervals ranging from 4 to 8 weeks between surgery and radiation therapy (Nixon et al. 1994; level V evidence).

There are a number of conflicting reports regarding the risk of recurrence following delay in radiation therapy after lumpectomy:

A review was conducted of 508 cases of patients with stage I or II breast cancer treated with breast irradiation after lumpectomy (Slotman et al. 1994; level V evidence). At a median follow-up of 5.7 years, the rate of local recurrence was 1.7% among patients who started radiation within 7 weeks after surgery and 5.6% among those with a longer interval ($p < 0.05$). In a Cox proportional-hazard analysis, the interval between surgery and radiation remained predictive of local recurrence ($p = 0.003$).

A review was performed of 1962 cases of women at low risk for recurrence who did not receive chemotherapy (Froud et al. 2000; level V evidence). At a median follow-up of 5.9 years, they found no difference in ipsilateral breast recurrence for intervals between surgery and radiation therapy of 0–20 weeks. However, the risk of distant recurrence was significantly higher with intervals of more than 12 weeks between surgery and the start of radiation therapy.

2. Sequencing of chemotherapy and breast RT

On the basis of the studies shown below, the authors conclude that the optimal sequencing of chemotherapy and RT is not clearly defined and that there is no evidence that concurrent treatment results in a better outcome, whilst concurrent treatment results in an increased chance of toxic effects, especially with anthracycline-containing regimens.

The 2001 update of a study by Recht and associates reported the results for 244 patients treated with lumpectomy who were randomly assigned to receive radiation therapy before or after chemotherapy. The median follow-up was 11.3 years. There was no statistically significant difference in time to any failure, time to distant metastases or time to death between the two groups. The recurrence rates by site of first failure were also similar between the two groups (local recurrence 15% v. 13%, respectively; distant recurrence 26% v. 32%, respectively) (level II evidence). This study was relatively underpowered to detect differences in failure patterns.

The timing of radiation therapy has been considered in other studies, with inconsistent results (level V evidence) (Antoniades et al. 1993; Buchholz et al. 1993; Buzdar et al. 1993; Hartsell et al. 1992; Recht et al. 1991).

In several trials designed to evaluate adjuvant chemotherapy regimens after BCS, radiation

therapy was delayed until chemotherapy was completed, without any apparent increase in local recurrence (level I evidence) (Fisher et al. 1990; Levine et al. 1998; Wallgren et al. 1996, Gore et al. 1987).

Several case series have shown that when chemotherapy and radiation therapy are given concurrently, the potential for increased acute and late adverse effects of radiation therapy, including a worse cosmetic outcome, is increased, especially when anthracycline-based regimens are used (level III evidence; Gore et al. 1987, Hoogenraad et al. 1992; Abner et al. 1991).

General comments

Canadian guideline, underpinned by a systematic review of mixed study designs.

Literature search

A literature search was performed using MEDLINE from 1966 to October 2001 and CANCERLIT from 1983 to September 2001. A nonsystematic review of the literature was continued through April 2002. Search terms included the following: "breast neoplasms," "segmental mastectomy," "lumpectomy," "breast conservation," "radiotherapy," "irradiation," "clinical trials," "practice guidelines" and "meta-analysis." Bibliographies from recently published reviews were scanned and relevant articles retrieved.

Study quality assessment

The quality of the evidence was categorised into 5 levels based upon: Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95(Suppl):2S-4S.

International Breast Cancer Study Group . Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. International Breast Cancer Study Group. Journal of Clinical Oncology 15[4], 1385-1394. 1997.

Design

RCT (2 x 2 factorial comparison)
Country of origin: International
Evidence grade: 1+

Inclusion criteria

Post-menopausal patients with node-positive, unilateral breast cancer

Exclusion criteria

31 patients from non-compliant institutions;
21 patients who were ineligible due to advanced stage (8), stage N0 (2), medically unfit for randomisation (1), previous cancer (3), bilateral breast cancer (1), unclear resection margins (3), pre-menopausal status (4) and randomisation 12 weeks after surgery (1).

Population

N=1266 in total; N=610 in arm B + arm C from which data are applicable to this question.
Stage: T1a-T3a, pN1, M0
Median age 60 years (range 35-84 years).

Interventions

Aim: to study the use of tamoxifen (T) with and without cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy, and also the optimal sequencing of CMF when used with T.

All patients received primary surgery: total mastectomy or BCS (breast RT mandatory in cases of BCS). All patients received axillary dissection. Breast RT was given after the end of the first phase of chemotherapy, where applicable (see below).

Patients were randomly allocated to one of four adjuvant treatment plans:

Group A (n=306): T
Group B (n=302): T + early CMF
Group C (n=308): T + delayed CMF
Group D (n=296): T + early CMF + delayed CMF

Adjuvant therapy started within 6 weeks of surgery.

Tamoxifen was given for 5 years, or until relapse, whichever occurred first.

Early CMF was 3 cycles, repeated every 28 days i.e. months 1, 2 and 3 following surgery.

Delayed CMF was 3 cycles, given on months 9, 12 and 15 following surgery.

Outcomes
Disease-free survival Overall survival
Follow up
Outcomes reported at a median follow-up of 60 months.
Results
<p>Recurrence and survival outcomes</p> <p>5-year disease-free survival: Group B: T + early CMF: 64% Group C: T + delayed CMF: 59%</p> <p>5-year overall survival: Group B: T + early CMF: 74% Group C: T + delayed CMF: 74%</p> <p>Compliance with chemotherapy (grouped data for patients in all three chemotherapy arms)</p> <p>95% of patients in the early CMF groups (B and D) received some chemotherapy for at least 3 courses. 14% of patients assigned to delayed chemotherapy did not receive it due to relapse (5%), refusal (7%) or other reasons (2%).</p> <p>Rate of toxicity of grade 3 or worse (by individual chemotherapy-including randomised group)</p> <p>Group B: T + early CMF: 9.7% Group C: T + delayed CMF: 7.6% Group D: T + early CMF + delayed CMF: 17.1%</p>
General comments
<ul style="list-style-type: none"> • Randomisation was stratified according to: • Participating institution; • Type of surgery (mastectomy vs. BCS + RT); • ER status (positive vs. negative). <p>Randomisation process described. Power calculation performed, with planned sample size: 1200 patients to give 80% power to detect an 8% difference in disease-free survival. Treatment groups were balanced for age, race, type of primary surgery, number of positive nodes and tumour size.</p> <p>Only arms B and C are relevant subgroups for this question. Most analyses in this study are not relevant to this question due to confounding by treatment according to group A (no chemotherapy) and group D (additional cycles of chemotherapy).</p>

Analysis appears to be by intention-to-treat (not reported). Blinding of subjects not feasible; and not feasible in all instances for investigators.

Calais, Serin, Fourquet, Bosset & Favre . Randomized study comparing adjuvant radiotherapy (RT) with concomitant chemotherapy (CT) versus sequential treatment after conservative surgery for patients with stages I and II breast carcinoma: Long-term results. International Journal of Radiation Oncology Biology Physics 63[2], S53. 2005.
Design
RCT Country of origin: Evidence grade: 1+
Inclusion criteria
716 patients with breast cancer treated between February 1996 and April 2000.
Exclusion criteria
Not reported
Population
N=716
Interventions
All patients received conservative surgery with axillary dissection and were randomly allocated to two treatment arms as follows: 1. Arm A: sequential treatment with chemotherapy (CT) first followed by radiotherapy (RT) started 3 to 5 weeks after the final cycle of CT. 2. Arm B: CT administered concurrently with RT. Chemotherapy was based upon mitoxantrone, 5-fluorouracil and cyclophosphamide, 6 cycles were delivered with 21 days interval. RT regimen was 50 Gy to the breast in 5 weeks with 10 to 20 Gy boost added to the tumour bed with electrons or brachytherapy. The subclavicular area was irradiated when axillary dissection was positive.
Outcomes
Time to initiation of RT Treatment compliance Overall survival Disease-free survival Loco-regional control Late toxic effects
Follow up
Median 6.7 years (data included in the Cochrane Review by Hickey et al. 2006 had a follow-up period of 3 years).
Results

Time to initiation of RT

Mean time to initiation of RT was 170 days in arm A and 39 days in arm B ($p < 0.0001$).

Treatment compliance

RT compliance was similar in the 2 randomised arms in respect of total dose, treatment duration and treatment interruption. Compliance to CT was also comparable between arms. CT mean relative dose intensity was 94% in arm A and 92% in arm B. Oesophagitis of grade >1

was seen at a higher rate in arm B than in arm A (23% versus 7%, respectively).

Haematologic toxicity was also higher in arm B in respect of neutrophil count and haemoglobin level. The incidence of other acute toxic effects including skin toxicity was similar in the 2 arms. Two patients developed acute leukemia (one in each arm).

Disease related events

No differences were observed between the two arms in rates of overall survival, disease-free survival or loco-regional control.

For node-positive patients the survival rate without local and regional failure was significantly higher in arm B ($p < 0.035$). Other prognostic factors for disease-free survival were tumour grade, hormone receptor status, tumour margin status and in situ component.

Late toxicity

The incidence of late toxic effects (subcutaneous fibrosis, telengectasia, skin pigmentation, and breast atrophy) was higher in arm B than in arm A.

General comments

Conference abstract: trial included in the Cochrane Review by Hickey et al. 2006, but with shorter follow-up.

The 2 arms were equally balanced regarding to age, stage, performance status, histology, hormonal receptors, tumour margins, in situ component and axillary status.

Randomisation was stratified according to axillary status.

1. Toledano, Azria, Garaud, Fourquet, Serin, Bosset, Miny-Buffet, Favre, Le & Calais . Phase III trial of concurrent or sequential adjuvant chemoradiotherapy after conservative surgery for early-stage breast cancer: final results of the ARCOSEIN trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 25[4], 405-410. 2007.

2. Toledano, Garaud, Serin, Fourquet, Bosset, Breteau, Body, Azria, Le & Calais . Concurrent administration of adjuvant chemotherapy and radiotherapy after breast-conserving surgery enhances late toxicities: long-term results of the ARCOSEIN multicenter randomized study. *International Journal of Radiation Oncology, Biology, Physics* 65[2], 324-332. 2006.

Design

RCT
Country of origin: France
Evidence grade: 1 +

Inclusion criteria

716 patients with stages I and II breast cancer treated between February 1996 and April 2000 Surgical margins had to be negative before randomisation.

Exclusion criteria

Patients who received prior ipsilateral breast/axillary RT, ipsilateral breast reconstruction, augmentation/reduction mammoplasty, or those with synchronous bilateral breast tumors were excluded.
21 patients were excluded from the analysis after randomisation due to ineligibility

Population

N=716

Hormone receptor status:
ER+ or PR+: 462 (69%)
ER- and PR-: 205 (31%)

Menopausal status:
Menopausal: 287 (41%)
Premenopausal: 401 (58%)
Unknown 7 (1%)

NB Late toxicity data are based upon the following selected patient subgroup: of 571 patients who were alive without recurrence, 297 patients treated at the five largest institutions were invited to attend for assessment of late toxicity and cosmesis. 72% of these were assessed for these outcomes (n=214).

Interventions

Aim: to compare sequential CT followed by RT versus CT administered concurrently with RT.

All patients underwent complete gross excision and axillary dissection. Adjuvant treatment began within 6 weeks after surgery. Patients were randomised as follows:

1. Sequential CT-RT group (n=358): RT started 3 to 5 weeks after the last cycle of CT.
2. Concurrent CT-RT group (n=358) In the concurrent arm, RT started the day of the first CT cycle.

RT was delivered to the breast and, when indicated, to the regional lymphatics. The RT breast dose was 50 Gy in 2-Gy fractions, with a 10 to 20 Gy boost to the tumor bed at the discretion of each participating center. Lymph node RT was given at a total dose of 50 Gy in 25 Gy fractions in node-positive patients and in the case of central or medial tumor locations. RT to the internal mammary chain was left at the discretion of local RT guidelines. RT was interrupted if grade 3 cutaneous toxicity occurred.

The CT regimen consisted of mitoxantrone, fluorouracil and cyclophosphamide in six courses of 21 days each. CT was interrupted or stopped if haematologic side effects reached a specified threshold. No dose reductions were planned.

Post or perimenopausal women with ER+ or PR+ tumours received tamoxifen, which was started during or after RT at the discretion of the treating physician.

Outcomes

Disease free survival (time from randomisation to the first treatment failure or death without recurrence)
Adverse effects
Cosmetic results
Overall survival

Further details of assessment of outcomes for late toxicity (subgroup analysis, n=214; 2nd reference):

Late effects were assessed as a single event at the most recent follow-up visit (median follow-up 6.7 years) using the LENT-SOMA scale (which is scored upon an assessment of pain, arm/breast lymphoedema, fibrosis, telangiectasia, atrophy, retraction, ulceration, pigmentation).

General frequency definitions for LENT-SOMA assessment were as follows:

- Occasional = monthly
- Intermittent = weekly
- Persistent = daily
- Refractory = constantly

Other LENT-SOMA definitions/assessments were as follows:

- Pigmentation: 5-points scoring system (excellent, good, moderate, poor, very poor).
- Breast oedema: permanent swelling with an increased volume of the treated breast, either asymptomatic (without pain or any consequences) or symptomatic.
- Fibrosis: detected by palpation of the treated breast in comparison with the untreated side.
- Arm oedema: difference in circumference of the ipsilateral and controlateral arm 15 cm above and 10cm below the olecranon
- Management of arm oedema, the patient's statements were taken into account, even if no differences in circumference could be measured.
- Intensive physiotherapy: weekly therapy.
- Breast retraction and atrophy: volume loss caused by RT or RT and surgery
- Cardiac event: myocardial infarction or congestive heart failure.
- Radiation pneumonitis: cough, fever, and shortness of breath that occurred 2 to 9 months after the completion of RT.

Follow up

Median 60 months

For subgroup analysis of late effects (n=214): median 6.7 years (range 4.3-9 years)

Results

1. Recurrence and survival

5-year disease-free survival (all patients)

Sequential group: 80%

Concurrent group: 80%; p=0.83, Log-rank test

5-year overall survival (all patients)

Sequential group: 90%

Concurrent group: 91%, p=0.76, Log-rank test

5-year local recurrence free survival (all patients)

Sequential group: 92%

Concurrent group: 95%; p=0.76, Log-rank test

Local recurrence-free survival in the node negative subgroup (n=305)

Sequential group: 93%

Concurrent group: 93%, p=0.81, Log-rank test

Local recurrence-free survival in the node positive subgroup (n=389)

Sequential group: 91%

Concurrent group: 97%, p=0.02, Log-rank test; HR 0.61, 95% CI 0.38-0.93

2. Adverse effects

a) Acute effects

Acute locoregional toxicities were moderate in both arms. Oesophagitis was more frequent in the concurrent arm (115 v 89; P = .04). Acute systemic symptoms also were mild in both arms. Nausea/vomiting was significantly higher in the sequential treatment arm (248 v 235; P = .008), whereas anaemia was significantly more frequent in the concurrent arm (111 v 81; P = .02).

b) Late toxicity (subgroup analysis, n=214; 2nd reference):

Subcutaneous fibrosis, telangiectasia, skin pigmentation, and breast atrophy occurred at higher rates in the concurrent arm than in the sequential arm. Twenty patients experienced Grade 2 or higher subcutaneous fibrosis in concurrent arm versus 5 patients in the sequential arm (p = 0.003; see table below).

Twenty-five patients and 7 patients showed Grade 2 or higher telangiectasia in the concurrent arm and the sequential arm, respectively (p = 0.001; see table below).

Forty-four patients and 20 patients showed Grade 2 or higher breast atrophy in the concurrent arm and the sequential arm, respectively (p = 0.0006; see table below).

Thirty patients experienced Grade 3 or higher skin pigmentation in the concurrent arm versus 15 patients in the sequential arm (p = 0.02; no data shown).

No statistical difference was observed between the 2 arms concerning Grade 2 or higher breast oedema or arm lymphoedema (see table below).

A trend toward increased Grade 2 or higher pain was seen in the concurrent arm, but this was not statistically significant (p = 0.07; see table below).

No deaths due to late toxicity, ulceration or severe cardiac or pulmonary events were observed in any patient in either group.

Table: Radiotherapy late effects of the cutaneous and subcutaneous tissue scored by LENT-SOMA scale [n(patients)]

Effect	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	A	B	A	B	A	B	A	B	A	B
Atrophy	44	34	43	29	10	25	10	17	0	2
Telangiectasia	82	58	18	24	2	8	5	17	-	-
Fibrosis	64	54	38	33	5	14	0	6	-	-
Breast oedema	99	100	8	6	0	1	0	0	-	-
Pain	73	56	21	27	10	17	3	5	0	2
Lymphoedema	86	80	18	25	2	0	1	2	0	0
Managed pain	102	96	3	6	2	4	0	0	0	1
Managed lymphedema	99	102	0	0	2	1	6	4	0	0

Effect of length of follow-up in late-toxicity evaluation: rates of late toxicities (pain, breast edema, fibrosis, atrophy, lymphedema, telangiectases Grade 1 or higher or pigmentation Grade 2 or higher) as a function of interval between randomisation and clinical assessment.

Before 5 years follow-up, there was no statistically significant difference in late toxicity between randomised arms. From the six year follow-up point the difference in rate of late toxicities became statistically significant (see table below).

Arm	Extent of follow-up (years)				
	<5	<6	<7	<8	<9
Concurrent arm	5/7	27/40	37/60	58/90	68/107
Sequential arm	4/9	13/34	27/63	36/87	44/107
p (by Chi square)	0.34	0.01	0.04	0.003	0.01

General comments

Power calculation performed to derive a target sample of 680 participants. Randomisation was stratified for participating center and axillary node status.

The main baseline characteristics of the two groups were similar. Involved tumor margins were found more in the sequential arm (36 v 20; P = .03), whereas margin invasion with ductal carcinoma in situ was seen more in the concurrent arm (28 v 44; P = .08).

There was no difference between the two arms in terms of type of surgery, mainly tumorectomy and quadrantectomy. The median CT dose was similar in the two arms. RT treatment was interrupted in 123 patients overall, for varying reasons, without a difference between the two arms.

Loss to follow-up: n=13 (10 patients in the sequential arm and 3 in the concurrent arm).

Authors do not report concealment of allocation nor blinding, which would not be feasible for the primary outcomes. However assessment of late toxicity was made by a radiation oncologist who was blinded to treatment allocation.

The analysis of late toxicity outcomes is not an intention-to-treat analysis. For this assessment the LENT-SOMA instrument was applied in 40 patients initially by 2 physician staff members to synchronise the objective grading to optimise the interobserver reliability.

Hershman, Wang, McBride, Jacobson, Grann & Neugut . Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women. Breast Cancer Research and Treatment 99[3], 313-321. 2006.
Design
Retrospective cohort study Country of origin: USA Evidence grade: 2-
Inclusion criteria
5003 women identified from the Surveillance, Epidemiology and End-Results (SEER) & Medicare databases, of age 65 years and older, who were diagnosed with Stage I or II breast cancer from 1991 to 1999, and who received CT within 1 year of their diagnosis of breast cancer, but who did not receive RT prior to CT.
Exclusion criteria
<ul style="list-style-type: none"> • Women who did not participate in Medicare; • Women treated with adjuvant RT prior to CT; • Women who had a prior cancer diagnosed before age 65, a prior breast cancer or other cancer, end-stage renal disease, or a diagnosis without histologic confirmation.
Population
N=5003
Interventions
<p>Aim: to investigate factors that may contribute to delay in the receipt of adjuvant CT, and the effect of timeliness in the initiation of CT on overall survival among elderly women who did not receive prior RT.</p> <p>The interval from the date of the last surgical procedure within 6 months after the breast cancer diagnosis to the date of first CT was analysed as a categorical variable, with analysis groups arising as follows:</p> <ul style="list-style-type: none"> • <1 month (n=2361; 47%) • ≥1 to <2 months (n=1846; 37%) • ≥2 to <3 months (n=323; 6%) • ≥3 months (n=477; 10%)
Outcomes
Predictive demographic and tumour-related variables for a delay in CT (with delay defined as a time interval greater than 3 months (84 days) from the date of the last surgical procedure within 6 months after the breast cancer diagnosis to the date of first CT).

Breast cancer-specific survival and overall survival by demographic, tumour related and delay to CT variables.

The demographic and tumour-related variables included in analyses were: age, race, urban/rural habitation, breast cancer stage (I or II), hormone receptor status, grade, comorbidity score, marital status, type of hospital providing care, socioeconomic status, receipt of RT (subsequent to CT) and type of surgery (lumpectomy versus mastectomy).

Follow up

Minimum possible 12 months, maximum possible 9 years (no median reported; but some survival outcomes estimated at 5 years follow-up)

Results

1. Relationship between interval to CT and demographic and tumour-related variables

In univariate analysis, time interval between surgery, and chemotherapy initiation was statistically significantly associated with each of the clinical variables investigated [age, race, urban/rural habitation, breast cancer stage (I or II), hormone receptor status, grade, comorbidity score, marital status, type of hospital providing care, socioeconomic status, receipt of RT (subsequent to CT) and type of surgery (lumpectomy versus mastectomy)]; $p < 0.05$ for each variable.

In a linear regression analysis, older age, residence outside a metropolitan area, having a hormone receptor negative tumor, being unmarried, and having undergone a mastectomy were statistically significantly associated with an increased number of days between surgery and initiation of chemotherapy ($p < 0.05$). Advanced stage, subsequent treatment with radiation, and worse tumor grade were statistically significantly associated with shorter time to initiate chemotherapy $p < 0.05$.

2. Relationship between interval to RT and survival

Breast cancer specific survival was similar in patients who received chemotherapy within 1 month, 2 months, or within 3 months following surgery. Overall survival also did not differ among patients who started treatment in any of these time intervals.

Interval from surgery to CT dichotomised to delay (≥ 3 months) versus no delay (< 3 months)

The unadjusted 5-year cancer specific survival for patients who received CT within 3 months was 76% compared to 63% for those who delayed chemotherapy beyond 3 months.

In a multivariate analysis, the breast cancer specific mortality rate was higher among women who delayed chemotherapy 3 months or more following surgery (HR > 3 months < 1 month 1.69, 95% CI 1.31–2.19), as was the overall mortality rate (HR > 3 months < 1

month 1.46, 95% CI 1.21–1.75). The increased breast cancer specific mortality was also statistically significantly associated with advanced age, African American race, residence in a non-metropolitan location, estrogen receptor negative tumors, poorly differentiated tumors, increased number of comorbidities, being unmarried, and undergoing radiation therapy (p<0.05 in all cases).

Table: strength of effect of interval to initiation of CT on survival

Interval to initiation	Cancer specific survival		Overall survival	
	HR (95% CI)	p value	HR (95% CI)	p value
<1 month	Referent		Referent	
1–2 month	0.92 (0.78–1.09)	NS	1.00 (0.88–1.14)	NS
2–3 month	0.89 (0.64–1.25)	NS	1.08 (0.85–1.36)	NS
>3 month	1.69 (1.31–2.19)	p<0.01	1.46 (1.21–1.75)	p<0.01

General comments

Only women who received adjuvant chemotherapy within 12 months of their primary breast surgery were included, to ensure treatment was not for recurrent disease.

Distribution of interval to CT may differ in this US study to that of the UK. Study benefits from large size, but retrospective design cannot account for all confounding variables. Note that patients are a selected group: aged 65 years or more, and not treated with RT prior to CT.

Hershman, Wang, McBride, Jacobson, Grann & Neugut . Delay in initiating adjuvant radiotherapy following breast conservation surgery and its impact on survival. International Journal of Radiation Oncology Biology Physics 65[5], 1353-1360. 2006.
Design
Retrospective cohort study Country of origin: USA Evidence grade: 2-
Inclusion criteria
13,907 women identified from the Surveillance, Epidemiology and End-Results (SEER) & Medicare databases, of age 65 years and older, who were diagnosed with Stage I or II breast cancer from 1991 to 1999, and who received RT within 1 year of their diagnosis of breast cancer, but who did not receive chemotherapy.
Exclusion criteria
<ul style="list-style-type: none"> • Women who did not participate in Medicare; • Women treated with adjuvant chemotherapy; • Women who had a prior cancer diagnosed before age 65, a prior breast cancer or other cancer, end-stage renal disease, or a diagnosis without histologic confirmation; • Women who received radiological procedures coded as 'radiation planning', 'hyperthermia', and 'nuclear medicine'.
Population
N=13,907
Interventions
<p>Aim: to investigate factors that may contribute to delay in the receipt of adjuvant RT, and the effect of timeliness in the initiation of RT on overall survival among elderly women not receiving chemotherapy.</p> <p>The interval from the date of the last surgical procedure within 6 months after the breast cancer diagnosis to the date of first RT was analysed as a categorical variable, with analysis groups arising as follows:</p> <ul style="list-style-type: none"> • <1 month (n=7966; 57%) • ≥1 to <2 months (n=4664; 34%) • ≥2 to <3 months (n=800; 5%) • ≥3 months (n=477; 3%)
Outcomes
Predictive demographic and tumour-related variables for a delay in RT (with delay defined

as a time interval greater than 3 months (84 days) from the date of the last surgical procedure within 6 months after the breast cancer diagnosis to the date of first RT).

Breast cancer-specific survival and overall survival by demographic, tumour related and delay to RT variables.

The demographic and tumour-related variables included in analyses were: age, race, urban/rural habitation, breast cancer stage (I or II), hormone receptor status, grade, comorbidity score, marital status, type of hospital providing care, socioeconomic status.

Follow up

Minimum possible 12 months, maximum possible 10 years (no median reported; but some survival outcomes estimated at 5 years follow-up)

Results

1. Relationship between interval to RT and demographic and tumour-related variables

In univariate analysis, interval between surgery and RT was statistically significantly associated with each of the explanatory variables (age, race, urban/rural habitation, breast cancer stage (I or II), hormone receptor status, grade, comorbidity score, marital status, type of hospital providing care, socioeconomic status).

Multivariate analysis (linear regression model): Odds ratios for an interval between surgery and RT of ≥ 3 months:

Variable	OR	p value
Age at diagnosis		
65–69	Referent	
70–74	1.03 (0.78–1.36)	NS
75–79	1.24 (0.94–1.63)	NS
80+	1.48 (1.11–1.87)	p<0.05
Race		
White	Referent	
Black	1.29 (0.88–1.64)	NS
AJCC stage		
I	Referent	
II	1.75 (1.44–2.13)	p<0.05
Hormone receptor		
ER and PR negative	Referent	
ER and/or PR positive	1.16 (0.82–1.86)	NS
Unknown		
Grade		
Well/Moderately	Referent	

differentiated		
Poorly differentiated	1.48 (1.18–1.64)	p<0.05
Metropolitan residence		
Yes	Referent	
No	1.48 (1.00–2.19)	p<0.05
Comorbidity score		
0	Referent	
1	1.09 (0.86–1.39)	NS
2	2.06 (1.56–2.72)	p<0.05
Marital status		
No (<i>sic</i>)	Referent	
Yes (<i>sic</i>)	0.71 (0.59–0.87)	p<0.05
Teaching hospital		
No	Referent	
Yes	0.97 (0.74–1.26)	NS
Socioeconomic status		
Lowest quintile	Referent	
2nd quintile	0.89 (0.65–1.23)	NS
3rd quintile	1.02 (0.74–1.39)	NS
4th quintile	0.97 (0.70–1.33)	NS
Highest quintile	1.07 (0.78–1.46)	NS

2. Relationship between interval to RT and survival

Patients who received RT within 1–2 months, 2–3 months, or >3 months after surgery were compared with those who initiated postsurgical radiation within 1 month. Both overall survival and breast cancer–specific survival were similar in patients who received RT within 1 month, 2 months, or within 3 months after surgery (no data shown).

a) Hazard ratios for survival by interval from surgery to RT and other demographic/tumour-related variables

Variable	Cancer-specific survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Interval to RT						
<1 month	1.00			1.00		
1-2 months	0.84	0.69-1.02	NS	0.87	0.80-0.96	0.005
2-3 months	1.16	0.82-1.64	NS	1.06	0.89-1.23	NS
≥3 months	3.81	2.98-4.87	NS	1.91	1.63-2.23	<0.0001
Age at diagnosis						
65–69	1.00			1.00		
70–74	1.14	0.90-1.45	NS	1.33	1.17-1.51	<0.0001

75–79	1.31	1.03-1.66	0.03	1.74	1.53-1.97	<0.0001
80+	2.22	1.74-2.83	<0.0001	3.14	2.76-3.56	<0.0001
Race						
White	1.00			1.00		
Black	1.25	0.90-1.72	NS	0.96	0.79-1.14	NS
Metropolitan residence						
Yes	1.00			1.00		
No	1.45	1.04-2.02	0.03	1.08	0.89-1.30	NS
AJCC stage						
I	1.00			1.00		
II	3.33	2.82-3.93	<0.0001	1.58	1.45-1.72	<0.0001
Hormone receptor						
ER and PR negative	1.00			1.00		
ER and/or PR positive	0.43	0.35-0.54	<0.0001	0.68	0.60-0.77	<0.0001
Unknown	0.53	0.41-0.69	<0.0001	0.72	0.62-0.83	<0.0001
Grade						
Well/Moderately differentiated	1.00			1.00		
Poorly differentiated	2.69	2.22-2.62	<0.0001	1.49	1.35-1.64	<0.0001
Comorbidity score						
0	1.00			1.00		
1	1.34	1.09-1.64	0.006	1.78	1.62-1.97	<0.0001
2	2.14	1.64-2.77	<0.0001	3.09	2.75-3.47	<0.0001
Marital status						
No (<i>sic</i>)	1.00			1.00		
Yes (<i>sic</i>)	0.73	0.62-0.87	0.0003	0.82	0.75-0.89	<0.0001
Teaching hospital						
Yes	1.00			1.00		
No	0.66	0.52-0.85	0.001	0.84	0.75-0.95	<0.0001
Socioeconomic status						
Lowest quintile	1.00			1.00		
2nd quintile	1.30	0.99-1.70	NS	0.92	0.81-1.05	NS
3rd quintile	1.14	0.86-1.52	NS	0.89	0.78-1.02	NS
4th quintile	1.13	0.84-1.53	NS	0.82	0.71-0.94	0.005
Highest quintile	1.36	1.03-1.81	0.03	0.88	0.77-1.01	NS

Interval from surgery to RT dichotomised to delay (≥ 3 months) versus no delay (< 3

months)

The unadjusted 5-year survival for women who received RT within 3 months of surgery was 81% compared with 67% for those who delayed RT beyond 3 months (no p value reported)

In a multivariate analysis, overall mortality rates were higher among women who delayed RT 3 months or more after surgery (HR 1.61; 95% CI, 1.42–1.82), as were cancer-specific mortality rates (HR 2.14; 95% CI, 1.79 –2.57).

General comments

Distribution of interval to RT may differ in this US study to that of the UK. Study benefits from large size, but retrospective design cannot account for all confounding variables. Note that patients are a selected group: aged 65 years or more, and not treated with chemotherapy.

Delay from surgery to radiotherapy

<p>Benchalal, M., Le Prise, E., De Lafontan, B., Berton-Rigaud, D., Belkacemi, Y., Romestaing, P., Peignaux, K., Courdi, A., Monnier, A., Montcuquet, P., Goudier, M. J., Marchal, C., Chollet, P., badie-Lacourtoisie, S., Datchary, J., Veyret, C. & Kerbrat, P. (2005) Influence of the time between surgery and radiotherapy on local recurrence in patients with lymph node-positive, early-stage, invasive breast carcinoma undergoing breast-conserving surgery - Results of the French adjuvant study group. <i>Cancer</i>, 104: 240-250.</p>
Design
Retrospective re-analysis of 7 RCTs. (Level 3 evidence). France
Inclusion criteria
Women with operable lymph node positive breast cancer. The women enrolled in one of seven RCTs WHO performance status 2 or less, normal liver, kidney and blood test results, no cardiac dysfunction.
Exclusion criteria
Metastatic disease, inflammatory or locally advanced breast cancer, history of cardiac disease or previous malignancy, serious physical or mental co-morbidity. Previous radiotherapy, hormone therapy or chemotherapy for breast carcinoma. Start of adjuvant treatment greater than 42 days after surgery.
Population
1831 patients, age 22 to 84. Most were tumour stage I to IIB
Interventions
All women received BCS with axillary dissection (at least 5 nodes removed). Women received either epirubicin based chemotherapy ± tamoxifen, tamoxifen only or no systemic therapy. Radiotherapy was started within 30 days of the third chemotherapy cycle in 2 trials (n=567) and within 30 days of the last chemotherapy cycle in the other 5 trials (n=789) or after BCS in women not receiving chemotherapy (n=475). The RT dose to the breast ranged from 45 to 55 Gy (conventionally fractionated) with a 10 to 15 Gy boost to the primary tumour site. Some women received RT to the superclavicular area, internal mammary chain and axillary area.
Outcomes
Local recurrence.
Follow up
Median follow up in the 7 trials ranged from 76 months to 138 months. Patients underwent clinical and lab tests every 6 months for the first 5 years and then yearly thereafter.
Results

Local recurrence: timing of radiotherapy (after 3 courses of chemotherapy vs. after 6 courses of chemotherapy vs. after BCS) was not a significant predictor of local recurrence in a multivariate Cox-regression, which included pathologic tumour size, use of hormone therapy and number of chemotherapy courses as covariates.

The hazard ratios for local recurrence between the three RT groups were: after 6th cycle vs. after BCS 1.18 (95% CI 0.69 to 1.67), after 6th cycle vs. after 3rd cycle 1.29 (95% CI 0.93 to 1.65).

General comments

Due to differences in trial protocols there were systematic differences between the systemic therapy received by the different RT-timing groups. Possibly addressed by the use of systemic treatment as a covariate in the analysis. RT timing was not measured directly as a continuous variable, only estimated indirectly from the type of systemic therapy received.

Jobsen, J. J., van der Palen, J., Ong, F. & Meerwaldt, J. H. (2006) Timing of radiotherapy and survival benefit in breast cancer. <i>Breast Cancer Research and Treatment</i> , 99: 289-294.
Design
Prospective cohort study. Netherlands (Quality 2-)
Inclusion criteria
Patients with stage I or II node negative breast carcinoma treated with BCS and radiotherapy in the Twente-Achterhoek region between 1983 and 2003.
Exclusion criteria
Any adjuvant systemic therapy, synchronous bilateral breast cancer.
Population
1446 patients
Interventions
BCS, with level I to III axillary clearance (or sentinel lymph node procedure from 2000 onwards). RT was 50 Gy to the whole breast (2 Gy fractions) followed by a 14 or 15 Gy boost to the tumour bed. Patients were divided into 3 groups depending on timing of radiotherapy after surgery: 1 to 36 days (n=506) – group 1 37 to 53 days (n=483) – group 2 54 to 112 days (n=484) – group 3
Outcomes
Local recurrence, Disease Specific Survival
Follow up
Length of follow up ranged from 5 to 265 months (median 90 months). Survival analysis included follow up to 120 months.
Results
Local recurrence Multivariate Cox regression of local recurrence was done using margin status, age group, metachronous contralateral breast cancer and RT timing group as covariates. RT timing group was not a significant predictor of local recurrence (HR not reported). Disease Specific Survival Multivariate Cox regression of DSS was done using, age group, family history, in situ carcinoma, histology, tumour size, ER/PR receptor status, lymph-angioinvasion, lumpectomy-axillary delay and RT timing group as covariates. Death from breast cancer was less likely in RT timing group 2 than group 1 (HR 0.6, 95%

CI 0.4 to 1.0), and less likely in group 3 than group 1 (HR 0.3, 95% CI 0.14 to 0.6). This suggested that shorter delay from BCS to RT was a risk factor for death from breast cancer (although there is a strong risk of bias, see below).

General comments

Delay between BCS and RT was also correlated with year of treatment. Women treated in the 1983 to 1993 time period were more likely to be in group 1 than those treated in the 1999 to 2003 period and this confounds the results. Year of treatment does not appear to have been included in the multivariate models.

RT delay categorized into 3 groups, rather than considered a continuous variable. Only variables significant on univariate analysis were included in the multivariate model.

Mikeljevic, J. S., Haward, R., Johnston, C., Crellin, A., Dodwell, D., Jones, A., Pisani, P. & Forman, D. (2004) Trends in postoperative radiotherapy delay and the effect on survival in breast cancer patients treated with conservation surgery. *British Journal of Cancer*, 90: 1343-1348.

Design

Cohort. UK (Quality 2+)

Inclusion criteria

Female breast cancer patients included in the Northern and Yorkshire Cancer registry, diagnosed between 1986 and 1998.

Exclusion criteria

No surgery, mastectomy, no RT, preoperative RT, delay from surgery to RT of more than 6 months.

Population

7800 women

Interventions

BCS, radiotherapy . 23% had chemotherapy and 82% had hormonal therapy.

Outcomes

Overall survival.

Follow up

5 years

Results

Patients were divided into 6 groups for analysis. Adjusted relative risks for death were calculated using age, stage, grade, deprivation index, time period and chemotherapy as covariates

Surgery-RT interval (weeks)	5 year survival (95% CI)	Adjusted RR(95% CI)
1 to 4	80% (79 to 83%)	1.00
5 to 6	80% (78 to 82%)	1.04 (0.91 to 1.19)
7 to 8	84% (83 to 86%)	0.99 (0.85 to 1.15)
9 to 12	84% (83 to 86%)	1.04 (0.89 to 1.22)
13 to 19	81% (79 to 84%)	1.16 (0.96 to 1.40)
20 to 26	76% (71 to 80%)	1.49 (1.16 to 1.92)

There was a statistically significant increase in the relative risk of death in patients whose RT was delayed for 20 to 26 weeks from surgery, when compared to those who had RT within a month of surgery.

General comments

Registry data, it was not always clear whether RT was given as adjuvant or salvage therapy (especially true with longer delays).

Delay from surgery to the start of chemotherapy

Sanchez, C. J., Ruiz, A., Martin, M., Anton, A., Munarriz, B., Plazaola, A., Schneider, J., del Prado, P. M., Alba, E. & Fernandez-Aramburo, A. (2007) Influence of timing of initiation of adjuvant chemotherapy over survival in breast cancer: A negative outcome study by the Spanish breast cancer research group (GEICAM). <i>Breast Cancer Research and Treatment</i> , 101: 215-223.																							
Design																							
Cohort study Country of origin: Spain Evidence grade: 2-																							
Inclusion criteria																							
Women included in a multicentre cohort study, with stage I-III breast cancer, who received surgery and adjuvant chemotherapy (N=7342). Women were treated between 1990 and 1997																							
Exclusion criteria																							
Missing data on timing of surgery and chemotherapy (N=4560). Male patients, neoadjuvant therapy.																							
Population																							
N=2782																							
Interventions																							
Surgery with curative intent and adjuvant chemotherapy.																							
Outcomes																							
Disease free survival, overall survival																							
Follow up																							
Not reported. Outcomes analyzed to 5 years after treatment																							
Results																							
Women were divided into four chemotherapy-timing groups for analysis.																							
<table border="1"> <thead> <tr> <th>Delay from surgery to chemo (weeks)</th> <th>n</th> <th>5 yr DFS (%)</th> <th>5 yr OS (%)</th> </tr> </thead> <tbody> <tr> <td><3</td> <td>637</td> <td>72.5</td> <td>85.5</td> </tr> <tr> <td>3 to 6</td> <td>1624</td> <td>76.1</td> <td>87.7</td> </tr> <tr> <td>6 to 9</td> <td>295</td> <td>72.5</td> <td>84.7</td> </tr> <tr> <td>>9</td> <td>226</td> <td>77.1</td> <td>89.9</td> </tr> </tbody> </table>				Delay from surgery to chemo (weeks)	n	5 yr DFS (%)	5 yr OS (%)	<3	637	72.5	85.5	3 to 6	1624	76.1	87.7	6 to 9	295	72.5	84.7	>9	226	77.1	89.9
Delay from surgery to chemo (weeks)	n	5 yr DFS (%)	5 yr OS (%)																				
<3	637	72.5	85.5																				
3 to 6	1624	76.1	87.7																				
6 to 9	295	72.5	84.7																				
>9	226	77.1	89.9																				
Using a Cox-regression model, delay from surgery to chemotherapy group was not a significant predictor of overall survival, with known prognostic factors included as covariates (HR not reported). This was also the case when delay was considered as a																							

continuous variable.

General comments

Poor reporting of multivariate model, only statistically significant predictors are reported

Lohrisch, C., Paltiel, C., Gelmon, K., Speers, C., Taylor, S., Barnett, J. & Olivotto, I. A. (2006) Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *Journal of Clinical Oncology*, 24: 4888-4894.

Design

Cohort
Country of origin: Canada
Evidence grade: 2-

Inclusion criteria

Women aged 90 years or less referred to the British Columbia Cancer Agency between 1989 and 1998 with stage I or II breast cancer and known pathologic nodal status. All received adjuvant chemotherapy.

Exclusion criteria

Locally advanced or metastatic disease, those who could not be linked to a pharmacy database. Chemotherapy started more than 24 weeks after surgery. Neoadjuvant chemotherapy. Relapse within 12 weeks of surgery. Delay >17 weeks between diagnosis and surgery. Prior or synchronous breast cancer

Population

N=2594

Interventions

Surgery with curative intent. Adjuvant chemotherapy (standard regimens included: AC, FAC-CAF, CMF)

Outcomes

Recurrence free survival, overall survival

Follow up Median follow up was 6.2 years

Results

Patients were divided into four chemotherapy timing groups for analysis

Delay from surgery to chemo (weeks)	n	5 yr RFS (%) (95% CI)	5 yr OS (%) (95% CI)
0 to 4	993	73.9 (71.0 to 76.5)	83.5 (81.1 to 85.7)
>4 to 8	1272	78.7 (76.3 to 80.9)	85.1 (82.9 to 86.9)
>8 to 12	217	82.4 (76.5 to 86.9)	88.7 (83.6 to 92.3)
>12 to 24	112	69.3 (59.7 to 77.0)	78.4 (69.5 to 85.0)

On univariate (log-rank) analysis there was a statistically significant difference between groups in both RFS and DFS (P=0.004 and P=0.013 respectively).

On multivariate analysis delay from surgery to chemotherapy between 12 and 24 weeks was an independent predictor of overall survival (HR=1.6, 95% CI 1.2 to 2.3), with tumour size, nodal status, age and LVI as covariates.

General comments

Relatively few patients in the 12 to 24 week group, only 4% of the overall cohort.

Shannon, C., Ashley, S. & Smith, I. E. (2003) Does timing of adjuvant chemotherapy for early breast cancer influence survival? <i>Journal of Clinical Oncology</i> , 21: 3792-3797.			
Design			
Prospective case series Country of origin: UK Evidence grade: 3			
Inclusion criteria			
Patients treated with adjuvant anthracycline based chemotherapy at the Royal Marsden Hospital between 1990 and 2001, either in clinical trials or on the basis of service guidelines.			
Exclusion criteria			
None reported			
Population			
N=1161			
Interventions			
Surgery: breast conserving surgery (N=911), mastectomy (N=250) Adjuvant anthracycline based chemotherapy: combinations including epirubicin (N=686), CMF or mitoxantrone and methotrexate (N=475) Adjuvant endocrine treatment (N=974) Local radiotherapy (N=846)			
Outcomes			
Disease free survival (DFS), overall survival (OS), both measured from the date of first surgery.			
Follow up			
Median 39 months (range 12 to 147 months)			
Results			
Patients were divided into 2 chemotherapy timing groups for analysis: within 3 weeks of surgery versus 3 or more weeks after surgery.			
	<u>Surgery to Chemotherapy delay group</u>		
	<3 weeks	3 or more weeks	Log-rank P
5 yr DFS	70%	72%	0.4
5 yr OS	82%	84%	0.2
DFS			
A Cox-proportional hazards model was used to adjust for known prognostic factors of pathologic size, nodal status, number of involved nodes, grade vascular invasion, ER status, type of chemotherapy and use of endocrine therapy. The timing of chemotherapy			

(within 3 weeks versus 3 weeks) was not an independent predictive factor of disease free survival (HR not reported).

OS

A Cox-proportional hazards model was used to adjust for known prognostic factors. The timing of chemotherapy (within 3 weeks versus 3 weeks) was not an independent predictive factor of overall survival (HR not reported).

When chemotherapy timing was considered as a continuous variable, it was still not an independent predictor of survival (HR not reported). Similarly when a 4 week and 5 week cut-offs were used to categorise patients there was still no effect of chemotherapy timing on survival.

General comments

Slightly higher rate of mastectomy in the late chemotherapy group than in the early group (24% vs. 17%, $p=0.01$).

Cold, S., Durning, M., Ewertz, M., Knoop, A. & Moller, S. (2005) Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). *British Journal of Cancer*, 93: 627-632.

Design

Re-analysis of RCTs, observational evidence
Country of origin: Denmark
Evidence grade: 3

Inclusion criteria

Patients with early breast cancer entered into Danish Breast Cancer Cooperative Group adjuvant chemotherapy trials between 1977 and 1999

Exclusion criteria

Delay of more than 89 days between surgery and chemotherapy, missing pathological data

Population

N=7501

Interventions

Breast surgery, not specified in detail
Adjuvant chemotherapy: classical CMF (N=352), CMF (N=6065) or CEF (N=1084). All included patients started chemotherapy within 13 weeks of surgery.
Radiotherapy, (N=3555) not specified in detail
Endocrine therapy, not reported

Outcomes

Overall survival

Follow up

Not reported

Results

Overall survival

Patients were divided into 4 chemotherapy to surgery delay groups for analysis. Multivariate analysis of overall survival was adjusted for known prognostic factors: age, tumour size, number of nodes, histological type, malignancy grade and receptor status.

For patients receiving classical CMF adjuvant chemotherapy

Start of chemotherapy	Adjusted HR (95% CI)
1 to 3 weeks	1
4 weeks	0.929 (0.441 to 1.957)
5 weeks	1.549 (0.761 to 3.149)

6 to 13 weeks	1.588 (0.856 to 2.948)
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For patients receiving CMF adjuvant chemotherapy

Start of chemotherapy	Adjusted HR (95% CI)
1 to 3 weeks	1
4 weeks	1.021 (0.903 to 1.155)
5 weeks	0.891 (0.782 to 1.012)
6 to 13 weeks	1.002 (0.884 to 1.136)

For patients receiving CEF adjuvant chemotherapy

Start of chemotherapy	Adjusted HR (95% CI)
1 to 3 weeks	1
4 weeks	1.218 (0.800 to 1.854)
5 weeks	1.045 (0.716 to 1.525)
6 to 13 weeks	1.238 (0.861 to 1.782)

The timing of the start of chemotherapy after surgery was not an independent predictive factor for overall survival.

General comments

Colleoni, M., Bonetti, M., Coates, A. S., Castiglione-Gertsch, M., Gelber, R. D., Price, K., Rudenstam, C. M., Lindtner, J., Collins, J., Thurlimann, B., Holmberg, S., Veronesi, A., Marini, G. & Goldhirsch, A. (2000) Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group. *Journal of Clinical Oncology*, 18: 584-590.

Design

Re-analysis of RCTs
 Evidence grade: 3
 Country: International

Inclusion criteria

Women enrolled in one of three international RCTs between 1978 and 1993. Premenopausal, positive axillary lymph nodes. Data available on ER levels.

Exclusion criteria

Oophorectomy. Patients who did not start chemotherapy.

Population

N=1788

Interventions

Surgery, not specified in detail
 Adjuvant chemotherapy, classical CMF
 Endocrine therapy and radiotherapy not reported

Outcomes

Disease free survival (DFS),

Follow up

Median follow up was 7.7 years.

Results

Patients were divided into two chemotherapy timing groups for analysis: within 3 weeks after surgery versus 3 or more weeks after surgery.

Multivariate analysis of disease free survival was done, adjusting for number of positive axillary nodes, tumour size, age and vessel invasion.

The effect of chemotherapy timing (within 3 weeks after surgery versus 3 or more weeks) on disease free survival is summarized below using hazard ratios and stratified by ER group.

ER group	N	Adjusted HR (95% CI)
Combined	1788	0.88 (0.76 to 1.03)

ER negative	226	0.60 (0.39 to 0.92)
ER 1 to 9	379	0.92 (0.63 to 1.33)
ER 10 or more	1183	0.91 (0.76 to 1.10)

Overall, the timing of the start of chemotherapy after surgery was not an independent predictive factor for disease free survival. In the sub-group of ER negative women disease free survival was significantly lower in those who started chemotherapy later than 3 weeks after surgery.

Chapter 5 – Adjuvant systemic therapy

5.1 In premenopausal patients with breast cancer, what are the benefits of adjuvant ovarian suppression/ablation?

Short Summary

There is a large volume of randomised trials of ovarian ablation and ovarian suppression in women with early breast cancer, and numerous high-quality systematic reviews are also available. Broadly, the literature describes two types of intervention: either ovarian ablation (by surgery or radiotherapy) or ovarian suppression using luteinising hormone releasing hormone agonist (LHRHa), each used adjuvant to surgery to the breast.

Evidence from systematic reviews of randomised trials, meta-analyses of individual patient data from randomised trials and further published randomised trials is suggestive of the following effects of ovarian ablation (by oophorectomy or radiotherapy) or suppression (by LHRH agonist).

Ovarian ablation or suppression versus none: In premenopausal women with breast cancer that is ER positive or with unknown ER status, ovarian ablation or suppression is beneficial compared to no ovarian treatment in terms of recurrence (respective rates 47% and 52%, $p < 0.0001$) and breast cancer mortality (respective rates 40% and 44%, $p < 0.004$), both assessed at 15 years follow-up (Early Breast Cancer Trialists' Collaborative Group 2005).

Ovarian ablation and the role of chemotherapy: The most recent evidence from a meta-analysis of individual patient data suggests that ovarian ablation has a benefit in terms of recurrence and survival over no ablation in premenopausal women, with or without chemotherapy (EBCTCG 2005). An earlier meta-analysis performed by the same group found that this benefit exists in the absence of chemotherapy, but not where adjuvant chemotherapy is given (EBCTCG 1998). Randomised trials that were not included in these reviews have demonstrated equivalence in terms of 10 year recurrence and survival between ovarian ablation and chemotherapy, with tamoxifen used in some randomised arms (Nomura *et al.* 1999; Thomson *et al.* 2002). An RCT was able to show no advantage of additional goserelin after a risk-adapted chemotherapy with respect to event free survival in hormone receptor negative patients (Kaufmann *et al.* 2007).

LHRHa versus no systemic therapy: A relatively small meta-analysis ($n=338$) found no difference in recurrence or survival, comparing LHRH agonists with no systemic therapy (Cuzick *et al.* 2007). From a well conducted RCT, premenopausal women with operable breast cancer showed a 5 and 10 year disease free survival and overall survival rates were significantly improved following adjuvant oophorectomy and tamoxifen (Love *et al.* 2008).

LHRHa versus chemotherapy: A larger meta-analysis (n=3184) in the same study found LHRH agonists to be equivalent to chemotherapy in terms of recurrence and survival (Cuzick *et al.* 2007).

LHRHa plus tamoxifen versus LHRH alone or tamoxifen alone: A Cochrane Review indicates that recurrence and mortality are reduced in premenopausal women treated with a LHRHa combined with tamoxifen compared to women treated with either drug alone (Sharma *et al.* 2007). In contrast a meta-analysis of individual patient data found no difference in recurrence or death following recurrence arising from treatment with LHRHa plus tamoxifen versus tamoxifen alone (Cuzick *et al.* 2007).

LHRHa with or without tamoxifen in addition to chemotherapy: Evidence from a narrative Cochrane Review and meta-analysis of randomised trials indicates that recurrence and mortality are reduced in premenopausal women with ER positive tumours who are treated with a LHRHa, with or without tamoxifen, in addition to chemotherapy (Sharma *et al.* 2007; Cuzick *et al.* 2007).

LHRHa with or without tamoxifen versus chemotherapy: Evidence from a narrative Cochrane Review and meta-analysis of randomised trials indicates that LHRHa, with or without tamoxifen, are as effective as chemotherapy for premenopausal women with ER positive tumours, in terms of recurrence and mortality (Cuzick *et al.* 2007; Sharma *et al.* 2007)

Side effects and quality of life:

Evidence from randomised trials suggests that ovarian ablation, ovarian suppression and chemotherapy each have adverse side effects and each can induce menopausal symptoms, including amenorrhoea (Brunt *et al.* 2004a; Groenvold *et al.* 2006; Schmid *et al.* 2007; Love *et al.* 1999; Sharma *et al.* 2007; Celio *et al.* 2002). A randomised comparison of oophorectomy and tamoxifen versus observation in Vietnamese women found that menopausal symptoms resulted from oophorectomy and tamoxifen within the first twelve months from start of treatment (Love *et al.* 1999). A Cochrane Review cited trials which found that side effects are more severe following LHRH agonist plus tamoxifen compared to tamoxifen alone (Sharma *et al.* 2007). Health-related quality of life tends to favour ovarian ablation or suppression over chemotherapy, whereas acute adverse effects appear to be worse following chemotherapy. In contrast, menopausal symptoms (for example hot flushes) appear to be worse following ablation or suppression, than following chemotherapy, and with earlier onset. Amenorrhoea can be longer lasting following chemotherapy compared with LHRH agonist (Brunt *et al.* 2004a; Groenvold *et al.* 2006; Sharma *et al.* 2007; Schmid *et al.* 2007). In one study a self assessment of tolerability by patients favoured LHRH agonist over CMF chemotherapy during the first 6 months, but with comparable tolerability at two years (Schmid *et al.* 2007).

PICO

Population	Intervention	Comparison	Outcome
<p>Premenopausal patients with early invasive breast cancer. Including: Receptor positive and Receptor negative</p> <p>Note: Patients with breast cancer who have had ovarian suppression/ablation without chemotherapy will also be considered.</p>	<ul style="list-style-type: none"> • Ovarian suppression (LHRH & oophorectomy) ± chemotherapy • Ovarian ablation • Zoladex 	<ul style="list-style-type: none"> • No treatment • Chemotherapy with or without Tamoxifen 	<ul style="list-style-type: none"> • Disease-free survival (DFS) • Overall survival (OS) • Contralateral breast cancer • Quality of life (SE profile) • Psychological morbidity

Evidence Summary

Population: The population of interest is women with early breast cancer who are pre-menopausal, and the included studies have good applicability in this regard. Some studies estimated menopausal status using a threshold of age <50 years (Early Breast Cancer Trialists' Collaborative Group 1998; Early Breast Cancer Trialists' Collaborative Group 2005).

ER status is likely to be an important factor in assessing outcomes following ovarian ablation or suppression. Many trials are directed at patients with ER positive tumours. There appears to be more benefit arising from ovarian ablation or suppression in the ER positive subset, and one study offered different randomised treatment plans to patients according to ER status, with ovarian treatment possible as a randomly allocated treatment only in ER positive cases (Nomura *et al.* 1999).

Interventions: Broadly, the literature describes two types of intervention: either ovarian ablation (by surgery or radiotherapy) or ovarian suppression using luteinizing hormone releasing hormone (LHRH) agonists, each used adjuvant to surgery to the breast. Some studies present results separately for the two types of intervention, or report only one intervention (e.g. LHRH agonists alone).

Some authors use the terms ablation and suppression inconsistently or interchangeably (Brunt *et al.* 2004b; Groenvold *et al.* 2006). In terms of this question as set out in PICO format, ovarian ablation (by surgery or ovarian radiotherapy) and ovarian suppression (by LHRH agonist) may be regarded as equivalent procedures. The comparison of interest is ovarian ablation or suppression versus no adjuvant treatment, or versus adjuvant chemotherapy or hormone therapy.

Some of the randomised trials that contribute data to the cited systematic reviews were conducted decades ago, particularly trials of ovarian ablation by surgery or radiotherapy. Such trials may have used older adjuvant chemotherapy regimens which differ from modern regimens.

Outcomes: The included studies focus heavily on recurrence and survival outcomes, particularly the systematic reviews, but tend less to report side effect data. The Cochrane Review of ovarian ablation (Early Breast Cancer Trialists' Collaborative Group 1998) reported in brief that ablation has major adverse side effects. Additional papers from RCTs published subsequent to the systematic reviews have been sought, as have RCTs that have reported additional side effect data. Even so, side effect and quality of life data may be underrepresented in the selected studies.

Other factors: Other publications were sought from randomised trials which meet the following criteria:

- Studies that did not contribute data to the EBCTCG dataset
- Studies published of trials included in the EBCTCG-based systematic reviews which subsequently publish data with longer follow-up e.g. (Schmid *et al.* 2007)
- Studies that publish data on psychosocial or quality of life outcomes; such outcomes were not reported in the EBCTCG-based systematic reviews.

Evidence:

1. Ovarian ablation or suppression versus control

The systematic review of RCTs and meta-analysis of individual patient data by (Early Breast Cancer Trialists' Collaborative Group 2005) compared ovarian ablation (by RT or oophorectomy) or suppression with LHRH agonists versus no ovarian treatment (with or without other adjuvant systemic therapy) in women with tumours that were ER positive or of unknown ER status. Results at 15 years follow-up based on analysis of 7601 women of age , entry age <50 years at trial entry indicated a benefit in favour of ablation/suppression in terms of recurrence and breast cancer mortality (Early Breast Cancer Trialists' Collaborative Group 2005):

Recurrence:

Ablation or suppression: 47.3%

Control: 51.6%

Logrank 2p=0.00001 (Early Breast Cancer Trialists' Collaborative Group 2005)

Breast cancer mortality:

Ablation or suppression: 40.3%

Control: 43.5%

Logrank 2p=0.004 (Early Breast Cancer Trialists' Collaborative Group 2005)

2. Ovarian Ablation versus control

A Cochrane review was published that was based upon the EBCTCG dataset and which compared ovarian ablation (by surgery or RT) versus control (Early Breast Cancer Trialists' Collaborative Group 1998). On the basis of the odds ratios shown below, ovarian ablation resulted in statistically significant benefits in terms of recurrence-free survival and overall survival in the subgroup of patients who did not receive chemotherapy, but with no benefit in the subgroup of patients treated with chemotherapy.

Recurrence-free survival in the absence of chemotherapy: Ovarian ablation versus control: OR 0.75; 95% CI 0.64-0.88; $p=0.0005$

Recurrence-free survival in the presence of chemotherapy: Ovarian ablation versus control: OR 0.90; 95% CI 0.75-1.08; $p=0.2$

Total (recurrence-free survival; $n=2174$): Ovarian ablation versus control: OR 0.82; 95% CI 0.72-0.92

Overall survival in the absence of chemotherapy: Ovarian ablation versus control: OR 0.76; 95% CI 0.65-0.89

Overall survival in the presence of chemotherapy: Ovarian ablation versus control: OR 0.92; 95% CI 0.75-1.12

Total (overall survival; $n=2174$): Ovarian ablation versus control: OR 0.82; 95% CI 0.72-0.92

For the reported odds ratios the review does not specify whether they represent patients of age <50 years. However the review concluded that ovarian ablation improves long term survival in pre-menopausal patients with early breast cancer, but also has major adverse effects and is unlikely to be of benefit to post-menopausal women (Early Breast Cancer Trialists' Collaborative Group 1998).

A subsequent publication from the same group (Early Breast Cancer Trialists' Collaborative Group 2005) provided another meta-analysis of individual patient data, comparing ovarian ablation versus control at a mean follow-up of 8 years. The risk ratio for recurrence in women of age < 50 years (ablation: control) was 0.83 (95% CI 0.73-0.93), $2p=0.0005$ i.e. a statistically significant effect in favour of ablation, where some patients received chemotherapy and others did not. The risk ratio for mortality in women of age < 50 years (ablation: control) was 0.86 (95% CI 0.76-0.96), $2p=0.01$. Again, this represents a statistically significant effect in favour of ablation, where some patients received chemotherapy and others did not.

A randomised controlled trial by (Groenvold *et al.* 2006) measured health-related quality of life during the 2 years following randomisation to either CMF chemotherapy versus ovarian ablation by oophorectomy in 196 premenopausal women with oestrogen or progesterone receptor positive breast cancer. Functional and symptom-related aspects of QOL based upon EORTC QLC-C30 mean scores tended to favour ablation when measured up to month five from randomisation: statistically significant differences in mean score in favour of ablation were seen for cognitive function, social function, constipation, fatigue, nausea and vomiting, dyspnoea, sleep, loss of appetite and global health/QOL. In contrast the diarrhoea outcome favoured chemotherapy, but only in the first month. For all EORTC QLC-C30 outcomes after five months there were no differences between groups. For physical symptoms outcomes assessed using the DBCG 89 scale, statistically significant differences in score favoured ablation for use of a wig, anticipatory nausea, regular bleedings, bleedings, urinary incontinence, weight gain (>2kg), hair loss and sore mouth. Some of these differences persisted until, or became apparent at approximately two years follow-up. In contrast, statistically significant differences favoured chemotherapy for hot flushes/sweats and to a lesser extent satisfaction with appearance, but with no difference persisting beyond 9 months. There was no difference between randomised arms for HAD anxiety score over the two year period, whereas HAD depression score favoured ablation at month 3 and at month 5 (Groenvold *et al.* 2006).

The UKCCR ABC randomised controlled trial included a randomised comparison of ovarian suppression (not further specified) or chemotherapy versus none, with tamoxifen in all cases, in 199 Pre/peri-menopausal women with early breast cancer; QOL outcomes were presented in an abstract (Brunt *et al.* 2004a). The addition of chemotherapy was associated with worse QOL during the first 9 months for depression ($p=0.007$), role function ($p=0.003$) and global QOL ($p=0.001$) and a trend to worse QOL for body image concerns ($p=0.02$), and sexual enjoyment ($p=0.08$). Systemic side effects ($p=0.001$) and menopausal problems ($p=0.02$) were worse over 30 months. The addition of ovarian suppression resulted in increased menopausal symptoms ($p<0.0001$), depression ($p=0.05$) and anxiety ($p=0.04$) over 30 months but no deterioration in role function, global QOL, body image or sexual function (Brunt *et al.* 2004a).

A randomised controlled trial reported in abstract form by (Celio *et al.* 2002) compared surgical oophorectomy versus FEC chemotherapy, with Tamoxifen in both arms, in 109 women with invasive, hormone receptor (ER or PR) positive, node-positive breast cancer. Poor accrual resulted in the study being stopped prematurely. All patients in the chemotherapy arm completed all cycles, but only 46 out of 55 patients received more than 95% of the total planned chemotherapy dose. Grade 3-4 neutropenia occurred in 12% of patients, and 75% of normally menstruating patients experienced amenorrhoea persisting after chemotherapy. With a median follow-up of 68 months, there were 10 (18%) vs. 4 (7%)

recurrences and 6 (11%) vs. 3 (5%) deaths in the oophorectomy and chemotherapy arms, respectively.

A randomised controlled trial compared oophorectomy and tamoxifen versus observation (with oophorectomy and tamoxifen initiated if metastatic disease was subsequently detected) in 709 premenopausal Vietnamese women with operable breast cancer of stage I-IIIa (Love *et al.* 2002). In an intention-to-treat analysis at a median 3.6 years follow-up, disease-free survival ($p=0.0003$) and overall survival ($p=0.0477$) were higher in the intervention group compared to the control group. Disease-free survival estimated at 5 years by Kaplan-Meier analysis was 75% in the intervention group and 58% in the observation group. Considering only the ER positive subgroup at a median 3.6 years follow-up, disease-free survival ($p=0.001$) and overall survival ($p=0.01$) were higher in the intervention group compared to the control group. Considering only the ER negative subgroup at a median 3.6 years follow-up, there was no statistically significant difference in disease-free survival or overall survival between the intervention group and the control group. The same authors undertook a sub-study on side effects of treatment in 482 women (Love *et al.* 1999). In the first 12 months from randomisation, the occurrence and severity of hot flashes, vaginal discharge and vaginal pruritus favoured the observation arm, to a statistically significant level. An excess of vasomotor symptoms persisted in women treated with oophorectomy and tamoxifen over three years of follow-up although at 3 years only 23% of treated women had these symptoms, and the majority of these were of grade 1 intensity. While over time small numbers of observation group patients developed recurrent disease and received oophorectomy and tamoxifen treatment and developed associated symptoms, these events do not significantly alter the distribution of vasomotor symptoms between groups. No women stopped tamoxifen because of toxicity.

From a well conducted RCT, premenopausal women with operable breast cancer showed a 5 and 10 year disease free survival and overall survival rates were significantly improved following adjuvant oophorectomy and tamoxifen (Love *et al.* 2008). Disease free Survival and Overall Survival: With a median follow-up of 7.0 years and from intent-to-treat analyses, a significant difference in disease free survival (DFS) ($P= 0.0003$) and overall survival (OS) ($P= 0.0002$) was found, which favoured the intervention group.

- 5-year DFS was 74% in adjuvant group and 61% in observation groups (95% CI for difference, 7% - 21%)
- 10-year DFS was 62% in adjuvant group and 51% in observation groups (95% CI for difference, 4% - 22%).
- 5-year OS rates were 78% in adjuvant group and 71% in observation groups (95% CI for difference, 1% - 21%)
- 10-year OS rates were 70% in adjuvant group and 52% in observation group (95% CI for difference, 6% - 34%).
- The DFS: HR (hazard ratio) for adjuvant versus observation groups = 0.65 (95% CI, 0.51 - 0.82)

- For OS : HR= 0.62 (95% CI, 0.48 - 0.80). (Based on a univariate Cox proportional hazards model)

ER status: For women with known estrogen receptor (ER) status (n = 470), the adjuvant treatment effect was more marked in ER+ women.

- A Cox proportional hazards model was designed which included the DFS outcome using treatment, ER status and the treatment by ER interaction as the predictors.
- Estimates from the model indicated that the treatment benefit decreased over time for ER+ patients.
- Using the model estimates and ER+/observation patients as the referent group, the hazard ratio for recurrence for ER+ patients undergoing treatment increased from 0.49 (95% CI, 0.31 to 0.75) at year 3 to 1.10 (95% CI, 0.58 to 2.06) at year 8.
- When considering the significant ER status by treatment interaction, a smaller effect of treatment for ER- patients was not significant (P=0.46 for DFS and 0.29 for OS). The 95%CI for the hazard ratio comparing treatment and observation among ER patients for DFS = 0.56 to 1.29 (authors claim that this CI is not narrow enough to rule out a clinically important effect of treatment in this subgroup)

In a randomised controlled trial reported by (Nomura *et al.* 1999) 789 premenopausal Japanese women with operable breast cancer of stage I-IIIa were randomised according to their ER status. Women with ER positive tumours were randomly allocated to either oophorectomy and Tamoxifen, chemotherapy (mitomycin and cyclophosphamide) or chemotherapy and Tamoxifen. Women with ER negative tumours were randomly allocated to either chemotherapy or chemotherapy and Tamoxifen. At a median follow-up of 10 years in patients with ER positive tumours there were no significant differences in relapse-free survival (p=0.15) or overall survival (p=0.42) among the oophorectomy plus Tamoxifen, chemotherapy, and chemotherapy plus Tamoxifen arms. At a median follow-up of 10 years in women with ER negative tumours there were no significant differences in relapse-free survival (p=0.97) or overall survival (p=0.85) between chemotherapy and chemotherapy plus Tamoxifen arms.

A randomised controlled trial compared ovarian ablation with CMF chemotherapy in 332 premenopausal patients with stage II breast cancer, recruited between 1980 and 1990 (Thomson *et al.* 2002). At a median follow-up of 10.7 years there was no statistically significant difference in overall survival between randomised arms: HR (ablation:CMF) 1.01, 95% CI 0.74-1.37, p=0.96, nor in event-free survival: HR (ablation:CMF) 0.95, 95% CI 0.71-1.26, p=0.7. There was also no difference between randomised groups for these outcomes when the subgroup of patients with ER positive tumours were analysed, or those with ER negative tumours.

3. Ovarian suppression with LHRH agonists

a) LHRH agonist versus no systemic therapy

The meta-analysis by Cuzick et al. 2007 found no statistically significant difference in the risk of recurrence or death following recurrence on the basis of 5 trials comparing LHRH agonist versus no systemic therapy (n=338):

HR (recurrence: LHRH agonist:no systemic therapy) 0.72; 95% CI 0.49-1.04; p=0.08.

HR (death after recurrence: LHRH agonist:no systemic therapy) 0.82; 95% CI 0.47-1.43; p=0.49 (Cuzick *et al.* 2007).

An RCT was able to show no advantage of additional goserelin after a risk-adapted chemotherapy with respect to event free survival in HR-negative patients (Kaufmann *et al.* 2007). Event Free Survival: The unadjusted hazard ratio (HR) of goserelin versus control pooling HR-negative and HR-positive patients was 0.92 (95% CI, 0.70– 1.21; calculated as 95.66% CI to account for two interim analyses; P = 0.54).

In HR-negative pts: adjusted HR (goserelin versus control) = 1.01 (CI, 0.72–1.42; P = 0.97).

In HR-positive pts: adjusted HR (goserelin versus control) = 0.77 (CI, 0.47–1.24; P = 0.27).

Overall survival: 5-year OS rates of all pts are estimated as 86% in the goserelin group and 85% in the control group. 104 (13%) deaths observed up to time of report (authors' note - it is too early for any definite analysis of OS)

Tolerability and adverse events: Goserelin was discontinued for medical reasons (other than recurrence or death) in 24 pts.

In the control group: Serious adverse events related to chemotherapy were reported in 17 pts

In the goserelin group: Serious adverse events related to therapy were reported in 14 pts

General comments: Overall, this study is underpowered for both the HR-negative and HR-positive population, the results do not indicate an advantage of additional goserelin after a risk-adapted chemotherapy with respect to EFS in HR-negative patients.

b) LHRH agonist versus chemotherapy

The meta-analysis by Cuzick *et al.* 2007 found no statistically significant difference in the risk of recurrence or death following recurrence on the basis of 4 trials comparing LHRH agonist versus chemotherapy (n=3184):

HR (recurrence: LHRH agonist:CT) 1.04; 95% CI 0.92-1.17; p=0.52

HR (death after recurrence: LHRH agonist:CT) 0.93; 95% CI 0.79-1.10; p=0.40 (Cuzick *et al.* 2007).

One of these trials, the TABLE study, recently reported results with a longer median follow-up of 5.8 years (Schmid *et al.* 2007). 599 premenopausal women with ER positive breast tumors of stage II or IIIA were randomly allocated to leuporelin acetate or to CMF chemotherapy. There was no significant difference in recurrence-free survival arising from treatment with leuporelin versus CMF. 5-year RFS rates were 63.9% for leuporelin and 63.4% for CMF (HR, 1.03; P=0.83). Survival favoured leuporelin treatment over CMF (HR, 1.50; 95% CI, 1.13 to 1.99; P=0.005) with 5-year survival rates of 81.0% and 71.9%, respectively. There was also a trend for a higher breast cancer-related mortality in the CMF group (CMF, 39.5%; leuporelin, 28.9%; P=0.05). Amenorrhea was reported in 88% of leuporelin patients by 6 months and more than 95% during the remaining 2-year treatment period, compared with 43.9% of CMF patients after 6-months of chemotherapy and 62.1% at 2 years. The onset of amenorrhea was earlier in the leuporelin group (mean, 22±38 days) compared to the CMF group (mean, 110±151 days). Amenorrhea was reversible within 1 year of stopping leuporelin in 45% of patients. In patients treated with CMF, the rate of amenorrhea steadily increased from 51.5% after 1 year to 62.1% after 2 years and 72.7% after 5 years. Symptoms of oestrogen suppression such as hot flashes and increased sweating were more common in patients treated with leuporelin, whereas acute adverse effects of chemotherapy such as nausea, vomiting, diarrhea, asthenia, and alopecia were reported more frequently in patients treated with CMF. An overall self assessment of tolerability by participants showed markedly better results for leuporelin during the first 6 months. At 6 months, 16.0% and 56.8% of patients in the leuporelin group rated the treatment tolerability as "very good" or "good," respectively, compared with 15.6% and 37.3% in the CMF group. After the end of chemotherapy, assessments improved markedly in the CMF group. At 2 years, self-assessments of tolerability were comparable in both arms.

c) Integration of LHRH agonists into adjuvant hormonal therapy

The Cochrane systematic review by (Sharma *et al.* 2007) concluded on the basis of four trials of approximately 5000 participants, that recurrence and mortality are reduced in premenopausal women treated with the LHRH agonist goserelin combined with tamoxifen compared to women treated with either drug alone. The authors stated that longer follow-up is needed to estimate the benefits more reliably and that insufficient data are available for a meta-analysis comparing tamoxifen versus goserelin as sole adjuvant therapy. (Sharma *et al.* 2007)

The systematic review by Cuzick *et al.* 2007 did perform a meta-analysis of five trials comparing LHRH agonist plus tamoxifen versus tamoxifen alone (n=1011). There was no statistically significant difference in the risk of recurrence or death following recurrence:

HR (recurrence: LHRH agonist + tamoxifen: tamoxifen) 0.85; 95% CI 0.67-0.20; p=0.2

HR (death after recurrence: LHRH agonist + tamoxifen: tamoxifen) 0.84; 95% CI 0.59-1.19; p=0.33 (Cuzick *et al.* 2007)

d) LHRH agonists with or without tamoxifen in addition to chemotherapy

The Cochrane systematic review by (Sharma *et al.* 2007) concluded on the basis of six trials that recurrence and mortality are reduced in premenopausal women with ER positive tumours who are treated with a LHRH agonist, with or without tamoxifen, in addition to chemotherapy.

The systematic review by Cuzick *et al.* 2007 performed a meta-analysis of 13 trials comparing the addition of LHRH agonist to chemotherapy with or without tamoxifen (n=2741). The results favoured adding LHRH agonist in terms of recurrence and mortality following recurrence:

HR (recurrence: Addition of LHRH agonist to CT ± Tamoxifen: CT ± Tamoxifen) 0.88; 95% CI 0.77-0.99; p=0.04.

HR (death after recurrence: Addition of LHRH agonist to CT ± Tamoxifen: CT ± Tamoxifen) 0.85; 95% CI 0.73-0.99; p=0.04 (Cuzick *et al.* 2007).

Cuzick *et al.* 2007 also performed meta-analyses for the same comparison but based upon subgroups according to participants age (≤40 years and >40 years). The results of these analyses confirmed the benefit of adding an LHRH agonist to chemotherapy (with or without tamoxifen) in terms of recurrence and mortality following recurrence in women of age ≤40 years. There was no evidence for a similar benefit in women of age 40 years or more:

Recurrence (9 trials)

Age ≤ 40 years:

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.75; 95% CI 0.61-0.92; p=0.01 (Cuzick *et al.* 2007)

Age > 40 years:

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.96; 95% CI 0.82-1.13; p=0.63 (Cuzick *et al.* 2007)

Death after recurrence (8 trials)

Age ≤ 40 years:

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.72; 95% CI 0.55-0.93; p=0.01 (Cuzick *et al.* 2007)

Age > 40 years (8 trials):

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.93; 95% CI 0.75-1.14; p=0.47 (Cuzick *et al.* 2007)

e) LHRH agonists with or without tamoxifen versus chemotherapy

The Cochrane systematic review by (Sharma *et al.* 2007) concluded on the basis of six trials that LHRH agonists, with or without tamoxifen, are as effective as chemotherapy for premenopausal women with ER+ tumours, in terms of recurrence free survival and overall survival. Hormone therapy had fewer distressing side effects than the regimens of chemotherapy assessed in these trials (Sharma *et al.* 2007).

The systematic review by Cuzick *et al.* 2007 performed a meta-analysis of three trials comparing LHRH agonist plus Tamoxifen versus chemotherapy (n=1577) and found no statistically significant difference in recurrence or mortality following recurrence:

HR (recurrence: LHRH agonist + Tamoxifen: CT) 0.90; 95% CI 0.75-1.08; p=0.25
HR (death after recurrence: LHRH agonist + Tamoxifen: CT) 0.89; 95% CI 0.69-1.15; p=0.37 (Cuzick *et al.* 2007).

Updated 2018

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EVIDENCE TABLES

Systematic reviews of randomised trials

Citation
Cuzick, Ambroisine, Davidson, Jakesz, Kaufmann, Regan & Sainsbury . Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 369[9574], 1711-1723. 2007.
Design
Systematic review of RCTs and meta-analysis of individual patient data. Country of origin: various Evidence grade: 1+
Inclusion criteria
Aim: to perform a meta-analysis based on individual patient data to present an updated overview of the evidence, dealing only with trials in which LHRH agonists were assessed, and focusing specifically on results for patients known to be hormone-receptor-positive. Eligible studies had to provide an assessment of the randomised addition of an LHRH agonist to an adjuvant therapy or a randomised comparison between a systemic treatment and an LHRH agonist. In some trials, ovarian suppression was done with a range of techniques; the authors only included trials in which more than half the treatments were with an LHRH agonist.
Exclusion criteria
Patients with unknown hormone receptor status.
Population
N=11, 906
Interventions
The randomised addition of an LHRH agonist was studied in the context of no other systemic adjuvant therapy (five trials), tamoxifen in both arms (five trials), chemotherapy in both arms (seven trials), or chemotherapy and tamoxifen in both arms (four trials). A second set of trials assessed a chemotherapy regimen versus an LHRH agonist (four trials), and a third group assessed chemotherapy versus an LHRH agonist combined with tamoxifen (three trials). No trials had assessed the question of chemotherapy versus an LHRH agonist, with tamoxifen in both arms. LHRH agonists studied:

Goserelin (13 trials)
Triptorelin (2 trials)
Leuprorelin (1 trial)

Chemotherapy, where given was most often CMF-based followed by anthracycline-based (with no use of taxanes).

Duration of LHRH agonist was most often 2 years, but 18 months, 3 years and 5 years duration were also studied.

Outcomes

Recurrence (defined as the first reappearance of breast cancer at any site: local or regional, contralateral, or distant)

Death following recurrence

Meta-analysis was performed for log hazard ratios and their variances, and results presented using Kaplan-Meier charts.

Follow up

Median 6.8 years

Results

1.) LHRH agonist versus no systemic therapy (5 trials; n=338)

HR (recurrence: LHRH agonist:no systemic therapy) 0.72 95% CI 0.49-1.04
p=0.08

HR (death after recurrence: LHRH agonist:no systemic therapy) 0.82 95% CI 0.47-1.43 p=0.49

2.) LHRH agonist + tamoxifen versus tamoxifen (5 trials; n=1011)

HR (recurrence: LHRH agonist + tamoxifen: tamoxifen) 0.85; 95% CI 0.67-0.20; p=0.2

HR (death after recurrence: LHRH agonist + tamoxifen: tamoxifen) 0.84; 95% CI 0.59-1.19; p=0.33

3.) Addition of LHRH agonist to chemotherapy with or without tamoxifen (13 trials; n=2741)

HR (recurrence: Addition of LHRH agonist to CT ± Tamoxifen: CT ± Tamoxifen) 0.88; 95% CI 0.77-0.99; p=0.04

HR (death after recurrence: Addition of LHRH agonist to CT ± Tamoxifen: CT ± Tamoxifen) 0.85; 95% CI 0.73-0.99; p=0.04

4.) LHRH agonist versus chemotherapy (4 trials; n=3184)

HR (recurrence: LHRH agonist:CT) 1.04; 95% CI 0.92-1.17; p=0.52

HR (death after recurrence: LHRH agonist:CT) 0.93; 95% CI 0.79-1.10; p=0.40

5.) LHRH agonist + Tamoxifen versus chemotherapy (3 trials; n=1577)

HR (recurrence: LHRH agonist + Tamoxifen: CT) 0.90; 95% CI 0.75-1.08; p=0.25

HR (death after recurrence: LHRH agonist + Tamoxifen: CT) 0.89; 95% CI 0.69-1.15; p=0.37

6.) Contributions of individual trials for addition of LHRH agonist to chemotherapy with or without tamoxifen by age

A) Recurrence, age ≤ 40 years; CT ± Tamoxifen versus CT ± Tamoxifen + LHRH (9 trials)

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.75; 95% CI 0.61-0.92; p=0.01

B) Recurrence, age > 40 years; CT ± Tamoxifen versus CT ± Tamoxifen + LHRH (9 trials)

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.96; 95% CI 0.82-1.13; p=0.63

C) Death after recurrence, age ≤ 40 years; CT ± Tamoxifen versus CT ± Tamoxifen + LHRH (8 trials)

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.72; 95% CI 0.55-0.93; p=0.01

D) Death after recurrence, age > 40 years; CT ± Tamoxifen versus CT ± Tamoxifen + LHRH (8 trials)

HR (CT ± Tamoxifen + LHRH: CT ± Tamoxifen) 0.93; 95% CI 0.75-1.14; p=0.47

General comments

In all trials, treatments were given in an unblinded open-label fashion.

No assessment of heterogeneity is made as part of the meta-analysis. A recent Cochrane Review (Sharma et al. 2007) did not perform a meta-analysis on data from largely the same studies due to unsuitability for meta-analysis.

Comparisons were made by intention-to-treat within the subgroups of hormone-receptor-positive (ie, oestrogen-receptor positive or progesterone-receptor positive, or both) and hormone-receptor-negative (ie, oestrogen-receptor negative and progesterone receptor negative, or oestrogen-receptor negative and progesterone-receptor unknown) patients. Cutoffs for hormone-receptor positivity were as used in the original trials.

Literature search strategy: used PubMed and Springer Link databases and

the database held by the Oxford overview group.

Keywords: “LHRH agonist”, “luteinising hormone- releasing hormone”, “breast cancer”, “adjuvant trials”.

Abstracts from major breast cancer meetings examined to identify all trials that assessed an LHRH agonist in at least one arm of a randomised adjuvant trial for early breast cancer.

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Citation
<p>Early Breast Cancer Trialists' Collaborative Group . Ovarian ablation for early breast cancer. Cochrane Database of Systematic Reviews: Reviews 1998 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000485</p> <p>1. Cochrane database of systematic reviews [2]. 1998. Chichester (UK), John Wiley & Sons, Ltd.</p>
Design
<p>Systematic review of RCTs and meta-analysis of individual patient data. Country of origin: Various Evidence grade: 1+</p>
Inclusion criteria
<p>Aim: to review randomised trials that began recruiting before 1990 and compared the ablation or suppression of ovarian function, sometimes with the addition of prednisone, versus no such adjuvant treatment.</p> <p>NB: the 12 included trials all began before 1980, and all achieved ovarian ablation by radiotherapy or surgery.</p>
Exclusion criteria
<p>Although eligible for inclusion, trials that evaluated ovarian suppression using LHRH agonists provided insufficient data so were not included.</p>
Population
<p>N=3456 Aged <50 years: 2102 Aged >=50 years: 1354</p>
Interventions
<p>Trials that compared the ablation or suppression of ovarian function were eligible, sometimes with the addition of prednisone, versus no such adjuvant treatment.</p> <p>NB - only studies of ovarian ablation by surgery or RT were included in the analyses because data in 4 trials of LHRH agonists were immature at the time of publication.</p> <p>In seven trials the ovarian ablation and control groups received no routine cytotoxic chemotherapy, in one there were randomisations both for cytotoxic therapy and for ovarian ablation in a "factorial" design, and in four trials both groups were scheduled to receive a common cytotoxic chemotherapy regimen (after ablation, in those allocated this treatment).</p>

Outcomes
<p>Time to contralateral breast cancer, first local recurrence, first distant recurrence, last known vital status. The cause of death was requested for women who had died without any record of distant recurrence.</p> <p>Because cytotoxic chemotherapy can itself produce partial or complete ovarian suppression in premenopausal women, separate analyses are also presented of ovarian ablation in the absence and in the presence of chemotherapy.</p>
Follow up
15 Years
Results
<p>REPORTED ODDS RATIOS BASED ON INDIVIDUAL PATIENT DATA</p> <p>Recurrence-free survival in the absence of chemotherapy Ovarian ablation versus control: OR 0.75; 95% CI 0.64-0.88; p=0.0005</p> <p>Recurrence-free survival in the presence of chemotherapy Ovarian ablation versus control: OR 0.90; 95% CI 0.75-1.08; p=0.2</p> <p>Total (recurrence-free survival; n=2174): Ovarian ablation versus control: OR 0.82; 95% CI 0.72-0.92</p> <p>Overall survival in the absence of chemotherapy Ovarian ablation versus control: OR 0.76; 95% CI 0.65-0.89</p> <p>Overall survival in the presence of chemotherapy Ovarian ablation versus control: OR 0.92; 95% CI 0.75-1.12</p> <p>Total (overall survival; n=2174): Ovarian ablation versus control: OR 0.82; 95% CI 0.72-0.92</p> <p>FURTHER DATA FROM NARRATIVE</p> <p>1. WOMEN AGED UNDER 50 AT RANDOMISATION</p> <p>RECURRENCE-FREE SURVIVAL Among women aged under 50, by year 15, there were 6.0 (SD 2.3) fewer events (recurrences or deaths) per 100 women allocated ovarian ablation (45.0 vs 39.0% event free 15 years after randomisation, logrank 2p=0.0007). Proportionally, ovarian ablation reduced the event rate by about one-fifth 18.5% [SD 5.5], both in the first 5 years (i.e., years 0-4) and in later years. The proportional reduction in events appeared to be similar in trials of ablation</p>

by surgery (18%;SD 8) or by radiotherapy (19%; SD 8), but the numbers of patients were not sufficient for this apparent similarity to be reliably informative.

OVERALL SURVIVAL

At 15 years follow-up the absolute difference between groups for overall survival (52.4 vs 46.1% still alive at 15 years after randomisation) was similar to that for recurrence-free survival. This represents an average of 6.3 (SD 2.3) fewer deaths per 100 women treated in all the trials. Again, although the proportional reduction in mortality was about the same in the earlier as in the later years, most of the absolute difference in overall survival appeared during the first 5 years. When these recurrence-free and survival analyses were further subdivided, no material differences between the benefits at ages under 40 or 40-49 were apparent (data not shown).

POSSIBLE INFLUENCE OF CYTOTOXIC CHEMOTHERAPY

Analyses were subdivided by whether or not women in both treatment groups were to receive routine cytotoxic chemotherapy. The proportional improvement in recurrence-free survival among women aged under 50 at randomisation was 25% (SD 7) in the absence of chemotherapy but only 10% (9) in its presence (p=NS).

Similarly, the proportional improvement in survival was 24% (7) in the absence but only 8% (10) in the presence of chemotherapy. Again the number of deaths were too small to assess any such modifications of the size of the survival effects reliably.

In the trials of ovarian ablation in the absence of routine chemotherapy, only 20 (2%) of the 1169 women aged under 50 were classified as postmenopausal at randomisation. Hence, if the analyses are restricted to premenopausal women only (according to the definition used in each trial), the findings are virtually unchanged, with ovarian ablation producing a proportional improvement in recurrence-free survival of 27% (7) in the absence of chemotherapy.

POSSIBLE INFLUENCE OF NODAL STATUS IN TRIALS WITHOUT CYTOTOXIC CHEMOTHERAPY

The indirect comparisons between the size of benefit in the absence and in the presence of cytotoxic chemotherapy are strongly confounded by nodal status, and vice versa. Almost all of the node-negative women (473 of 502) aged under 50 were entered into ovarian ablation trials in the absence of chemotherapy, whereas almost all of the women in the trials in the presence of chemotherapy (904 of 933) were node-positive. Hence, the relevance of nodal status can be assessed only in the ovarian ablation trials in which chemotherapy was not routinely given. As would be expected, the 473 women classified as node-negative (either by axillary clearance or just by axillary sampling) had a better prognosis than the remaining 696 women classified as node-positive (or of unknown nodal status). Because the number of women

studied was not large, the separate effects of ovarian ablation in node-positive and node-negative women cannot be estimated reliably. But, whether or not nodes were involved, ovarian ablation in the absence of chemotherapy was associated with significant improvements in recurrence-free survival and in overall survival. The proportional risk reductions for node-positive and for node-negative women were similar, but the absolute risk reduction was non-significantly greater for node-positive women (figure not reproduced). Most of the patients in these trials were randomised before 1970, and most survivors have been followed up to beyond 1990, so there is information beyond year 15. Even during this late period, the annual death rates, taking all women together, remained lower among those who had been allocated ablation (2.6% [SD 0.3]) than among the controls (3.9% [0.5]). This observation provides some reassurance against the later emergence of any substantial hazards.

ER STATUS IN TRIALS WITH CYTOTOXIC CHEMOTHERAPY

ER measurements on the primary tumour were available for most women aged under 50 at entry in four of the five trials in which both randomised groups received chemotherapy, but not for any women in trials of ovarian ablation in the absence of chemotherapy. Among the 194 women with “ER poor” primary tumours, there was no apparent difference between ablation plus chemotherapy versus chemotherapy alone, either in recurrence-free survival (logrank O-E 0.3, variance 26.9, not significant) or in overall survival (logrank O-E 1.9, variance 24.0, no significant). Among the 550 women with “ER-positive” primary tumours, however, ablation plus chemotherapy appeared to be more effective than chemotherapy alone, both for recurrence-free survival (logrank OE -9.5, variance 67.0, odds reduction 13% [SD 11]) and for overall survival (logrank O-E -9.2, variance 50.5, odds reduction 17% [SD 13]), but these differences were not statistically significant.

CAUSE SPECIFIC MORTALITY

Most studies were able to supply some cause-specific mortality information. Among women aged under 50 at randomisation who died without a distant recurrence of their breast cancer being recorded, 116 were classified as having died of non-breast-cancer causes. After allowance has been made (EBCTCG 1995) for those allocated ablation surviving longer, and therefore being at more prolonged risk of death from other causes, there was no significant difference between the treatment groups in vascular deaths (22/929 ablation vs 20/824 controls in trials with data, logrank OE -1.6, variance 9.5, not significant), in other non-breast-cancer deaths (44/929 vs 30/824, logrank O-E -0.2, variance 16.5, not significant) or in all non-breast-cancer deaths.

CONTRALATERAL BREAST CANCER

The suppression of ovarian function might be expected to reduce the incidence of contralateral breast cancer. But, even in the aggregate of all

available trials, there was not enough information to confirm or refute this suggestion (30 contralateral breast cancers as first event among 712 women allocated ablation vs 32 among 679 controls in trials with data, logrank O-E - 2.8, variance 15.1, not significant).

WOMEN AGED 50 OR ABOVE AT ENTRY

Because ovarian function is generally substantially less at older than at younger ages, any effects of ovarian ablation might be expected to be much less. Of the 1354 women aged 50 or above when randomised, 1018 were reported to have died and a further 48 to have had a distant or local recurrence. Despite these large numbers of events, there was no significant difference between the treatment groups in recurrence-free survival or in overall survival. By year 15 after randomisation there were 3.1 (SD 2.6) fewer recurrences or deaths per 100 women allocated ovarian ablation (32.0 vs 28.9% alive with no history of local or distant recurrence, logrank O-E -17.6, variance 225.9, not significant) and 2.5 (SD 2.7) fewer deaths per 100 (36.9 vs 34.5% alive, logrank O-E -8.9, variance 223.8, not significant).

General comments

This review was first published in the Lancet (EBCTCG 1996) and has been reproduced with the permission of the journal.

Review does not report adverse effects of ovarian ablation, which are noted as considerable under 'Implications for practice' and 'Implications for research'.

Only studies of ovarian ablation by surgery or RT were included in the analyses because data in 4 trials of LHRH agonists were immature at the time of publication.

Literature search strategy: not reported. References provided to EBCTCG publications which describe trial identification procedures.

Being a Cochrane Review, this systematic review has passed a quality assessment by the Cochrane Collaboration. However based on this document alone it is not possible to see precisely how the primary studies were identified, nor to relate included studies to subsequently published papers, which may provide more recent data.

Statistical methods described.

Citation
Early Breast Cancer Trialists' Collaborative Group . Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365[9472], 1687-1717. 2005.
Design
Systematic review of RCTs and meta-analysis of individual patient data. Country of origin: various Evidence grade: 1+
Inclusion criteria
All randomised trials of chemotherapy and hormone therapy in patients with early breast cancer that had started by 1995 (trial data for ovarian ablation by surgery or RT or suppression with LHRH agonists cited here).
Exclusion criteria
Not reported.
Population
N=4317; N=7601 for different analyses.
Interventions
Ovarian ablation by surgery or RT (in women of age <50 years) or ovarian suppression with LHRH agonists versus no adjuvant ovarian treatment, or as a randomised addition to chemotherapy (CT).
Outcomes
Recurrence (defined as the first reappearance of breast cancer at any site, and so includes second primary breast cancers and local or distant recurrences of the original cancer)
Breast cancer mortality
Follow up
5-year outcomes for ablation alone. 15-year outcomes for ablation/LHRH agonists combined

Results

1. Ovarian ablation by RT or oophorectomy (excludes LHRH agonists); mean follow-up 8 years

Table: recurrence/woman-years: ratio of recurrence events (ablation: control)

Category	Ratio (ablation:control)	SE	95% Confidence interval		2p value
			LWR	UPR	
Ovarian ablation (Chi square 7.7; p=0.05)					
OA versus nil					
Age <40	0.70	0.17	0.37	1.03	
Age 40-49	0.67	0.08	0.51	0.83	
OA + CT versus CT					
Age <40	0.96	0.11	0.74	1.18	
Age 40-49	0.90	0.08	0.74	1.06	
Total	0.83	0.05	0.73	0.93	0.0005

Table: breast cancer mortality/women: ratio of annual death rates (ablation: control)

Category	Ratio (ablation:control)	SE	95% Confidence interval		2p value
			LWR	UPR	
Ovarian ablation (Chi square 10.6; p=0.01)					
OA versus nil					
Age <40	0.71	0.16	0.40	1.02	
Age 40-49	0.68	0.09	0.50	0.86	
OA + CT versus CT					
Age <40	1.04	0.13	0.79	1.29	
Age 40-49	0.98	0.09	0.80	1.16	
Total	0.86	0.05	0.76	0.96	0.01

2. Ovarian ablation by RT or oophorectomy or suppression with LHRH agonists in women with ER: positive or ER: unknown tumours; 15-year

outcomes, n=7601, entry age <50

Recurrence:

Ablation or suppression: 47.3%

Control: 51.6%

Logrank 2p=0.00001

Breast cancer mortality:

Ablation or suppression: 40.3%

Control: 43.5%

Logrank 2p=0.004

General comments

Data for ovarian suppression by LHRH agonists are more up to date in the meta-analysis by Cuzick et al. 2007.

Data identification strategy:

This study uses data that are centrally collated by the EBCTCG from every woman in all randomised trials of the treatment of early breast cancer that had, at the time of the analysis, already been running for at least 5 years. The present report is of the final results from the year 2000 EBCTCG meta-analyses of the trials of systemic adjuvant treatments (chemotherapy, endocrine therapy, or chemoendocrine therapy) that had begun in or before 1995. The preliminary analyses were presented and discussed at a meeting in September, 2000, of the trial investigators. Since then, the data have been extensively checked for internal consistency and completeness and amended or updated through correspondence with the relevant trialists.

Meta-analysis was by a non-fixed effect method; analyses were by intention-to-treat. The Chi square and associated p values indicate some heterogeneity in results.

Citation
Sharma, Hamilton & Beith . LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane database of systematic reviews [3]. 2007. Chichester (UK), John Wiley & Sons, Ltd.
Design
Systematic review of RCTs Country of origin: Various. Evidence grade: 1++
Inclusion criteria
Randomised controlled trials of LHRH agonists (Buserelin, Goserelin, Leuprolide, Nafarelin and Triptorelin). Premenopausal women with a histological diagnosis of early breast cancer. Early breast cancer is defined as operable breast cancer (TNM stage 1 and stage 2) and premenopausal is defined as women less than 50 years of age.
INCLUDED STUDIES
13 RCTs were included, which address the role of LHRH agonists in the adjuvant treatment of pre-menopausal women with ER+ early breast cancer as follows:
1. Integration into adjuvant hormonal therapy
<ul style="list-style-type: none"> • three trials compared an LHRH agonist versus tamoxifen (Norwegian Study, ZBCSG Trial B, ZIPP) • three trials compared an LHRH agonist versus combined LHRH agonist and tamoxifen (ECOG 5188 INT-0101, ZBCSG Trial B, ZIPP) • two trials compared combined LHRH agonist and tamoxifen versus tamoxifen (ZBCSG Trial B, ZIPP)
2. Integration into adjuvant chemo-hormonal therapy
<ul style="list-style-type: none"> • three trials compared an LHRH agonist versus CMF chemotherapy (IBCSG VIII, TABLE, ZEBRA) • no trials comparing LHRH agonists to other chemotherapeutic regimens were identified • two trials compared combined LHRH agonist and tamoxifen versus CMF chemotherapy (ABCSG 5, GROCTA 02) and one trial compared combined LHRH agonist and tamoxifen versus an anthracycline-based chemotherapy regimen (FASG 06) • one trial compared an LHRH agonist versus chemotherapy followed by

an LHRH agonist (IBCSG VIII)

- five trials compared chemotherapy versus chemotherapy followed by an LHRH agonist (ECOG 5188 INT-0101, GABG IV-B-93, IBCSG VIII, Pretoria, ZIPP)
- three trials compared chemotherapy versus chemotherapy followed by combined LHRH agonist and tamoxifen (ECOG 5188 INT-0101, MAM 01 GOCSI, ZIPP)

3. Comparison with ovarian ablation by surgery or radiotherapy

- no trials were identified comparing an LHRH agonist versus surgical or radiotherapeutic ovarian ablation in the adjuvant setting.

METHODOLOGICAL QUALITY OF STUDIES

Study	Global quality rating	Allocation concealment rating
Norwegian Study	B1	A
ZBCSG Trial B	Not assigned	B
ZIPP	A	A
ECOG 5188 INT-0101	Not assigned	B
IBCSG VIII	A	A
TABLE	A	B
ZEBRA	A	A
ABCSG 5	B1	B
GROCTA 02	B1	A
FASG 06	Not assigned	B
GABG IV-B-93	Not assigned	B
Pretoria	Not assigned	B
MAM 01 GOCSI	A	A

Exclusion criteria

Women with locally advanced or metastatic disease.

Population

N=11,000

Interventions

Aims: to review randomised trials that test the use of LHRH agonists in adjuvant therapy for women with early breast cancer.

The specific objectives of the review are:

1. to make the following comparisons:

- a.any LHRH agonist versus any LHRH agonist plus tamoxifen
- b.any LHRH agonist versus CMF (or other chemotherapy)
- c.any LHRH agonist versus ovarian ablation
- d.any LHRH agonist versus any LHRH agonist plus chemotherapy

2. To describe the best available evidence on the optimum duration of LHRH treatment

3. To discuss the long term impact of amenorrhoea

4. To discuss:

- a.restoration of fertility following ovarian suppression
- b.HER-2+ ER+ disease
- c.women with familial breast cancer syndromes (not cited here)

Outcomes

1. Overall survival (time from date randomised to date of death due to any cause)
2. Disease-free survival (time from date randomised to first recurrence or death)
3. Quality of life
4. Toxicity

Follow up

Reported for 3 trials as follows:

- ZEBRA: median 72 months
- IBCSG VIII: median 84 months
- MAM-01: median 72 months

Results

Reviewers' conclusions

For premenopausal women with early breast cancer who are not known to be ER-, the use of an LHRH agonist, with or without tamoxifen as adjuvant therapy is likely to lead to a reduction in the risk of a recurrence and a delay in death. If the treatment decision is a choice between the use of an LHRH agonist and chemotherapy, the evidence in this review suggests that recurrence free survival and overall survival will be similar following both treatments for ER+ women, but with fewer or less severe adverse effects from the LHRH agonist. However, for ER- women, chemotherapy is likely to lead to a reduction in the risk of recurrence and a delay in death compared to an LHRH agonist. The LHRH agonist for which there is most evidence is

goserelin, given as a 3.6mg depot subcutaneously every 28 days for a couple of years.

1. Integration of LHRH agonists into adjuvant hormonal therapy (4 trials, n≈5000)

Summary: Taken together, the trials point to reductions in recurrence and death for premenopausal women who take goserelin combined with tamoxifen compared to either drug alone, as adjuvant treatment for breast cancer, but longer follow-up of the women is needed to estimate any benefits more reliably. Insufficient data have been presented to date for a meta-analysis that would inform reliably a choice between either tamoxifen or goserelin as sole adjuvant therapy.

a) LHRH agonist versus tamoxifen

- ZIPP trial (2x2 factorial design): the proportion of patients who experienced at least one side effect was 56% among patients allocated goserelin alone and 41% among patients receiving tamoxifen alone. The most common side effect was hot flushes (26% versus 17%). The only other side effect reported by more than 10 patients in either group was weight gain (4% versus 7%).
- Norwegian trial: After a median follow up of 88 months, patients randomised to goserelin had a non-statistically significantly higher risk of recurrence than those allocated to tamoxifen (RR: 1.10, 95% CI 0.81 to 1.48, P=0.56) and of death (RR: 1.16, 95% CI 0.80 to 1.69, P=0.42).
- ZBCSG Trial B: there was a non-statistically significant improvement in recurrence free survival for patients allocated goserelin (HR: 0.87, 95% CI 0.47-1.63) while, based on four deaths, overall survival was non-statistically significantly worse (HR: 2.10, 95% CI 0.38 to 11.49).

b) LHRH agonist versus LHRH agonist and tamoxifen

- ZIPP trial (2x2 factorial design): after a median follow up of 66 months, patients randomised to tamoxifen (which includes those randomised to no goserelin) had significantly better event free survival (HR: 0.79, 95% CI 0.68 to 0.92) and non-significantly better overall survival (HR: 0.83, 95% CI 0.68 to 1.02) compared to those randomised to no tamoxifen. Side effects were experienced by 56% of patients allocated goserelin alone and by 65% of patients allocated goserelin and tamoxifen. The most common side effect was hot flushes (26% versus 44%), followed by weight gain (4% versus 11%).
- ECOG 5188 INT-0101: after a median follow up of 115 months, recurrence free survival was statistically significantly better for patients randomised to tamoxifen in addition to chemotherapy and goserelin (68%) versus chemotherapy and goserelin alone (60%) (HR: 0.73, P<0.01). Overall survival was non-statistically significantly better (76% versus 73%, HR: 0.91, P=0.21).

- ZBCSG Trial B: no data

c) Tamoxifen and LHRH agonist versus tamoxifen

- ZIPP trial (2x2 factorial design): After a median follow up of 66 months, patients randomised to goserelin had significantly better recurrence free survival (73%) and overall survival (86%) than those allocated to no goserelin (68% and 83%, respectively). These correspond to a hazard ratio of 0.80 (95% CI 0.69 to 0.82, P=0.002) for recurrence free survival and 0.81 (95% CI 0.67 to 0.99, p=0.038) for overall survival. These overall effects of goserelin versus no goserelin were reported to be similar in women who received tamoxifen, either electively or by randomisation. Subgroup analyses have also been reported on the basis of ER status, with benefits for goserelin compared to no goserelin in recurrence free survival and overall survival for women in each of the three subgroups (ER-, ER+ or ER-unknown). However, these subgroup analyses are much less powerful than the overall results, most are non-significant and there is insufficient evidence from the ZIPP trial to assess differences in effect among ER subgroups in the presence of tamoxifen. The proportion of patients who experienced at least one side effect in the ZIPP trial was 65% among patients randomised to tamoxifen and goserelin and 41% among patients allocated to tamoxifen alone. The most common side effects were hot flushes (44% versus 17%) and weight gain (11% versus 7%).
- ZBCSG Trial B: No data.

2. Integration of LHRH agonists into adjuvant chemo-hormonal therapy

a) LHRH agonists with or without tamoxifen versus chemotherapy

Summary: Taken together, these trials show that LHRH agonists, with or without adjuvant tamoxifen, are as effective as chemotherapy for premenopausal women with ER+ tumours, in terms of recurrence free survival and overall survival. The trials also show that the hormonal therapy has fewer distressing side effects than the forms of chemotherapy assessed in these trials.

i) LHRH versus chemotherapy

- ZEBRA Trial: At a median follow-up of 72 months, patients randomised to goserelin had significantly worse recurrence free survival (55.2%) than those allocated to chemotherapy (60.0%) (HR: 1.18, 95% CI 1.02 to 1.37, P=0.029), and worse overall survival (HR: 1.21, 95% CI 0.99 to 1.49, P=0.067). However, a highly significant interaction was found between treatment and ER status (P=0.0016 for recurrence free survival). Patients who were ER+ had similar recurrence free survival and overall survival in both treatment groups (HR for recurrence free survival for goserelin versus CMF: 1.01, 95% CI 0.84 to 1.20, P=0.94;

HR for overall survival: 0.99, 95% CI 0.76 to 1.28, $P=0.92$) with the worse outcome for goserelin treated patients being due to the effect in the ER- patients (HR for recurrence free survival: 1.76, 95% CI 1.27 to 2.44, $P=0.0006$; HR for overall survival: 1.77, 95% CI 1.19 to 2.63, $P=0.0043$) and ER-unknown patients (HR for recurrence free survival: 2.00, 95% CI 1.07 to 3.75, $P=0.026$; HR for overall survival: 1.81, 95% CI 0.81 to 4.05, $P=0.14$). After six months of treatment in ZEBRA, amenorrhoea was more common in patients treated with goserelin (95%) than with chemotherapy (59%). However, after three years, 23% of patients who had received goserelin remained amenorrhoeic compared with 77% of patients treated with chemotherapy. The incidence of adverse reactions, including menopausal side effects, hot flushes, vaginal discharge and vaginal soreness, was similar in both groups (in total, goserelin: 42.6%; chemotherapy: 48.0%). These side effects tended to resolve within a year after stopping goserelin but persisted in the chemotherapy group for the 30 months under investigation. A special assessment of quality of life was done in 86 of the 102 centres, involving 1010 of the randomized patients. Early benefits were noted during months 3 to 6 of treatment for women in the goserelin group. However, at 1, 2 and 3 years, there were no significant differences between the two treatment groups.

- IBCSG VIII trial: CMF alone versus CMF followed by goserelin versus goserelin alone. At a median follow-up of 84 months, there were no significant differences between the treatment groups in disease free survival or overall survival. The five-year disease free survival was 79% (95% CI 75% to 84%) for goserelin alone and 82% (95% CI 78% to 86%) for chemotherapy alone. In the comparison of goserelin versus chemotherapy, the relative risk for disease free survival was 1.13 (95% CI 0.83 to 1.53, $P=0.44$). However, an interaction was found between treatment and ER status. ER+ patients in both the goserelin group and the chemotherapy group had similar disease free survival (5-year DFS: 81%, 95% CI 76% to 87% in both groups; RR: 0.97, 95% CI 0.66 to 1.42, $P=0.86$). In contrast, ER- patients had worse disease free recurrence in the goserelin group (73%, 95% CI 64% to 81%) compared to the chemotherapy group (84%, 95% CI 77% to 91%) (RR: 1.52, 95% CI 0.89 to 2.58, $P=0.12$). Toxicities of grade 3 or worse were experienced by 4.7% of patients allocated to goserelin alone (mostly weight gain) and by 18.8% of patients during chemotherapy (mostly leucopenia, neutropenia and nausea or vomiting).
- IBCSG VIII trial: At 36 months follow-up, amenorrhoea was induced in 90% of patients under 40 years of age within three months of starting goserelin and continued until the end of goserelin treatment, when menses resumed in almost all women. Amenorrhoea happened more slowly among younger women allocated to chemotherapy, being observed in 50% of these patients by the end of six cycles of CMF. Menses resumed in 15% of the patients in the chemotherapy alone

group but amenorrhea continued for 35-40% of women in this group throughout the three years of observation. Among women aged 40 years or older, amenorrhoea was induced in more than 90% of patients within three months of starting goserelin, continued until the end of goserelin treatment, and menses resumed in about half the women. Amenorrhoea due to chemotherapy was observed sooner than among the younger women, affecting 80-90% of these patients by the end of six cycles of CMF, nearly all of whom remained amenorrhoeac throughout the three years of observation. Patients in the goserelin alone group showed a marked improvement or less deterioration in various quality of life indicators during the first six months than those allocated chemotherapy. There were no differences at 36 months, apart from in hot flashes which were more problematic for women in the chemotherapy alone group than the goserelin alone group.

- TABLE study (patients who were not known to be ER or ER+ patients): No significant differences were found between the treatments on either recurrence-free survival or overall survival. The 2-year disease free survival was 59.1% for women allocated leuprorelin, compared to 45.3% for women allocated chemotherapy. All women in the leuprorelin group became amenorrhoeic during treatment, compared to 90.4% of women treated with chemotherapy. The most common adverse events were low-grade hot flushes, weight gain and increased sweating among the leuprorelin patients and alopecia, nausea and vomiting among the chemotherapy patients. The overall assessment of tolerability by patients was markedly better after three and six months of treatment in the leuprorelin group, but there was no significant difference between the two groups at two years.

ii) LHRH and tamoxifen versus chemotherapy

- ABCSG 5 Trial (most women ER+): after a median follow up of 60 months, patients randomised to goserelin and tamoxifen had significantly better recurrence free survival (81%) than those allocated to chemotherapy (76%) ($P=0.037$). Overall survival was non-significantly better in the hormonal therapy group (92%) than the chemotherapy group (90%) ($P=0.195$). Hot flushes were the main side effect for patients in the goserelin and tamoxifen group: 91% of patients experienced at least one. The side effects of chemotherapy were typical of CMF: nausea (81%), alopecia (55%) and hot flushes (54%).
- GROCTA 02 trial (mostly ER+ women; for one third of the women in the hormonal therapy group, ovarian ablation was achieved by surgery or radiotherapy, instead of goserelin): After a median follow up of 76 months, there were no significant differences in recurrence free survival (HR: 0.94, 95% CI 0.60 to 1.47, $P=0.80$) or overall survival (HR: 0.69, 95% CI 0.36 to 1.33, $P=0.30$) between patients randomised to goserelin and tamoxifen versus those randomised to chemotherapy. This is based on a total of 82 relapses and 39 deaths. All women

treated with goserelin became amenorrhoeic during treatment, but menses returned in 20% within six months of stopping therapy. In the chemotherapy group, 68% of women became amenorrhoeic during treatment and remained so even after the treatment stopped. Hot flushes were the main side effect for patients in the goserelin and tamoxifen group (experienced by approximately 60% of patients) compared to nausea (70%), leukopenia (40%) and alopecia (40%) in the chemotherapy group.

- FASG 06 trial (women with hormone responsive breast cancer): after a median follow up of 54 months, recurrence free survival was 91.7% in the hormonal therapy group and 80.9% in the chemotherapy group. This difference is non-significant ($P=0.12$). The difference was also non-significant for overall survival ($P=0.18$) being 97.0% and 92.9%, respectively. All women treated with triptorelin became amenorrhoeic during treatment compared to 41.5% in the chemotherapy group.

b) LHRH agonists with or without tamoxifen in addition to chemotherapy

Summary: Taken together, these trials point to reductions in recurrence and death for premenopausal women with ER+ tumours who take LHRH agonists, with or without tamoxifen, in addition to chemotherapy as adjuvant treatment for breast cancer.

i) LHRH versus Chemotherapy and LHRH agonist

- IBCSG VIII Trial (2/3 women ER+): The five-year disease free survival was 87% (95% CI 83% to 91%) for chemotherapy followed by goserelin and 79% (95% CI 75% to 84%) for goserelin alone. The relative risk for chemotherapy followed by goserelin versus goserelin alone was 0.71 (95% CI 0.52 to 0.99, $P=0.04$). However, as noted above, an interaction was found between treatment and ER status. ER- patients appeared to derive much more benefit from the combination of chemotherapy and goserelin than ER+ patients. Among ER- patients, the disease free recurrence was 88% (95% CI 82% to 94%) in the chemotherapy and goserelin group compared to 73% (95% CI 64% to 81%) in the goserelin alone group (RR: 0.49, 95% CI 0.28 to 0.87, $P=0.01$). Whereas, among ER+ patients, the disease free survival was 86% (95% CI 82% to 91%) in the chemotherapy and goserelin group versus 81% (95% CI 76% to 87%) in the goserelin alone group (RR: 0.86, 95% CI 0.56 to 1.26, $P=0.40$).
- IBCSG VIII: At 36 months follow-up, amenorrhoea was induced in 90% of patients under 40 years of age within three months of starting goserelin and continued until the end of goserelin treatment, when menses resumed in almost all women. Amenorrhoea happened more slowly among younger women during chemotherapy, being observed in 50% of these patients by the end of six cycles of CMF, and increasing to 90% within a few months of starting goserelin. Menses resumed in many women when they stopped goserelin but were still absent for 35-

40% of women in this group at month 36. Among women aged 40 years or older, amenorrhoea was induced in more than 90% of patients within three months of starting goserelin, continued until the end of goserelin treatment, and menses resumed in about half the women. Amenorrhoea due to chemotherapy was observed sooner than among the younger women, affecting 80-90% of these patients by the end of six cycles of CMF, increasing to nearly all women after the first couple of months of goserelin, almost all of whom remained amenorrhoeac at month 36. Patients in the goserelin alone group showed a marked improvement or less deterioration in various quality of life indicators during the first six months than those receiving chemotherapy but there were no differences in quality of life at 36 months between the groups allocated chemotherapy followed by goserelin versus goserelin alone.

ii) Chemotherapy and LHRH agonist versus chemotherapy

- ZIPP Trial: After a median follow up of 66 months, the primary analyses of goserelin versus no goserelin (regardless of the presence or absence of chemotherapy) showed that patients randomised to goserelin had significantly better recurrence free survival (73%) and overall survival (86%) than those allocated to no goserelin (68% and 83%, respectively). These correspond to a hazard ratio of 0.80 (95% CI 0.69 to 0.82, $P=0.002$) for recurrence free survival and 0.81 (95% CI 0.67 to 0.99, $P=0.038$) for overall survival. Exploratory analyses of interactions between the effects of goserelin, the use of chemotherapy and ER status found an apparent improvement in recurrence free survival in ER+ patients in the presence of chemotherapy (0.83, 95% CI 0.62 to 1.10) and a worsening in ER- patients in the presence of chemotherapy (1.19, 95% CI 0.83 to 1.71). However, these subgroup results are not significantly heterogeneous and do not provide sufficient evidence to support or refute true differences in effect between these subgroups.
- ECOG 5188 INT-0101 (premenopausal women who had node positive breast cancer and were ER+); goserelin and tamoxifen versus goserelin versus no hormonal therapy: after a median follow up of 115 months, patients randomised to the addition of goserelin to chemotherapy had non-significantly better recurrence free survival (60%) than those allocated chemotherapy alone (57%) (HR: 0.93 $p=0.25$) and non-significantly better overall survival (73% versus 70%, HR: 0.88, $P=0.14$).
- The IBCSG VIII trial (CMF alone versus CMF followed by goserelin versus goserelin alone): at a median follow-up of 84 months, there were no significant differences between the treatment groups in disease free survival or overall survival. The five-year disease free survival was 82% (95% CI 78-86) for chemotherapy alone, and 87% (95% CI 83-91) for chemotherapy followed by goserelin. In the comparison of the combination of chemotherapy and goserelin versus

chemotherapy, the relative risk for disease free survival was 0.80 (95% CI 0.57-1.11, $p=0.17$). This was similar in both the ER+ and ER- subgroups (RR: 0.80, 95% CI 0.54-1.19, $p=0.26$; and RR: 0.75, 95% CI 0.40-1.39; $p=0.35$, respectively). Among women under 40 years of age at diagnosis, amenorrhoea occurred gradually during the six months of chemotherapy, reaching 50% in both the chemotherapy alone and the chemotherapy to be followed by goserelin group after the six cycles. Among the former, menses resumed in 15% of the patients but amenorrhoea continued for 35-40% of women in this group throughout the three years of observation. Among the women who received goserelin after their chemotherapy, 90% of the group were amenorrhoeac after a few months of this drug. Menses resumed in many women when they stopped goserelin but were still absent for 35-40% of women in this group at month 36. Among women aged 40 years or older, amenorrhoea due to chemotherapy was observed sooner than among the younger women, affecting 80-90% of these patients by the end of six cycles of CMF. Among the older women who started goserelin after six months of chemotherapy, nearly all of them were amenorrhoeac after the first couple of months of goserelin, almost all of the group remained so at month 36. Quality of life was similar for patients in both groups through the first six months (when, of course, all were receiving chemotherapy) and at 36 months.

- GABG-IV-B-93 trial (60% of the 776 women in the trial were ER-): 5-year event free survival (all patients) was 71.3% (95% CI 66.3% to 76.3%) in the chemotherapy and goserelin group compared to 67.6% (95% CI 62.2% to 73.0%) in the chemotherapy alone group. This is equivalent to a hazard ratio of 0.92 (95% CI 0.70 to 1.21, $P>0.5$).
- Pretoria trial (premenopausal women; CMF versus CMF followed by depo-buserelin): the differences between the treatments on disease free survival and overall survival are non-significant in this relatively small trial, with a disease free interval of 6.8 years for women in the combination therapy group compared to 6.2 years for women in the chemotherapy alone group.

iii) Chemotherapy and LHRH agonist and tamoxifen versus chemotherapy

- ZIPP trial: no acceptable data due to non-randomised comparisons.
- ECOG 5188 INT-0101 trial (premenopausal women who had node positive breast cancer and were ER+); goserelin and tamoxifen versus goserelin versus no hormonal therapy: after a median follow up of 115 months, patients randomised to the addition of goserelin and tamoxifen to chemotherapy had better recurrence free survival (68%) than those allocated chemotherapy alone (57%) and better overall survival (76% versus 70%). However, the associated hazard ratios and significance tests for this comparison have not been published.
- MAM 01 GOCSI (chemotherapy plus goserelin and tamoxifen versus

chemotherapy alone): after a median follow-up of 72 months, the estimated probability of being disease free at five years was significantly higher for the chemotherapy, goserelin and tamoxifen group (64%), compared to the chemotherapy alone group (53%), corresponding to a hazard ratio of 0.74 (95% CI 0.56 to 0.99, P=0.04). The benefits appeared greater for women with ER+/ER-unknown tumours (HR: 0.73) than for women with ER- tumours (HR: 0.89) but the interaction between treatment effect and ER status was not significant. The estimated 5-year overall survival was 82% for the chemo-hormonal therapy group, and 80% for the women who were allocated to chemotherapy alone (HR: 0.84, 95% CI 0.54 to 1.32).

iv) LHRH versus ovarian ablation by surgery or radiotherapy

No trials were identified comparing an LHRH agonist versus ovarian ablation by surgery or radiotherapy in the adjuvant setting.

General comments

A. Literature search strategy:

The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group was searched. Studies coded as "early breast cancer" and "endocrine therapy" were extracted for consideration. In addition, the reference lists of related literature reviews and the list of reports of trials maintained by the Early Breast Cancer Trialists' Collaborative Group were checked. Handsearches were performed of the proceedings of the annual meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium in 2005 and 2006.

B. Assessing trials for eligibility

The eligibility criteria were applied to each potentially eligible trial identified. In the first instance, trial publications were used to assess each trial's eligibility. If a trial had not been published, the necessary information was sought from the trial protocol or from the principal investigator of the trial.

C. Quality Control

Two reviewers independently assessed each potentially eligible trial for inclusion in the review and quality. A third reviewer resolved any differences of opinion regarding eligibility or quality.

D. Data extraction and Analysis

A single reviewer extracted data describing the trial and patients' baseline characteristics. Two independent reviewers extracted data on outcomes (including follow-up times). The most complete dataset feasible was assembled from the published reports of the trials. Results of included studies have not been combined in a meta-analysis because this was not judged appropriate or possible. Instead results are presented according to their primary papers.

E. Assessing the Methodological Quality of the Included Studies

Two independent reviewers appraised the design and conduct of each trial to assess its susceptibility to bias. Methodological quality was assessed using a modified subset of the Methods for Evaluating Research and Guideline Evidence (MERGE) criteria (Liddle 1996). The following aspects of each trial were considered:

- a. concealment of treatment allocation
- b. generation of the allocation sequence
- c. comparability between groups at the baseline
- d. inclusion of all randomised participants in the analysis
- e. withdrawals from the trial
- f. valid assessment of endpoints.

A global quality score was assigned to each trial:

A: all or most the evaluation criteria from the MERGE checklist are fulfilled.

Where evaluation criteria are not fulfilled, the conclusions of the study are thought very unlikely to alter.

B1: some evaluation criteria from the MERGE checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought unlikely to alter.

B2: some evaluation criteria from the MERGE checklist are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought likely to alter.

C: few or no evaluation criteria are fulfilled. Where evaluation criteria are not fulfilled or are not adequately described, the conclusions of the study are thought very likely to alter.

Where the two reviewers differed in their quality assessment, arbitration from a third reviewer was sought.

Randomised controlled trials

Citation
Groenvold, Fayers, Petersen & Mouridsen . Chemotherapy versus ovarian ablation as adjuvant therapy for breast cancer: impact on health-related quality of life in a randomized trial 5. Breast cancer research and treatment. 98[3], 275-284. 2006.
Design
Randomised controlled trial Country of origin: Denmark, UK, Norway Evidence grade: 1-
Inclusion criteria
<p>Aim: to provide a detailed comparison of the impact of CMF chemotherapy versus ovarian ablation by oophorectomy on health-related quality of life during the 2 years following randomization.</p> <p>Participants: premenopausal women with primary, histologically proven estrogen or progesterone receptor positive breast cancer. All patients had axillary lymph node metastases and/or tumours larger than 50 mm.</p> <p>Accrual period for the entire RCT: January 1990-May 1998</p> <p>The quality of life sub-study was opened June 1, 1991 and included the patients randomized in the DBCG 89-b trial in Denmark until a predefined number of approximately 300 patients was reached. Inclusion was stopped February 6, 1996 when 317 patients had been included; follow-up was continued till 1998.</p>
Exclusion criteria
<ul style="list-style-type: none">• Patients with evidence of distant metastases• Patients with prior or concomitant malignant disease• Patients whose disease recurred within the study period (i.e. the first 2 years after randomization).• Patients who did not fill in all the 6 questionnaires• Eligible patients for whom no data was collected due to administrative errors (n=23)• Eligible patients who selected the other treatment to the one to which they were randomised (i.e. non-intention-to-treat).
Population
N=196
Interventions

Patients underwent lumpectomy or mastectomy, both with axillary dissection. Patients were randomly assigned to one of two adjuvant therapies:

1. CMF Chemotherapy (n=87): (nine cycles of intravenous cyclophosphamide, methotrexate, fluoracil given every 3 weeks for approximately 6 months)
2. Ovarian ablation (n=109): achieved by ovarian radiation in 107 of 109 patients (pelvic irradiation with a total dose of 15 Gy given as 5 daily fractions or in 2 cases, surgical oophorectomy. Ablation was performed 3–5 weeks after randomization)

Outcomes

QOL outcomes were assessed by questionnaire by mail 1 month after randomization. If the patient filled in the questionnaire booklet, identical booklets were sent to the patient 3, 5, 9, 15, and 24 months after randomization.

For women in the ovarian ablation group, the first assessment at 1 month approximately corresponds to the completion of their treatment. For women in the chemotherapy group the first three assessments (1, 3, and 5 months after randomization) reflect the treatment period.

The questionnaire consisted of 69 items, including:

- EORTC QLQ-C30 for use in cancer clinical trials: The Danish EORTC QLQC30 was validated in two studies.
- Hospital Anxiety and Depression Scale (HADS).
- DBCG 89: developed for this study to cover issues identified as relevant but not included in the two standard questionnaires, including physical symptoms and social outcomes.

Follow up

Outcomes reported until 2 years from randomisation.

Results

1. Functional and symptom-related aspects of QOL: Based upon EORTC QLQ-C30 mean scores at 1, 3, 5, 9, 15 and 24 months from randomisation

NB: Mean scores are not shown. Direction of effect is shown as either ND; p=NS: 'No difference; p value not statistically significant ($p > 0.05$)' or for statistically significant differences between arms: FA: 'favours ablation' or FCT: 'favours chemotherapy'.

Questionnaire item	Direction of effect (p value)					
	month 1	month 3	month 5	month 9	month 15	month 24
Physical	ND;	ND;	ND;	ND;	ND;	ND;

function	p=NS	p=NS	p=NS	p=NS	p=NS	p=NS
Role function	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Emotional function	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Cognitive function	FA; p<0.01	FA; p<0.01	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Social function	ND; p=NS	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Global health/QOL	FA; p<0.01	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Fatigue	ND; p=NS	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Nausea and vomiting	FA; p<0.01	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Pain	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Dyspnoea	ND; p=NS	ND; p=NS	FA; p<0.05	ND; p=NS	ND; p=NS	ND; p=NS
Sleep	FA; p<0.05	ND; p=NS	FA; p<0.01	ND; p=NS	ND; p=NS	ND; p=NS
Loss of appetite	FA; p<0.05	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Constipation	FA; p<0.001	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Diarrhoea	FCT; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Financial difficulties	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS

2. Physical symptoms outcomes (DBCG 89) and Hospital Anxiety and Depression Scale (HADS)

NB: Mean scores aren't shown. Direction of effect is shown as either ND; p=NS: 'No difference; p value not statistically significant (p>0.05)' or for statistically significant differences between arms: FA: 'favours ablation' or FCT: 'favours chemotherapy'.

Questionnaire item	Direction of effect (p value)					
	month 1	month 3	month 5	month 9	month 15	month 24
Sore mouth	FA; p<0.001	FA; p<0.001	FA; p<0.001	ND; p=NS	ND; p=NS	FA; p<0.01
Hot	ND;	FCT;	FCT;	FCT;	ND;	ND;

flushes/sweats	p=NS	p<0.001	p<0.001	p<0.001	p=NS	p=NS
Anticipatory nausea	FA; p<0.01	FA; p<0.001	FA; p<0.001	FA; p<0.01	FA; p<0.05	FA; p<0.01
Satisfaction with appearance	ND; p=NS	ND; p=NS	FCT; p<0.01	ND; p=NS	ND; p=NS	ND; p=NS
Energy	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Regular bleedings	ND; p=NS	FA; p<0.001	FA; p<0.001	FA; p<0.001	FA; p<0.001	FA; p<0.01
Bleedings	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	FA; p<0.001	FA; p<0.001
Urinary incontinence	ND; p=NS	ND; p=NS	FA; p<0.01	ND; p=NS	ND; p=NS	ND; p=NS
Weight gain >2kg	ND; p=NS	ND; p=NS	FA; p<0.05	FA; p<0.05	ND; p=NS	ND; p=NS
Hair loss	FA; p<0.001	FA; p<0.001	FA; p<0.001	FA; p<0.001	FA; p<0.001	ND; p=NS
Wear wig	ND; p=NS	FA; p<0.05	FA; p<0.001	ND; p=NS	ND; p=NS	ND; p=NS
Sexual interest	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Had sex in last month	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Vaginal dryness	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Vaginal discharge	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Employed	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
Full time job	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
HAD: anxiety	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS	ND; p=NS
HAD: depression	ND; p=NS	FA; p<0.05	FA; p<0.05	ND; p=NS	ND; p=NS	ND; p=NS

General comments

Limitations in applicability: results are based upon patients who were recurrence-free throughout the 2 years and those who returned all six questionnaires (with possible selection biases).

The paper uses the term oophorectomy inaccurately because it states that 107 of 109 patients in the ovarian ablation arm had ablation by RT.

The content of the questionnaire was validated as follows:

- literature review
- identification of potential issues to be included in the questionnaire
- validation of the selection of issues against patient interviews
- combination of standard questionnaires and ad hoc developed items
- pilot testing the combination of questionnaires

13 patients randomized to ovarian ablation and one patient randomized to chemotherapy did not receive the allocated treatment because they selected the other treatment. These patients were excluded (i.e. non-intention-to-treat) as the authors report that this would mean that the description of quality of life outcome of ovarian ablation would include patients receiving chemotherapy and vice versa.

Updated 2018

Citation
Brunt, Bliss, Benghiat, Dawson, Dewar, Harnett, Hopwood P, Lawrence & Trask . The impact on quality of life of adding chemotherapy (CT) or ovarian suppression (OS) to adjuvant tamoxifen (TAM): Outcomes from the UK NCRI Adjuvant Breast Cancer (ABC) trial [abstract] 34. Annual Meeting Proceedings of the American Society of Clinical Oncology , 729. 2004.
Design
Randomised controlled trial: QOL outcomes from a sub-study within the UK NCRI ABC trial (cited from ASCO meeting abstract) Country of origin: UK, Malta, New Zealand and countries in the Middle East and Asia. Evidence grade: 1-
Inclusion criteria
Aim: the ABC Trial evaluates whether adjuvant chemotherapy and/or ovarian suppression add to the benefits of prolonged (5 years) tamoxifen for women with early breast cancer. Women with early breast cancer were recruited between the years 1993 and 2000.
Exclusion criteria
Not reported.
Population
N=436 (247 in +/-CT comparison, 199 in +/-ovarian suppression comparison). Median age 49 (range 28-79).
Interventions
Patients were randomly allocated to two treatment plans as follows: <ol style="list-style-type: none"> 1. Pre/peri-menopausal women: CT and/or ovarian suppression versus none (where all patients receive tamoxifen) 2. Post-menopausal women: CT versus none (where all patients receive tamoxifen) <p>In the Quality of life (QOL) sub-study, patients reported QOL using the EORTC QLQ-C30, BR23 breast cancer module, Hospital Anxiety and Depression Scale (HADS) and Menopausal Symptom Scale (MSS), before randomisation and at 3, 6, 9, 18, 30, 48 and 72 months.</p>
Outcomes
QOL outcomes including systemic and menopausal symptoms, mood, sexual functioning, body image, role functioning and global QOL.
Follow up
Available from accrual period (1993-2006) to 2006 i.e. minimum 6 years.

Results

The addition of CT was associated with worse QOL during the first 9 months for depression ($p=0.007$), role function ($p=0.003$) and global QOL ($p=0.001$) and a trend to worse QOL for body image concerns ($p=0.02$), and sexual enjoyment ($p=0.08$). Systemic side effects ($p=0.001$) and menopausal problems ($p=0.02$) were worse over 30 months.

The addition of ovarian suppression resulted in increased menopausal symptoms ($p<0.0001$), depression ($p=0.05$) and anxiety ($p=0.04$) over 30 months but no deterioration in role function, global QOL, body image or sexual function.

Authors' conclusions: adverse QOL counters the potential benefits of additional CT; therefore treatment choice should consider possible health gains and QOL losses. The negative QOL effect of OS is paralleled by a lack of clinical benefit in the ABC trial.

General comments

Although this trial was identified by the team that compile the EBCTCG dataset, the EBCTCG list of trials indicates that data are unavailable, so citing this report is useful (See Appendix; EBCTCG codes 93A3, 93A4 and 93A6).

Compliance with QL forms was high; 99.8% at baseline ranging to 86.3% at 30 months.

Updated 2018

Citation
Celio, Buzzoni, Longarini, Gattinoni, Prtale, Denaro, Oriana S & Bajetta . Surgical oophorectomy (Ovx) and tamoxifen (T) versus chemotherapy (FEC) and T in premenopausal, node-positive breast cancer 31. Annals of Oncology 13[Suppl 5], 37. 2002.
Design
Randomised controlled trial (Abstract) Country of origin: Italy Evidence grade: 1-
Inclusion criteria
Aim: to measure the clinical benefit of complete oestrogen blockade compared to anthracycline-containing chemotherapy (CT) in premenopausal patients with early-stage breast cancer.
Exclusion criteria
Amenorrhoea lasting more than 1 year or cardiac dysfunction.
Population
N=109 women with invasive, receptor positive (ER or PR), node-positive breast cancer. Median age was 48 (37-57) years. Of all patients, 76% had fewer than 4 positive axillary nodes, and 80% had both ER+ and PR+ tumours.
Interventions
Patients (patients) were randomised to receive either A) surgical oophorectomy and Tamoxifen 20 mg/d for 5 years (n=54) B) 6 cycles of FEC (5FU 750 mg/m ² , epirubicin 75 mg/m ² , Cyclophosphamide 500 mg/m ²) every three weeks and T for 5 years (n=55). Local radiotherapy was mandatory in case of breast conservation. In the two arms, 58% of patients underwent breast-conserving surgery.
Outcomes
Recurrence and mortality (crude rates)
Follow up
Median 68 (55-81) months
Results
Tolerability and side effects of chemotherapy All patients in the CT arm completed all cycles, but only 46 patients received more than 95% of the total planned dose. Grade 3-4 neutropenia occurred in 12% of patients, and 75% of normally menstruating patients experienced

amenorrhea persisting after CT.

With a median follow-up of 68 (55-81) months, we observed 10 (18%) vs. 4 (7%) recurrences and 6 (11%) vs. 3 (5%) deaths in the A and B arms, respectively.

Authors' conclusions: After a median follow-up of six years, the very low number of events suggests good clinical benefit with both treatments. Large randomized trials are needed for final recommendations regarding the relative worth of either treatment modality in the premenopausal adjuvant setting.

General comments

The unexpected poor accrual resulted in the study being stopped prematurely in 1997. No statistical analysis performed, presumably due to small sample size. Unlikely to add value in the light of the cited systematic reviews.

Updated 2018

Citation
<p>Love, Nguyen, Nguyen, Nguyen & Havighurst . Symptoms associated with oophorectomy and tamoxifen treatment for breast cancer in premenopausal Vietnamese women 32. Breast cancer research and treatment. 58[3], 281-286. 1999.</p> <p>Love, Duc, Allred, Binh, Dinh, Kha, Thuan, Mohsin SK, Roanh, Khang, Tran, Quy, Thuy, Thé, Cau, Tung, Huong, Quang, Hien, Thuong, Shen, Xin, Zhang, Havighurst TC, Yang, Hillner & Demets . Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer 16. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 20[10], 2559-2566. 2002.</p>
Design
<p>Randomised controlled trial Country of origin: Vietnam, China Evidence grade: 1+</p>
Inclusion criteria
<p>Aim: to evaluate disease-free and overall survival in Vietnamese women with early operable breast cancer following adjuvant oophorectomy and tamoxifen versus observation, with oophorectomy and tamoxifen given at the onset of metastatic disease.</p> <p>Premenopausal women with operable breast cancer; T\geq2cm; Stage I-IIIa with a treatment plan of mastectomy.</p>
Exclusion criteria
<p>Distant metastasis; post-menopausal status.</p>
Population
<p>N=709 [n=482 for the sub-study on side effects]</p>
Interventions
<p>All patients underwent mastectomy and axillary node clearance.</p> <p>Patients were randomised as follows:</p> <p>Intervention arm (n=356): underwent oophorectomy under the same anaesthetic as that for mastectomy (2 patients underwent ovarian ablation by RT), and then five years of tamoxifen.</p> <p>Observation arm (n=353): did not receive oophorectomy or tamoxifen and were observed, with oophorectomy and tamoxifen initiated if metastatic disease was subsequently detected.</p>

In either arm adjuvant chest wall RT was permitted; 50Gy in 2Gy/day fractions, with axillary RT given in node-positive cases.

Outcomes

Disease-free survival

Overall survival

Side effects of treatment (At each of these visits, physicians asked each about 10 symptoms and completed a one-page symptom questionnaire, which inquired about, listed, and described specific grades of toxicity to note if present. The specific symptoms were edema, nausea, pruritus vulvae, hot flashes frequency and intensity, vaginal bleeding, discharge and dry ness, depression, skin rash, and changes in mood [with irritable, sad spells] frequency and intensity).

Follow up

Patients were seen at 3-month intervals for 3 years, then 6-monthly.

Median follow-up 3.6 years

Results

Treatment received

124/353 = 35.1% of women in the observation group experienced disease recurrence

Actual treatment received was as follows:

Treatment	Intervention group (n=356)	Observation group (n=124 with recurrence)
Oophorectomy plus tamoxifen	93%	23%
Tamoxifen alone	3.9%	52%
Oophorectomy alone	-	1%
Neither oophorectomy not tamoxifen	3.1%	19%
Unknown	-	5%
Total	100%	100%

Recurrence and survival

In an itention-to-treat analysis at a median 3.6 years follow-up, disease-free survival ($p=0.0003$) and overall survival ($p=0.0477$) were higher in the intervention group compared to the control group. Disease-free survival estimated at 5 years by Kaplan-Meier analysis was 75% in the intervention group and 58% in the observation group.

Considering only the ER positive subgroup at a median 3.6 years follow-up,

disease-free survival ($p=0.001$) and overall survival ($p=0.01$) were higher in the intervention group compared to the control group.

Considering only the ER negative subgroup at a median 3.6 years follow-up, there was no statistically significant difference in disease-free survival or overall survival between the intervention group and the control group.

Side effects reported in the first 12 months (subgroup: first 482 randomised subjects)

Symptom	Randomised arm	Hot flash grade					p value
		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	
Hot flash frequency	Observation	220 (91)	20 (18)	3 (1)	0 (0)	0 (0)	0.001
	Oophorectomy + Tamoxifen	54 (23)	79 (33)	101 (42)	1 (0.4)	4 (1.7)	
Hot flash intensity		Hot flash intensity scale (#/day)					
		0 (None)	1-2 (Warm)	3-5 (Sweating)	6-9 (Damp clothes)	≥10 (Wet clothes)	
	Observation	220 (91)	22 (9)	1 (0.4)	0 (0)	0 (0)	0.001
Oophorectomy + Tamoxifen	54 (23)	138 (58)	41 (17)	2 (0.8)	4 (1.7)		
Vaginal discharge	Observation	230 (95)	8 (3)	3 (1)	2 (1)	0 (0)	0.001
	Oophorectomy + Tamoxifen	205 (89)	16 (7)	7 (3)	11 (5)	0 (0)	
Genital pruritus	Observation	237 (98)	2 (1)	4 (2)	0 (0)	0 (0)	0.02
	Oophorectomy + Tamoxifen	219 (92)	12 (5)	8 (3)	0 (0)	0 (0)	

Hot flash frequency and intensity over 3 years

Hot flash outcome	Time point (months)	Grade 1				Grade 2				Observation cases with toxicity (who were treated with intervention)	p
		Intervention		Observation		Intervention		Observation			
		%	n	%	n	%	n	%	n	n	
Frequency	3	27	61	4	9	31	71	0	1	0	0.0001
	6	33	69	3	6	20	42	0	0	0	0.0001
	12	26	46	5	8	3	6	1	1	4	0.0001
	18	13	18	4	6	3	4	0	0	3	0.025
	24	13	16	3	4	1	1	3	3	6	0.019
	30	18	17	7	6	2	2	0	0	5	0.07
	36	22	16	3	2	1	1	0	0	2	0.017
Intensity	3	52	118	4	9	7	16	0	1	-	0.0001
	6	52	108	3	6	2	4	0	0	-	0.0001
	12	25	44	5	8	4	7	1	1	-	0.0001
	18	13	18	3	4	3	5	1	1	-	0.012
	24	11	14	4	5	3	4	2	2	-	0.059
	30	14	14	6	5	3	3	1	1	-	0.0063
	36	18	13	3	2	5	4	0	0	-	0.0008

Narrative to support tabulated side effects data

Only three of the symptoms enquired about – hot flashes, vaginal discharge, and genital pruritus – were found in the first 12 months to be more frequent in women

treated with adjuvant oophorectomy and tamoxifen.

During the first 12 months 77% of women randomised to oophorectomy/tamoxifen versus 9% of those randomised to observation had some hot flash toxicity, and 44% of those randomised to treatment reported toxicity in numbers of hot flashes of grade 2 or more (3–5 hot flashes per day or more) as compared to 1% of women randomised to observation. Hot flashes of intensity to produce sweating occurred in 20% of treated women versus less than 1% of observation subjects. Vaginal discharge and genital pruritus were about twice as common in tamoxifen-treated patients, and these two side effects were significantly associated ($p < 0.0001$).

An excess of vasomotor symptoms persisted in treated women over three years of follow-up although by that time only 23% of treated women had these symptoms, and the majority of these were of grade 1 intensity. While over time small numbers of observation group patients developed recurrent disease and received oophorectomy and tamoxifen treatment and developed associated symptoms, these events do not significantly alter the pattern or the strength of the association of vasomotor symptoms and initial oophorectomy tamoxifen therapy over time.

No women who began tamoxifen and who have not had recurrence have stopped tamoxifen because of toxicity.

General comments

The study design permits the risk that some patients with tumours ≥ 2 cm in size that are found subsequently to be benign, undergo oophorectomy.

Randomisation achieved by sealed envelope, using permuted block design; stratified for nodal status and tumour size. Where patients were found on review to belong within a different randomisation strata, the assigned treatment was continued (there were 35 such errors). Analysis was by intention-to-treat.

Compliance with randomised treatment is poor, especially in the observation arm in cases with recurrent disease.

8 patients received no primary treatment for their breast cancer. 23 patients were lost to follow-up (7 in intervention group, 34 patients had no evidence of invasive disease on pathology review (12 in observation group; $p = 0.08$).

Study sample size/power calculation performed, which indicated a sample size of 700.

The only statistically significant differences in patient-tumour variables at study outset are:

Pathological tumour size:

Intervention: 3.22 cm
Observation: 3.37 cm; $p=0.0091$

ER positive (%)

Intervention: 55.7

Observation: 67.95; $p=0.012$ NB ER status was evaluated for 67% of all patients.

Data on side effects were missing for 1, 1, 2, 2, 3, 4, and 6 subjects at the 3, 6, 12, 18, 24, 30, and 36-month time points, respectively. The authors report that these missing data did not significantly influence the results presented.

Updated 2018

Citation
Nomura, Tsutsui, Murakami & Takenaka . [A randomized study of adjuvant treatments for operable breast cancer patients stratified by estrogen receptor and menopausal status]. [Japanese] 76. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 26[5], 643-649. 1999.
Design
Randomised controlled trial Country of origin: Japan Evidence grade: 1-
Inclusion criteria
Patients with operable breast cancer of stage I-IIIa between 1978 and 1991
Exclusion criteria
Not known
Population
N=1579 in the total trial; 789 for whom results are cited (i.e. premenopausal patients)
Interventions
All patients underwent mastectomy and were randomly allocated to the following strategies according to their ER status and menopausal status: Premenopausal patients; ER positive: <ol style="list-style-type: none"> 1. Oophorectomy + Tamoxifen (n=154) 2. Chemotherapy (CT, mitomycin and cyclophosphamide) (n=157) 3. CT + Tamoxifen (n=151) Premenopausal patients; ER negative: <ol style="list-style-type: none"> 1. CT (n=165) 2. CT + Tamoxifen (n=162) Postmenopausal patients; ER positive: <ol style="list-style-type: none"> 1. Tamoxifen 2. CT 3. CT + Tamoxifen Postmenopausal patients; ER negative: <ol style="list-style-type: none"> 1. CT 2. CT + Tamoxifen Patients with unknown ER status:

1. CT
2. CT + Tamoxifen

Outcomes

Relapse-free survival
Overall survival

Follow up

Median 10 years

Results

At a median follow-up of 10 years in ER-positive, premenopausal patients there were no significant differences in relapse-free survival ($p=0.15$) or overall survival ($p=0.42$) among the oophorectomy + Tamoxifen, CT, and CT + Tamoxifen arms

At a median follow-up of 10 years ER-negative, premenopausal patients showed no significant differences in relapse-free survival ($p=0.97$) or overall survival ($p=0.85$) between CT and CT + Tamoxifen arms.

Table: recurrence and survival outcomes in premenopausal patients (separate randomisations for patients with ER+ tumours and for those with ER- tumours)

	Adjuvant therapy	Recurrence			Multiple cancer			Death		
		n/N	%	p	n/N	%	p	n/N	%	p
ER+	Chemotherapy	19/157	12	0.2	9/157	6	0.541	22/157	14	0.5
	Oophorectomy + Tamoxifen	31/154	20		5/154	3		28/154	18	
	Chemotherapy + Tamoxifen	24/151	16		6/151	4		21/151	14	
ER-	Chemotherapy	28/165	17	0.9	9/165	6	0.449	28/165	17	0.7
	Chemotherapy + Tamoxifen	27/162	17		6/162	4		25/162	15	

General comments

Most of the narrative is available only in Japanese language; data extracted from tables and figures with English language annotation.

Data are cited from two randomisation strategies; one for premenopausal patients with ER+ tumours and one for premenopausal patients with ER- tumours.

Graded as 1- as a cautious approach, because the reviewer is unable to read Japanese.

Citation
Thomson, Twelves, Mallon & Leake . Adjuvant ovarian ablation vs CMF chemotherapy in premenopausal breast cancer patients: Trial update and impact of immunohistochemical assessment of ER status 100. Breast 11[5], 419-429. 2002.
Design
Randomised controlled trial Country of origin: UK Evidence grade: 1+
Inclusion criteria
Patients with pathologically confirmed stage II breast cancer enrolled between March 1980 and May 1990.
Exclusion criteria
Not reported.
Population
N=332
Interventions
Patients were randomised to receive either ovarian ablation or CMF chemotherapy after undergoing mastectomy or conservation surgery: <ul style="list-style-type: none"> 1. Ovarian ablation (n=167) 2. CMF chemotherapy (n=165) <p>In addition, in a 2x2 factorial study design, patients were randomly allocated to either treatment with prednisolone or no prednisolone (no data cited).</p>
Outcomes
Overall survival (endpoint: death from any cause) Event-free survival (endpoint: death or recurrence: local, regional or distant; contralateral disease was included as distant recurrence)
New, non-breast cancer primary tumours were not included as events.
Kaplan–Meier analyses were used to plot survival curves, obtain survival point estimates and produce two-tailed log-rank statistical significance tests of equality of the survival curves. Cox’s proportional hazards models were fitted to obtain hazard ratios with 95% confidence intervals.
ER subgroup data are cited for 270 patients for whom ligand-binding assays were available (non-intention-to-treat). Numerous ER-based classifications were studied, outcome data are cited by ER subgroup as follows:

ER negative: <20 fmol/mg
 ER positive: ≥20fmol/mg

Follow up

Median 10.7 years (range: 0.5, 20.1)

Results

Overall survival: all randomised patients

Randomised arm	Deaths	HR: ablation:CMF	95% CI	p, log-rank test
Ovarian ablation	80	1.01	0.74-1.37	0.96
CMF chemotherapy	81			

Overall survival: ER positive patients (concentration ≥20fmol/mg)

Randomised arm	Deaths	HR: ablation:CMF	95% CI
Ovarian ablation	30	0.82	0.50-1.33
CMF chemotherapy	36		

Overall survival: ER negative patients (concentration <20fmol/mg)

Randomised arm	Deaths	HR: ablation:CMF	95% CI
Ovarian ablation	34	1.23	0.75-2.02
CMF chemotherapy	29		

Event-free survival: all randomised patients

Randomised arm	Events (death or recurrence)	HR: ablation:CMF	95% CI	p, log-rank test
Ovarian ablation	91	0.95	0.71-1.26	0.70
CMF chemotherapy	98			

Event-free survival: ER positive patients (concentration ≥20fmol/mg)

Randomised arm	Events (death or recurrence)	HR: ablation:CMF	95% CI
Ovarian ablation	37	0.77	0.50-1.19
CMF chemotherapy	47		

Event-free survival: ER negative patients (concentration <20fmol/mg)

Randomised arm	Events (death or recurrence)	HR: ablation:CMF	95% CI
Ovarian ablation	35	1.10	0.69-1.76
CMF chemotherapy	34		

General comments

Randomisation method: through a central office by telephone between March 1980 and May 1990 with treatment options allocated from computer-generated lists of random numbers.

The randomised groups did not differ appreciably in terms of most patient and tumour-related variables. Slightly more women whose tumours had an ER concentration of <20 fmol/mg were randomised to receive ovarian ablation than CMF (54/136 and 60/135, respectively).

Randomisation violations:
There were 43 patients (13%) who did not receive the systemic therapy to which they had been randomised. Of these women, two had CMF instead of ovarian ablation and six received ovarian ablation rather than CMF. Three further women received tamoxifen in place of CMF and three had it in place of ovarian ablation. Another 11 women randomised to CMF received no systemic treatment and 11 randomised to ovarian ablation had no systemic therapy. The remaining seven violations were in relation to the prednisolone randomisation.

Narrative in paper implies that not all patients gave informed consent prior to being accrued on this trial: "According to accepted practice at the start of the trial in 1980, the participating clinician made the decision whether to seek informed consent from each patient." Alternatively this could be interpreted as meaning that not all patients were considered for the trial, which may introduce a selection bias.

All analyses were performed according to the randomised intention to treat groups.

There was no interaction between the two treatment comparisons comprising the 2 by 2 design (P=0.26 for all deaths; Cox model).

Citation
Schmid, Untch, Kosse, Bondar, Vassiljev, Tarutinov, Lehmann, Maubach, Meurer, Wallwiener & Possinger . Leuprorelin acetate every-3-months depot versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant treatment in premenopausal patients with node-positive breast cancer: the TABLE study. Journal of Clinical Oncology 25[18], 2509-2515. 2007.
Design
Randomised controlled trial: TABLE study Country of origin: Germany, Ukraine Evidence grade: 1+
Inclusion criteria
Aim: to evaluate the efficacy and tolerability of the 3-monthly depot LHRH agonist leuprorelin acetate (LAD-3M) as adjuvant treatment of premenopausal patients with early, node-positive breast cancer. Participants were premenopausal women with histologically confirmed stage II or IIIA breast cancer, treated at 71 participating centers between September 1995 and November 1998. Patients had to have between one and nine involved axillary lymph nodes, with at least 10 lymph nodes being examined. Initially, patients were required to have ER-positive tumors or tumors with unknown ER status. In March 1998, an amendment was issued, requesting positive ER status for enrollment (ie, patients with unknown ER status were ineligible thereafter).
Exclusion criteria
Patients were ineligible if they had received ovarian ablation, adrenalectomy, or hypophysectomy. Further exclusion criteria included systemic treatment of cancer within 6 months before enrollment, hormone treatment (apart from contraceptives) within 2 weeks before entry, regular steroid therapy, endocrine abnormalities, severe concurrent medical conditions, and impaired renal function. Pregnant or lactating women were ineligible. Five patients in each treatment group did not receive the allocated study medication and were excluded from ITT and safety analysis. Accordingly, the ITT population and the safety population included 589 patients. Another 63 patients (LAD-3M, n=24; CMF, n=39) were excluded from the primary efficacy population because of premature termination of study treatment or relevant protocol violations. Thus, the primary efficacy population consisted of 526 patients: 270 patients randomly assigned to LAD-3M and 256 to CMF.
Population
N=589
Interventions

A total of 599 patients were randomly assigned to treatment within 6 weeks of surgery as follows:

1. LAD-3M(n=299): 2 years of treatment with the 3-monthly depot LHRH-agonist leuprorelin acetate
2. CMF(n=300): six cycles of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil

Outcomes

- Relapse-free survival (RFS)
- Overall survival (OS)
- Adverse events
- Oestrogen suppression
- Menstrual status
- Subjective state of health

Follow up

Median 5.8 years

Results

Treatment compliance

Treatment compliance was high in both arms. A total of 277 (94.2%) patients received at least two doses of LAD-3M, 255 patients (86.7%) received four doses, and 237 (80.6%) patients all eight doses of LAD-3M. The majority of patients without recurrence in the first 6 months completed all six cycles of CMF(93.2%). Cycles of CMF were delayed or dose reduced in 2% of courses.

Recurrence and survival

With a median follow-up of 5.8 years, there were 269 recurrences and 197 deaths. Sites of recurrence and types of events are as follows:

Sites of First Treatment Failure According to Treatment at Median Follow-Up of 5.8 Years (exploratory two-sided Fisher test)

Outcome	Total (n=589)	LAD-3M (n=294)		CMF (n=295)		p
		No.	%	No.	%	
Recurrence:	269	126	42.9	143	48.5	0.186
• Distant	156	73	24.8	83	28.1	0.401
• Local	35	26	8.8	9	3.1	0.003
• Unspecified	77	26	8.8	51	17.3	0.003
• Contralateral	11	6	2.0	5	1.7	0.772
• 2 nd malignancy	4	1	0.3	3	1.0	0.624
Deaths						

• Any cause	197	83	28.2	114	38.6	0.009
• Breast cancer-specific	189	82	27.9	107	36.3	0.034

There was no significant difference in RFS between LAD-3M and CMF. The ITT 5-year RFS rates were 63.9% for LAD-3M and 63.4% for CMF (HR, 1.03; P=0.83). Similar results were obtained for the PP analysis (HR, 1.02; P=0.88).

Exploratory survival analysis favored LAD-3M treatment over CMF (HR, 1.50; 95% CI, 1.13 to 1.99; P=0.005) with 5-year survival rates of 81.0% and 71.9%. Survival differences began to emerge after 2 years of follow-up. There was also a trend for a higher breast cancer-related mortality in the CMF group (CMF, 39.5%; LAD-3M, 28.9%; P=0.05).

Effects of Treatment on Menstrual Function

Amenorrhea was reported in 88% of LAD-3M patients by 6 months and more than 95% during the remaining 2-year treatment period, compared with 43.9% of CMF patients after 6-months of chemotherapy and 62.1% at 2 years. The onset of amenorrhea was earlier in the LAD-3M group (mean, 22±38 days) compared to the CMF group (mean, 110±151 days).

Amenorrhea was reversible within 1 year of stopping LAD-3M in 45% of patients. In patients treated with CMF, the rate of amenorrhea steadily increased from 51.5% after 1 year to 62.1% after 2 years and 72.7% after 5 years. Further analysis by age showed that more than 90% of patients younger than 40 years at trial entry had normal menstrual function 1 year after the completion of therapy, compared with approximately 70% of patients between 40 and 45 years and 40% of patients older than 45 years.

Tolerability

Adverse effects were generally of low or moderate intensity. Symptoms of estrogen suppression such as hot flashes and increased sweating were more common in patients treated with LAD-3M, whereas acute adverse effects of chemotherapy such as nausea, vomiting, diarrhea, asthenia, and alopecia were reported more frequently in patients treated with CMF:

Incidence of adverse effects during the first 2 years (%)

Adverse effect	LAD-3M (n=294)		CMF (n=295)		p
	All grades	Grade 3/4	All grades	Grade 3/4	
Nausea/vomiting	11.6	0.3	69.8	21.0	<0.01
Mucositis	2.4	0	11.2	1.0	<0.01

Diarrhoea	4.4	1.4	12.9	7.8	<0.01
Infection	13.5	2.7	10.5	1.7	0.26
Fatigue	44.6	1.4	67.1	3.1	<0.01
Hot flushes	83.7	16.3	49.5	6.8	<0.01
Oedema	16.7	2.0	10.2	0.7	0.02
Alopecia	9.5	1.0	43.1	5.4	<0.01

The overall self assessment of tolerability by the patients showed markedly better results for LAD-3M during the first 6 months. At 6 months, 16.0% and 56.8% of patients in the LAD-3M group rated the treatment tolerability as “very good” or “good,” respectively, compared with 15.6% and 37.3% in the CMF group. After the end of chemotherapy, assessments improved markedly in the CMF group. At 2 years, self-assessments of tolerability were comparable in both arms.

General comments

This RCT is included in the Cochrane systematic review by Sharma et al. 2007, but this subsequently published paper provides longer follow-up data (5-year outcomes versus 2-year outcomes).

Patients were randomly assigned in a 1:1 ratio to one of the two treatment groups using a stratified random permuted block design (block size 4). Random assignment was performed centrally according to the order in which information on potential patients was received by fax. Patients were stratified by study center.

There were no significant differences between the groups with respect to any characteristic.

Blinding to, and concealment of allocation not feasible: open label study.

Scale used for self assessment of tolerability is not fully reported.

<p>Kaufmann, M., Graf, E., Jonat, W., Eiermann, W., Vescia, S., Geberth, M., Conrad, B., Gademann, G., Albert, U. S., Loibl, S., von, M. G., Schumacher, M. & German Adjuvant Breast Cancer Study Group (2007) A randomised trial of goserelin versus control after adjuvant, risk-adapted chemotherapy in premenopausal patients with primary breast cancer - GABG-IV B-93. <i>European journal of cancer (Oxford, England : 1990)</i>, 43: 2351-2358.</p>
<p>Design: RCT, 1+ Country: Germany</p> <p>Aim: To investigate the effectiveness of goserelin compared to no further treatment, after risk-adapted chemotherapy in premenopausal patients with HR negative breast cancer.</p>
<p>Inclusion criteria Premenopausal women with histological diagnosis of breast cancer and either hormone receptor (HR)-negative (node-negative and node-positive) patients were included (stage pT1–3, N0–N3, M0; no prior surgical, systemic or radiation therapy for breast cancer; Karnofsky index P60). Patients were recruited from 66 centres all over Germany.</p>
<p>Exclusion criteria Major exclusion criteria were distant metastases, T4 tumours; incomplete surgical resection; resection of <10 axillary lymph nodes; simultaneous contralateral breast cancer; previous malignancy except basal cell carcinoma of the skin or carcinoma in situ of the cervix uteri; pregnancy or lactation and randomisation not within 28 days of definitive primary surgery.</p>
<p>Population 776 patients (pts) were randomised:</p> <ul style="list-style-type: none"> • 465 pts were HR-negative (241 in the control arm, 224 in the goserelin arm), • 311 pts were HR positive (151 in the control arm, 160 in goserelin arm). <ul style="list-style-type: none"> • HR-negative sub-population 32% of the pts were up to 40 years old and the majority (62%) were nodal negative. • Tumours were greater than 2 cm in largest diameter in 52% and histological grade 3 was found in 59% of the tumours in this subgroup. • Baseline characteristics were reported to be well balanced across both groups
<p>Interventions Goserelin (Zoladex® 3.6 mg subcutaneously every four weeks for two years) or no further treatment after a risk-adapted adjuvant chemotherapy.</p> <p>– Risk-adapted adjuvant chemotherapy = either three cycles of CMF (cyclophosphamide 500 mg/m², methotrexate 40 mg/m² and 5-fluorouracil 600 mg/m², IV day 1, 8, every 4 weeks) for patients with 0–3 positive lymph nodes or four cycles of EC (epirubicin 90 mg/m² and cyclophosphamide 600 mg/m², IV every 3 weeks) followed by three cycles CMF in patients with 4–9 positive lymph nodes.</p>
<p>Outcomes</p>

- The primary outcome: event free survival (EFS) - defined as time from definitive primary surgery to the first event of failure (locoregional recurrence, metastases, second primaries including contralateral breast cancer, or death). The first event of failure was classified as isolated locoregional recurrence if locoregional recurrence occurred at least 4 weeks before an event at a distant site.
- The treatment effect on EFS was estimated as the hazard ratio in a Cox model with a two-sided 95% CI. P-values were based on two-tailed Wald tests.
- The secondary outcome: overall survival (OS) - defined as the interval from definitive primary surgery to death of any cause.
- Tolerability and adverse events

Follow Up

- Follow-up examinations were scheduled every 3 months for the first 2 years, every 6 months up to year 5, and annually after this point.
- The median follow-up of 5.5 years (HR-negative) and 4 years (HR-positive). Completeness of follow-up was 88–90%. With regard to event-free survival, 215 events had been observed so far. 143 events occurred in HR-negative pts.

Results

Event Free Survival

For all pts 5-year EFS rates are estimated:

71% (95% CI, 66–76%) in the goserelin group

68% (95% CI, 62–73%) in the control group.

The unadjusted hazard ratio (HR) of goserelin versus control pooling HR-negative and HR-positive patients was 0.92 (95% CI, 0.70–1.21; calculated as 95.66% CI to account for two interim analyses; P = 0.54).

In HR-negative pts: adjusted HR (goserelin versus control) = 1.01 (CI, 0.72–1.42; P = 0.97).

In HR-positive pts: adjusted HR (goserelin versus control) = 0.77 (CI, 0.47–1.24; P = 0.27).

Overall survival

- 5-year OS rates of all pts are estimated as 86% in the goserelin group and 85% in the control group.
- 104 (13%) deaths observed up to time of report (authors' note - it is too early for any definite analysis of OS)

Tolerability and adverse events

Goserelin was discontinued for medical reasons (other than recurrence or death) in 24 pts.

In the control group:

Serious adverse events related to chemotherapy were reported in 17 pts (leucopenia/thrombopenia- 5, emesis/nausea- 2, seroma- 2, abscess- 2, and thrombophlebitis, hyponatremia, stomatitis, vitiligo, infection, fever 1, respectively).

In the goserelin group:

Serious adverse events related to therapy were reported in 14 pts:

- 6 during chemotherapy (wound healing disorders- 2, and emesis/nausea, paravasation, leucopenia, infection 1 respectively),
- 8 during or after goserelin treatment (psychiatric disorders 3, erysipelas 2, wound pain, endometrial hyperproliferation, mastopathy 1, respectively).

No patient died during study medication.

General comments

Overall, this study is underpowered for both the HR-negative and HR-positive population, the results do not indicate an advantage of additional goserelin after a risk-adapted chemotherapy with respect to EFS in HR-negative patients.

Technical Issues:

Randomisation reported, no allocation concealment reported and intention to treat analysis was conducted but not described clearly. A power calculation was conducted wrt event free survival (EFS). From prior research EFS would be 60% at five years in the control group. Therefore, 190 events would be required to detect a hazard ratio of 0.67 for goserelin versus control, i.e. an improvement to about 71% in the goserelin group, with a power of 80% using a two-sided log-rank test at the level $\alpha = 5\%$. With four years of planned recruitment and two years additional follow-up, at least 700 patients would have to be included.

Updated 2019

Love, R. R., Van, D. N., Quy, T. T., Linh, N. D., Tung, N. D., Shen, T. Z., Hade, E. M., Young, G. S. & Jarjoura, D. (2008) Survival after adjuvant oophorectomy and tamoxifen in operable breast cancer in premenopausal women. *Journal of Clinical Oncology*, 26: 253-257.

Design: RCT , 1+

Country: RCT (report of mature results from original study, Love et al 2002)

Aim: This study reports the mature results of the original study (which aimed to evaluate the effectiveness of oophorectomy and tamoxifen versus observation), and focuses on the differential effects of treatment by ER status.

Inclusion criteria

Premenopausal women with operable breast cancer; T \geq 2cm; Stage I-IIIa with a treatment plan of mastectomy.

Exclusion criteria

Distant metastasis; post-menopausal status

Population

N=709

Interventions

1. Intervention arm (n=356): underwent oophorectomy, and then five years of tamoxifen.

2. Observation arm (n=353): did not receive oophorectomy or tamoxifen and were observed (oophorectomy and tamoxifen were initiated if metastatic disease was subsequently detected)

- Details of patient recruitment and entry criteria have been previously published (Love et al 2002).
- This study reports data from an extended follow-up of patients.
- Patients were scheduled visits every 3 to 6 months for the first 5 years after random assignment, and annually thereafter.
- Tamoxifen was provided at each visit for the first 5 years. Extending the median follow-up time to 7.0 years, as compared with 3.6 years in the original report Love et al (2002).
- For patients without events, median follow-up was 7.9 years (first quartile, 6.6 years; third quartile, 9.5 years).

Outcomes

- Overall survival (OS) - calculated from the date of random assignment until the date of death from any cause
- Disease-free survival (DFS) time - measured from the date of random assignment until the date of disease recurrence or death before recurrence

Results

Disease free Survival and Overall Survival

- From the intent-to-treat analyses (using all registered cases), a significant difference in DFS and OS was found, which favoured the treatment group (log-rank test P values=

0.0003 and 0.0002, respectively.)

- 5-year DFS was 74% in adjuvant group and 61% in observation groups (95% CI for difference, 7% - 21%)
- 10-year DFS was 62% in adjuvant group and 51% in observation groups (95% CI for difference, 4% - 22%).
- 5-year OS rates were 78% in adjuvant group and 71% in observation groups (95% CI for difference, 1% - 21%)
- 10-year OS rates were 70% in adjuvant group and 52% in observation group (95% CI for difference, 6% - 34%).
- The DFS: HR (hazard ratio) for adjuvant versus observation groups = 0.65 (95% CI, 0.51 - 0.82)
- For OS : HR= 0.62 (95% CI, 0.48 - 0.80). (Based on a univariate Cox proportional hazards model)

ER status

For women with known estrogen receptor (ER) status (n = 470), the adjuvant treatment effect was more marked in ER+ women.

- A Cox proportional hazards model was designed which included the DFS outcome using treatment, ER status and the treatment by ER interaction as the predictors.
- Estimates from the model indicated that the treatment benefit decreased over time for ER+ patients.
- Using the model estimates and ER+/observation patients as the referent group, the hazard ratio for recurrence for ER+ patients undergoing treatment increased from 0.49 (95% CI, 0.31 to 0.75) at year 3 to 1.10 (95% CI, 0.58 to 2.06) at year 8.

DFS

- Kaplan-Meier survival curves showed that for ER+ women, the DFS probabilities for adjuvant-treatment patients were 83% at 5 years, 82% at 7 years, and 66% at 10 years; compared with 62%, 56%, and 50%, respectively, for the observed patients.

OS

- OS probabilities were 87% at 5 years, 84% at 7 years, and 80% at 10 years, for adjuvant treatment, compared with 76%, 65%, 51% in the observation group, respectively.
- When considering the significant ER status by treatment interaction, a smaller effect of treatment for ER- patients was not significant (P=0.46 for DFS and 0.29 for OS). The 95%CI for the hazard ratio comparing treatment and observation among ER patients for DFS = 0.56 to 1.29 (authors claim that this CI is not narrow enough to rule out a clinically important effect of treatment in this subgroup.)

General comments

Author's conclusions:

In premenopausal women with operable breast cancer not selected for estrogen receptor status or with oestrogen receptor-positive tumors, 5- and 10-year DFS and OS rates are significantly improved following adjuvant oophorectomy and tamoxifen.

5.2.1 What is the role of aromatase inhibitors (AIs) as adjuvant therapy in post-menopausal women with hormone receptor positive breast cancer?

5.2.2 Which subgroups of post menopausal breast cancer patients should receive Aromatase Inhibitors as adjuvant therapy?

There are several high quality RCTS and systematic reviews of RCTS that report the role of aromatase inhibitors (AIs) as adjuvant therapy in post-menopausal women with hormone receptor positive breast cancer.

Anastrozole

Disease free survival is significantly increased with anastrozole compared to tamoxifen either as first line adjuvant treatment or after tamoxifen. Prior chemotherapy (CMF, anthracyclines or taxanes) reduces the disease free survival advantage of anastrozole (Boccardo *et al.* 2005; Buzdar *et al.* 2006; Buzdar and Cuzick 2006; Dowsett *et al.* 2005; Forbes *et al.* 2008; Hind *et al.* 2007; Howell *et al.* 2005; Jakesz *et al.* 2005; Kaufmann *et al.* 2007). For hormone receptor positive patients DFS favoured the anastrozole group and in the hormone receptor negative subgroup there was no difference (Forbes *et al.* 2008).

There is no difference in overall survival either as first adjuvant treatment or after tamoxifen (Boccardo *et al.* 2005; Buzdar *et al.* 2006; Dowsett *et al.* 2005; Forbes *et al.* 2008; Hind *et al.* 2007; Howell *et al.* 2005; Jakesz *et al.* 2005). However in contrast, Kaufmann *et al.* (2007) showed a significant improvement in survival for patients in the anastrozole group when the benefits of switching to anastrozole after 2 years of tamoxifen treatment were compared with continuing on tamoxifen for 5 years.

The risk of disease recurrence is significantly reduced with anastrozole and is reported to be independent of nodal status, tumour size or prior chemotherapy. All ER positive patients showed a benefit but there was no statistical difference between the progesterone receptor (PR) positive or PR negative subgroup (Boccardo *et al.* 2005; Buzdar *et al.* 2006; Dowsett *et al.* 2005; Forbes *et al.* 2008; Hind *et al.* 2007; Howell *et al.* 2005; Jakesz *et al.* 2005; Kaufmann *et al.* 2007). When patients who were disease free at the end of receiving 5 years of adjuvant tamoxifen (with or without the aromatase inhibitor, amino-glutethimide, for the first 2 years of therapy) were randomly assigned to receive either 3 years of anastrozole or no further treatment; the disease free survival was statistically improved with significantly fewer recurrences. The risk of contralateral breast cancer is significantly reduced only if anastrozole is given as first line adjuvant treatment; it is not significantly different if given after Tamoxifen (Boccardo *et al.* 2005; Buzdar *et al.* 2006; Dowsett *et al.* 2005; Forbes *et al.* 2008; Hind *et al.* 2007; Howell *et al.* 2005; Jakesz *et al.* 2005; Kaufmann *et al.* 2007).

Time to progression was significantly increased for ER positive/PR negative tumours. The data for ER positive/PR positive tumours were significantly different from ER positive/PR negative tumours (non-overlapping confidence intervals). There is no statistical significant difference in the risk of distant disease. Forbes *et al.* (2008) and Kaufmann *et al.* (2007) both showed that statistically fewer patients on anastrozole experienced distant disease recurrence.

There were statistically significant adverse events, with a significant increased in risk of bone fracture with anastrozole compared to tamoxifen. However women treated with tamoxifen were at significantly increased risk of endometrial cancer, deep venous and venous thromboembolic events and ischaemic cerebrovascular events compared to anastrozole.

Letrozole

The BIG 1-98 trial (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008) compared letrozole versus tamoxifen in the initial adjuvant setting; and the MA-17 trial (Goss *et al.* 2005, 2007; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008) compared, letrozole versus placebo in the extended adjuvant setting following standard adjuvant treatment with tamoxifen. For monotherapy arm of the BIG 1 98 trial and the MA-17 trial, disease free survival was significantly improved with letrozole compared to tamoxifen for lymph node-positive tumours (Crivellari *et al.* 2008; Coates *et al.* 2007; Goss *et al.* 2005, 2007, 2008; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008).

When letrozole was compared to placebo disease free survival showed a significant improvement with letrozole. Over time (6 months to 4 years) the difference in the risk of progression significantly increased in the letrozole group compared to the placebo group. (Goss *et al.* 2005, 2007; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008). When patients in the placebo arm of the MA-17 trial were subsequently offered letrozole and then compared to those who did not take the letrozole (placebo arm), disease free survival was improved (Goss *et al.* 2008).

Overall survival was not statistically different between letrozole and tamoxifen (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008). Overall survival was not statistically different between letrozole and the placebo groups (Goss *et al.* 2005, 2007; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008). Over time any difference in risk (significant or not) disappears. When patients in the placebo arm of the MA-17 trial were subsequently offered letrozole and then compared to those who did not take the letrozole (placebo arm), the overall survival adjusted hazard ratio was 0.30 for the letrozole arm.

Risk of contralateral breast cancer did not report statistically significant results; letrozole vs tamoxifen: 0.4% vs 0.7% (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008). Risk of contralateral breast cancer when letrozole was compared to placebo showed no difference for time to recurrence (Goss *et al.* 2005, 2007; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008). There was a reduction in contralateral breast cancer in the letrozole arm of the Goss *et al.* (2008) trial.

There were fewer thromboembolic events with letrozole compared with tamoxifen but there was a significantly higher risk of bone fracture and some cardiac events with letrozole. (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008). The incidence of bone fractures, observed more often in the letrozole group, did not differ by age. In elderly patients, letrozole had a significantly higher incidence of any grade 3 to 5 non-fracture adverse event compared with tamoxifen. Incidence of bone fractures was higher among patients treated with letrozole. Differences were not significant for thromboembolic or cardiac adverse events (Crivellari *et al.* 2008)

There was a significantly higher incidence of osteoporosis but no difference in the fracture rate with letrozole compared to placebo. (Goss *et al.* 2005, 2007; Hind *et al.* 2007; Ingle *et al.* 2006; Muss *et al.* 2008). There were statistically significantly more self-reported new diagnoses of osteoporosis with letrozole compared with placebo. There were significantly more clinical fractures in the women who took letrozole and there was a non-significant difference in the number of cardiac events occurring between the groups. Thromboembolic events occurred rarely in both groups.(Goss *et al.* 2008).

The time to any disease recurrence was significantly decreased with letrozole compared to tamoxifen or placebo. (Crivellari 2008; Coates 2007; Goss 2005, 2007, 2008; Hind 2007; Ingle 2006; Muss 2008; Thurlimann 2005; Rasmussen 2008).

There was no significant difference between letrozole and tamoxifen with respect to quality of life (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005; Rasmussen *et al.* 2008).

When letrozole was compared to placebo; the disease free survival for ER positive/PR positive tumours was significantly increased with letrozole. For ER positive/PR negative tumours the reported data had very wide confidence intervals spanning the line of no effect as well as that of the ER positive/PR positive tumours (Goss *et al.* 2005; Muss *et al.* 2008). When letrozole was compared to placebo, lymph node-positive and lymph node-negative women had significantly improved disease free survival (Goss *et al.* 2005). Goss *et al.* (2007) demonstrated a significant benefit in disease free survival in this subgroup and significant benefits were also observed for distant disease-free survival and overall survival versus placebo. When letrozole was compared to tamoxifen the

lymph node-negative tumour data also had very wide confidence intervals which spanned a line of no effect as well as that for the lymph node-positive data (Crivellari *et al.* 2008; Coates *et al.* 2007; Hind *et al.* 2007; Thurlimann *et al.* 2005). These findings make it very difficult to interpret nodal status outcomes. Letrozole significantly improved disease free survival compared with placebo for both lymph node-negative and lymph node-positive patients younger than 60 years and for patients with negative nodes ≥ 70 years old (Muss *et al.* 2008). When letrozole was compared with placebo in lymph node positive patients the results indicated a significant improvement in distant disease free survival in those aged 60 to 69 years and a significant improvement in overall survival for those aged ≥ 70 years (Muss *et al.* 2008).

Exemestane

Disease free survival was significantly increased with exemestane compared with tamoxifen and nodal status did not affect outcome. (Coombes *et al.* 2004; 2007; Eisen *et al.* 2008; Hind *et al.* 2007).

Overall survival was not significantly different between exemestane or tamoxifen or between exemestane and placebo (Coombes *et al.* 2004; Eisen *et al.* 2008; Hind *et al.* 2007). A modest improvement in overall survival was reported for patients who switch to exemestane after 2–3 years on tamoxifen (Coombes *et al.* 2007).

There was a significant increase in bone fractures with exemestane (Coombes *et al.* 2004; Eisen *et al.* 2008; Hind *et al.* 2007).

The risk of contralateral breast cancer was significantly decreased with exemestane. Endocrine events decreased for all women with no difference between exemestane or tamoxifen. Disease free survival was significantly increased for women with ER positive histology regardless of PR status (Coombes *et al.* 2004; Hind *et al.* 2007). Significant improvements in overall survival were reported in the update Coombes (2007) study when receptor-negative patients were excluded. There is difficulty with interpretation of results in order to determine the outcomes for ER/PR status (Coombes *et al.* 2004; Hind *et al.* 2007).

A decision modelling exercise found that women with ER positive/ PR positive tumours gained more benefit from over 10 years by starting with tamoxifen then crossing over to an aromatase inhibitor whereas women with ER positive/ PR negative gained benefit from initial treatment with an aromatase inhibitor (Coombes *et al.* 2004; Hind *et al.* 2007).

PICO Tables:

What is the best timing/ sequencing of aromatase inhibitors and the duration of treatment as adjuvant therapy in post menopausal women with hormone receptor positive breast cancer?

Patients	Interventions	Comparisons	Outcomes
<p>Post menopausal patients with early invasive hormone receptor positive breast cancer who have completed definitive surgery</p> <p>ER, PR and HER2, individually and combined (ER+ alone, PR+ alone, Her2+ alone, ER+ with PR+/PR-/Her2+/Her2- /both PR+ & Her2+ and PR+ with ER- /Her2+/Her2-)?</p> <p>node – and + patients because node – can be high risk in other ways e.g. high grade, vascular invasion, HER2+</p> <p>Would not separate node +ve and –ve groups</p>	<p>Adjuvant therapy with:</p> <p>Arimidex</p> <p>Letrozole</p> <p>Exemestane</p>	<p>Tamoxifen</p> <p>Other Als</p> <p>Nil</p> <p>Chemotherapy</p> <p>Most comparisons will be with Tam or Als</p>	<p>Disease-free survival (DFS)</p> <p>Overall survival (OS)</p> <p>Contralateral breast cancer</p> <p>Quality of life (SE profile)</p> <p>Psychological morbidity</p> <p>Health Economics</p>

Which subgroups of post menopausal breast cancer patients should receive Als as adjuvant therapy?

Patients	Interventions	Comparisons	Outcomes
<p>Post menopausal patients with early invasive hormone receptor positive breast cancer ?who</p>	<p>Aromatase inhibitors:</p> <p>Arimidex</p> <p>Letrozole</p> <p>Exemestane</p>	<p>Nil</p> <p>Tamoxifen</p>	<p>Disease-free survival (DFS)</p> <p>Overall survival (OS)</p> <p>Contralateral</p>

have completed definitive surgery (Node + and -)			breast cancer Quality of life (SE profile) Psychological morbidity Health Economics
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Evidence Summary

The literature search was limited to papers published between 2005 and 2008. The content of evidence available was mainly primary RCTs and secondary analyses of data from these trials. The studies were directly relevant to postmenopausal women with early breast cancer and ER + status aged up to 80 years. Analyses were included in the review when conducted on women with PR+ and PR – status since emerging trial data suggests that PR status does not affect the performance of aromatase inhibitors (AIs). Findings from women who were ER negative were also included, where reported, for comparison.

Anastrozole

Event Free Survival (EFS) improved in the anastrozole group compared with tamoxifen in both RCTs of women with ER positive tumours (Boccardo *et al* 2005, ITA; Jakesz *et al* 2005, ARNO-95/ABCSG-8). The hazard ratio for time to recurrence of all breast cancer events was found to be significantly lower in the ER+/PR- subgroup than the ER+/PR+ subgroup from one analysis (Dowsett *et al* 2005, ATAC). Another subgroup analysis from a different trial found that the risk of recurrence did not depend on PR status (Jakesz *et al* 2005).

The ITA trial found that the benefit of anastrozole in preventing recurrence was independent of tumour size, grade, number of involved nodes and prior chemotherapy [HR 0.35 (0.18-0.69) p=0.002]. Whilst the ARNO-95/ABCSG-8 trial found the benefit of anastrozole was independent of nodal status, age at surgery, or progesterone receptor positivity. The benefit was greatest in the ER+/PR- subgroup (HR 0.42) than the ER+/PR+ subgroup (HR 0.66) although the difference between these two hazard ratios was not statistically significant from confidence intervals [ER+/PR+ HR 0.66 (0.46-0.93) p=0.017; ER+/PR- HR 0.42 (0.19-0.92) p=0.029].

Distant metastases free survival was improved (HR 0.49) for women taking anastrozole in the largely ER+ ITA trial. Contralateral breast cancer incidence was low in the two studies that reported this outcome (ITA trial 0.8%; 0.9%).

One small case series assessed joint symptoms experienced with anastrozole (Ohsako *et al.* 2005). Joint symptoms were more common in patients who had prior chemotherapy. Hormonal therapy did not influence joint symptoms.

Table 4.2.2.1 Outcomes from Anastrozole trials

Study	N patients	HR status	Outcomes		
ITA Boccardo <i>et al</i> 2005 Quality 1+	448	ER+ 397 89% ER- 2 <1% ERuk or missing 49 11% PR status not reported	EFS HR 0.35 (0.20-0.63) p=0.0002	Distant metastasis free survival HR 0.49 (0.22-1.05) p=0.06 Disease recurrence The benefit of anastrozole was independent of tumour size, grade, number of involved nodes and prior chemotherapy. HR 0.35 (0.18-0.69) p=0.002	Contralateral breast cancer Anastrozole n=1 Tamoxifen n=2
ATAC Dowsett <i>et al</i> 2005 Quality 1+	9366	ER+/PgR+ 5709 71% ER+/PgR- 1372 17%	Time to recurrence (all br ca events) ER+/PR+ HR 0.84 (0.69-1.02) p=0.07 ER+/PR- HR 0.43 (0.31-0.61) p<0.0001		
ARNO-95 and ABCSG-8 Jakesz <i>et al</i> 2005 Quality 1+	3224	ER+/PR+ 2519	EFS HR 0.60 (0.44–0.81) p=0.0009	Risk of recurrence Benefit of anastrozole not dependent on nodal status, age at surgery, or progesterone	Contralateral recurrences n=28/177 events (16%) Anastrozole n=12 Tamoxifen n=16

		78%		receptor positivity.	
		ER+/PR- 17%	564	ER+/PR+ HR 0.66 (0.46- 0.93) p=0.017	
				ER+/PR- HR 0.42 (0.19- 0.92) p=0.029	
HR = Hazard Ratio					
EFS = Event Free Survival					
ER = Estrogen Receptor					
PR = Progesterone Receptor					

Letrozole

Disease Free Survival (DFS) improved in the letrozole group compared to placebo or tamoxifen in two RCTs for women with ER+ tumours. The largest gains occurred in the placebo controlled trial compared with the tamoxifen controlled trial, and this was also reflected in subgroup analyses. The PR+ subgroup benefited the most compared with placebo in one trial (Goss *et al* 2007, MA.17); the benefit was similar in PR+ and PR- subgroups in another trial when compared with tamoxifen (Thurlimann *et al* 2005, BIG I-98). DFS in lymph node positive and negative patients improved over time compared with placebo in a trend analysis (Ingle *et al* 2006, MA.17). Both lymph node positive and negative patients on letrozole had improved DFS compared to placebo in one trial (Goss *et al* 2005). However this benefit in DFS was only observed in lymph node positive patients when compared with tamoxifen in another trial (Thurlimann *et al* 2005).

There was no improvement in Overall Survival (OS) over all patients when letrozole was compared with either placebo or tamoxifen. However OS was improved in a subgroup of ER+/PR+ women when compared to placebo (Goss *et al* 2007). This benefit was not observed in ER+/PR- women. Another subgroup analysis in the same trial found improved OS in lymph node positive women, but not in lymph node negative women (Goss *et al* 2005).

Time to any recurrence was significantly reduced with letrozole compared to tamoxifen in the BIG I-98 trial [HR 0.72]. Time to distant recurrence was also significantly reduced with letrozole in the BIG I-98 trial [HR 0.73 (0.60-0.88) *P* = 0.001]. Time to contralateral recurrence was not significant compared to placebo in the MA.17 trial [HR 0.63].

Table 4.2.2.2 Outcomes from Letrozole trials

Study	N patients	HR status	Outcomes		
			DFS	OS	Contralateral breast cancer
MA.17 Goss <i>et al</i> 2005 (1++) Goss <i>et al</i> 2007 (1+) Ingle <i>et al</i> 2006 (1+)	5148	ER+/PR+ (n=3809) 73.4% ER+/PR- (n=636) 12.3% (ER or PR) status: Positive 5035 (97.4%) Negative 8 (0.15%) Lymph node status: Positive 2360 (45.6%) Negative 2568 (49.7%)	Overall pts: HR 0.58 (0.45-0.76) Subgroups: ER+/PR+ HR 0.49 (0.36-0.67) ER+/PR- HR 1.21 (0.63-2.34) Lymph node +ve: HR 0.61 (0.45-0.84) Lymph node -ve: HR 0.45 (0.27-0.73) At 48 months (trend): Overall HR 0.19 p<0.0001 Lymph node	Overall pts: HR 0.82 (0.57-1.19) Subgroups: ER+/PR+ HR 0.58 (0.37-0.90) ER+/PR- HR 1.52 (0.54-4.30) Lymph node +ve: HR 0.61 (95% CI 0.38-0.98) P = 0.04 Lymph node -ve HR 1.52 (0.76-3.06) At 48 months (trend): Overall HR 0.79 p0.33 Lymph node +ve: HR 0.40 p0.038 Lymph node -ve: HR 2.75 p0.34	Annual incidence Hormone Receptor +ve: 3.0/1000 on letrozole 4.8/1000 on placebo NS Time to contralateral recurrence: HR 0.63 (0.18-2.21) P = 0.12

			+ve: HR 0.24 p0.0004		
			Lymph node - ve: HR 0.43 p0.027		
BIG I-98 Thurlimann <i>et al</i> 2005 (1++)	8010	ER+/PR+ 5055 (63.1%) ER+/PR- 1631 (20.4%)	Overall pts: HR 0.81 (0.70- 0.93) p=0.003 ER+/PR+ HR 0.84 (0.69- 1.03) P=0.09 ER+/PR- HR 0.83 (0.62- 1.10) P=0.18 Lymph Node +ve HR 0.71(0.59- 0.85) P<0.001 Lymph Node - ve HR 0.96(0.76- 1.21) P=0.75	Overall pts: HR 0.86 (95% CI 0.70- 1.06) p=0.16	Contralateral breast cancer n=43 (0.5%) Letrozole n=16 Tamoxifen n=27 Time to any recurrence: HR 0.72 (95% CI 0.61-0.86) p<0.001

Exemestane

One RCT compared exemestane vs. tamoxifen. There was a significant benefit of exemestane over tamoxifen in DFS overall patients. Subgroups that benefited the most were ER+, PR+, PR-, lymph node positive and lymph node negative patients (Coombes *et al* 2004). Exceptions were ER-ve or unknown status, and PR status unknown where there were no significant differences in the Hazard Ratios between exemestane and tamoxifen. The benefit of exemestane compared to tamoxifen was not influenced by whether patients received prior HRT or chemotherapy. Overall Survival was not statistically significantly different between exemestane and tamoxifen overall patients. Contralateral breast cancer incidence was significantly reduced in patients on exemestane compared to tamoxifen.

Table 4.2.2.3 Outcomes from the exemestane trial

Study	N patients	HR status	Outcomes		
			DFS	OS	Contralateral breast cancer
IES Coombes	4742	ER+/PR+ 2619 (55.2%) ER+/PR- 735 (15.5%)	Overall pts: HR 0.67 (0.56 - 0.82) p<0.001	Overall HR 0.89 (0.67-1.17) p=0.41	Incidence HR 0.44 (0.20- 0.98) p=0.04 Favours

<p><i>et al/2004</i></p> <p>Quality 1++</p>		<p>ER- 59 (1.2%)</p> <p>Lymph node status: Node negative: n=2422 (51.1%) Node positive: 1-3 nodes n=1421 (30%) Node positive: ≥4 nodes n=651 (13.7%)</p>	<p>Subgroups:</p> <p>HR status: ER+ HR0.64 (0.52-0.79) ER-ve or uk HR0.85 (0.57-1.29) PR+ HR0.66 (0.51-0.87) PR-ve HR0.58 (0.38-0.90) PRuk HR0.67 (0.39-1.16)</p> <p>Lymph node status: Negative HR0.68 (0.48-0.95) +ve 1-3 HR0.71 (0.51-0.98) +ve ≥4 HR0.58 (0.42-0.81)</p>		<p>exemestane N=29 Exemestane n=9</p> <p>Tamoxifen n=20</p>	
<p>Coombes 2007 (In Eisen 2008)</p>	<p>women who had completed two or three years Tamoxifen to receive either exemestane or further Tamoxifen for a total of five years.</p>	<p>Overall in the ITT group:</p> <ul style="list-style-type: none"> unadjusted hazard ratio (HR) for disease-free survival = 0.76 (95% CI 0.66–0.88; p=0.0001) - in favour of exemestane. 	<p>Adjusting for potential confounders:</p> <ul style="list-style-type: none"> ITT analysis: HR= 0.85 (95% CI 0.71–1.01); p=0.07; Oestrogen-receptor-positive and oestrogen-receptor-unknown 	<p>Time to distant recurrence (HR: 0.83; 95% CI: 0.71-0.99) were significantly improved with exemestane.</p>	<p>time to recurrence (HR: 0.70; 95% CI: 0.58-0.83)</p>	<p>Time to contralateral breast cancer (HR: 0.57; 95% CI: 0.33-0.98),</p>

		<p>Translating to a 3.3% (95% CI 1.6–4.9) absolute improvement in disease-free survival at 2.5 years after randomisation, and a 3.4% (0.1–6.8) improvement 5 years after randomisation.</p> <ul style="list-style-type: none"> • Both node positive and node negative were in favour of exemestane with respect to improved disease-free survival • ER+ and ER+PgR+ were in favour of exemestane • ER+PgR– and ER unknown both did not have a significant difference b/n exemestane and tamoxifen • Age 60–69 years 	<p>group: HR= 0.83, 0.69– 0.99; p=0.04</p>			
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		<p>favoured exemestane</p> <p>In the oestrogen-receptor-positive and oestrogen-receptor-unknown group, very similar results were obtained, with a HR = 0.75 (95% CI 0.65–0.87; p=0.0001). For the oestrogen-receptor-positive and oestrogen-receptor unknown group, the absolute improvement at 2.5 years = 3.5% (95% CI 1.8–5.1) and at 5 years = 3.5% (0.1–6.9).</p>				
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Meta-analysis

A meta-analysis (Rubio *et al* 2007, quality 1+) pooled trials of any Aromatase Inhibitor and examined the subgroups by when the AI was administered (at the same time as the group receiving tamoxifen; sequentially after tamoxifen; and after 5 years of tamoxifen). The studies showed the consistent benefits of AIs at different adjuvant treatment stages for DFS and OS. However different AIs were grouped together and no subgroup analyses were performed.

Guidelines

The ASCO guideline (Winer *et al* 2005, Quality 4) recommended that adjuvant therapy for postmenopausal women with hormone receptor-positive breast

cancer should include an aromatase inhibitor in order to lower the risk of tumour recurrence.

Decision analysis

A decision modelling study (Punglia *et al* 2006, Quality 4) using data on anastrozole from the ATAC and ARNO/ABCSCG trials for women with ER+/PR+ and ER+/PR- tumours was conducted to assess whether different treatment strategies may provide benefit to these particular subgroups. The findings were that patients with ER+/PR+ tumours achieved optimal 10-year DFS estimates with tamoxifen followed by a crossover to AI therapy, whereas patients with ER+/PR- tumours gained more benefit when treatment was initiated with an AI.

A summary table of all outcomes is shown below:

Table 4.2.2.4 Summary of all outcomes

Study	Comparison	DFS	OS	Distant DFS	Recurrence	Contralateral breast cancer
Anastrozole						
Lancet 2005 (ATAC Trialist Gp)	Anastrozole vs. Tamoxifen				HR 0.74 (95% CI 0.64–0.87) p=0.0002 all HR +ve	Incidence in HR +ve 53%, 95% CI (25–71), p=0.001
Dowsett 2005 Subgroup analysis N=9366	Anastrozole vs. Tamoxifen ER+/PgR+ 5709 71% ER+/PgR- 1372 17%				Time to recurrence (all Breast Cancer events): ER+/PgR+ HR 0.84 (0.69-1.02) p=0.07 ER+/PgR- HR 0.43 (0.31-0.61) p<0.0001	
Jakesz 2005 (2 RCT)s N=3224	Anastrozole vs. Tamoxifen ER+/PR+ 2519; 78% ER+/PR- 564; 17%	Event FS HR 0.60 (95% CI 0.44–0.81) p=0.0009			Risk of recurrence: Benefit of anastrozole not dependent on nodal status, age at surgery, or progesterone receptor positivity ER+/PR+ HR 0.66 (0.46-0.93) p=0.017 ER+/PR- HR 0.42 (0.19-0.92) p=0.029	Contralateral recurrences n=28/177 events (16%) Anastrozole n=12 Tamoxifen n=16
Boccardo 2005 N= 448 ITA	Anastrozole vs. tamoxifen Hormone status: ER+ 397 89% ER- 2 <1% ERuk or missing 49 11%	EFS HR 0.35 (0.20-0.63) p=0.0002		Distant metastases free survival HR 0.49 (0.22-1.05) p=0.06	Disease recurrence: The benefit of anastrozole was independent of tumour size, grade, number of involved nodes and prior chemotherapy. HR 0.35 (0.18-0.69) p=0.002	Contralateral recurrences n=3 Anastrozole n=1 Tamoxifen n=2

Study	Comparison	DFS	OS	Distant DFS	Recurrence	Contralateral breast cancer
Letrozole						
Goss 2007 N=5187 MA.17	Letrozole vs. placebo ER+/PR+ (n=3809) 73.4% ER+/PR- (n=636) 12.3%	All subgroups: HR 0.58 (0.45-0.76) ER+/PR+ HR 0.49 (0.36-0.67) ER+/PR- HR 1.21 (0.63-2.34)	All subgroups: HR 0.82 (0.57-1.19) ER+/PR+ HR 0.58 (0.37-0.90) ER+/PR- HR 1.52 (0.54-4.30)	All subgroups: HR 0.60 (0.43-0.84) ER+/PR+ HR 0.53 (0.35-0.80) ER+/PR- HR 1.25 (0.56-2.80)		
Goss 2005 N=5187 MA.17	Letrozole vs. placebo Hormone receptor (ER or PR) status: Positive 5035 (97.4%) Negative 8 (0.15%) Lymph node status: Positive 2360 (45.6%) Negative 2568 (49.7%)	Local or distant recurrence or contralateral breast cancer (HR+ve): HR 0.58 (95% CI = 0.45 to 0.76) Distant DFS: HR = 0.60, (95% CI = 0.43 to 0.84; P = 0.002) DFS Lymph node +ve: HR 0.61 (0.45- 0.84) Lymph node -ve: HR 0.45 (0.27- 0.73)	Death from any cause: HR 0.82 (95% CI 0.57-1.19) p=0.3 OS Lymph node +ve: HR 0.61 (95% CI 0.38-0.98) P = 0.04 Lymph node -ve: HR 1.52 (0.76-3.06)	HR = 0.60, (95% CI = 0.43 to 0.84; P = 0.002)	Time to contralateral recurrence: HR = 0.63, (95% CI = 0.18 to 2.21; P = 0.12)	Annual incidence HR +ve: 3.0/1000 on letrozole 4.8/1000 on placebo NS
Ingle 2006 N=5187 MA.17	Letrozole vs. placebo Hormone receptor (ER or PR) status:	DFS at 48 months compared to 6 mths (trend analysis)	OS at 48 months (trend analysis) Lymph node +ve:	DDFS at 48 months (trend analysis) Lymph node +ve:		

	<p>Positive 5035 (97.4%) Negative 8 (0.15%)</p> <p>Lymph node status: Positive 2360 (45.6%) Negative 2568 (49.7%)</p>	<p>Lymph node +ve: HR 0.24 p0.0004</p> <p>Lymph node -ve: HR 0.43 p0.027</p>	<p>HR 0.40 p0.038</p> <p>Lymph node -ve: HR 2.75 p0.34</p>	<p>HR 0.24 p0.0005</p> <p>Lymph node -ve: HR 0.18 p0.22</p>		
<p>Thurliman n 2005 N=8010 BIG I-98</p>	<p>Letrozole vs. tamoxifen</p> <p>Hormone status: ER+/PR+ 5055 (63.1%) ER+/PR- 1631 (20.4%)</p>	<p>DFS HR 0.81 (95% CI 0.70-0.93) p=0.003</p> <p>ER+/PR+ HR 0.84 (95% CI 0.69-1.03) P=0.09</p> <p>ER+/PR- HR 0.83 (95% CI 0.62-1.10) P=0.18</p> <p>Node -ve HR 0.96(0.76- 1.21) P=0.75</p> <p>Node +ve HR 0.71(0.59- 0.85) P<0.001</p>	<p>HR 0.86 (95% CI 0.70-1.06) p=0.16</p>	<p>Time to distant recurrence : HR 0.73 (95% CI 0.60-0.88) p=0.001</p>	<p>Time to recurrence: HR 0.72 (95% CI 0.61-0.86) p<0.001</p>	<p>Contralateral breast cancer n=43 (0.5%) Letrozole n=16 Tamoxifen n=27</p>

Study	Comparison	DFS	OS	Distant DFS	Recurrence	Contralateral breast cancer
Exemestane						
Coombes 2004 N=4742 IES	Exemestane vs. Tamoxifen ER+/PR+ 2619 (55.2%) ER+/PR- 735 (15.5%) ER- 59 (1.2%) Lymph node status: Node negative: n=2422 (51.1%) Node positive: 1-3 nodes n=1421 (30%) Node positive: ≥4 nodes n=651 (13.7%)	Overall HR 0.67 (95% CI 0.56-0.82) p<0.001 Favours exemestane. HR status: ER+ HR0.64 (0.52-0.79) ER-ve or uk HR0.85 (0.57-1.29) PR+ HR0.66 (0.51-0.87) PR-ve HR0.58 (0.38-0.90) PRuk HR0.67 (0.39-1.16) Lymph node status: Negative HR0.68 (0.48-0.95) +ve 1-3 HR0.71 (0.51-0.98) +ve ≥4 HR0.58 (0.42-0.81)	Overall HR 0.89 (95% CI 0.67-1.17) p=0.41			Incidence: HR 0.44 (95% CI 0.20-0.98) p=0.04 Favours exemestane N=29 Exemestane n=9 Tamoxifen n=20
Coombes 2007 (In Eisen 2008)	women who had completed two or three years Tamoxifen to receive either exemestane or further Tamoxifen	Overall in the ITT group: ● unadjusted hazard ratio (HR) for disease-free survival =	Adjusting for potential confounders: ● ITT analysis: HR= 0.85 95% CI 0.71-	Time to distant recurrence (HR: 0.83; 95% CI: 0.71-0.99) were significantly improved with exemestane	time to recurrence (HR: 0.70; 95% CI: 0.58-0.83)	Time to contralateral breast cancer (HR: 0.57; 95% CI: 0.33-0.98),

	for a total of five years.	<p>0.76 (95% CI 0.66–0.88; p=0.0001) - in favour of exemestane. Translating to a 3.3% (95% CI 1.6–4.9) absolute improvement in disease-free survival at 2.5 years after randomisation, and a 3.4% (0.1–6.8) improvement 5 years after randomisation.</p> <ul style="list-style-type: none"> • Both node positive and node negative were in favour of exemestane with respect to improved disease-free survival • ER+ and ER+PgR+ were in favour of exemestane • ER+PgR– and ER unknown both did not have a significant difference 	<p>1.01); p=0.07;</p> <ul style="list-style-type: none"> • Oestrogen-receptor-positive and oestrogen-receptor-unknown group: HR= 0.83, 0.69–0.99; p=0.04 	e.		
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		<p>b/n exemestane and tamoxifen</p> <ul style="list-style-type: none"> • Age 60–69 years favoured exemestane <p>In the oestrogen-receptor-positive and oestrogen-receptor-unknown group, very similar results were obtained, with a HR = 0.75 (95% CI 0.65–0.87; p=0.0001). For the oestrogen-receptor-positive and oestrogen-receptor-unknown group, the absolute improvement at 2.5 years = 3.5% (95% CI 1.8–5.1) and at 5 years = 3.5% (0.1–6.9).</p>				
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Study	Comparison	DFS	OS	Distance DFS	Recurrence	Contralateral breast cancer
Meta-analysis						
Rubio 2007 (Meta analysis)	AI vs tamoxifen or placebo administered at different	Overall studies OR 0.75 (0.69-0.81) p<0.00001	Overall studies OR 0.88 (0.80-0.98) P=0.02			

	stages. Als: anastrozole, letrozole or exemestane	Significant heterogeneity	Heterogeneity not significant			
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Chlebowski, R.T., Gelber,R., et al (2005) American Society of Clinical Oncology
Technology Assessment on the Use of Aromatase Inhibitors As Adjuvant
Therapy for Postmenopausal Women With Hormone Receptor—Positive Breast
Cancer: Status Report 20114 – Journal of Clinical Oncology, 23 column 3 pp619-
629

Evidence Tables

Systematic Review

Study Identification:	Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. Health Technol Assess 2007; 11(26).
Design:	Systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	RCTs (postmenopausal women, histologically confirmed invasive breast cancer, completed primary surgery)
Intervention:	Systematic review of RCT of primary adjuvant, sequenced or switch strategies of AI vs Tam
Primary adjuvant	<p>ATAC: T1: anastrozole 1 mg/day for 5 years from surgery, or after CT (n 3125). T2: tamoxifen 20 mg/day for 5 years from surgery, or after CT (n 3116). T3: anastrozole 1 mg/day + tamoxifen 20 mg/day for 5 years from surgery, or after CT (n 3125)</p> <p>BIG 1-98: T1: letrozole (2.5 mg/day) for 5 years T2: letrozole (2.5 mg/day) for 2 years, then tamoxifen (20 mg/day) for 3 years; (T1 + T2, n 4003) T3: tamoxifen (20 mg/day) for 5 years T4: tamoxifen (20 mg/day) for 2 years, then letrozole (2.5 mg/day) for 3 years (T3 + T4, n 4007)</p> <p>Unplanned switch</p> <p>GABG : Following 2 years of adjuvant tamoxifen T1: anastrozole (1 mg/day), 3 years (n 1618) T2: tamoxifen (20 or 30 mg/day), 3 years (n 1606)</p> <p>ITA: T1: anastrozole (1mg/day) for 2—3 years (n 223) T2: tamoxifen for 2—3 years (20 mg/day) (n 225)</p> <p>IES: T1: exemestane 25 mg/day for 2—3 years (n 2362) T2: tamoxifen 20/30 mg/day for 2—3 years (n 2380)</p> <p>Extended adjuvant</p> <p>MA-17: T1: letrozole (2.5 mg/day) oral (n 2593) T2: oral placebo (n 2594)</p> <p>ABCSG: T1: anastrozole 1 mg/day for 36 months T2: no treatment</p>
Outcomes:	DFS, OS
Follow-up:	ATAC median 68 months; BIG 1-98 median 26; GABG median 28 months; ITA median 36 months; IES median 31 months; MA-17 30 months; ABCSG median 60 months

Results:	<p>A meta-analysis of three trials found a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Significant improvements in overall survival are yet to be demonstrated in other strategies. Compared with 5 years' tamoxifen, disease-free survival (disease recurrence or death from any cause) was significantly improved in the primary adjuvant setting with anastrozole and letrozole, and with an exemestane switching strategy. Other trials did not report this outcome. Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole and letrozole, anastrozole switching, extended adjuvant anastrozole or letrozole. The AIs and tamoxifen have different side-effect profiles, with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in postmenopausal women. There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies.</p>
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OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:		
<i>Primary adjuvant strategies</i>		
<p>The 60-month primary adjuvant anastrozole strategy (ATAC) resulted in a difference in DFS that was significant at the 5% level (HR = 0.87, 95% CI 0.78 to 0.97, p = 0.01). In the tamoxifen group 79.0% of participants were alive and disease free versus 81.3% in the anastrozole group: rounding figures up, an extra 2.4% of participants receiving anastrozole benefited from the treatment. For one extra woman to be alive and disease free over 68 months, 41 women would have to be treated using anastrozole. The difference in DFS was significant at the 5% level when only women whose disease had been hormone receptor- positive (HR = 0.83, 95% CI 0.73 to 0.94, p = 0.005) were analysed. In the tamoxifen group, 83.8% of participants were alive and disease free versus 80.9% in the anastrozole group: rounding figures up, an extra 2.9% of participants receiving anastrozole benefited from the treatment. For one extra woman to be alive and disease free over 68 months, 34 women would have to be treated using anastrozole.</p>		
<p>The 60-month primary adjuvant letrozole strategy (BIG 1-98) resulted in a difference in DFS that was significant at the 5% level (HR = 0.81, 95% CI 0.70 to 0.93, p = 0.003). In the tamoxifen group, 89.3% of participants were alive and disease free versus 91.2% in the letrozole group: an extra 1.9% of participants receiving letrozole benefited from the treatment. For one extra woman to be alive and disease free over 26 months, 52 women would have to be treated using letrozole.</p>		
<i>Switching strategies</i>		
<p>Neither the GABG nor ITA reported DFS as defined in this report.</p>		
<p>The 24-36-month anastrozole switching strategy (Jonat meta-analysis) resulted in a difference in DFS that was significant at the 5% level (HR = 0.59, 95% CI 0.48 to 0.74, p < 0.000 1). It was not clear whether the necessary summary statistics were available to calculate the ARR and NNT</p>		
<p>The 24- 36-month exemestane switching strategy (IES) resulted in a difference in DFS that was significant at the 5% level (HR = 0.73, 95% CI 0.62 to 0.86, p = 0.000 1). In the tamoxifen group, 85.1% of participants were alive and disease free compared with 89.0% in the exemestane group: after rounding, an extra 3.8% of participants receiving exemestane benefited from the treatment. For one woman to benefit from exemestane, 26 women would have to be treated using it.</p>		
<i>Extended adjuvant strategies</i>		
<p>Neither of the included studies that evaluated extended adjuvant strategies reported DFS as defined in this review.</p>		
Overall Survival:		
<i>Primary adjuvant strategies</i>		
<p>The 60-month primary adjuvant anastrozole strategy (ATAC) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.97, 95% CI 0.85 to 1.12,p = 0.7). In the tamoxifen group, 13.6% of participants died versus 13.3% in the anastrozole group; an extra 0.3% of participants receiving anastrozole benefited from the treatment. For every death prevented over 68 months, 354 women would have to be treated using anastrozole. Overall survival rates for the</p>		

hormone receptor-positive population were similar. The difference in “time to breast cancer death” was not significant at the 5% level (HR = 0.88, 95% CI 0.74 to 1.05, p = 0.2). In the tamoxifen group, 8.6% of participants died of breast cancer versus 7.6% in the anastrozole group: an extra 1% of participants receiving anastrozole benefited from the treatment. For every breast cancer death to be prevented over 68 months, 101 women would have to be treated using anastrozole. The outcome for the hormone receptor-positive population was similar

The 60-month primary adjuvant letrozole strategy (BIG 1-98) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.86, 95% CI 0.70 to 1.06, p = 0.16). In the tamoxifen group, 4.8% of participants died versus 4.1% in the letrozole group: an extra 0.6% of participants receiving letrozole benefited from the treatment. For every death prevented over 26 months, 155 women would have to be treated using letrozole. The difference in “death following cancer event” (data from conference presentation only⁷²) was significant at the 5% level (HR not reported). In the tamoxifen group, 3.8% of participants died following a cancer event versus 2.8% in the letrozole group: an extra 1.1% of participants receiving letrozole benefited from the treatment. For every death following a cancer event to be prevented over 26 months, 93 women would have to be treated using letrozole.

Switching strategies

One study evaluating a 36-month anastrozole switching strategy (GABG) demonstrated a difference in overall survival that was not significant at the 5% level (HR not reported). In the tamoxifen group, 3.7% of participants died versus 2.8% in the anastrozole group: an extra 0.9% (95% CI -1.1 to 2.8%) of participants receiving anastrozole benefited from the treatment. For every death to be prevented over 28 months, 113 women would have to be treated using anastrozole. The difference in “deaths: breast cancer related” was not significant at the 5% level (HR not reported). In the tamoxifen group, 1.9% of participants died following a cancer event versus 1.5% in the anastrozole group: an extra 0.4% (95% CI -1.0 to 1.9%) of participants receiving anastrozole benefited from the treatment. For every breast cancer-related death to be prevented over 28 months, 226 women would have to be treated using anastrozole.

Another study evaluating a 24—36-month anastrozole switching strategy (ITA) did demonstrate a difference in overall survival that was borderline significant at the 5% level (HR not reported). In the tamoxifen group, 4.4% of participants died versus 1.8% in the anastrozole group: 2.7% (95%CI 1.0-4.3%) of participants receiving anastrozole benefited from the treatment. For every death prevented over 36 months, 38 women would have to be treated using anastrozole. In the tamoxifen group, 3.1% of participants died as a result of breast cancer versus 1.8% in the anastrozole group: an extra 1.3% (95% CI -0.2 to 2.8%) of participants receiving anastrozole benefited from the treatment. For one death from breast cancer to be prevented, 76 women would have to be treated using anastrozole.

The 24-36-month anastrozole switching strategy (Jonat. meta-analysis) resulted in a difference in overall survival that was significant at the 5% level (HR = 0.71, 95% CI 0.52 to 0.98, p = 0.038). It was not clear whether the necessary summary statistics were available to calculate the ARR and number-needed-to-treat (NNT).

The 24-36-month exemestane switching strategy (IES) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.83, 95% CI 0.67 to 1.02, p = 0.08). In the tamoxifen group, 7.9% of participants died versus 6.4% in the exemestane group: an extra 1.5% (-0.7 to 3.6%) of participants receiving exemestane benefited from the treatment. For every death prevented over 37 months, 68 women would have to be treated using exemestane. The difference in “breast cancer-

free survival” was significant at the 5% level when reported at 31 months (HR = 0.63, 95% CI 0.51 to 0.77, $p < 0.001$). An HR was not available in the conference presentation of the 37-month follow-up but, in the intervening period, the “breast cancer-related” death rate had risen from 2.8 to 5.2% in the tamoxifen group and from 2.3 to 4.0% in the exemestane group. At 37 months, an extra 1.2% of participants receiving exemestane benefited from the treatment. For every breast cancer-related death to be prevented over this period, 82 women would have to be treated using exemestane.

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17) resulted in a difference in overall survival that was not significant at the 5% level (HR 0.82, 95% CI 0.57 to 1.19). In the placebo group, 2.4% of participants died versus 2.0% in the letrozole group: an extra 0.4% (-0.8 to 1.6%) of participants receiving letrozole benefited from the treatment. For death to be prevented, 235 women would have to be treated using letrozole. The difference in overall survival was significant at the 5% level when they analysed only women whose disease had been node-positive (HR 0.61, 95% CI 0.38

to 0.98). The ARR and NNT for this subgroup were not estimable, because event numbers were not reported. The difference in “breast cancer as cause of death” was not significant at the 5% level (HR not reported). In the placebo group, 0.9% of participants died as a result of breast cancer versus 0.6% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment. For one death from breast cancer to be prevented, 431 women would have to be treated using letrozole.

Contralateral breast cancer:

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC) resulted in a difference in the rate of contralateral breast cancers that was significant at the 5% level (odds ratio 0.58, 95% CI 0.38 to 0.88, $p = 0.01$). In the tamoxifen group, 1.9% of participants developed cancer in the contralateral breast compared with 1.1% in the anastrozole group: an extra 0.8% of participants receiving anastrozole benefited from the treatment. For contralateral breast cancer to be prevented in one extra woman over 68 months, 126 women would have to be treated using anastrozole. The difference

in the hormone receptor-positive population was also significant at the 5% level (odds ratio 0.47, 95% CI 0.29 to 0.75, $p = 0.001$). In the tamoxifen group, 2.0% of participants developed cancer in the contralateral breast compared with 1.9% in the anastrozole group: an extra 1.0% of participants receiving anastrozole benefited from the treatment. For contralateral breast cancer to be prevented in one extra hormone receptor-positive woman over 68 months, 93 such women would have to be treated using anastrozole.

It is not clear whether the 60-month primary adjuvant letrozole strategy (BIG 1-98) resulted in a difference in the rate of contralateral breast cancers which was significant at the 5% level (HR not reported). In the tamoxifen group, 0.7% of participants had an event compared with 0.4% in the letrozole group: an extra 0.3% (95% CI not estimable) of participants benefited from receiving letrozole. For contralateral breast cancer to be prevented in one extra woman over 26 months, 333 women would have to be treated using letrozole.

Switching strategies

It is not clear whether the study evaluating a 36-month anastrozole switching strategy (GABG) demonstrated a difference in the rate of contralateral breast cancers that was significant at the 5%

level (HR not reported). In the tamoxifen group, 1.0% of participants had an event compared with 0.7% in the anastrozole group: an extra 0.3% of participants receiving anastrozole benefited from the treatment. To prevent contralateral breast cancer in one additional woman over 28 months, 396 women would have to be treated using anastrozole.

It is not clear whether the study evaluating a 24-36-month anastrozole switching strategy (ITA) demonstrated a difference in the rate of contralateral breast cancer which was significant at the 5% level (HR not reported). In the tamoxifen group, 0.9% of participants developed a contralateral compared with 0.4% in the anastrozole group: rounding down, contralateral cancer was prevented in an additional 4.0% of participants receiving anastrozole. For every contralateral cancer prevented over 24-36 months, 227 women would have to be treated using anastrozole.

The 24-36-month exemestane switching strategy (IES) resulted in a difference in the rate of contralateral breast cancer that was significant at the 5% level (HR = 0.50, 95% CI 0.26 to 0.97, p = 0.04). In the tamoxifen group, 1.1% of participants had an event compared with 0.5% in the exemestane group: contralateral breast cancer was prevented in an additional 0.6% of participants receiving exemestane. For contralateral cancer to be prevented in one additional woman over 37 months, 173 women would have to be treated using exemestane.

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17) resulted in a difference in DR that was not significant at the 5% level (HR = 0.63, 95% CI 0.18 to 2.21, p not reported). In the placebo group, 1.1% of participants had an event versus 0.7% in the letrozole group: contralateral breast cancer was prevented in an additional 0.4% of participants receiving letrozole treatment. For each additional contralateral cancer to be prevented over 30 months, 236 women would have to be treated using letrozole.

It is unclear whether the 36-month extended adjuvant anastrozole strategy (ABC SG) resulted in a difference in the rate of contralateral breast cancers that was significant at the 5% level (HR not reported). In the placebo group, 2.1% of participants developed a cancer in the contralateral breast versus 1.6% in the anastrozole group: an extra 3.3% of participants remained disease free as a result of receiving anastrozole treatment. For each additional contralateral cancer to be prevented over 60 months, 172 women would have to be treated using anastrozole.

Quality of Life (including side-effects):

Adverse events: bone health

Primary adjuvant strategies

At 33 months, the relative risk of a fracture in the 60-month primary adjuvant anastrozole strategy was already 1.59 (95% CI not reported, p < 0.0001), with 115 (3.7%) women in the tamoxifen arm and 183 (5.9%) in the anastrozole arm experiencing a fracture (ATAC trial). By 68 months, 7.7% of participants in the tamoxifen group had experienced a fracture compared with 11.0% in the anastrozole group: an extra 3.3% of participants receiving anastrozole were harmed by the treatment. One extra woman would experience a fracture over 68 months for every 30 women treated using anastrozole. The odds ratio for hip fracture, the subcategory most frequently associated with mortality, was not significant (1.20, 95% CI 0.74 to 1.93, p = 0.5).° In the tamoxifen group, 1.0% of participants experienced a hip fracture compared with 1.2% in the anastrozole group: an extra 0.2% of participants receiving anastrozole experienced a hip fracture. One extra woman would experience a hip fracture over 68 months for every 514 women treated with anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98) resulted in a difference in the fracture

rate that was significant at the 5% level (HR not reported, $p < 0.001$) favouring tamoxifen. In the tamoxifen group, 4.0% of participants experienced a fracture compared with 5.7% in the letrozole group: an extra 1.7% of participants receiving letrozole were harmed by the treatment. One extra woman would experience a fracture over 26 months for every 60 women treated using letrozole. The HR for hip fracture was not reported.

Switching strategies

The 36-month anastrozole switching strategy (GABG) resulted in a difference in the fracture rate that was significant at the 5% level (HR not reported; $p = 0.015$). In the tamoxifen group, 1.0% of participants experienced a fracture compared with 2.1% in the anastrozole group: an extra 1.1% of participants receiving anastrozole were harmed by the treatment. One extra woman would experience a fracture over 36 months for every 90 women treated using anastrozole. The hip fracture rate was not reported.

The study evaluating a 24—36-month anastrozole switching strategy (ITA) demonstrated no difference in the fracture rate: 0.9% of women in each arm experienced a fracture (HR not reported). The hip fracture rate was not reported.

It is not clear whether the 24-36-month exemestane switching strategy (IES) resulted in a difference in fracture rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 2.3% of participants experienced a fracture compared with 3.1% in the exemestane group: an extra 0.8% of participants receiving exemestane were harmed by the treatment. One extra woman would experience a fracture over 36 months for every 118 women treated using exemestane.

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17) did not result in a difference in the fracture rate that was significant at the 5% level (HR not reported, $p = 0.25$). In the placebo group, 4.6% of participants experienced a fracture compared with 5.3% in the letrozole group: an extra 0.7% of participants receiving letrozole were harmed by the treatment. One extra woman would experience a fracture over 30 months for every 141 women treated using letrozole. The hip fracture rates were 0.003% in the placebo group and 0.002% in the letrozole group. The rate of new osteoporosis was highly significant at a median follow-up of 30 months (letrozole 8.1%; placebo 6.0%; $p = 0.003$), whereas at the previous follow-up (median 2.4 years, or 28.8 months)⁹² it had been a non-significant trend (letrozole 5.8%; placebo 4.5%; $p = 0.07$).

Quality of Life - including side-effects (contd.):

Adverse events: cardiovascular events

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC) reported “ischaemic cardiovascular disease”. There was no significant difference between the arms [anastrozole, 127/3092 (4.1%); tamoxifen, 104/3094 (3.4%); HR 1.23, 95% CI 0.95 to 1.60, $p = 0.1$]. ATAC also reported “ischaemic cerebrovascular events”, which does not separate Grade 4 events, such as stroke, from Grade 3 conditions, such as TIA: the results found that there were significantly more events in the tamoxifen arm (anastrozole, 62/3092; tamoxifen, 88/3094; HR 0.70, 95% CI 0.50 to 0.97, $p = 0.03$). They also reported “venous thromboembolic events” (anastrozole, 87/3092; tamoxifen, 140/3094; HR 0.61,

95% CI 0.47 to 0.80, $p = 0.0004$) and deep venous thromboembolic events (anastrozole, 48/3092; tamoxifen, 74/3094; HR 0.64, 95% CI 0.45 to 0.93, $p = 0.02$).

The 60-month primary adjuvant letrozole strategy (BIG 1-98) reported differences in the number of thromboembolic events that were significant at the 5% level [letrozole, 61/3975 (1.5%); tamoxifen, 140/3988 (3.5%); HR not reported, $p < 0.001$], favouring letrozole. There were no significant differences in all cardiac events, but there was a significant difference in Grade 3-5 cardiac events [letrozole, 85/3975 (2.1%); tamoxifen, 44/3988 (1.1%); HR not reported, $p = 0.000372$], favouring tamoxifen. There was no significant difference in ischaemic heart disease, but there was a significant difference in cardiac failure [letrozole, 31/3975 (0.8%); tamoxifen, 14/3988 (0.4%); $p = 0.01$] and “other cardiac events” [letrozole, 19/3975 (0.5%); tamoxifen, 8/3988 (0.2%); $p = 0.04$]. There were more deaths without recurrence in the letrozole arm (55 versus 38 in the tamoxifen arm), including three times as many from cardiac events (16 versus five).⁷¹ There was no significant difference between arms in the recording of cardiovascular accident (CVA) or transient ischaemic attack (TIA) events.

Switching strategies

One study evaluating a 36-month anastrozole switching strategy (GABG) reported no significant difference in myocardial infarction or “embolism”. There was a significant difference in thromboses favouring anastrozole, 3/1602; tamoxifen, 12/1597, $p = 0.034$).

Another study evaluating a 24–36-month anastrozole switching strategy (ITA) reported no significant difference between treatments in terms of “cardiovascular disease” or “venous disorders”. The 24-36-month exemestane switching strategy (IES) reported “cardiovascular disease other than myocardial infarction”. It also reported separately “thromboembolic disease” and “thromboembolic events”, but did not define what these categories included. Thromboembolic disease was significantly more frequent in the tamoxifen arm (exemestane, 24/2309; tamoxifen, 45/2332; $p = 0.003$). Thromboembolic events were reported as significantly more frequent in the tamoxifen arm (exemestane, 30/2309; tamoxifen, 55/2332; $p = 0.007$). Deaths from vascular (exemestane, 12/2362; tamoxifen, 6/2380), cardiac (exemestane, 10/2362; tamoxifen, 8/2380), thrombotic (exemestane, 1/2362; tamoxifen, 1/2380) or pulmonary (exemestane, 0/2362; tamoxifen, 1/2380) causes were recorded separately (HR and p -values not reported). In the updated analysis (median follow-up 37 months; data from conference presentation⁸⁹) there were twice as many deaths from vascular causes in women in the exemestane arm (0.6% versus 0.3%) and twice as many myocardial infarctions (0.9% versus 0.4%, $p = 0.02$, but non-significant, presumably due to multiple significance testing). Conversely, there was more thromboembolic disease in the tamoxifen arm (3.3%) than in the exemestane arm (1.9%), and this difference was significant at the 5% level ($p < 0.001$).

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17) reported that cardiovascular “events” or “disease” were observed in 149 (5.8%) and 144 (5.6%) of patients in the letrozole and placebo arms, respectively ($p = 0.76$). This includes potentially fatal events, such as myocardial infarction and stroke, and also nonfatal conditions such as angina and TIA. Thromboembolic events were reported as a subcategory of CVD with pulmonary embolism, the potentially fatal event, not separated out from other non-fatal conditions. There were five cardiovascular-related deaths and two fatal strokes in women receiving letrozole and five cardiovascular-related deaths and one fatal stroke in women receiving placebo.

No data were available for this outcome from the study evaluating the 36-month extended adjuvant anastrozole strategy.

Quality of Life - including side-effects (contd.):

Adverse events: gynaecological

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported; $p = 0.02$). In the tamoxifen group, 0.8% of participants developed endometrial cancer compared with 0.2% in the anastrozole group: after rounding, an extra 0.5% of participants receiving anastrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 68 months, 187 women would have to be treated using anastrozole. In the tamoxifen group, 10.2% of participants experienced a vaginal bleeding compared with 5.4% in the anastrozole group: an extra 4.8% of participants receiving anastrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 68 months, 21 women would have to be treated with anastrozole. The authors also observed a fourfold increase in hysterectomy rates (anastrozole, 1.3%; tamoxifen, 5.1%; $p < 0.0001$).

The 60-month primary adjuvant letrozole strategy (BIG 1-98) did not result in a difference in the rate of “invasive endometrial cancers” that was significant at the 5% level (HR not reported, $p = 0.18$). In the tamoxifen group, 0.3% of participants developed endometrial cancer compared with 0.1% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 26 months, 500 women would have to be treated using letrozole. In the tamoxifen group, 6.6% of participants experienced a vaginal bleeding compared with 3.3% in the letrozole group: an extra 3.3% of participants receiving letrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 26 months, 30 women would have to be treated with letrozole.

Switching strategies

It is not clear whether the 36-month anastrozole switching strategy (GABG) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 0.4% of participants developed endometrial cancer compared with 0.1% in the anastrozole group: after rounding, an extra 0.4% of participants receiving anastrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 36 months, 266 women would have to be treated using anastrozole. The GABG study analysed vaginal bleeding and discharge as one outcome: there was no significant difference between treatment arms.

The study evaluating a 24-36-month anastrozole switching strategy (ITA) did not report the incidence of endometrial cancer or vaginal bleeding. The Jonat meta-analysis did not report the incidence of endometrial cancer or vaginal bleeding.

It is not clear whether the 24-36-month exemestane switching strategy (IES) resulted in a difference in endometrial cancer rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 0.5% of participants developed endometrial cancer compared with 0.2% in the exemestane group: after rounding, an extra 0.3% of participants receiving exemestane benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 31 months, 399 women would have to be treated using exemestane. In the tamoxifen group, 5.5% of participants experienced vaginal bleeding compared with 4.0% in the exemestane group: after rounding, an extra

1.5% of participants receiving exemestane benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 31 months, 66 women would have to be treated using exemestane.

Extended adjuvant strategies

It is unclear whether the 60-month extended adjuvant letrozole strategy (MA-17) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported). In the placebo group, 0.4% of participants developed endometrial cancer compared with 0.2% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 30 months, 369 women would have to be treated using letrozole. In the placebo group, 7.6% of participants experienced a vaginal bleeding compared with 5.6% in the letrozole group: an extra 2.0% of participants receiving letrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 30 months, 51 women would have to be treated with anastrozole.

Endometrial cancer and vaginal bleeding rates were not reported by the study evaluating a 36-month extended adjuvant anastrozole strategy (ABCSSG).

Adverse events: gynaecological

Study Identification:	Ellis, M.J., Rigden, C.E. - Initial versus sequential adjuvant aromatase inhibitor therapy: a review of the current data – Current Medical Research and Opinion, 2006 22, 12, pp2479-2487	
Design:	systematic review of RCTs evidence level 1++	
Country / Setting:	international	
Population:	Reports of 6 RCT (ATAC, BIG1-98, ARNO 95, ABCSG8, ITA, IES)	
Intervention:	Interventions in each of the trials (reported elsewhere) reviewed to compare efficacy and safety data for AI's in initial adjuvant and switched adjuvant settings.	
Outcomes:	DFS, total events, QOL	
Follow-up:	Reported elsewhere	
Results:	In the upfront adjuvant setting, anastrozole and letrozole have both demonstrated a significant DFS benefit over tamoxifen. Upfront therapy with a nonsteroidal AI appears to be most critical for patients at risk of an early relapse, illustrated by the finding that upfront letrozole provided a significant early DFS advantage over tamoxifen only in patients with node-positive disease (HR = 0.71, p < 0.001). With respect to safety, both strategies have similar adverse event profiles.	
OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:		
<i>Upfront AI therapy:</i>		
ATAC trial – anastrozole demonstrated a significant benefit in DFS (HR=0.87, p=0.01)		
Subgroup analysis suggested a more pronounced DFS benefit for anastrozole in the ER+/PR- subgroup (HR = 0.43) than in the ER+/PR+ subgroup (HR = 0.84)		
BIG1-98 - median follow-up showed a 19% improvement in DFS (HR = .0.81; p = 0.003), an estimated absolute increase for 5-year DFS by 2.6% with letrozole compared to tamoxifen. A significant benefit in DFS was only observed in higher-risk patients, i.e., those with node-positive disease (HR = 0.71, p < 0.001)		
<i>Adjuvant switch therapy:</i>		
IES trail – already received tamoxifen therapy for 2-3 years. At a median follow-up of 55.7 months, the results show that exemestane therapy after 2-3 years of tamoxifen therapy significantly improved DFS compared with the standard 5 years of tamoxifen treatment (HR = 0.76, p = 0.0001)		
ARNO95/ABCSG8 - After a median follow-up of 28 months, patients in the anastrozole group had a 40% decrease in the risk for an event compared with the tamoxifen group (67 events for anastrozole vs. 110 events for tamoxifen, for an HR 0.60; p = 0.009).		
IES –patients who had 2-3 (plus) years of tamoxifen followed by 2-3 years of anastrozole (n = 223) experienced a significantly reduced risk of relapse (HR 0.35, p = 0.001) compared with those patients who had only received tamoxifen for 5 years (n = 225).		
Overall Survival:		
<i>Upfront AI therapy:</i>		
ATAC trial – Although there was an absolute reduction in breast cancer deaths, it was not		

significant, and at 68 months of follow-up, there was no significant difference in overall survival between the ER+PR+ and ER+PR- groups (HR = 0.97; p = 0.7). In the hormone receptor positive population there were only 5 fewer deaths in the anastrozole vs tamoxifen arm BIG1-98 - Fewer overall deaths occurred in the letrozole arm when compared with the tamoxifen arm (166 vs. 192), which translated into a non-significant 14% decrease in the relative risk for breast cancer mortality (p = 0.16).

General comments: Differences in patient populations, definitions of end points, and prior tamoxifen usage between the trials discussed necessitates careful interpretation.

Study Identification:	Mouridsen, H.T., Incidence and management of side effects associated with aromatase inhibitors in the adjuvant treatment of breast cancer in postmenopausal Women: Current Medical Research and Opinion; Aug 2006; 22, 8; ProQuest Medical Library pg1609
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	
Intervention:	See above
Outcomes:	QOL including side-effects
Follow-up:	See population
Results:	Als alone and sequenced after tamoxifen are an appropriate option for adjuvant endocrine therapy for most postmenopausal patients with hormone-responsive breast cancer. The incidence of endometrial cancer and thromboembolic events is significantly lower with an AI than with tamoxifen. However, there is a small but significant increase in the risk of osteoporosis and fractures with AI therapy. Monitoring and management of bone loss associated with AI treatment are essential. A potential negative effect on the cardiovascular system, specifically on lipid metabolism, has not been conclusively demonstrated. No significant differences in overall quality of life were observed in studies comparing AIs with tamoxifen or placebo. The most commonly reported adverse events associated with adjuvant AI therapy include hot flushes and musculoskeletal complaints arthralgia

OUTCOME OF INTEREST	COMPARISON	RESULT
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Disease-free survival: Reported elsewhere

Overall Survival: Reported elsewhere

Contralateral breast cancer: Reported elsewhere

Quality of life (including side effects):

Reported incidences of cardiac events

Study	Follow-up (months)	Symptoms	AI(%)	Tam(%)	P
ATAC	33.3	Ischemic CVD	2.5	1.9	0.14
BIG 1-98	25.8	Cardiac Event	4.1	3.8	0.61
IES	30.6	Cardiovascular other than MI, MI	42.6,1.0	39.2,0.4	0.11,NI
ABCSG/ARNO	28	MI	<1(n=3)	<1(n=2)	1.0

Reported incidences of thromboembolic events

Study	Follow-up(months)	AI(%)	Tam(%)	P
ATAC	33.3	2.1	3.5	0.0006
BIG 1-98	25.8	1.5	3.5	<0.001
IES	30.6	1.0	1.9	0.003
ABCSG/ARNO	28	<1(n=3)	<1(n=12)	0.034

Reported incidences of endometrial cancer and gynaecological symptoms

Study	Follow-up (months)	Symptoms	AI(%)	Tam(%)	P
ATAC	33.3	Endometrial cancer	0.1	0.5	0.02
		Bleeding	4.5	8.2	<0.0001
		Discharge	2.8	11.4	<0.0001
BIG 1-98	25.8	Endometrial cancer	0.1	0.3	0.18
		Bleeding	3.3	6.6	<0.0001
		Discharge	2.3	9.1	<0.0001
IES	30.6	Endometrial cancer	0.2	0.5	NI
		Bleeding	4.0	5.5	0.05
ABCSG/ARNO	28	Endometrial cancer	<1(n=1)	<1(n=7)	0.069
		Bleeding/discharge	18	17	0.94

Reported incidences of fractures and osteoporosis

Study	Follow-up (months)	Symptoms	AI(%)	Tam(%)	P
ATAC	33.3	Fracture	5.9	3.7	<0.0001
BIG 1-98	25.8	Fracture	5.7	4.0	<0.001
IES	30.6	Fracture, osteoporosis	3.1,7.4	2.3,5.7	0.08,0.05
ABCSG/ARNO	28	Fracture	2.0	1.0	0.015

Reported incidences of arthralgia

Study	Follow-up(months)	AI(%)	Tam(%)	P
ATAC	33.3	27.8	21.3	<0.0001
BIG 1-98	25.8	20.3	12.3	<0.001
IES	30.6	5.4	3.6	0.01
ABCSG/ARNO	28	NR	NR	-

Psychological morbidity: not reported

General comments: -

Study Identification:	Winer, E.P, Hudis, C., Burstein, H.I., Wolff, A.C., Pritchard, K.I., Ingle, J.N., Chlebowski, R.T., Gelber, R., et al -American Society of Clinical Oncology Technology Assessment on the Use of Aromatase Inhibitors As Adjuvant Therapy for Postmenopausal Women With Hormone Receptor—Positive Breast Cancer: Status Report 20114 – Journal of Clinical Oncology, 2005,23 column 3 pp619-629
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	4 RCT of AI vs tamoxifen or placebo in early breast cancer hormone receptor positive ATAC: n=9366; ITA: n=426; IES: n=4742; MA17: n=5187
Intervention:	ATAC: tamoxifen vs anastrozole vs tamoxifen + anastrozole ITA: anastrozole sequential to 2-3 year course of tamoxifen IES: tamoxifen vs exemestane sequential to 2-3 year course tamoxifen MA17: letrozole vs placebo sequential to 5 year course of tamoxifen
Outcomes:	Rate of recurrence, distant recurrence, total events
Follow-up:	ATAC: median 33.3 months; ITA: median 24 months; IES: median 30.6 months; MA17: median 26.8 months
Results:	Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor—positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, or 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor—negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized.

OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:		
ATAC: HR for recurrence A vs T is 0.82(0.70-0.96; p=0.014)		
ITA: HR for recurrence 0.36 (0.17-0.75; p=0.006)		
IES: HR for recurrence 0.68 (0.56-0.82; p=0.00005)		
MA17: HR for recurrence L vs P 0.57 (0.43-0.75; p=0.00008)		
Overall Survival:		
+		
Contralateral breast cancer: Not reported other than included in total events (recurrence, contralateral breast cancer or death)		
ATAC: total events anastrozole 413 tamoxifen 472		
ITA: total events anastrozole 10 tamoxifen 26		
IES: total events exemestane 183 tamoxifen 266		
MA17: total events letrozole 92 placebo 94		
Quality of life (including side effects): Not reported		
Psychological morbidity: Not reported.		
General comments:		

Study Identification:	Scott,L.J., Keam,S.J., Letrozole In Postmenopausal Hormone-Responsive Early-Stage Breast Cancer Drugs 200ts 66 (3): 353-362
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	Postmenopausal women with hormone responsive early stage breast cancer (8000 mean age 61 years; range 38—90 years;5000)
Intervention:	BIG1-98 trial once daily letrozole 2.5mg vs once daily tamoxifen 20mg; MA17 trial once daily letrozole 2.5mg
Outcomes:	DFS, QOL
Follow-up:	Median 25.8 months; 30 months
Results:	<p>As first-line adjuvant therapy in 8000 postmenopausal women with hormone-responsive, early stage breast cancer, once-daily letrozole 2.5mg significantly prolonged disease-free survival (DFS; primary endpoint) and reduced the risk of relapse at distant sites relative to once-daily tamoxifen 20mg in the ongoing Breast International Group 1-98, double-blind, multinational trial. Extended adjuvant therapy with once-daily letrozole 2.5mg significantly prolonged DFS relative to placebo treatment in the MA-17 trial in 5000 postmenopausal women who were disease free after 4.5—6 years of tamoxifen therapy for hormone-responsive, early-stage breast cancer.</p> <p>Letrozole treatment for up to 5 years was generally well tolerated in this clinical setting. As first-line treatment, relative to tamoxifen, letrozole was associated with a significantly lower incidence of venous thromboembolic events, vaginal bleeding, hot flushes and night sweating, whereas the incidence of cardiac failure, bone fractures and arthralgia was higher in letrozole recipients.</p>

OUTCOME OF INTEREST	COMPARISON	RESULT
<p>Disease-free survival: BIGT trial prospectively planned subgroup analyses, there were significantly (all $p < 0.05$) fewer DFS events in letrozole than tamoxifen recipients who were aged <65 ($n = 5143$; 187 vs 230 events; HR 0.82; 95% CI 0.67, 0.99) or ≥ 65 years ($n = 2867$; 164 vs 198 events; HR 0.79; 95% CI 0.64, 0.97), tumour $>2\text{cm}$ ($n = 2973$; 190 vs 251 events; HR 0.76; 95% CI 0.63, 0.92), node positive ($n = 3311$; 205 vs 274 events; HR 0.71; 95% CI 0.59, 0.85), mastectomy ($n = 3452$; 223 vs 271 events; HR 0.76; 95% CI 0.64, 0.91), radiotherapy - yes ($n = 5744$; 227 vs 273 events; HR 0.82; 95% CI 0.69, 0.98) no ($n = 2258$; 124 vs 155 events; HR 0.77; 95% CI 0.61, 0.98) chemotherapy - yes ($n = 2024$; 92 vs 126 events; HR 0.70; 95% CI 0.54, 0.92).</p>		
<p>The magnitude of the beneficial reduction in the risk of disease recurrence with letrozole treatment was similar in estrogen receptor-positive women, irrespective of whether they were progesterone receptor PR-positive (179 vs 208 events with tamoxifen; DFS HR 0.84; 95% CI 0.69, 1.03, $p = 0.09$), PR-negative (89 vs 107 events; DFS HR 0.83; 95% CI 0.62, 1.10, $p = 0.18$) or PR status unknown (70 vs 92 events; DFS HR 0.72; 95% CI 0.53, 0.98, $p = 0.04$)</p>		
<p>MA17 trial; 122 events in the letrozole vs 193 in the placebo group; HR 0.62; 95% CI 0.49, 0.78, $p = 0.00003$) Notably, in a prospectively planned subgroup analysis of lymph node-positive patients, letrozole significantly ($p < 0.05$) reduced the risk of disease recurrence by 39% (DFS HR 0.61; 95% CI 0.45, 0.84), distant recurrence by 47% (distant DFS HR 0.53; 95% CI 0.36, 0.78) and overall survival by 39% (HR 0.61; 95% CI 0.38, 0.98)</p>		
<p>In a separate analysis evaluating the relationship between the duration of letrozole therapy in the extended adjuvant setting and hazard for recurrence of disease, the benefits of letrozole to placebo treatment increased as the duration of treatment increased. There was a significant ($p < 0.0001$) reduction in the HR for DFS (primary endpoint) from 0.52 (95% CI 0.40, 0.64) at 12 months to 0.19 (95% CI 0.04, 0.34) at 4 years in the placebo/letrozole group. Similarly, the distant DFS HR was reduced from 0.43 to 0.21 ($p = 0.0013$).</p>		
<p>Overall Survival: There was no between group difference in terms of 4-year overall survival rates (95.4% vs 95.0%); the HR for the risk of death from any cause was 0.82 (95% CI 0.57, 1.19).</p>		
<p>Contralateral breast cancer: Not reported other than DDFS</p>		
<p>Quality of life (including side effects): In the MA-17 trial, there was generally no significant difference in the frequency or nature of adverse events that occurred in the letrozole ($n = 2572$) and placebo groups ($n = 2577$) although there was a slightly higher incidence of treatment discontinuation because of adverse events in the letrozole group (4.9% vs 3.6%, $p = 0.019$).</p>		

Approximately 97% of all treatment- emergent adverse events were grade 1 or 2 according to the National Cancer Institute's common toxicity criteria. The frequency of cardiovascular events (5.8% vs 5.6%), hypercholesterolaemia (16% vs 16%) and endometrial cancer (0.2% vs 0.4%) was similar in both groups.

Hot flushes (58% vs 54%, $p = 0.003$), arthralgia (25% vs 21%, $p < 0.001$), myalgia (15% vs 12%, $p = 0.004$), anorexia (6% vs 4%, $p = 0.039$) and alopecia (5% vs 3%, $p = 0.01$) occurred significantly more frequently in letrozole than placebo recipients, whereas significantly fewer letrozole recipients experienced vaginal bleeding (6% vs 8%, $p = 0.005$). In addition, although the incidence of new self-reported osteoporosis increased in letrozole recipients compared with placebo recipients (8.1% vs 6%, $p = 0.003$), there was no difference between the two treatment groups in the proportion of patients experiencing a clinical fracture during the study period (5.3% vs 4.6%)

Psychological morbidity: Not reported.

General comments:

Study Identification:	Boccardo, F., Rubagotti, A., Aldrighetti, D., Buzzi, F., et al - Switching to an Aromatase Inhibitor Provides Mortality Benefit in Early Breast Carcinoma-Cancer 2007 109:6 pp1060-1067
Design:	Pooled analysis of RCTs evidence level 1+
Country / Setting:	Italy
Population:	Post-menopausal women with ER+ tumours and node + disease
Intervention:	Pooled analysis of 2 prospective multi-centre trials with the same study design and identical inclusion criteria: tamoxifen for 2 or 3 years + randomisation to continuing tamoxifen for 2 or 3 years or switch to aminoglutethimide or anastrozole.
Outcomes:	Mortality
Follow-up:	GROCTA 4B median 61 months, ITA median 64 months
Results:	All-cause mortality (HR 0.61 [0.42—0.88] p= .007) and breast cancer-related mortality (HR 0.61 [0.39— 0.94] p = .025) was significantly improved in women who switched to AG or ANA. On the contrary, even though more women in the tamoxifen group appeared to have died in the absence of obvious disease recurrence, there was no significant difference between groups in breast cancer-unrelated mortality. The probability of death increased over time both for the women who died after breast cancer recurrence and for those who died before disease recurrence. However, the average time before death was about double for women in the latter group compared with those in the former group (average time before death being 96 and 54 months, respectively). Multivariate analysis shows that patient age, tumour size, allocated treatment, and nodal status, in that order, were independent predictors of the risk of dying.
General comments: Both trials were concluded without having reached the planned recruitment size and therefore lack statistical power to analyse the impact of switching on mortality. In GROCTA 4B trial the aminoglutethimide is no longer in use for the treatment of cancer.	

Study Identification :	Buzdar, A.U., Guastalla, J.P., Nabholz, J.M., Cuzick, J. Impact of Chemotherapy Regimens Prior to Endocrine Therapy: Results From the ATAC (Anastrozole and Tamoxifen, Alone or in Combination) Trial – Cancer 2006, 107:3, pp. 472-480
Design:	RCT; evidence level 1++
Country / Setting:	International
Population:	1345 patients from the ATAC trial population who have received prior chemotherapy

Intervention:	5 years tamoxifen alone vs. anastrozole alone – impact of prior chemotherapy sub-study: chemotherapy regimens divided into 3 subgroups: 1) CMF only; 2) anthracycline-containing regimens (anthracycline or anthracycline and CMF); and 3) other chemotherapy regimens, including taxane-containing combinations.											
Outcomes:	Time to recurrence											
Follow-up:	Median 68 months											
Results:	<p>On the basis of the 5-year Completed Treatment Analysis, the ATAC trial does not indicate that the relative treatment benefits of anastrozole differ significantly between patients who received prior chemotherapy and those who did not. No evidence was found for an interaction between prior chemotherapy and anastrozole (HR, 0.89 vs. 0.74 for those with or without prior chemotherapy, respectively; $p = .21$ for interaction).</p> <p>For those with prior chemotherapy, the HR of anastrozole when compared with that of tamoxifen shifted from 0.98 (95% CI, 0.76—1.28) at 47 months' median follow-up to 0.89 (95% CI, 0.71—1.12) at 68 months' median follow-up and was closer to the overall treatment effect (HR, 0.79; 95% CI, 0.70—0.90). No differences according to type of chemotherapy were seen, and a benefit for anastrozole was also apparent for patients receiving prior CMF (HR 0.89; 95% CI, 0.63—1.24).</p>											
<table border="1"> <thead> <tr> <th data-bbox="120 1020 711 1058">OUTCOME OF INTEREST</th> <th data-bbox="711 1020 1084 1058">COMPARISON</th> <th data-bbox="1084 1020 1502 1058">RESULT</th> </tr> </thead> <tbody> <tr> <td data-bbox="120 1094 711 1570"> <p>Time to recurrence: At 68 months' median follow-up, the previously reported potential treatment interaction between patients who had received prior chemotherapy and those who had not was no longer apparent (HR, 0.89 vs. 0.74 for those with or without prior chemotherapy, respectively; $p = 0.21$ for interaction). A longer time to recurrence was maintained for anastrozole than for tamoxifen in the anthracycline containing (HR, 0.92; 95% CI, 0.60—1.40) and taxane containing (HR, 0.85; 95% CI, 0.52—1.38) subgroups. This is now evident for the CMF subgroup (HR, 0.89; 95% CI, 0.63—1.24) Adjusting for chemotherapy type had almost no effect on the time to recurrence analysis in the intent-to-treat population (unadjusted HR, 0.79; 95% CI, 0.70—0.90 vs. adjusted HR, 0.79; 95% CI, 0.69—0.90) trends for the hormone-receptor-- positive patient population: CMF (n = 470; HR, 0.95; 95% CI, 0.63—1.44), anthracycline-containing (n =401; HR, 1.10; 95% CI, 0.67—1.80), and other, including taxane-containing (n = 208; HR, 0.81; 95% CI, 0.46—1.40).</p> </td> <td data-bbox="711 1094 1084 1570"></td> <td data-bbox="1084 1094 1502 1570"></td> </tr> <tr> <td colspan="3" data-bbox="120 1606 1502 1675"> <p>Effect of Prior Chemotherapy regimen on HR for time to recurrence (intent to treat population)</p> </td> </tr> <tr> <td colspan="3" data-bbox="120 1682 1502 1717"> <p>General comments: -</p> </td> </tr> </tbody> </table>	OUTCOME OF INTEREST	COMPARISON	RESULT	<p>Time to recurrence: At 68 months' median follow-up, the previously reported potential treatment interaction between patients who had received prior chemotherapy and those who had not was no longer apparent (HR, 0.89 vs. 0.74 for those with or without prior chemotherapy, respectively; $p = 0.21$ for interaction). A longer time to recurrence was maintained for anastrozole than for tamoxifen in the anthracycline containing (HR, 0.92; 95% CI, 0.60—1.40) and taxane containing (HR, 0.85; 95% CI, 0.52—1.38) subgroups. This is now evident for the CMF subgroup (HR, 0.89; 95% CI, 0.63—1.24) Adjusting for chemotherapy type had almost no effect on the time to recurrence analysis in the intent-to-treat population (unadjusted HR, 0.79; 95% CI, 0.70—0.90 vs. adjusted HR, 0.79; 95% CI, 0.69—0.90) trends for the hormone-receptor-- positive patient population: CMF (n = 470; HR, 0.95; 95% CI, 0.63—1.44), anthracycline-containing (n =401; HR, 1.10; 95% CI, 0.67—1.80), and other, including taxane-containing (n = 208; HR, 0.81; 95% CI, 0.46—1.40).</p>			<p>Effect of Prior Chemotherapy regimen on HR for time to recurrence (intent to treat population)</p>			<p>General comments: -</p>		
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<p>Effect of Prior Chemotherapy regimen on HR for time to recurrence (intent to treat population)</p>												
<p>General comments: -</p>												

Randomised controlled trials:

Study Identification :	Buzdar, A.U., and Jack Cuzick, J. -Anastrozole as an Adjuvant Endocrine Treatment for Postmenopausal Patients with Breast Cancer: Emerging Data, Clinical Cancer Research, 2006, 12:3, pt. 2, pp 1037-1048	
Design:	RCT; evidence level 1++	
Country / Setting:	International	
Population:	6,241 post-menopausal women with early breast cancer were randomized between the two monotherapy arms (intent-to-treat population). Mean age 64 years; 61% lymph node negative, 84% hormone receptor positive, and 64% tumor \leq 2 cm in maximum diameter	
Intervention:	5 years tamoxifen alone vs anastrozole alone	
Outcomes:	DFS, OS, AESAE,	
Follow-up:	Median 68 months	
Results:	Using an aromatase inhibitor as initial adjuvant therapy is a better option than switching to an aromatase inhibitor after 2 years of tamoxifen. Treatment with anastrozole showed superior disease-free survival, time to recurrence, and time to distant recurrence, as well as contralateral recurrence benefits, compared with tamoxifen. Without adjuvant treatment, the recurrence rate observed over 5 years is 26.5% in women with ER+ disease, a rate that is reduced to 15.1% with tamoxifen. The efficacy benefits for anastrozole are over and above the benefits seen with tamoxifen and lead to a further 3.3% absolute reduction in the risk of recurrence at 5 years for patients receiving anastrozole compared with those receiving tamoxifen. The main features are suppression by anastrozole of the early peak of recurrence observed with tamoxifen treatment and continued hazard reduction throughout the entire treatment period, which seems to extend beyond the end of treatment. Therefore, waiting for 2 to 3 years before switching from tamoxifen to anastrozole will result in some patients developing recurrences that could have been prevented by initial adjuvant treatment with anastrozole. Adverse events judged by the investigator to be treatment related were significantly less common with anastrozole than with tamoxifen, as were treatment-related serious adverse events. Withdrawals due to adverse events were significantly less frequent for anastrozole than tamoxifen.	
OUTCOME OF INTEREST	COMPARISON	RESULT
<p>Disease-free survival: Disease-free survival was significantly greater in the anastrozole group compared with the tamoxifen group in the intent-to-treat population (HR. 0.87; 95% CI 0.78-0.97; $p = 0.01$) and in the hormone receptor—positive population (HR. 0.83; 95% CI, 0.73-0.94; $p = 0.005$), with a 17% lesser risk of recurrence and an absolute difference of 3.3% between treatment arms in hormone receptor— positive patients at a median follow-up of 68 months.</p> <p>Overall Survival: Although there was no material difference for overall survival ($p = 0.7$ in both the intent-to-treat and hormone receptor— positive populations; HR. 0.97; 95% CI, 0.85-1.12 and HR. 0.97; 95% CI, 0.83-1.14, respectively), there was a nonsignificant trend in favor of anastrozole for time to breast cancer death ($p = 0.2$ in both the intent-to-treat and hormone receptor—positive populations; HR, 0.88; 95% CI, 0.74-1.05 and HE, 0.87; 95% CI, 0.70-1.09, respectively).</p> <p>Contralateral breast cancer: Not reported other than time to recurrence. The advantage of anastrozole in reducing the risk of recurrence was more pronounced in the estrogen receptor—</p>		

<p>positive (ER+)/PR-negative (PR—) group (HR. 0.43; 95% CI, 0.31-0.61) than in the ER+/PR+ group (HR, 0.43; 95% CI, 0.69-1.02;).</p> <p>Quality of life (including side effects): Treatment-related adverse events leading to death that occurred while receiving study treatment numbered 6 (0.2%) in the anastrozole group and 10 (0.3%) in the tamoxifen group (difference between groups not significant, p = 0.5).</p> <p>Psychological morbidity: Not reported.</p> <p>General comments: -</p>
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Study Identification :	Howell,A., Cuzick,J., Baum,M., Buzdar,A., Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet, 2005 365, 9453 pp.60-62
Design:	RCT; evidence level 1++
Country / Setting:	International
Population:	9366 Post-menopausal women with hormone receptor positive localised breast cancer Baseline patients characteristics; see ATAC trial
Intervention:	A double-blind randomised trial, compared 5 years of the aromatase inhibitor anastrozole alone with tamoxifen alone, or the combination, as adjuvant therapy in 9366 postmenopausal women with localised breast cancer.
Outcomes:	DFS, time to recurrence, distant metastases, contralateral breast cancer
Follow-up:	5 years median 68 months
Results:	5 years of anastrozole should be considered as the preferred initial adjuvant endocrine treatment for post- menopausal women with hormone-receptor-positive localised breast cancer. anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0.87, 95% CI 0.78—0.97, p=0 .01) and time-to-recurrence (402 vs 498, 0-79, 0-70—0-90, p=0 .0005), and significantly reduced distant metastases (324 vs 375, 0.86, 0-74—0.99, p=0 .04) and contralateral breast cancers (35 vs 59, 42% reduction, 12—62, p=0 .01).

OUTCOME OF INTEREST	COMPARISON	RESULT
<p>Disease-free survival: Treatment with anastrozole led to significant improvements compared with tamoxifen for disease-free survival (575 vs 651 events, hazard ratio 0.87, 95% CI 0.78—0.97, p=0.01) and time-to-recurrence (402 vs 498 0.79, 0.70—0.90, p=0.0005). A greater advantage was seen in disease-free survival (0.83, 0.73—0.94, p=0.005) and in time-to-recurrence (0.74, 0.64—0.87, p=0.0002) in hormone-receptor-positive patients. This 26% risk reduction over tamoxifen for time-to-recurrence is in addition to the 47% risk reduction previously shown for 5 years of tamoxifen versus placebo in adjuvant studies. No significant differences were noted in effect according to subgroup at the 1% level, and the hazard rate was lower for anastrozole in all subgroups except for patients who were hormone-receptor-negative or whose hormone-receptor status was unknown.</p>		
<p>Overall Survival: Overall survival was similar for anastrozole and tamoxifen (hazard ratio 0.97, 95% CI 0.85—1.12, p=0.7); a 12% reduction in deaths from breast cancer in the anastrozole group was not significant (0.88, 0.74—1.05; p=0.2). However, since the trial population had a relatively good prognosis (5695 [61%] of patients were lymph-node-negative and 5959 [64%] had tumours 2cm or smaller in diameter), it is too early to expect a difference in survival.</p>		
<p>Contralateral breast cancer: The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen (all patients 35 vs 59, 42% reduction, 95% CI 12 - 62, p=0.01; hormone-receptor-positive patients 53%, 25—71, p=0.001). Since tamoxifen shows a 50% reduction in the occurrence of these tumours in hormone-receptor-positive patients compared with placebo, the findings from the ATAC study suggest that anastrozole treatment might prevent 70—80% of hormone-receptor-positive tumours in women at high risk of breast cancer.</p>		
<p>Quality of life (including side effects): Withdrawals due to adverse events were significantly less common with anastrozole (344, 11.1%) than with tamoxifen (442, 14.3%; p=0.0002). Drug-related serious adverse events were also significantly less common with anastrozole (146, 4.7%) than with tamoxifen (271, 9.0%; p<0.0001). Treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes, and vaginal discharge, compared with tamoxifen.</p>		
<p>Psychological morbidity: Not reported.</p>		
<p>General comments: -</p>		

Study Identification :	Thurlimann, B., Keshaviah,A., Coates, AS., Mouridsen, H., Mauriac, L., Forbes, JF. Et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer N Engl J Med, Vol.353(26),2005 pp2747-2757
Design:	RCT; evidence level 1++
Country:	International
Population:	8010 postmenopausal women with hormone-receptor-positive breast cancer
Intervention:	The Breast International Group (BIG) 1-98 study is a randomized, phase 3, double-blind trial that compared five years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor-positive breast cancer:letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. This analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment.
Outcomes:	DFS local recurrence contralateral breast cancer regional recurrence
Follow-up:	Median 25.8 months
Results:	In postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites. Five-year disease-free survival estimates of 84.0 percent and 81.4 percent, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (hazard ratio, 0.81; 95 %CI, 0.70 to 0.93; P=0.003), especially the risk of distant recurrence (hazard ratio, 0.33; 95 %CI, 0.60 to 0.88; P=0.001). Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and Cardiac events and of hypercholesterolemia.

OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:		Disease-free survival was significantly greater in the letrozole group than in the tamoxifen group (HR, 0.81; 95 %CI, 0.70 to 0.93; p=0.003 by the log-rank test), especially reducing recurrence at distant sites (HR, 0.73; 95 %CI, 0.60 to 0.88; p=0.001 by the log-rank test). The five-year estimates of disease-free survival were 84.0% in the letrozole group and 81.4% in the tamoxifen group. A beneficial effect of letrozole was also seen in analyses comparing the two monotherapy groups. Subgroup analyses of DFS showed a greater effect of letrozole than of tamoxifen among patients who received chemotherapy, those who did not receive radiotherapy, and those with involved axillary lymph nodes. 5 year DFS rate among patients with node-positive cancer was 77.9% in the letrozole group and 71.4% in the tamoxifen group; the value among patients with node-negative cancer was 88.7% in both groups. The beneficial effect of letrozole on disease-free survival was similar for all combinations of estrogen-receptor and progesterone-receptor status.
Overall Survival:		The overall survival did not differ significantly between groups.
Contralateral breast cancer:		Significantly fewer events were reported in the letrozole group 16 (0.4%) compared to the Tamoxifen group 27 (0.7%)
Quality of life (including side effects):		More patients in the letrozole group than in the tamoxifen group reported at least one protocol-specified adverse event of any grade (2912 patients vs. 2554 patients), but the number of patients with life-threatening or fatal protocol-specified adverse events was similar in the two groups (67 of 3975 [1.7%] and 69 of 3988 [1.7%], respectively). Fractures were significantly more frequent in the letrozole group than in the tamoxifen group (5.7% vs. 4.0%, p<0.001) (Table 3), with a significantly shorter time to a first fracture reported within four weeks after the end of treatment (P<0.001). As compared with tamoxifen, letrozole was associated with fewer thromboembolic events (1.5% vs. 3.5%, p<0.001), a lower rate of vaginal bleeding (3.3% vs. 6.6%, p<0.001), fewer endometrial biopsies (72 of 3089 women [2.3%] vs. 288 of 3157 women [9.1%], p<0.001), and fewer invasive endometrial cancers (4 of 3089 women [0.1%] vs. 10 of 3157 women [0.3%], p=0.18).
Psychological morbidity:		Not reported.

Study Identification :	Coates, A., Keshaviah,A., Thurliman, B., Mouridsen, H., Mauriac, L., Forbes, J.F., et al Five Years of Letrozole Compared With Tamoxifen as Initial Adjuvant Therapy for Postmenopausal Women with Endocrine-Responsive Early Breast Cancer: Update of Study BIG 1-98: Journal of Clinical Oncology 2007,25,5 pp 486-492
Design:	RCT; evidence level 1++
Country / Setting:	International
Population:	4922 of the 8,028 postmenopausal women with receptor- positive early breast cancer randomly assigned (double-blind) to the BIG 1-98 trial
Intervention:	5 years of continuous adjuvant therapy with either letrozole (2.5mg daily) or tamoxifen (20mg daily)
Outcomes:	DFS, OS, Systemic DFS, Time to recurrence, time to distant recurrence,
Follow-up:	Median 51 months
Results:	The present updated analysis, which was limited to patients on monotherapy arms in BIG 1-98, yields results similar to those from the previous primary analysis but more directly comparable with results from other trials of continuous therapy using a single endocrine agent At a median follow-up time of 51 months, 352 DFS events were observed among 2,463 women receiving letrozole and 418 events among 2,459 women receiving tamoxifen. This reflected an 18% reduction in the risk of an event (HR, 0.82, 95%CI, 0.71 to 0.95; p= .007). No predefined subsets showed differential benefit. Adverse events were similar to previous reports. Patients on tamoxifen experienced more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding. Patients on letrozole experienced more bone fractures, arthralgia, low-grade hypercholesterolemia, and cardiovascular events other than ischemia and cardiac failure.

OUTCOME OF INTEREST**COMPARISON****RESULT**

Disease-free survival: 352 DFS events were recorded among the 2,463 patients assigned to letrozole, and 418 DFS events were recorded among the 2,459 patients assigned to tamoxifen. The hazard ratio for DFS was 0.82 (95%CI, 0.71 to 0.95; p= .007), and the 5-year DFS survival estimates were 84.0% and 81.1% for letrozole and tamoxifen, respectively.

Overall Survival: 194 OS events were recorded among the letrozole patients compared to 211 in tamoxifen patients.
(HR 0.91, 95%CI 0.75-1.11, p=0.35)

Contralateral breast cancer: Not reported other than time to recurrence and time to distant recurrence .

Quality of life (including side effects): More patients receiving letrozole, compared with patients receiving tamoxifen, reported at least one adverse event of any grade (2,292 patients v 2,165 patients, respectively) and at least one life-threatening or fatal adverse event (113 of 2,448 patients [4.6%] v 92 of 2,447 patients [3.8%], respectively).

Psychological morbidity: Not reported.

General comments: -

Study Identification :	Ingle, JN., Tu, D., Pater, JL., Martino, S., Robert, NJ., Muss, HB., et al. Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial. <i>Breast Cancer Research and Treatment</i> (2006) 99:295—300
Design:	RCT; evidence level 1++
Country / Setting:	International
Population:	5187 postmenopausal women that established letrozole to be of value in reducing recurrence of breast cancer when given in the extended adjuvant therapy setting after about 5 years of tamoxifen. Hormone receptor status was positive in 97.4%, negative in 0.15% and unknown or missing in 2.4%. 2360 women had node-positive status and 2568 had node-negative status.
Intervention:	Randomized to letrozole, 2.5 mg orally daily, or placebo with a planned treatment duration of 5 years. Prior adjuvant tamoxifen therapy for 4.5—6 years for a histologically confirmed breast cancer that was estrogen receptor and/or progesterone receptor positive defined as ≥ 10 fmol/mg protein by a biochemical assay or positive by immunohistochemical stain or hormone receptor unknown.
Outcomes:	DFS, DDFS, OS
Follow-up:	median 48 months
Results:	<p>Longer duration of letrozole treatment is associated with greater benefit in the extended adjuvant therapy setting at least out to about 48 months.</p> <p>Considering all patients, HRs for events in DFS and DDFS progressively decreased over time, favoring letrozole, with the trend being significant ($p < 0.0001$ and $p = 0.0013$, respectively) whereas the trend for OS was not significant.</p> <p>Considering the 2360 patients with node-positive status, the HRs for DFS, DDFS and OS all decreased over time with tests for trend all showing significance ($p = 0.0004$, 0.0005 and 0.038, respectively).</p> <p>Considering the 2568 patients with node-negative status, the HRs for DFS decreased over time with the test for trend being significant ($p = 0.027$) whereas the HRs for DDFS and OS showed no significant change over time.</p>

OUTCOME OF INTEREST**COMPARISON****RESULT**

Disease-free survival: The HR for an event in DFS decreased in all patients from 0.59 at 6 months to 0.19 at 48 months with the decreasing trend in HRs being significant ($p < 0.0001$). For node-positive cohort, the HR decreased from 0.66 at 6 months to 0.24 at 48 months with the decreasing trend in HRs being significant ($p = 0.0004$). For node-negative cohort the HR decreased from 0.72 at 6 months to 0.43 at 48 months with the decreasing trend in HRs being significant ($p = 0.027$).

Overall Survival: For all patients, the HRs were similar between 6 months (HR = 0.87) and 48 months (HR = 0.79) and the test for trend in HRs was not significant ($p = 0.33$). For node positive patients, the HR for death decreased from 0.64 at 6 months to 0.40 at 48 months with the decreasing trend in HRs being significant ($p = 0.038$). For node negative patients, the HRs likewise were similar between 6 months (HR = 2.50) and 48 months (HR = 2.75) and the test for trend was not significant ($p = 0.34$).

Contralateral breast cancer: Not reported other than DDFS.

Quality of life (including side effects): Not reported.

Psychological morbidity: Not reported.

General comments: -

Study Identification :	Mann, BS., Johnson, JR., Kelly, R., Sridhara, R., Williams, G., Pazdur, R.- Letrozole in the Extended Adjuvant Treatment of Postmenopausal Women with History of Early-Stage Breast Cancer Who Have Completed 5 Years of Adjuvant Tamoxifen. Clin Cancer Res 2005:11 (16)
Design:	RCT; evidence level 1+
Country / Setting:	International
Population:	5187 Postmenopausal women with history of hormone receptor — positive or unknown early-stage breast cancer that had been surgically removed, who had completed 5 years of adjuvant tamoxifen within 3 months before randomization, free of breast cancer recurrence, ECOG status of ≤ 2 , life expectancy of ≥ 5 years, adequate bone marrow and liver functions.
Intervention:	Randomized to letrozole, 2.5 mg orally daily, or placebo with a planned treatment duration of 5 years. Prior adjuvant tamoxifen therapy for 4.5— 6 years for a histologically confirmed breast cancer that was estrogen receptor and/or progesterone receptor positive defined as ≥ 10 fmol/mg protein by a biochemical assay or positive by immunohistochemical stain or hormone receptor unknown.
Outcomes:	DFS, DDFS, OS
Follow-up:	median 48 months
Results:	Letrozole administration led to a statistically significant prolongation in DFS. No statistically significant improvement in overall survival was observed. Hot flushes, arthralgia/arthritis, myalgia, and new diagnosis of osteoporosis were more common on letrozole. Frequency of fractures and cardiovascular ischemic events was not significantly different. A statistically significant mean decrease in bone mineral density in the hip occurred at 24 months on letrozole.

OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:	DFS:122 events on letrozole and 193 events on placebo were observed (HR, 0.62; 95%CI, 0.49-0.78; p=0.00003).	
Overall Survival:	No statistically significant improvement in OS was observed. 68 and 78 deaths in the letrozole and the placebo arms, respectively (HR, 0.87; 95%CI, 0.63-1.21).	
Contralateral breast cancer:	Not reported other than DDFS. Distant disease-free survival DDFS also improved with letrozole, 55 vs92 events (HR, 0.61; 95% CI. 0.44-0.84; p=0.003).	
Quality of life (including side effects):	Hot flushes, arthralgia/arthritis, and myalgia were significantly more common in the letrozole arm (50% vs 43%, 28% vs 22%, and 10% vs 7%, respectively; p < 0.001 for each comparison).	
	Incidence of new diagnosis of osteoporosis reported by the patients was significantly higher in the letrozole arm, both while on treatment (6.4% vs 4.9%, p = 0.02) and at any time after randomization (6.9% vs 5.5%, p = 0.042).	
	The frequency of fractures was not significantly different between the two groups (5.9% vs 5.5%, p = 0.6196).	
Psychological morbidity:	Not reported.	
General comments:	- Short duration of treatment and follow-up precluded assessment of long-term safety and efficacy.	

Cohort Studies:

Study Identification :	Whelan, T.J., Goss, P.E., Ingle, J.N., Pater, J.L., Tu, D., Pritchard, K., et al Assessment of Quality of Life in MA. 17: A Randomized, Placebo-Controlled Trial of Letrozole After 5 Years of Tamoxifen in Postmenopausal Women: Journal of Clinical Oncology official journal of the American Society of Clinical Oncology, 2005, 23, 28, pp. 6931-6940	
Design:	Cohort study, evidence level 2++	
Country / Setting:	International	
Population:	3,612 (69.9%) participating in the QOL substudy of MA17 trial comparing letrozole with placebo after adjuvant tamoxifen: 1,799 allocated to placebo and 1,813 allocated to letrozole.	
Intervention:	Mean change scores from baseline were compared between groups for summary measures and domains in the short form 36-item Health Survey (SF-36) and the Menopause Specific Quality of Life Questionnaire (MFNQOL) at baseline, 6 months, and annually. A response analysis compared the proportion of patients who demonstrated an important change in QOL	
Outcomes:	QOL	
Follow-up:	5 years	
Results:	Letrozole did not have an adverse impact on overall QOL. Small effects were seen in some domains consistent with a minority of patients experiencing changes in QOL compatible with a reduction in estrogen synthesis. No differences were seen between groups in mean change scores from baseline for the SF-36 physical and mental component summary scores at 6, 12, 24, and 36 months. Small (< 0.2 standard deviations) but statistically significant differences in mean change scores from baseline were seen for the SF-36 domains of physical functioning (12 months), bodily pain (6 months) and vitality (6 and 12 months), and the MENQOL vasomotor (6, 12, and 24 months) and sexual domains (12 and 24 months). On the response analysis, a significant difference was seen between groups for the bodily pain domain (percentage of patients reporting a worsening of QOL, 47% placebo v 51% letrozole; P = .009) and the vasomotor domain (22% placebo v 29% letrozole; p = .001).	
OUTCOME OF INTEREST	COMPARISON	RESULT
Disease-free survival:	Not reported	
Overall Survival:	Not reported	
Contralateral breast cancer:	Not reported.	
Quality of life (including side effects):	Significant predictors for worsening in quality of life for SF-36 physical component summary (PCS) included: age 50 to 59 v < 49 years, odds ratio [OR] = 1.70, p = .0008 60 to 69 v < 49 years, OR = 2.04, p = .0001	

≥ 70 v < 49 years, OR = 2.56, $p < .0001$
and baseline PCS score (OR 1.03; $p < .0001$)

Sole predictor for worsening of the SF-36 mental component summary (MCS) was the baseline MCS score (OR = 1.05; $p < .0001$).

For the SF-36 bodily pain domain, predictors included

age 50-59 v < 49 years, OR = 1.71, $p = .0004$

60 to 69 v < 49 years, OR = 1.51, $p = .007$

70 v < 49 years, OR 1.72, $p = .0006$

baseline bodily pain score (OR = 1.02; $p < .0001$)

and treatment (OR = 1.27; $P = .002$)

Predictors for worsening in the MENQOL vasomotor domain included

age (≥ 70 v < 49 years, OR = 0.54; $p = .0003$),

baseline vasomotor score (OR=0.86; $p < .0001$),

and treatment (OR = 1.46; $p < .0001$).

Symptom analysis

No. of patients experiencing being 'very bothered' by a specific symptom

Quality of life response analysis

Psychological morbidity: Not reported.

Study Identification :	Fallowfield, L.J., Bliss, J.M., Porter, L.S., Price, M.H., Snowdon, C.F., Jones, S.E., Coombes, R.C., Hall, E., - Quality of Life in the Intergroup Exemestane Study: A Randomized Trial of Exemestane Versus Continued Tamoxifen After 2 to 3 Years of Tamoxifen in Postmenopausal Women With Primary Breast Cancer – Journal of Clinical Oncology 2006, 24 column 6 pp910-917
Design:	Cohort study; evidence level 2++
Country / Setting:	International
Population:	582 postmenopausal women with early-stage, operable invasive breast cancer, had completed their primary treatment (surgery ± radiotherapy ± chemotherapy) according to local practice, and had received 2 to 3 years of adjuvant tamoxifen before enrolment. Baseline Demographic and Clinical Characteristics
Intervention:	This is a QOL subsidy of the IES trial (switched from tamoxifen to exemestane or continue with tamoxifen until 5 years of treatment were completed) QOL was measured using the Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire (version 3), together with an endocrine symptom subscale (ES) questionnaire (FACT-B+ES) The FACT-B is a 38 item questionnaire with six subscales assessing physical (seven items), social (seven items), emotional (six items), and functional (seven items) well being, relationship with doctor (two items), and additional concerns more specific to women with breast cancer (nine items). The ES was designed for use with the FACT-B and comprises 18 items. Four other items (sleep, fatigue, nervousness, and nausea) are already included in the FACE B. Patients indicated how true a statement had been for them over the past 7 days using a 5-point scale as follows: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All items receive equal weighting.
Outcomes:	Trial Outcome Index (TOI- the sum of the scores from the 23 items of the physical and functional wellbeing and the breast cancer subscales), total FACT-B+ES (reflecting overall QOL) and ES (reflecting burden of endocrine symptoms)
Follow-up:	60 months
Results:	The switch from tamoxifen to exemestane neither increased nor decreased endocrine symptoms present after 2 to 3 years of tamoxifen; the switch also did not initiate significant reports of new symptoms. Results indicate that the clinical benefits of exemestane over tamoxifen are achieved without significant detrimental effect on QOL. QOL was generally good and stable over 2 years, with no clinically meaningful differences found between groups in TOI or ES. Prevalence of severe endocrine symptoms at trial entry was high for vasomotor complaints and sexual problems, which persisted for both groups during the study. No significant differences between groups were seen for any endocrine symptoms apart from vaginal discharge, which was more pronounced with tamoxifen (p < .001).

OUTCOME OF INTEREST**COMPARISON****RESULT**

Disease-free survival: Not reported

Overall Survival: Not reported

Contralateral breast cancer: Not reported

Quality of life (including side effects): There were no significant treatment *differences in TOI scores* over the total time period from 3 to 24 months (mean TOI score for patients allocated to tamoxifen was 0.89 points higher than the score for patients in the exemestane group; 95%CI, -0.22 to 1.99).

There were no significant within-group changes in TOI for patients in the tamoxifen arm. Neither group displayed clinically meaningful mean changes at any time point, and the repeated-measures analysis suggested that, irrespective of treatment, TOI did not change significantly with time.

The proportions of patients who maintained a clinically meaningful TOI point increase from baseline at all the points and, thus, had a sustained improvement were 3.9% for exemestane (95%CI, 2.0% to 6.9%) and 4.7% for tamoxifen (95%CI, 2.5% to 7.9%) (p=.64).

The proportions of patients who had a clinically meaningful sustained decrease at each time point compared with baseline were 2.5% for exemestane (95%CI, 1.0% to 5.1%) and 3.6% for tamoxifen (95%CI, 1.8% to 6.6%) (p = .43).

There was no significant difference between treatment groups in **ES change** scores over time. At individual time points, no difference was seen at 6 months (mean difference [exemestane - tamoxifen] = -0.79; 95%CI, -2.02 to 0.44; p= .21) or at any other time point. Irrespective of treatment, mean ES scores increased (ie, endocrine symptoms decreased) over time.

Patients in the exemestane and tamoxifen arms had significantly higher ES scores compared with baseline (ie, fewer endocrine symptoms) at 9, 12, 18, and 24 months (all p≤0.01)

Total FACT-B +ES. No significant differences in total FACTB+ES scores were seen by treatment group or over time after adjustment for baseline score and known prognostic factors. There were no significant differences between treatment groups at 6 months (mean difference [exemestane - tamoxifen] = -3.08; 95% CI, -6.10 to -0.06; p= .05) or at any other time point. The only statistically significant within-treatment group change was seen at 6 months for patients in the exemestane arm, although this change was not clinically meaningful (mean change = -3.12; 95% CI, -5.37 to -0.87; p= .007).

Psychological morbidity: Not reported.

Guideline

Study Identification:	Thuerlimann, B., Koeberle, D., Senn, H.J., Guidelines for the adjuvant treatment of postmenopausal women with endocrine-responsive breast cancer: Past, present and future recommendations EUROPEAN JOURNAL OF CANCER 43 (2007) 46—52	
Design:	Guideline; evidence level 4	
Country / Setting:	Switzerland	
Population:	Guideline developed on the systematic review of RCT	
Intervention:	ATAC (comparing tamoxifen and anastrozole alone or in combination) BIGT 1-89 MA17 (comparing letrozole and tamoxifen alone or in combination)	
Outcomes:	DFS, relapse rates	
Follow-up:	Up to 5 years	
Results:	<p>It has been suggested that patients with ER-positive/PgR-negative, and/or HER-2--positive tumours appear to have an increased benefit with AI therapy compared with tamoxifen therapy. Retrospective, exploratory data from ATAC trial suggest that a benefit of anastrozole over tamoxifen is confined to the ER-positive/PgR-negative subgroup (for time to recurrence, hazard ratio (HR) = 0.84 versus 0.45, respectively).</p> <p>In contrast, data from assessment of ER/PgR in the BIG 1-98 trial show a benefit of letrozole irrespective of PgR status. The analysis of nearly 4400 tumours has shown that the small group of patients with HER-2 overexpression/amplification in the tumour had a higher rate of recurrence with both treatments. PgR status in ER-positive tumours did not predict responsiveness to letrozole when compared with tamoxifen. Thus, at present, neither HER-2 status nor PgR status help to select letrozole over tamoxifen for postmenopausal patients with ER-positive tumours.</p>	
	OUTCOME OF INTEREST	COMPARISON
	Disease-free survival – not reported	RESULT
	Overall survival – not reported	
	Contralateral breast cancer – benefit of anastrozole over tamoxifen in the ER-positive/PgR-negative subgroup, reported as time to relapse hazard ratio (HR) = 0.84 versus 0.45, respectively).	
	Quality of life – not reported	
	Psychological morbidity – not reported	
	General comments: -	

Gines Rubio J, Fernandez Cortez F, Rifa Ferrer J. [A meta-analysis of the effectiveness of aromatase inhibitors as adjuvant treatment for postmenopausal patients with breast cancer]. [Spanish]. Farmacia Hospitalaria 2007 Jan;31(1):5-16.

Design: Meta-analysis of RCTs (2000-2005)

Level 1+

Country: Spain setting:

Aim: To evaluate the efficacy and safety of aromatase inhibitors (AIs) as adjuvant hormonal therapy for postmenopausal patients with hormone receptor positive breast cancer compared with tamoxifen therapy, or as a subsequential treatment to this therapy.

Inclusion criteria

RCT phase III studies of AIs compared with tamoxifen.

Trials where an AI was given after 5 years of tamoxifen treatment.

Search of MEDLINE database between years 2000 and Dec 2005.

Papers from ASCO and SABCS conferences.

Exclusion criteria

Population

Postmenopausal women with hormone receptor positive early stage breast cancer.

Interventions

AI and tamoxifen treatments were compared either directly after surgery or following 2-3 years of treatment with tamoxifen.

Trials that incorporated the administration of an AI after 5 years of tamoxifen treatment as a continuation of hormone therapy.

Outcomes

DFS (defined as interval between randomisation and either disease recurrence or death with no recurrence)

OS (interval between randomisation and death due to any cause)

Side effects.

Follow up -

Results

7 studies were included:

ATAC 2005 Anastrozole

BIG 1-98 2005 Letrozole

IES 2004 Exemestane

ITA 2005 Anastrozole

ABCSG 8 and ARNO 95 combined (2005) Anastrozole

Ma.17 2005 Letrozole

ABCSG-6a 2005 (abstr) Anastrozole

Meta-analysis was conducted using the Mantel-Haenszel fixed effects model for DFS and OS. Analysis of subgroups was conducted by stratification into when the AI was administered (at the same time as the group receiving tamoxifen; sequentially after tamoxifen; and after 5 years of tamoxifen).

DFS

Seven studies reported DFS. AIs were shown to increase DFS in comparison to tamoxifen as a first-line therapy (MH OR = 0.83; 95% CI: 0.76-0.92) and when administered sequentially for 2-3 years following 2-3 years of tamoxifen treatment (MH OR = 0.65; 95% CI: 0.57-0.75). Use after 5 years of tamoxifen therapy also increased DFS (MH OR = 0.63; 95% CI: 0.51-0.77). The overall effect of AIs was significant in improving DFS (MH OR 0.75; 95% CI 0.69-0.81) $p < 0.00001$, however statistical heterogeneity was present between studies (I^2 65%).

Meta-analysis for DFS outcomes

Study	AI n/N	Control n/N	OR (95% CI)	p value
AI monotherapy vs. tamoxifen				
ATAC	575/3125	651/3116	0.85 (0.75-0.97)	0.0133
BIG 1-98	282/4003	346/4007	0.80 (0.68-0.94)	0.0082
<i>Combined:</i> Q =0.36; p 0.5506 I^2 0% no heterogeneity			0.83 (0.76-0.92)	0.0004
Sequential: Tamoxifen-AI vs. tamoxifen				
IES	262/2352	353/2372	0.72 (0.60-0.85)	0.0001
ITA	27/223	60/225	0.38 (0.22-0.62)	0.0001
ABCSG-8/ARNO95	88/1618	138/1606	0.61 (0.46-0.81)	0.0005
<i>Combined:</i> Q =5.93; p 0.0516 I^2 66% Significant heterogeneity			0.65 (0.57-0.75)	<0.0001
AI after 5 years of tamoxifen				
MA.17	125/2583	194/2587	0.63 (0.50-0.79)	0.0001
ABCSG-6a	30/387	56/469	0.62 (0.39-0.99)	0.044
<i>Combined:</i> Q =0.00; p 0.96 I^2 0% no heterogeneity			0.63 (0.51-0.77)	<0.0001
Overall effect	125/2583	194/2587	0.75 (0.69-0.81)	<0.00001
I^2 65% Significant				

heterogeneity
P=0.008

Forest Plot of DFS outcomes for RCTs:

OS

Five studies reported OS. A statistically significant improvement in OS was obtained when the AI was administered following 2-3 years of tamoxifen treatment (MH OR = 0.77; 95% CI: 0.64-0.94). The difference was not significant when the AI was administered instead of tamoxifen as first-line therapy (MH OR = 0.93; 95% CI: 0.83-1.05) from two studies of different pharmaceuticals (Anastrozole and Letrozole). The overall effect of AIs was significant in improving OS (MH OR 0.88; 95% CI 0.80-0.98) p=0.02, and no statistical heterogeneity was present between studies (I² 14%).

Meta-analysis for OS outcomes

Study	AI n/N	Control n/N	OR (95% CI)	p value
AI monotherapy vs. tamoxifen				
ATAC	411/3125	420/3116	0.97 (0.84-1.12)	0.70
BIG 1-98	166/4003	192/4007	0.86 (0.70-1.06)	0.16
<i>Combined:</i> Q =0.87; p 0.35 I ² 0% No significant heterogeneity			0.93 (0.83-1.05)	0.27
Sequential: Tamoxifen-AI vs. tamoxifen				
IES	152/2352	187/2372	0.81 (0.65-1.01)	0.0589
ITA	9/223	17/225	0.51 (0.22-1.18)	0.1167
ABCSG-8/ARNO95	45/1618	59/1606	0.75 (0.51-1.11)	0.1528
<i>Combined:</i> p 0.58 I ² 0% No heterogeneity			0.77 (0.64-0.94)	0.008
Overall effect	783/11321	875/11326	0.88 (0.80-0.98)	0.02
I ² 13.6% No significant heterogeneity P=0.33				

Forest plot of OS outcomes from RCTs: see figure in paper

Toxicity

There was no subgroup analysis for toxicity effects.

Anastrozole

Anastrozole showed a lower incidence of gynaecological and vascular events. However, bone fractures, mainly spinal fractures, and arthralgias were significantly higher (this data is from the ATAC trial comparing anastrozole with tamoxifen alone or in combination with tamoxifen). Gastrointestinal problems and alterations in lipid metabolism were also significantly higher with anastrozole than with tamoxifen (ITA study).

Letrozole

The incidence of arthralgias, myalgias, hot flashes, anorexia, and alopecia was found to be significantly higher in patients treated with letrozole than placebo. The incidence of osteoporosis appeared to be higher with letrozole than with placebo, although the difference was not statistically significant when measuring the number of bone fractures. Patients receiving placebo had a higher incidence of vaginal bleeding than those treated with letrozole. There were no differences observed in the incidence of cardiac events between the letrozole group and the placebo group.

Exemestane

Exemestane showed fewer thromboembolic events and gynaecological side-effects, as well as a lower incidence of second primary tumours. However, musculoskeletal toxicity, diarrhoea, and sight problems are more frequent with exemestane. The incidence of osteoporosis appeared to be higher in the exemestane group although the difference was not statistically significant when measuring the number of bone fractures. A higher number of myocardial infarctions occurred in the exemestane group compared with tamoxifen (1 vs. 0.4%, respectively) although the difference was not statistically significant.

Author conclusions

In comparison with tamoxifen, AIs reduce the incidence of thromboembolic and gynaecologic events, although they increase bone toxicity. The clinical studies evaluated show the consistent benefits of AIs at different adjuvant treatment stages; however, we have been unable to establish the optimum moment for their introduction due to the absence of direct comparisons between the different strategies. We now need to focus on the selection of patient sub-groups which could benefit from their use as a first-line therapy, the long-term toxicity of AIs, and their capacity to increase OS, regardless of the strategy followed, after a longer monitoring period. In light of the evidence available, bearing in mind certain limitations, we propose criteria for the use of AIs in daily clinical practice.

General comments –

$I^2 > 50\%$ indicates substantial statistical heterogeneity.

The overall effects (ORs) of AIs for DFS and OS were not reported in the paper, these were obtained by transferring the data to Review Manager.

Subgroup analyses were not performed. This study was included to show the effects of AIs on outcomes from the major RCTs comparing tamoxifen or placebo with AIs.

Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of **ABCSG trial 8 and ARNO 95** trial.[see comment]. Lancet 2005 Aug 6;366(9484):455-62.

Design: Analysis of data from 2 RCTs (1996-2003)

Level

1+

Country: Austria, setting:

Aim: To investigate whether women who received a period of adjuvant tamoxifen would benefit from being switched to anastrozole.

Inclusion criteria

ABCSG-8 postmenopausal women \leq 80 years

ARNO-95 postmenopausal women \leq 75 years

All had histologically verified, locally radically treated invasive or minimally invasive breast cancer without previous chemotherapy, hormone therapy, or radiotherapy, tumour infiltration of up to ten (ABCSG trial 8) or nine (ARNO 95) lymph nodes, and absence of organ metastases.

Exclusion criteria

Exclusion criteria for both trials were indeterminate menopausal status (or menopausal status maintained by medication), presence of secondary malignant disease, tumour infiltration of skin or breast muscle (T4 tumours), and presence of other concomitant serious medical conditions.

Population number of patients = 3224 analyzed

(ABCSG- 8 N=2262

ARNO 95 N=962)

HR status:

Randomization was to either continue tamoxifen (n=1606) or switch to anastrozole (n=1618).

	Tamoxifen	Anastrozole
ER+/PgR+	1247 (78%)	1272 (79%)
ER+/PgR-	281 (18%)	283 (18%)
ER-/PgR+	39 (2%)	28 (2%)
Unknown	39 (2%)	35 (2%)

Interventions

Postmenopausal women with hormone-sensitive early breast cancer who had completed 2 years adjuvant oral tamoxifen (20 or 30 mg daily) were randomised to receive 1 mg oral anastrozole (n=1618) or 20 or 30 mg tamoxifen (n=1606) daily for the remainder of their adjuvant therapy.

Patients had modified radical mastectomy or breast-conserving surgery with axillary lymph-node dissection or sentinel lymph-node biopsy (with or without radiotherapy),

followed by adjuvant tamoxifen therapy started within 6 weeks (ABCSG trial 8) or 4 weeks (ARNO 95) of surgery or radiotherapy. Two years of adjuvant oral tamoxifen therapy was completed.

Outcomes

Event-free survival – event defined as local or distant metastasis, or contralateral breast cancer

Distant recurrence free survival

Tolerability

Follow up

Median follow-up 28 months (95% CI 26-30)

At the time of disclosure of trial data 882 (55%) of patients on anastrozole and 884 (55%) on tamoxifen had completed 5 years of treatment.

Results

Analysis was by intention to treat. Hazard ratios (HR) were calculated from the Cox proportional-hazards regression model.

Event free survival

Higher in patients on anastrozole (67 events) than those continuing treatment with tamoxifen (110 events).

HR 0.60 (95% CI 0.44–0.81, $p=0.0009$) favouring anastrozole at 3 years after switching.

HR for first events was 0.59 (0.44–0.81, $p=0.0008$).

Event-free survival 3 years after switching:

92.7% (SD 0.81) for the tamoxifen group and 95.8% (SD 0.65) for the anastrozole group.

Absolute benefit of 3.1% at 3 years for anastrozole.

Distant metastases

62% of recurrences (110/177)

3% for women on anastrozole

5% for women on tamoxifen

HR 0.61 95% CI 0.42–0.87, $p=0.0067$

Corresponds to a 39% decrease in risk of metastases for women switching to anastrozole.

Recurrence

More recurrences occurred in the tamoxifen group than the anastrozole group.

Contralateral recurrences $n=28$ (16%)

Ipsilateral recurrences $n=41$ (23%)

Summary table of events

	Tamoxifen	Anastrozole	Total
Total N of events	110	67	177
Locoregional events	24	20	44

Distant metastases	75	46	121
Contralateral events	16	12	28
Deaths:			
Breast cancer related	31	24	55
Non-breast cancer related	28	21	49

Overall survival

At 3 years OS was marginally higher in patients on anastrozole (97%) than tamoxifen (96%), but not statistically significant p=0.16.

Risk of recurrence after stratification by nodal status, tumour grade, age and receptor status

None of the subgroup analyses were statistically significant between each component but the authors suggested from the Forest plot that women with G1, G2 and Gx lobular tumours (n=3044) responded better to anastrozole than tamoxifen compared to women with G3 tumours (however it should be noted that the G3 group was small (n=167), and had a wide confidence interval).

Overall the benefit of switching to anastrozole compared with remaining on tamoxifen was not dependent on nodal status, age at surgery, or progesterone receptor positivity. (Univariate analysis).

Author conclusions

These data lend support to a switch from tamoxifen to anastrozole in patients who have completed 2 years' adjuvant tamoxifen.

General comments –

This study was included in the meta-analysis by Rubio (2007). It was added to this table because of the subgroup analyses.

Subgroup analysis

Dowsett M, Cuzick J, Wale C, Howell T, Houghton J, Baum M. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis-generating study.[see comment]. J Clin Oncol 2005 Oct 20;23(30):7512-7		
Design: Analysis of RCT data	(1996 - ?)	Level 1+
Country: UK, setting:		

Aim:

To retrospectively assess the effect of PgR status on time to recurrence (TTR) in the arimidex, tamoxifen, alone and in combination (ATAC) trial.

Inclusion criteria

Postmenopausal women with histologically proven, operable, invasive breast cancer who had completed primary surgery and radiotherapy or chemotherapy (when given).

Exclusion criteria

Population number of patients = 9366 total

Interventions

The **ATAC** trial is a (1:1:1) randomized, double-blind trial of adjuvant use of 1 mg of anastrozole versus 20 mg of tamoxifen versus a combination of the two for 5 years in postmenopausal women with early invasive breast cancer. After the first analysis, with a median 33 months follow-up, the combination arm was discontinued and patients were offered the opportunity to switch to anastrozole or tamoxifen.

TTR was compared between the three treatment groups (tamoxifen and anastrozole; and between tamoxifen and the combination as used in the trial) for subgroups defined by ER and PgR status using Cox's proportional hazards model, with and without adjustment for baseline variables. Subgroups analyzed were ER+/PgR+ and ER+/PgR- (n=7081). Patients with ER+/PgRuk (n=518) were also included in the analysis. (uk=unknown)

Variables analyzed were:

nodal status (negative or unknown; one to three nodes positive; greater than three nodes positive)

tumour size (≤ 2 cm; > 2 cm)

tumour grade (well differentiated, moderately differentiated, poorly differentiated, or undifferentiated)

previous adjuvant chemotherapy (no; yes).

All significant baseline variables were included in multivariate models.

Outcomes

Time to recurrence (TTR)

Breast cancer events (includes contralateral tumour incidence)

Follow up

Median follow-up at time of analysis was 68 months.

Results

Results from an associated report in the Lancet (Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment

for breast cancer. *Lancet* 2005; 365: 60–62) found that the hazard ratio for time to recurrence of all hormone receptor positive women in the study was:

Hazard ratio 0.74 (95% CI 0.64–0.87) p=0.0002 Risk reduction = 26%

This same study reported the incidence of contralateral breast cancer as substantially reduced by anastrozole compared with tamoxifen (all patients 35 vs. 59, 42% reduction, 95% CI 12–62, p=0.01; hormone-receptor-positive patients 53%, 25–71, p=0.001).

In the present analysis hazard ratios (HR) for breast cancer events were compared by different receptor groups for anastrozole, tamoxifen and for the combination of both:

		Breast cancer events			An vs. Tam	Comb vs Tam
		Anastrozole	Tamoxifen	Combined		
	N of patients	N %	N %	N %	HR 95% CI p	HR 95% CI p
ER+/PgR+	5709	191 10	222 12	205 11	0.84 (0.69-1.02) 0.07	0.95 (0.78-1.15) 0.6
ER+/PgR-	1372	50 11	102 24	102 21	0.43 (0.31-0.61) <0.001	0.87 (0.66-1.15) 0.3
ER-/PgR+	220	17 27	25 33	22 27	0.79 (0.43-1.47) 0.5	0.84 (0.47-1.49) 0.5
ER-/PgR-	703	66 28	79 32	71 32	0.90 (0.65-1.25) 0.5	1.08 (0.78-1.48) 0.7
ER+/PgRuk	518	22 13	20 11	24 14	1.29 (0.71-2.37) 0.4	1.34 (0.74-2.43) 0.3
ERuk/PgRuk	743	46 19	47 19	49 19	0.96 (0.64-1.44) 0.8	0.98 (0.65-1.46) 0.9
Other	101	Not	reported			
Total	9366	402 12.9	498 16.0	479 15.3	0.79 (0.70-0.90)	0.97 (0.86-1.10)

					0.0005	0.6
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Figures in **bold** font were statistically significant

The Hazard Ratio of breast cancer events was significantly lower for the ER+/PgR- group [0.43 (95% CI, 0.31 to 0.61)]. This is equivalent to a reduction of 57% in breast cancer events on anastrozole compared with tamoxifen.

After adjusting for baseline nodal status, tumour size, tumour grade and use of adjuvant chemotherapy before hormonal adjuvant therapy the HRs were:

ER+/PgR+ 0.83 95% CI (0.68-1.00)

ER+/PgR- 0.45 95% CI (0.32-0.63) equivalent to a 55% reduction in breast cancer events with anastrozole.

TTR is shown as Kaplan-Meier curves in Figure 1 (A) for the ER+/PgR+ subgroup and (B) for the ER+/PgR- subgroup. (Taken from the paper).

The TTR for the anastrozole-treated group was better than either the tamoxifen or combination-treated arms in both subgroups. The outcomes for the tamoxifen and combination arms were similar. The difference in TTR with anastrozole was greater for the ER+/PgR- subgroup than the ER+/PgR+ subgroup. For comparison, the outcome of patients treated with anastrozole was only marginally worse in the ER+/PgR- subgroup (11% had a recurrence) than the ER+/PgR+ subgroup (10% had a recurrence) over 68 months.

A further analysis was made excluding the contralateral tumour incidence from the recurrence rates:

		Breast cancer events excluding contralateral tumours							
		<i>Anastrozole</i>		<i>Tamoxifen</i>		<i>Combination</i>	<i>An vs. Tam</i>	<i>Comb vs Tam</i>	
	N of patients	N	%	N	%	N	%	HR 95% CI p	HR 95% CI p
ER+/PgR+	5709	174	9	186	10	173	9	0.92 (0.75-1.13) 0.4	0.96 (0.78-1.18) 0.7
ER+/PgR-	1372	43	10	91	21	90	18	0.42 (0.29-0.60)<0.001	0.87 (0.65-1.16) 0.3
Total	9366	367	11.7	439	14.1	425	13.6	0.83 (0.72-0.95) 0.007	0.98 (0.86-1.12) 0.7

Author conclusions

Time to recurrence was longer for anastrozole- than tamoxifen-treated patients in both ER+/PgR+ and ER+/PgR- subgroups, but the benefit was substantially greater in the PgR- subgroup. As this was an "exploratory" analysis, this effect should be considered as hypothesis generating and assessed prospectively in other trials comparing the adjuvant use of an aromatase inhibitor with tamoxifen.

General comments –

The authors noted that this analysis was exploratory in nature and hypothesis generating.

Ingle JN, Tu D, Pater JL, Martino S, Robert NJ, Muss HB, et al. Duration of letrozole treatment and outcomes in the placebo-controlled **NCIC CTG MA.17** extended adjuvant therapy trial. *Breast Cancer Research & Treatment* 2006;99(3):295-300.

Design: RCT (1996-2002) Level 1+
Country: USA, Canada, Belgium, Switzerland, UK, setting: Multicentre
Aim: Analyses were conducted to examine the relationships between duration of treatment on MA.17 and outcomes.

Inclusion criteria

Previous adjuvant tamoxifen therapy for 4.5 – 6 years;
Histologically confirmed primary breast cancer;
A tumour that was positive for estrogen receptor (ER), progesterone receptor (PR), or both;
Discontinuation of tamoxifen therapy less than 3 months before enrollment;
An Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (scored on a scale of 0 to 4, with lower scores indicating better function);
Life expectancy of more than 5 years;
Postmenopausal status

Exclusion criteria

Population number of patients = 5187 (17 excluded)

Letrozole n=2593 (2583 analyzed)

Placebo n=2594 (2587 analysed)

Hormone receptor status:

Positive 5035 (97.4%)

Negative 8 (0.15%)

Unknown 91 (1.8%)

Missing 36 (0.7%)

Node positive 2360 (45.6%)

Node negative 2568 (49.7%)

Interventions

Patients were stratified according to tumour hormone receptor status (ER- and/or PR-

positive or unknown), lymph node status (negative, positive, or unknown), and prior adjuvant chemotherapy (yes or no).

Randomized, double-blind, placebo-controlled trial of letrozole (2.5 mg orally daily) versus placebo (orally daily), given for a period of 5 years.

The hazard rates for disease-free survival (DFS), distant DFS (DDFS) and overall survival (OS) at 6, 12, 24, 36 and 48 months of follow-up and the hazard ratios (HRs) of letrozole to placebo were determined. The trend in HRs over time was tested based on a Cox model with a time-dependent covariate.

Outcomes

DFS reported at 6 monthly intervals between 6 and 48 months (test for trend analysis)

OS as above

Distant DFS as above

Subgroup analyses within these outcomes- node positive and node negative

Follow up Median follow-up of 30 months

Results

Considering all patients, HRs for events in DFS and DDFS progressively decreased over time in favour of letrozole. The trend was significant for DFS and DDFS, but not significant for OS.

In patients with node-positive status, the HRs for DFS, DDFS and OS all decreased over time with statistically significant tests for trend.

In patients with node-negative status, the HR for DFS showed a decreasing trend over time. Whilst the HRs for DDFS and OS showed no significant change over time.

Hazard ratios for node status subgroups at different time points are shown in the following table:

Subgroup	HR at 6 months	HR at 48 months	P value test for trend
Overall:			
DFS	0.59	0.19	<0.0001
DDFS	0.51	0.21	0.0013
OS	0.87	0.79	0.33
Node positive:			
DFS	0.66	0.24	0.0004
DDFS	0.45	0.24	0.0005
OS	0.64	0.40	0.038
Node negative			
DFS	0.72	0.43	0.027
DDFS	0.22	0.18	0.22
OS	2.50	2.75	0.34

Author conclusions: These analyses suggest that, at least out to about 48 months, longer duration of letrozole treatment is associated with greater benefit in the extended adjuvant therapy setting.

General comments –
Confidence intervals for HRs were not reported.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: **National Cancer Institute of Canada Clinical Trials Group MA.17**. J Clin Oncol 2007;25(15):2006-11.

Design: RCT (1998-2002) Level 1+

Country: USA, Canada, Belgium, Switzerland, UK setting: Multicentre

Aim: Retrospective analysis to assess the effect of the ER and PgR status of the primary tumour on DFS, distant DFS (DDFS), and OS in the MA.17 trial.

Inclusion criteria

These were reported in an earlier publication (Goss 2003). Postmenopausal women with histologically confirmed primary breast cancer. Tamoxifen discontinued < 3 months before enrolment. ECOG performance status 0, 1 or 2. Life expectancy > 5 years.

Exclusion criteria

Concurrent use of investigational drugs or prior or concurrent malignancy other than skin cancer or carcinoma in situ of the cervix.

Population number of patients = 5187 (ITT analysis)

4653 with known ER and PR receptor status.

534 at least one of two receptors of unknown status.

ER+/PR+ n=3809 (73%)

ER+/PR- n=636 (12%)

ER-/PR+ n=200 (4%)

ER-/PR- n=8

Interventions

The MA.17 trial was a randomized, double-blind placebo-controlled trial of extended adjuvant therapy with letrozole for 5 years in patients with breast cancer who were disease-free after standard adjuvant tamoxifen. Postmenopausal women (N=5,187) who had completed 4.5 to 6 years of tamoxifen were randomly assigned from August 1998 to September 2002.

Women were stratified based on tumour hormone-receptor status (positive or unknown), lymph node status (negative, positive, or unknown), and previous adjuvant chemotherapy (yes or no).

A Cox model with interaction terms was used to assess the differential treatment effects between ER+/PR+ and ER+/PR- groups, adjusting for nodal status and prior chemotherapy.

Outcomes

DFS - defined as time from randomization to time of any breast cancer recurrence

(breast, chest wall, nodal, or metastatic site), or contralateral breast cancer.
Distant DFS - defined as time from randomization to time of distant metastasis.
OS - defined as time from randomization to time of death from any cause.

Follow up

Median follow-up 30 months (range 1.5-61.4 months).

Results

Results of Hazard Ratios for Disease-Free Survival, Distant Disease-Free Survival, and Overall Survival by Hormone-Receptor Subset, adjusted for nodal status and prior chemotherapy are shown in the table:

		Events on Letrozole	Events on Placebo	
Subset	N (%)	n (%)	n (%)	HR (95% CI)
DFS				
ITT	5187 (100)	92 (3.6)	155 (6)	0.58 (0.45-0.76)
ER+/PR+	3809 (73)	60 (3)	117 (6)	0.49 (0.36-0.67)
ER+/PR-	636 (12)	19 (6)	17 (5)	1.21 (0.63-2.34)
ER-/PR+	200 (4)	4 (4)	5 (5)	0.56 (0.15-2.12)
ER-/PR-	8 (0)	-	-	-
DDFS				
ITT	5187 (100)	52 (2)	82 (3.2)	0.60 (0.43-0.84)
ER+/PR+	3809 (73)	36 (2)	65 (3)	0.53 (0.35-0.80)
ER+/PR-	636 (12)	13 (4)	11 (3)	1.25 (0.56-2.80)
ER-/PR+	200 (4)	3 (3)	4 (4)	0.55 (0.12-2.47)
ER-/PR-	8 (0)	-	-	-
OS				
ITT	5187 (100)	51 (2)	62 (2.4)	0.82 (0.57-1.19)
ER+/PR+	3809 (73)	31 (2)	52 (3)	0.58 (0.37-0.90)
ER+/PR-	636 (12)	9 (3)	6 (2)	1.52 (0.54-4.30)
ER-/PR+	200 (4)	3 (3)	1 (2)	2.16 (0.22-20.77)
ER-/PR-	8 (0)	-	-	-

Women with ER+/PR+ status on Letrozole benefited the most across all 3 outcomes (DFS, DDFS, OS). The smaller subgroup of ER+/PR- women benefited less (HR values), however, the confidence intervals were much wider. The difference in outcomes between women with ER+/PR+ receptor status and ER+/PR- receptor status was only statistically significant for DFS (p=0.02). Corresponding p values for DDFS and OS were p= 0.06 and p = 0.09 respectively.

Confidence intervals were very wide for the ER- subgroup since event rates were small.

Adjustments for nodal status and prior adjuvant chemotherapy did not alter the data.

Authors Conclusions

These results suggest greater benefit for letrozole in DFS, DDFS and OS in patients with ER+/PgR+ tumours, implying greater activity of letrozole in tumours with a functional ER. However, because this is a subset analysis and receptors were not measured centrally we caution against, using these results for clinical decision making.

General comments -

Randomized controlled trial

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from **NCIC CTG MA.17**. [see comment]. J Natl Cancer Inst 2005 Sep 7;97(17):1262-71.

Design: RCT (1998-2002) Level 1++

Country: USA, Canada, Belgium, Switzerland, UK. Setting: Multicentre

Aim: To present the final efficacy and toxicity results of the **MA.17** trial including all preplanned subset analyses, based on all events that occurred up to the unblinding of study participants in October 2003.

Inclusion criteria

Previous adjuvant tamoxifen therapy for 4.5 – 6 years;

Histologically confirmed primary breast cancer;

A tumour that was positive for estrogen receptor (ER), progesterone receptor (PR), or both;

Discontinuation of tamoxifen therapy less than 3 months before enrollment;

An Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (scored on a scale of 0 to 4, with lower scores indicating better function);

Life expectancy of more than 5 years;

Postmenopausal status.

Exclusion criteria

Population number of patients = 5187 (17 excluded)

Letrozole n=2593

Placebo n=2594

Hormone receptor status:

Positive 5035 (97.4%)

Negative 8 (0.15%)
 Unknown 91 (1.8%)
 Missing 36 (0.7%)

Interventions

Patients were stratified according to tumour hormone receptor status (ER- and/or PR-positive or unknown), lymph node status (negative, positive, or unknown), and prior adjuvant chemotherapy (yes or no).

Randomized, double-blind, placebo-controlled trial of letrozole (2.5 mg orally daily) versus placebo (orally daily), given for a period of 5 years.

Outcomes

DFS - time from randomization to the earliest recurrence of breast cancer (breast, chest wall, regional nodes, or distant metastasis) or a contralateral new primary breast cancer.

Distant DFS

OS- time from randomization to death by any cause

Incidence contralateral tumours

Toxic effects.

Follow up

The median follow-up of patients was 30 months, and the range was 1.5 to 61.4 months.

Results

At a median follow-up of 2.5 years there were:

247 breast cancer events;

113 deaths;

1115 and 503 patients followed for 40 and 48 months, respectively.

Summary of events in analysis of DFS

Event or Outcome	Letrozole N (%)	Placebo N (%)
All patients	2583	2587
Any event	92 (3.6)	155 (6)
All recurrences	75 (2.9)	127 (4.9)
Local breast recurrence	9	22
Local chest wall recurrence	2	8
Regional recurrence	7	3
Distant recurrence	52	82
Contralateral breast	17	28
4 year DFS	94.4% (95% CI 93.0-95.8)	89.8% (95% CI 87.9-91.8)

Absolute reduction DFS	4.6%	-
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Hazard Ratios

From Cox proportional hazards model of letrozole vs. placebo

Outcome	Hazard Ratio (95% CI)	Risk reduction
Local or Distant Recurrence or contralateral breast cancer (HR+ve)	0.58 (95% CI = 0.45 to 0.76)	42% favouring letrozole
Adjusted value for menopausal status and duration of tamoxifen treatment	Adjusted HR = 0.59 (95% CI =0.45 to 0.76)	
Distant DFS	HR = 0.60, (95% CI = 0.43 to 0.84; <i>P</i> = 0.002)	40% favouring letrozole
Time to contralateral breast cancer	HR = 0.63, (95% CI = 0.18 to 2.21; <i>P</i> = 0.12)	37.5% favouring letrozole (NS)

After adjusting for receptor status, lymph node status, and prior adjuvant treatment at random assignment, the stratified log rank test for the difference in DFS between subgroups was significant *P* <0.001. (not clear where the data for this statement appears in the paper).

Pre-specified subgroup analyses (Forest plot from paper) showed that DFS was better in the letrozole group than placebo in most subgroups, exceptions were the subgroups of patients with unknown hormone receptor status or unknown lymph node status, both had few patients.

HR positive patients were not subdivided by type of hormone receptor positivity, and could be ER+, PR+ or both.

Although Letrozole was more effective in increasing DFS compared with placebo in all subgroups the only subgroup where a significant difference between subgroup HRs was achieved was menopausal criteria (> 50 yrs at start of tamoxifen vs. other).

Contralateral Breast Cancer Incidence

Annual incidence:

3.0/1000 on letrozole

4.8/1000 on placebo

(difference = 1.8/1000; 95% CI -1.3 to 4.9 per 1000)

The incidence of contralateral breast cancer was lower in women receiving letrozole, but the difference was not statistically significant.

Overall survival

Summary of events for OS

Event or Outcome	Letrozole N (%)	Placebo N (%)
All patients	2583	2587
All deaths	51	62
Breast cancer deaths	16	22
Other primary malignancies (deaths)	9	11
Other conditions or circumstances (deaths)	24	28
Other deaths	1	0
4 year Overall survival	95.4% (95% CI 93.7-97.0)	95% (95% CI 93.5-96.4)
Absolute increase 4 yr OS	0.4%	-
Death from any cause	HR 0.82 (95% CI 0.57-1.19) p=0.3	
OS Lymph node positive	HR 0.61 (95% CI 0.38-0.98) P = 0.04	
OS Tamoxifen > 5 years	HR 0.56 (95% CI 0.33-0.97) P = 0.04	

The pre-specified subgroup analyses showed that letrozole improved OS compared to placebo in lymph node positive patients and those taking tamoxifen more than 5 years. A Forest plot of the subgroup analysis from the paper see table.

Women receiving letrozole experienced more hormonally related side effects than those receiving placebo, but the incidences of bone fractures and cardiovascular events were the same.

Author conclusions: Letrozole after tamoxifen is well-tolerated and improves both disease-free and distant disease-free survival but not overall survival, except in node-positive patients.

General comments –

Hormone receptor positivity includes oestrogen receptor, progesterone receptor or both.

Goss P. Breaking the 5-year barrier: Results from the **MA.17** extended adjuvant trial in women who have completed adjuvant tamoxifen treatment. European Journal of Cancer Supplement 1990 2006;4(9):10-5.

Design: RCT (1996-2002)

Level 1+

Country: USA, Canada, Belgium, Switzerland, UK, setting: multicentre

Aim: Summary of previous findings

Inclusion criteria As previously reported

Exclusion criteria

Women with significant co-morbid disease.

Population number of patients = 5187

Interventions

Outcomes

Quality of life (additional to previous reported outcomes).

Follow up

Results

Letrozole therapy was well tolerated.

More common in Letrozole gp

Hot flushes

Alopecia

Arthralgia

Myalgia

Anorexia

Fractures

Self-reported osteoporosis

More common in placebo gp

Vaginal bleeding

No differences were found between groups for the incidence of cardiovascular events (Letrozole n=149, 5.8%; Placebo n=144, 5.6%; p = 0.76); hypercholesterolaemia (Letrozole n=418, 16%; Placebo n=411, 16% p = 0.79) or global quality of life scores compared with placebo.

A MA.17 lipid substudy (Wasan 2005) that evaluated serum lipids at baseline, 6 months, 12 months and annually found that letrozole did not alter lipid profiles compared with placebo in non-hyperlipidaemic postmenopausal women.

Quality of Life

3612/5187 (70%) of patients participated in a QoL study.

Letrozole n=1813

Placebo n=1799

There was no adverse effect of letrozole on QoL after 36 months.

There were no differences in SF-36 physical and mental component summary scores at any time point between treatment arms.

Small statistically significant differences in mean change scores from baseline were observed in patients on letrozole for SF-36 domains:

physical functioning (12 months)

bodily pain (6 months)

vitality (6 and 12 months)

MENQOL vasomotor (6, 12 and 24 months)
sexual domains (12 and 24 months).

In the response analysis, significant differences between placebo and letrozole were observed in the proportions of patients reporting worsening of QoL for:
bodily pain (placebo 47%, letrozole 51%, $p = 0.009$)
vasomotor domain (placebo 22%, letrozole 29%, $p = 0.001$) (Whelan 2005).

General comments –

Subgroup analyses of QoL domains were not reported. The full report on QoL for the MA.17 trial is a separate paper (Whelan 2005) that was not included in the references for this topic.

Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.[see comment][erratum appears in N Engl J Med. 2006 May 18;354(20):2200 Note: Wardly, Andrew [corrected to Wardley, Andrew]]. N Engl J Med 2005 Dec 29;353(26):2747-57.

Design: RCT (1998-2003) **(BIG) 1-98** Level 1++

Country: Multinational, setting: multicentre

Aim: To compare letrozole monotherapy with tamoxifen monotherapy as initial adjuvant endocrine therapy as well as sequential treatment with the two agents in either order in postmenopausal women with hormone-receptor-positive breast cancer.

Inclusion criteria

Postmenopausal women with tumours positive for estrogen receptors, progesterone receptors, or both.

Primary surgery with clear margins.

Adequate haematological, renal and hepatic function.

Exclusion criteria

Metastatic disease

Previous or concurrent cancer

At least one month's adjuvant antiestrogen therapy

Systemic investigational drug treatment within 30 days before randomization

Population number of patients = 8010 (ITT analysis)

Letrozole n=4003

Tamoxifen n=4007

Median age 61 years (38-90)

Tumour size:<2cm n= 4957 (61.9%)

> 2cm n=2973 (37.1%)

Unknown or missing n=80 (1%)

Node status:

Negative (includes Nx) n=4587 (57.3%)

Positive n=3311 (41.3%)

Unknown or missing n=112 (1.4%)

Hormone receptor status:

ER+/PR+ n=5055 (63.1%)

ER+/PR- n=1631 (20.4%)

ER+/PRuk or missing n=1154 (14.4%)

ER-/PR+ n=143 (1.8%)

ERuk or missing/PR+ n=7 (0.1%)

Other n=20 (0.2%)

Interventions

The Breast International Group (**BIG**) 1-98 study was a randomized, phase 3, double-blind trial comparing five years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor-positive (ER+, PR+ or both) invasive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole.

This analysis compared the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment groups were included up to the time that treatments were switched.

Outcomes

DFS - defined as recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, non-breast cancer; or death without a prior cancer event.

DFS- excluding non-breast cancers

Time to recurrence - as DFS excluding second non-breast cancers, and censoring of deaths with no breast cancer recurrence

Time to distant recurrence – defined as time from randomization to first distant recurrence

OS- defined as time from randomization to death from any cause.

Systemic disease –free survival- defined as time from randomization to systemic recurrence (excluding local and contralateral-breast events), the occurrence of a second, non-breast cancer, or death from any cause.

Safety

Follow up

Median follow-up 25.8 months

Results

Summary of events (Letrozole vs. Placebo)

Event or Outcome	Letrozole N (%)	Tamoxifen N (%)	Hazard Ratio (95% CI)
All patients	4003	4007	
DFS events	351 (8.8)	428 (10.7)	0.81 (95% CI 0.70-0.93) p=0.003
5 Year DFS estimates	84%	81.4%	
Deaths without prior cancer event (included in DFS)	55 (1.4)	38 (0.9)	
Deaths from any cause	166 (4.1)	192 (4.8)	
Systemic DFS events (excludes local and contralateral breast events)	323 (8.1)	383 (9.6)	0.83 (95% CI 0.72-0.97) p=0.02
Overall survival	166 (2.1)	192 (2.4)	0.86 (95% CI 0.70-1.06) p=0.16
DFS excluding 2 nd nonbreast cancer	296 (7.4)	369 (9.2)	0.79 (95% CI 0.68-0.92) p=0.002
Local recurrence	21 (0.5)	37 (0.9)	
Contralateral breast cancer	16 (0.4)	27 (0.7)	
Regional recurrence	13 (0.3)	12 (0.3)	
Distant recurrence	177 (4.4)	232 (5.8)	
Second, non-breast cancer	69 (1.7)	82 (2.0)	
Time to recurrence	228 (5.7)	310 (7.7)	0.72 (95% CI 0.61-0.86) p<0.001
Time to distant recurrence	184	249	0.73 (95% CI 0.60-0.88) p=0.001

Subgroup analyses were reported for the following parameters – taken from the paper (the authors suggest caution in the interpretation of this data):

All subgroup analyses favoured letrozole compared to tamoxifen. The largest benefits of letrozole were in patients with node positive disease and those receiving chemotherapy, although differences between components of subgroups compared were not statistically significant (CIs overlap).

There were no significant differences between ER+/PR+ and ER+/PR- subgroups.

Event or Outcome	N of patients	Letrozole N (%)	Tamoxifen N (%)	Hazard Ratio (95% CI)
DFS				
Node negative (includes Nx)	4587	140 (3.0)	147 (3.2)	0.96 (0.76-1.21) p=0.75
Node positive	3311	205 (6.2)	274 (8.3)	0.71 (0.59-0.85) p<0.001
Chemotherapy				
Yes	2024	92 (4.5)	126 (6.2)	0.70 (0.54-0.92) p=0.01
No	5986	259 (4.3)	302 (5.0)	0.85 (0.72-1.00) p=0.06

Side effects

Event	Letrozole	Tamoxifen	
Adverse events (patients)	2912	2554	
Fatal adverse events	67/3975 (1.7%)	69/3988 (1.7%)	
Fractures	5.7%	4.0%	P<0.001
Thromboembolic events	1.5%	3.5%	P<0.001
Vaginal bleeding	3.3%	6.6%	P<0.001
Endometrial biopsies	72/3089 (2.3%)	288/3157 (9.1%)	P<0.001
Invasive endometrial cancers	4/3089 (0.1%)	10/3157 (0.3%)	P=0.18
Cholesterol (median change)	6 mths Letrozole 0% Tamoxifen 12%	12 mths 0% -13.5%	24 mths -1.8% -14.1%
Hypercholesterolaemia	43.6%	19.2%	
Cardiovascular events	3.7%	4.2%	

Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolemia.

Author conclusions:

In postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites.

Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the **Italian Tamoxifen Anastrozole Trial**. [see comment]. J Clin Oncol 2005 Aug 1;23(22):5138-47.

Design: RCT (1998-2002) Level 1+

Country: Italy, setting: Multicentre

Aim: To test the efficacy of switching postmenopausal patients who were already receiving tamoxifen to the aromatase inhibitor anastrozole.

Inclusion criteria

Postmenopausal women.

Histologically confirmed primary breast cancer.

Tumour ER positivity (confirmed- PR status not required)

Positive axillary nodes

No evidence of metastatic disease.

Exclusion criteria

Patients with any other cancer (except treated skin cancer, carcinoma in-situ of cervix)

Conditions that may jeopardize compliance to treatments.

Population number of patients = 448 enrolled – Intention to treat analysis

	Tamoxifen (n=225)	Anastrozole (n=223)
Age Median 63 years	43-77	38-76
ER +	194 (43%)	203 (45%)
ER -	-	2 (<1%)
Unknown or missing	31 (7%)	18 (4%)
Involved nodes:		
=<3	132 (29%)	152 (34%)
>3	91 (20%)	71 (16%)
Missing	2 (<1%)	-
Time on tamoxifen at randomization, months		
Median	28	28
Range	20-39	23-40

Interventions

The Italian Tamoxifen Anastrozole (ITA) trial was a phase III, randomized, multicenter trial including postmenopausal women who had already received 2 to 3 years of tamoxifen treatment. Patients were randomly assigned to receive continued tamoxifen treatment (20 mg/d) or to be switched to anastrozole (1 mg/d) for a total duration of 5 years of endocrine treatment.

Stratification was by participating centre and prior chemotherapy before randomization.

Women undergoing BCS treatment received thoracic wall irradiation. Few women undergoing mastectomy received thoracic wall irradiation (7 in tamoxifen group, 2 in anastrozole group).

Outcomes

Locoregional recurrence (ipsilateral breast, axilla, thoracic wall, other nodes)

Distant recurrence (excluding contralateral breast cancer)

Event free survival- included locoregional recurrence, distant metastases, second primary tumours (including contralateral breast cancer), and breast cancer-unrelated deaths (ie, deaths occurring in the absence of disease recurrence).

Deaths

Adverse events

Multivariate analyses of subgroups

Follow up Median 36 months (range 1-70 months)

Results

Events occurring in each arm are summarized in the following table:

Event	Tamoxifen (n=225)	Anastrozole (n=223)
Tumour recurrences:		
Locoregional	13	2
Distant metastases with or without locoregional recurrences	19	10
Secondary primary tumours:		
Contralateral breast	2	1
Endometrium	5	1
Other	3	3
Death without relapse	3	-
Total events	45	17 (P = 0.0002)
Breast cancer deaths	7	4

Women switched to anastrozole benefited most for EFS and recurrence FS, and had longer locoregional recurrence FS.

Hazard ratios for EFS, locoregional recurrence free survival and distant metastases-free survival are shown below:

Event	Hazard Ratio (95% CI)	P value
Event free survival	0.35 (0.20-0.63)	0.0002
Recurrence free survival	0.35 (0.18-0.68)	0.001
3 yr difference in Recurrence free survival	5.8% (95% CI 0.5-6.4)	
Locoregional recurrence free survival	0.15 (0.03-0.65)	0.003
Distant metastases-free survival	0.49 (0.22-1.05)	0.06

Disease-free, event free and local recurrence free survival were significantly longer in the

anastrozole group.

Multivariate analyses were conducted on a number of relevant subgroup variables for the risk of developing any event and disease recurrence. These findings are reported in the following table:

	Any event		Disease recurrence	
Subgroup	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
	p value		p value	
Treatment: Tamoxifen Anastrozole	1.0 0.36 (0.21-0.63) 0.0004		1.0 0.35 (0.18-0.69) 0.002	
Tumour size: ≤ 2cm > 2cm	1.0 1.86 (1.06-3.27) 0.03		1.0 1.67 (0.86-3.24)	0.1
Tumour grade: 1-2 3-Gx	1.0 1.23 (0.73-2.06)	0.4	1.0 1.44 (0.79-2.63)	0.2
N of involved nodes: ≤ 3 >3	1.0 1.48 (0.86-2.52) 0.15		1.0 1.64 (0.87-3.07)	0.1
Prior adjuvant chemotherapy: No Yes	1.0 1.29 (0.71-2.35)	0.4	1.0 1.87 (0.86-4.06)	0.1

The benefit of anastrozole compared with tamoxifen was independent of the other variables tested. (NB the multivariate analysis does not compare subgroups assigned to either drug, other than in the first row of the table)

A further analysis displayed as a Forest Plot for risk of recurrence found the benefit of anastrozole to be consistent across all subgroups (HR adjusted for tumour size, grade, number of involved nodes and treatment of primary tumour). There appears to be no statistically significant difference between the components of each subgroup.

Subgroup analysis of risk of recurrence:

Overall, more adverse events were recorded in the anastrozole group compared with the tamoxifen group (203 v 150, respectively; P = 0.04). However, more events were life threatening or required hospitalization in the tamoxifen group than in the anastrozole group (33 of 150 events v 28 of 203 events, P = 0.04).

Author conclusions: Switching to anastrozole after the first 2 to 3 years of treatment is well tolerated and significantly improves event-free and recurrence-free survival in

postmenopausal patients with early breast cancer.

Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Eng J Med* 2004; 350: 1081-92.

Design: RCT (1998-2003) Level 1++
Country: Multinational, setting: Multicentre
Aim: To investigate whether exemestane could prolong disease-free survival, as compared with continued tamoxifen therapy.

Inclusion criteria

Histologically confirmed, completely resected unilateral invasive breast carcinoma positive for estrogen receptors; postmenopausal; adjuvant tamoxifen therapy for at least two years but not more than three years and one month.

Exclusion criteria

Tumour with known negative estrogen-receptor status; evidence of local relapse or a distant metastasis since diagnosis; clinically significant skeletal, cardiac, or endocrine disorder; and the use of hormone-replacement therapy within four weeks before randomization.

Population number of patients = 4742 from 37 countries

Exemestane = 2362

Tamoxifen = 2380

Age 64.3 ± 8.3 years

Node negative n=2422 (51.1%)

Node positive 1-3 nodes n=1421 (30%)

Node positive =>4 nodes n=651 (13.7%)

Hormone receptor status:

ER+/PR+ n=2619 (55.2%)

ER+/PR- n=735 (15.5%)

ER+/PRuk or missing n=499 (10.5%)

ER- n=59 (1.2%)

ERuk or missing n=830 (17.5%)

Other n=20 (0.2)

PR status

PR+ n=2633 (55.5%)

PR- n=755 (15.9%)

PRuk or missing n=1354 (28.6%)

Interventions

The Intergroup Exemestane Study (**IES**) is an international, intergroup, phase 3, randomized, double-blind trial comparing the efficacy and safety of continued adjuvant tamoxifen therapy with that of exemestane therapy in postmenopausal women with primary breast cancer free of disease after receiving adjuvant tamoxifen for two to three years. Women were randomly assigned to receive oral exemestane (25 mg) or tamoxifen (20 mg) daily to complete a total of five years of adjuvant endocrine treatment.

Outcomes

Disease-free survival - defined as time from randomization to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause.

Overall survival

Incidence of contralateral breast cancer

Long term tolerability

Breast cancer-free survival (with censoring of deaths with no recurrence of breast cancer or a contralateral breast cancer).

Follow up

30.6 months (interquartile range, 23.9 to 36.6).

Results

449 first events (local or metastatic recurrence, contralateral breast cancer, or death)

183 in the exemestane group and 266 in the tamoxifen group.

Crude event numbers and adjusted Hazard Ratios are reported in the following tables:

Event	Exemestane n=2362	Tamoxifen n=2380	All patients N=4742
Events in DFS:			
Local recurrence	21	33	54
Distant recurrence	114	174	288
Primary ca in contralateral breast	9	20	29
Intercurrent death (no recurrence)	39	39	78
All events in DFS	183	266	449
Deaths:			
Any cause	93	106	199

Breast cancer related	54	67	121
Intercurrent	39	39	78
Second primary non-breast cancer	27	53	80

Event	Exemestane n=2362	Tamoxifen n=2380
DFS	HR 0.67 (95% CI 0.56 - 0.82) p<0.001	
DFS Absolute benefit at 3 years	4.7% (95% CI 2.6-6.8)	
DFS % at 3 years	91.5% (95% CI 90.0-92.7)	86.8% (95% CI 85.1-88.3)
Br ca free survival events	144	277
Breast cancer free survival	HR 0.62 (95% CI 0.5 – 0.76) p<0.001	
Distant DFS (unadj)	HR 0.66 (95% CI 0.52-0.83) P=0.0004	
Deaths	93	106
OS	HR 0.89 (95% CI 0.67-1.17) p=0.41	
Contralateral breast cancer	HR 0.44 (95% CI 0.20-0.98) p=0.04	

HR values were adjusted for ER status, nodal status, chemotherapy, use of HRT unless stated as unadjusted. All HRs favoured exemestane.

A subgroup analysis was performed for DFS. Most subgroups analysed favoured exemestane over tamoxifen as shown in the forest plot from the paper. Exceptions were ER-ve or unknown status, and PR status unknown.

Subgroup	Hazard Ratio for DFS
Hormone receptor status:	
ER+ (n=3853)	0.64 (0.52-0.79)
PR+ (n=2619)	0.66 (0.51-0.87)
PR- (n=735)	0.58 (0.38-0.90)
PR uk (n=499)	0.67 (0.39-1.16)

ER-ve or uk (n=889)	0.85 (0.57-1.29)
Nodal status:	
Negative (n=2422)	0.68 (0.48-0.95)
1-3 Positive nodes (n=1421)	0.71 (0.51-0.98)
≥ 4 Positive (n=651)	0.58 (0.42-0.81)
Previous HRT:	
Yes (n=1124)	0.63 (0.40-0.99)
No (n=3470)	0.69 (0.56-0.85)
Previous chemotherapy:	
Yes (n=1531)	0.69 (0.51-0.92)
No (n=3171)	0.67 (0.52-0.86)
All patients (N=4742)	0.67 (0.56-0.82)

Adverse events

Exemestane was associated with a higher incidence of:

- Arthralgia (p=0.005)
- Aches and pains (p=0.001)
- Diarrhoea (p<0.001)
- Osteoporosis (p=0.023)
- Visual disturbances (p=0.024)
- Headaches (p=0.035)

Symptoms more common with tamoxifen were:

- Gynaecological (p<0.001)
- Cramps (p=0.002)
- Thromboembolic disease (p=0.007)

Severe toxic effects of exemestane were rare.

Author conclusions:

Exemestane therapy after two to three years of tamoxifen therapy significantly improved disease-free survival as compared with the standard five years of tamoxifen treatment.

General comments –

Incidence of contralateral breast cancer and time to recurrence of contralateral breast cancer seem to have been used interchangeably in the paper.

Observational Studies (eg. Prospective Cohort or Retrospective Cohort or Case Series):

Ohsako T, Inoue K, Nagamoto N, Yoshida Y, Nakahara O, Sakamoto N. Joint symptoms: a practical problem of anastrozole. Breast Cancer 2006;13(3):284-288.

Design: NRS case series (2001-2005)

Level 3

Country: Japan, setting: Single clinic

Aim: Joint symptoms as adverse events of anastrozole in postmenopausal patients with breast cancer.

Inclusion criteria Postmenopausal ER+ breast cancer patients treated with anastrozole (1mg daily)

Exclusion criteria None specified

Population number of patients = 53

ER+

Interventions

Patient examination and interview whilst taking anastrozole

Outcomes

Incidence and grade of joint symptoms (examination and interview)

Follow up

Results

14/53 (26%) had joint symptoms:

13/14 (25% of total) had digital stiffness

3/14 (6% of total) had arthralgia of wrist and shoulders

Median time to onset of symptoms 5 months (1-19 months).

Joint symptoms were more common in patients who had prior chemotherapy.

Hormonal therapy did not influence joint symptoms.

Seven patients who discontinued anastrozole treatment showed improved symptoms. Five patients with grade 1 digital stiffness continued anastrozole treatment without additional treatment.

Other characteristics are shown in the table below:

Characteristic	Joint symptom		Multivariate analysis OR (95%CI)	P value
	+	-		
Age years	58.9 ± 9.7 (47-75)	64.8 ± 11.9 (43-83)	1.02 (0.93-1.11)	0.72

Prior therapy:				
Chemotherapy	9	12	9.94 (1.34-73.51)	0.02
No chemotherapy	5	27		
Hormonal therapy	6	20	3.08 (0.46-20.52)	0.24
No hormonal therapy	8	19		
Administration:				
Adjuvant	13	19	32.51 (2.63-401)	0.007
Metastatic	1	20		

Author conclusions: Benefits to patients may possibly be lost by discontinuation of anastrozole or changing to tamoxifen since the clinical superiority of anastrozole to tamoxifen has been reported. We should continue anastrozole in patients with low grade symptoms, while ensuring that patients are aware of the toxicity of anastrozole.

General comments –

There is no comparison group in this study.

DECISION ANALYSIS

Punglia RS, Kuntz KM, Winer EP, Weeks JC, Burstein HJ. The impact of tumor progesterone receptor status on optimal adjuvant endocrine therapy for postmenopausal patients with early-stage breast cancer: a decision analysis. Cancer 2006 Jun 15;106(12):2576-82.

Design: Decision analysis

Country: USA, setting:

Aim: To conduct a decision analysis using Markov modeling to determine whether treatment strategies of AI upfront or crossover therapy using tamoxifen and then an AI may differ among women with biologically determined breast cancer subtypes. A particular objective was to determine whether patients with ER+/PR- tumours may benefit from different strategies from patients with ER+/PR+ tumours.

Inclusion criteria

Model estimates obtained from:

EBC Trialist's Collaborative Group Overview of tamoxifen data

An update of the ATAC study (in abstract form)

The ARNO/ABCSG trial (included earlier in this table – Jakesz 2005)

Both RCTs compared the AI Anastrozole with tamoxifen.

Exclusion criteria

Population

Women treated with AIs vs tamoxifen

Interventions

Comparisons were of AI monotherapy or sequential treatment with tamoxifen followed by AI therapy with crossover at 2 years.

Markov models were used to simulate disease-free survival (DFS) separately among postmenopausal women with ER+/PR+ cancers and women with ER+/PR- cancers.

The models used risk of recurrence for patients receiving 5 years of tamoxifen as baseline, (defined in the Oxford overview analysis) and then factored in the selective gains achieved with the use of AI therapy in the different strategies.

Outcomes

Disease free survival

Follow up**Results**

Among patients with ER+/PR+ cancers, sequential therapy with tamoxifen with crossover to an AI after 2 years improved 10-year disease-free survival compared with 5 years of therapy with an AI monotherapy alone (84.3% vs. 82.2% and 68.8% vs. 64.8% for lymph node-negative and lymph node-positive patients, respectively). (see Table).

For women with ER+/PR- cancers, upfront treatment with an AI yielded improved 10-year DFS rates compared with sequential treatment with tamoxifen followed by an AI (90.5% vs. 88.2% for the lymph node-negative, and 80.1% vs. 76.1% for lymph node-positive groups respectively). (see Table).

Expected DFS for each treatment strategy

	Hazard Ratios			
	5 year DFS		10 year DFS	
Patient group	ER+/PR+	ER+/PR-	ER+/PR+	ER+/PR-
Lymph node -ve				
AI only	0.896	0.944	0.822	0.905
Year 2 crossover	0.902	0.917	0.843	0.882
Lymph node +ve				
AI only	0.791	0.887	0.648	0.801
Year 2 crossover	0.807	0.839	0.688	0.761

This data is also illustrated in the survival curves from the paper below:

Key:

A –Lymph Node negative

B- Lymph Node positive

Treatment AI alone red line

Sequential treatment with tamoxifen followed by AI purple line

ER+/PR+ solid lines

ER+/PR- dashed lines

Because this model used the same baseline recurrence rate for tamoxifen-treated patients with either PR+ or PR- tumours, the data showed the paradoxical outcome that patients with ER+/PR- tumours had better disease free survival than patients with ER+/PR+ tumours. This was corrected by identifying relative risks of recurrence for ER+/PR+ and ER+/PR- tumours in tamoxifen-treated patients from the San Antonio Breast Cancer Registry. The analysis was repeated for the impact of PR status on the risk of recurrence with tamoxifen. The treatment strategies did not change -patients with ER+/PR+ benefited from sequential tamoxifen/AI treatment, and ER+/PR- from AI monotherapy. However the resulting survival curves showed that patients who have tumours with PR expression have a better overall prognosis than patients with tumours lacking PR expression.

DFS with adjusted baseline risk of recurrence in tamoxifen treated patients with PR+ and PR - tumours.

Key:

A –Lymph Node negative

B- Lymph Node positive

Treatment AI alone red line

Sequential treatment with tamoxifen followed by AI purple line

ER+/PR+ solid lines

ER+/PR- dashed lines

Author conclusions

Modelling estimates suggested that the optimal endocrine treatment strategy may differ based on the biologic features of breast cancer tumours. Patients with ER+/PR+ tumours achieved optimal 10-year DFS estimates with tamoxifen followed by a crossover to AI therapy, whereas patients with ER+/PR- tumours fared best when they initiated treatment with AI.

General comments –

Studies from which data were obtained:

Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet*. 1998;351:1451-1467.

Howell A on behalf of the ATAC Trialists' Group. The ATAC ('Arimidex,' Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer—updated efficacy results based on a median follow-up of 5 years [abstract 1]. *Breast Cancer Res Treat*. 2004;88(Suppl 1);S7.

Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial.[see comment]. *Lancet* 2005 Aug 6;366(9484):455-62.

GUIDELINES

Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004.[see comment]. [Review] [50 refs]. J Clin Oncol 2005 Jan 20;23(3):619-29.

Design: Update of SR and Guideline recommendations
Country: USA, setting:

Level 4

Aim: To update the 2003 American Society of Clinical Oncology technology assessment on adjuvant use of aromatase inhibitors

Inclusion criteria

Exclusion criteria

Population

Interventions

Outcomes

Follow up

Results

Questions addressed by the panel related to this topic:

Are there specific patient populations that should receive initial therapy with an aromatase inhibitor in lieu of tamoxifen?

Postmenopausal women with a hormone receptor-positive invasive tumour should receive an aromatase inhibitor if there is a contraindication to tamoxifen.

Postmenopausal women who develop invasive breast cancer whilst receiving a selective estrogen receptor modulator (SERM) for either breast cancer risk reduction or bone loss, should be treated with an aromatase inhibitor.

There is a suggestion, from a subgroup analysis within the ATAC trial, that women with ER+, progesterone receptor-negative tumours may benefit more from initial therapy with an aromatase inhibitor. Although this subset analysis was retrospective, the number of events considered was relatively large.

Postmenopausal women with breast cancer over-expressing HER-2, have reported higher response rates for aromatase inhibitors when compared with tamoxifen in two randomized **neoadjuvant** trials. However, both studies included a very limited number of women with HER-2-positive tumours. The Panel recognized that debate continues regarding the optimal hormonal management of patients with HER-2-positive tumours. Based on available clinical evidence, the Panel recommended that HER-2 status not be considered when making choices about adjuvant hormonal therapy.

Do the Results of the MA-17 Trial Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women With Hormone Receptor–Positive Breast Cancer Who Have Completed a 5-Year Course of Tamoxifen?

This trial studied a population of postmenopausal women finishing 5 years of tamoxifen therapy. It demonstrated a statistically significant (43%) reduction in breast cancer events with the use of letrozole. Subset analyses suggested that patients with both node negative and node-positive disease derive benefit from letrozole in this setting. Because of the difference in residual risk of recurrence between high and low-risk patients, the absolute difference is larger for node-positive than node-negative cohorts. The most recent analysis revealed a small but statistically significant ($P=0.04$) survival benefit in patients with node-positive disease.

Based on findings from MA-17, postmenopausal women finishing 5 years of tamoxifen for ER-positive, early-stage breast cancer should consider treatment with an aromatase inhibitor. At present, a minimum of 2.5 years of therapy can be recommended based on the median follow-up from MA-17.

In decisions about the use of an aromatase inhibitor after completion of a five-year course of tamoxifen, clinicians and patients should consider the residual risk of recurrence and individual preferences. The survival advantage in the subset of women with node-positive disease is noteworthy and strengthens the argument for use of an aromatase inhibitor after tamoxifen in this patient population.

Do the Results of the IES and ITA Trials Provide Sufficient Evidence to Recommend the Use of an Aromatase Inhibitor in Postmenopausal Women With Hormone Receptor–Positive Breast Cancer Who Have Received Tamoxifen for 2 to 3 Years?

The IES and ITA trials compared 5 years of tamoxifen versus 2 to 3 years of tamoxifen followed by 2 to 3 years of an aromatase inhibitor among postmenopausal women with ER-positive early-stage breast cancer. Both studies showed that a change in treatment from tamoxifen to an aromatase inhibitor reduced the risk of breast cancer recurrence (risk reduction 32% in IES).

Subset analyses suggest similar relative benefits among women with node negative or node-positive primary breast cancer. The side effect profiles differed between aromatase inhibitor therapy versus continued tamoxifen therapy in predictable ways.

Based on the findings in the IES trial, with supporting evidence from the ITA trial, postmenopausal women concluding 2 to 3 years of tamoxifen therapy may consider cross-over to an aromatase inhibitor. Patients intolerant of aromatase inhibitors or unwilling to switch from tamoxifen should continue to receive tamoxifen for a total duration of 5 years based on previous randomized trials that demonstrated the benefits of a 5-year course of tamoxifen versus a shorter course.

Is There Any Role for the Aromatase Inhibitors in Women With Hormone Receptor–Negative Breast Cancer?

There is strong evidence that adjuvant hormonal therapy is effective only in patients with positive ER and/or progesterone receptors. Aromatase inhibitors have not been evaluated in the adjuvant setting for women with hormone receptor negative tumours. Hormone receptor studies should be performed on all primary invasive tumours to guide the use of adjuvant hormonal therapy. Women with hormone receptor–negative tumours should not receive an aromatase inhibitor as adjuvant therapy. The Panel noted that false-negative hormone receptor assays can occur and would encourage clinicians to repeat hormone receptor studies if the result is in question or is discordant with the clinical picture.

What Is Known About Bone and Musculoskeletal Toxicity Associated With the Aromatase Inhibitors?

Aromatase inhibitor use is associated with osteoporosis and fracture risk related to estrogen deprivation. In adjuvant trials, all three aromatase inhibitors have been associated with more fractures than tamoxifen or placebo (letrozole 3.6% v placebo 2.9%, $P=0.24$, Goss 2003; exemestane 3.1% v tamoxifen 2.3%, $P=0.08$, Coombes 2004; anastrozole 7.1% v tamoxifen 4.4%, $P<0.001$, Baum 2003). Clinical trial evidence indicates that intravenous bisphosphonate as well as oral bisphosphonates clodronate and risedronate, are effective in maintaining bone density in breast cancer patients on hormonal therapy and with therapy associated premature menopause.

In otherwise healthy women, a strong body of evidence supports early detection and therapy of osteoporosis. The ASCO bisphosphonate guideline identifies postmenopausal breast cancer patients who receive aromatase inhibitors to be at high risk for osteoporosis and recommends that they have baseline bone mineral density evaluation.

What Is Known About Vascular Complications and Endometrial Cancer in Women Treated on the Adjuvant Aromatase Inhibitors Trials?

Both anastrozole and exemestane were associated with significantly fewer endometrial cancers, as well as venous and arterial vascular events (pulmonary emboli and stroke), when compared with tamoxifen.

What Is Known About Overall Quality Of Life and Sexual Functioning in Women on Aromatase Inhibitors?

In general, there have been no major differences in symptoms influencing quality of life comparing anastrozole with tamoxifen (Baum 2003) or letrozole with placebo (Goss 2003). Fallowfield (Conference abstr 2002) have reported inferior sexual functioning in women randomly assigned to anastrozole compared with tamoxifen on the ATAC trial. In the IES study, women taking tamoxifen reported less vaginal dryness but more vaginal discharge compared with those on exemestane (Paridaens 2004; Conference abstr). Aromatase inhibitor effects on cognition or dementia have not been reported.

Hot flash frequency data was not measured in a standardized way and difficult to compare between studies.

RECOMMENDATIONS:

Based on results from multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumour recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include 5 years of aromatase inhibitors treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3, or 5 years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor-negative tumours should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their role in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized.

CONCLUSION:

The Panel believes that optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.

General comments –

The main focus of this guideline was the timing and sequencing of aromatase inhibitors. Some subgroup analyses were reported. Side effects of AIs were discussed and are covered in the related topic of timing and sequencing of AIs (topic 29c).

Carlson RW, Brown E, Burstein HJ, Gradishar WJ, Hudis CA, Loprinzi C, et al. NCCN Task Force report: Adjuvant therapy for breast cancer. Journal of the National Comprehensive Cancer Network 2006;4(SUPPL. 1):S.

Design: Guideline
Country: USA, setting:

Level 4

Inclusion criteria**Exclusion criteria****Population**

All stages of breast cancer.

Interventions

Adjuvant systemic therapy.

Only AI therapies are reported here.

Outcomes

Follow up

Results

The National Comprehensive Cancer Network (NCCN) first published the NCCN Breast Cancer Treatment Guidelines in 1996. The Guidelines address the treatment of all stages of breast cancer across the spectrum of patient care. Since adjuvant therapy for breast cancer has undergone a rapid evolution over the past few years the NCCN Breast Cancer Guidelines Panel was supplemented by additional experts to form the Adjuvant Therapy Task Force to provide a forum for extended discussion and expanded input to the adjuvant therapy recommendations for Breast Cancer Treatment Guidelines. One issue discussed was how age, menopausal status, and oestrogen receptor levels impact on the benefits from chemotherapy and endocrine therapy.

Aromatase inhibitors for postmenopausal women

Data from the ATAC trial suggested a greater benefit of anastrozole in patients with ER+/PR- tumours compared to ER+/PR+ tumours (Dowsett 2005). However, this was not observed in the initial analysis of the BIG 1-98 trial (Thurlimann 2005 abstract).

None of the studies using AIs in breast cancer treatment have led to a clear improvement in survival or quality of life. Also, none of the current trials directly compares initial, sequential or extended hormonal therapy.

Aromatase inhibitors and tamoxifen have differing side effect profiles. AIs are associated with lower risk of peripheral blood clots and endometrial cancer, but a greater risk of bone loss and bone fracture than tamoxifen. AI treatment can be associated with an arthralgia syndrome, hot flashes, night sweats and other menopausal symptoms. Quality of life analyses have been similar between AIs and tamoxifen, but patients on AIs have reported greater sexual dysfunction.

In 2004 the ASCO technology assessment on the use of AIs recommended that from results of multiple large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer should include an aromatase inhibitor. Neither the optimal timing nor duration of aromatase inhibitor therapy is established.

Rieber AG, Theriault RL. Aromatase inhibitors in postmenopausal breast cancer patients. *Journal of the National Comprehensive Cancer Network* 2005;3(3):309-14.

Design: Expert review

Level 4

Country: USA, setting:

Aim: Review of evidence supporting current NCCN guidelines for use of AI therapy in the treatment of hormone receptor-positive postmenopausal breast cancer patients.

Inclusion criteria

Exclusion criteria

Population

Postmenopausal HR+ breast cancer

Interventions

Anastrozole
Letrozole
Exemestane

Outcomes**Follow up****Results**

The National Comprehensive Cancer Network (NCCN) guidelines recommend the following algorithm for postmenopausal women with hormone receptor-positive breast cancer:

- Initial adjuvant endocrine treatment:
Anastrozole 1 mg daily for 5 years
- Treatment with tamoxifen for 2-4 years, discuss:
Exemestane 25 mg daily to complete 5 years of total therapy
Anastrozole 1 mg daily to complete 5 years of total therapy
- Treatment with tamoxifen for 4.5-6 years, discuss:
Letrozole 2.5 mg daily for 5 years

UPDATE EVIDENCE (literature search 2005 - June 2008)

<p>Goss PE., Ingle JN., Pater JL., Martino S., Robert NJ., Muss HB., Piccart MJ., Castiglione M., Shepherd LE., Pritchard KI., Livingston RB., Davidson NE., Norton L., Perez EA., Abrams JS., Cameron DA., Palmer MJ and Tu DS (2008) Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. <i>J Clin Oncol</i> 26: 1948-1955</p>
<p>Design: Cohort study as a follow up of MA-17 RCT (Ingle et al 2006), Evidence level 2+ Country: US Aim: The MA-17 trial reported the efficacy of letrozole (LET) started within 3 months of 5 years of adjuvant tamoxifen in postmenopausal hormone receptor–positive early-stage breast cancer. The trial was un-blinded, patients who received placebo (PLAC) were offered LET. This cohort study describes the outcomes of women assigned PLAC at the initial random assignment after un-blinding. The outcomes of the PLAC patients on MA.17 provides an opportunity to determine whether a later intervention with the aromatase inhibitor also might benefit the many breast cancer patients to whom it may apply.</p>
<p>Inclusion criteria As for original MA-17 trial</p>
<p>Exclusion criteria</p>
<p>Population 1. 1,579 women in the PLAC-LET group (median time from tamoxifen, 2.8 years) 2. 804 in the PLAC-PLAC group</p>
<p>Interventions Efficacy outcomes of women who chose LET (PLAC-LET group) were compared with those who did not (PLAC-PLAC group) by the hazard ratios and by P values calculated from Cox models that adjusted for imbalances between the groups.</p>
<p>Outcomes</p> <ul style="list-style-type: none">• Hazard ratio (HR) for disease recurrence• Disease-free survival (DFS)• Overall Survival• Toxicity analyses (only events that occurred after un-blinding)
<p>Results</p> <ul style="list-style-type: none">• Median follow-up of 5.3 years• Patients in the PLAC-LET group were younger; had a better performance status; and were more likely to have had node-positive disease, axillary dissection, and adjuvant chemotherapy than those in the PLAC-PLAC group. <p>DFS:</p> <ul style="list-style-type: none">• 31 patients (2.0%) in the PLAC-LET group had a DFS event compared with 39 patients (4.9%) in the PLAC-PLAC group• Adjusted HR = 0.37, 95%CI 0.23-0.61, P<0.0001. Which corresponded to a 63% reduction in disease recurrence for patients electing to cross over to LET from PLAC.

Distant DFS:

Adjusted HR= 0.39; 95% CI 0.20 - 0.74; P= 0.004. A significant 61% reduction in the risk of developing metastases was observed.

Contralateral primary breast cancer (CLBC):

- The annual incidence rate for new CLBC = 0.06 in the PLAC-LET group and 0.38 in the PLAC-PLAC group.
- Adjusted HR = 0.18; 95% CI 0.06 - 0.58; P = 0.004. Which corresponded to an 82% reduction in CLBC.

Overall Survival:

- Adjusted HR = 0.30 for the PLAC-LET compared with the PLAC-PLAC group, 95%CI 0.17 to 0.53 P<0.0001.

Toxicity:

- There were statistically significantly more self-reported new diagnoses of osteoporosis (PLAC-LET group (5.3% v 1.6%; P<0.0001)
- Significantly more clinical fractures occurred in the women who took LET (5.2% v 3.1%, P = 0.02).
- There was a non significant difference in the number of cardiac events occurring between the groups.
- Thromboembolic events occurred rarely in both groups.
- Other malignancies or bone marrow dysplasias was not different between the groups.

General comments

The question of whether the addition of LET more than 3 months after stopping tamoxifen is beneficial has been answered in part by this analysis of the crossover patients of the MA-17 trial and provides the only available information that can be used to inform this treatment decision.

The analysis reported here represents a self selected patient group to receive LET and so introduces patients selection bias. The authors caution that “the results to DFS and distant DFS should be viewed in the context of an adjusted, retrospective multivariate analysis and not as a prospective, randomised trial”

Forbes JF., Cuzick J., Buzdar A., Howell A., Tobias JS and Baum M (2008) Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncology* **9**: 45-53

Design: RCT, Evidence level 1+

Country: UK

Aim: To evaluate the efficacy and side-effects that may persist after 5 years of adjuvant treatment with an aromatase inhibitor. This study presents the long-term outcomes in the (ATAC) trial that compares anastrozole with tamoxifen after a median follow-up of 100 months.

Inclusion criteria

postmenopausal women with localised invasive breast cancer.

Exclusion criteria

Population

Interventions

anastrozole, n=3125; tamoxifen, n=3116; N= 6241

Outcomes

- Disease free survival (DFS)
- Time to recurrence (TTR)
- Incidence of new contralateral breast cancer (CLBC)
- Time to distant recurrence (TTDR)
- Overall survival (OS)
- Death after recurrence

Results

- Median follow-up of 100 months (range 0–126)
- Follow-up included 46 202 women-years of follow-up for patients receiving monotherapy
- Mean (SD) duration of treatment for patients receiving anastrozole = 4·11 years compared with 3·97 years for tamoxifen

DFS:

For all patients (intention to treat) HR = 0·90 (95%CI 0·82–0·99) P= 0·025, favouring anastrozole

For Hormone-receptor-positive patients: HR = 0·85 (95%CI 0·76–0·94) P= 0·003, favouring anastrozole

In the hormone-receptor-negative subgroup: DFS HR= 1·02 (0·78–1·33) p=0·9, no difference for this group

TTR:

For all patients (intention to treat) HR = 0·81 (95%CI 0·73–0·91) P= 0·0004 favouring anastrozole

For Hormone-receptor-positive patients: HR =0.76 (95%CI 0.67–0.87) P= 0.0001 favouring anastrozole

In the hormone-receptor-negative subgroup: HR= 0.96 (0.71–1.29) p=0.8.

TTDR:

For all patients (intention to treat) HR = 0.86 (95%CI 0.75–0.98) P= 0.022, favouring anastrozole

For Hormone-receptor-positive patients: HR = 0.84 (95%CI 0.72–0.97) P= 0.022 favouring anastrozole

CLBC:

For all patients (intention to treat) HR = 0.68 (95%CI 0.49–0.94) P= 0.020 favouring anastrozole

For Hormone-receptor-positive patients: HR = 0.60 (95%CI 0.42–0.85) P= 0.004 favouring anastrozole

Adverse events:

• Deaths after recurrence for all patients = 350 (anastrozole) and 382 (tamoxifen)

HR =0.91 (0.79–1.05) p=0.2

• For the hormone receptor- positive subgroup = 245 (anastrozole) and 269 (tamoxifen)

HR =0.90 (0.75–1.07) p=0.2

OS:

• No statistically significant difference was reported for OS

For the ITT population: 629 deaths (anastrozole); 624 deaths (tamoxifen)

HR =1.00 (0.89–1.12) p=0.99

After Treatment Outcomes:

Disease Recurrence:

• A lower recurrence rate for anastrozole compared with tamoxifen was maintained after treatment was completed, (esp. in hormone-receptor-positive patients)

• Absolute benefit = 2.8% (anastrozole, n=245 events; tamoxifen, n=312 events)

HR =0.77 (0.65–0.91) p=0.002

• At 5 years this difference increased to 4.8%

• At 9 years (anastrozole, 391 events, tamoxifen, 494 events): HR=0.76 (0.67–0.87) p=0.0001

After 5 years, for the hormone-receptor-positive patient population:

• 146 events in 2159 (7%) at-risk patients who received anastrozole

• 182 events in 2075 (9%) at-risk patients who received tamoxifen

• HR= 0.75 (0.61–0.94) p=0.01

→ Indicating that the carryover benefit after treatment completion with anastrozole is larger than that known to exist after tamoxifen.

Distant recurrence rates continued to diverge with increasing follow-up time:

• 1.3% lower for anastrozole compared with tamoxifen at year 5; 2.4% lower at year 9

For isolated contralateral tumours (as a first event): significantly lower with anastrozole

compared with tamoxifen (hormone-receptor-positive patients: HR=0.60 (0.42–0.85 p=0.004)

The HR recurrence favoured anastrozole for all subgroups based on baseline and treatment characteristics

- Subgroup of oestrogen receptor-positive and progesterone-receptor-negative patients with a significant benefit in favour of anastrozole (larger than for the oestrogen-receptor-positive and progesterone-receptor-positive subgroup) HR= 0.42 (95% CI 0.31-0.58)

Adverse events:

- No significant difference for deaths between the groups, however, death without recurrence were higher in patients receiving anastrozole.
- Serious adverse events were similar in both treatment arms
- Treatment-related serious adverse events were lower in those receiving anastrozole compared with those receiving tamoxifen during treatment and similar after treatment completion; OR =0.57 (0.47–0.68) p<0.0001
- Myocardial infarctions were similar in the two treatment groups (both during treatment and after its completion)
- Fewer cerebrovascular accidents reported for patients receiving anastrozole during treatment
- There was no significant difference in risk of cardiovascular morbidity between anastrozole and tamoxifen treatment groups.
- Endometrial cancer remained significantly lower in patients treated with anastrozole than with tamoxifen; OR= 0.21 (0.06–0.56) p=0.0004
- Fracture data was monitored in a blinded manner after treatment cessation: fracture rates were increased on anastrozole during treatment: incidence rate ratio (IRR) = 1.55 (1.31–1.83) p<0.0001. There was no significant difference after 5 years, off treatment: (IRR= 1.03 (0.81–1.31) p=0.79
- There was no significant difference in risk of mortality between anastrozole and tamoxifen treatment groups.

Kaufmann M., Jonat W., Hilfrich J., Eidtmann H., Gademann G., Zuna I and von MG (2007) Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. *J Clin Oncol* **25**: 2664-2670

Design: RCT, Evidence level 1+

Country: Germany

Aim: To evaluate the benefits of switching to anastrozole after 2 years of tamoxifen treatment, compared with continuing on tamoxifen for 5 years

This study has been reported by Jakesz et al 2005 (Lancet) which combined results from the ABCSG trial 8 (GABG) study. The report here describes results of only the ARNO 95 trial.

Inclusion criteria

Postmenopausal women (age \leq 75 years) with histologically verified, grade 1 to grade 3 invasive breast cancer (pT1-3, node negative, or up to nine tumour-infiltrated lymph nodes [pN0-2] and no distant metastases), who had undergone primary surgery (with or without radiotherapy) and had received 2 years of continuous adjuvant tamoxifen therapy (20 or 30 mg/d) without disease recurrence.

Exclusion criteria

Population

Randomly assigned n = 979

Tamoxifen: Allocated to treatment (n = 490) (*Intent-to-treat population*) - Received treatment (n = 452) (*Safety analysis population*) - Ongoing on study treatment (n = 182) - Completed study treatment (n = 175) - Ongoing on follow-up (n = 172)

Anastrozole: Allocated to treatment (n = 489) (*Intent-to-treat population*) - Received treatment (n = 445) (*Safety analysis population*) - Ongoing on study treatment (n = 170) - Completed study treatment (n = 185) - Ongoing on follow-up (n = 182)

Interventions

Patients were who had received 2 years of continuous adjuvant tamoxifen therapy were randomly assigned to receive: anastrozole (1 mg/d) or to continue with tamoxifen (20 or 30 mg/d) for 3 years in a 1:1 ratio.

Outcomes

- Disease recurrence
- Overall survival
- Serious adverse events

Results

Follow-up of live patients ranged from < 1 to ≥ 7 years when the database was closed. When the analysis was initiated, 42.5% of patients had completed the planned 5 years of adjuvant treatment (2 years of tamoxifen treatment plus 3 years of study therapy). Median follow-up time = 30.1 months and the median durations of exposure to anastrozole (26.8 months) and tamoxifen (27.4 months) during the randomized treatment period.

Recurrence:

- Switching to adjuvant anastrozole from adjuvant tamoxifen showed a statistically significant improvement in disease-free survival:
34% reduction in the relative risk of disease recurrence or death compared with continuing on tamoxifen: HR= 0.66; 95% CI, 0.44 to 1.00; P =0.049
- The estimate of disease-free survival at 3 years (completion of study treatment) showed an absolute difference of 4.2% in favor of anastrozole (93.5% for anastrozole and 89.3% for tamoxifen)
- Fewer patients who switched to anastrozole experienced first recurrence events of local or distant disease recurrence, contralateral breast cancer, or death compared with those who continued on tamoxifen (38 [7.8%] patients v 56 [11.4%] patients, respectively).
- Numerical results only showed an advantage in favour of anastrozole for the incidence of any recurrence event (local or distant recurrence, contralateral breast cancer - 1.4% in patients switched to anastrozole and 1.0% in patients who continued with tamoxifen.)

Survival and Disease-Free Survival:

- Anastrozole group had a 47% improvement in overall survival compared with continued tamoxifen group (HR= 0.53; 95% CI, 0.28 - 0.99; P=0.045)
- After adjustment for potential prognostic factors (age, tumor size and grade, lymph node status, and type of primary surgery), switching to adjuvant anastrozole from adjuvant tamoxifen still resulted in a statistically significant improvement in:
 - disease-free survival: HR= 0.61; 95% CI, 0.40 to 0.93; P =0.023)
 - overall survival: HR= 0.48; 95% CI, 0.25 to 0.91; P=0.026) compared with continuing on tamoxifen.

Safety:

- All of the patients in this study tolerated 2 years of treatment with tamoxifen.
- Less patients died after switching to anastrozole treatment (n = 15; 3.4%) compared with those patients who continued on tamoxifen (n=27; 6.0%)
- No serious adverse events with an outcome of death were observed.
- Fewer patients in anastrozole group reported serious adverse events (101/445; 22.7%) compared with those who remained on tamoxifen (139/452; 30.8%).
- This difference was mainly due to a greater number of patients in the tamoxifen group with serious endometrial events (OR =0.66; 95% CI, 0.49 -0.89; P =0.0065)

Rasmussen BB., Regan MM., Lykkesfeldt AE., Dell'Orto P., Del CB., Henriksen KL., Mastropasqua MG., Price KN., Mery E., Lacroix-Triki M., Braye S., Altermatt HJ., Gelber

RD., Castiglione-Gertsch M., Goldhirsch A., Gusterson BA., Thurlimann B., Coates AS., Viale G and Collaborative and International Breast Cancer Study Groups. (2008) Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1-98 randomised trial.[see comment]. *Lancet Oncology* **9**: 23-28

Design: RCT(subset report of BIG1-98 trial), Evidence level 1+

Country: International

Aim: To evaluate the benefit of letrozole versus tamoxifen according to the ERBB2 status of tumours.

Inclusion criteria

postmenopausal women with early breast cancer whose tumours were assessed by local pathologists as either ER-positive or PgR-positive, or both.

Exclusion criteria

Population

8010 patients randomised → 3650 (117 excluded absent or not assessable .:3533)centrally assessed as having ER present tumours→1782 in letrozole group / 1751 in tamoxifen group

Interventions

The BIG 1-98 trial consists of four treatment groups that compare 5 years of monotherapy with letrozole or tamoxifen, and sequential administration of one drug for 2 years followed by the other drug for 3 years.

Outcomes

Tumour assessment and associations with DFS and treatment group.

Results

- 7% of patients (257 of 3650) tumours were identified to be ERBB2-positive.

Patients with ERBB2-positive tumours were:

- younger than those with ERBB2-negative tumours ($p=0.04$) and were
- treated more frequently with mastectomy ($p=0.005$) and
- treated more frequently with chemotherapy ($p<0.0001$).

- ERBB2-positivity was associated with larger tumour size and higher tumour grade (both $p<0.01$), but not with positive lymph-node status ($p=0.10$), and was associated with lower ER and PgR expression (both $p<0.0001$)

Association of ERBB2 status and treatment with DFS in endocrine-responsive disease were based to the 3533 patients who had ER-present tumours assessed.

ERBB2 status was shown to be associated with DFS;

- 6.8% patients whose tumours were ERBB2-positive had a poorer outcome than those whose tumours were ERBB2-negative (HR= 2.09, 95% CI 1.59–2.76; $p<0.0001$),
- Estimated 4-year DFS of 75% (95% CI 68–80) ERBB2-positive and 88% (87–89) ERBB2-negative
- Letrozole improved DFS compared with tamoxifen regardless of ERBB2 status (ERBB2-positive tumours: HR 0.62 (95% CI 0.37–1.03); ERBB2-negative tumours: HR 0.72 (0.59–0.87))

- PgR status of the tumour was associated with DFS ($p < 0.0001$), but no statistical evidence of heterogeneity in the treatment effect existed ($p = 0.47$ for interaction); suggesting a consistent benefit of letrozole over tamoxifen regardless of PgR expression.
- When heterogeneity of the treatment effect according to PgR and ERBB2 status of the tumour was investigated; there was no statistically significant interaction ($p = 0.63$), suggesting improved DFS with letrozole compared with tamoxifen, regardless of PgR or ERBB2 status.

Crivellari D., Sun Z., Coates AS., Price KN., Thurlimann B., Mouridsen H., Mauriac L., Forbes JF., Paridaens RJ., Castiglione-Gertsch M., Gelber RD., Colleoni M., Lang I., Del ML., Gladiëff L., Rabaglio M., Smith IE., Chirgwin JH and Goldhirsch A (2008) Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1-98 trial. *J Clin Oncol* **26**: 1972-1979

Design: RCT: sub-study of BIG1-98 trial

Country: International

Aim: To evaluate the differences in efficacy, treatment completion, and adverse events (AEs) in elderly women receiving adjuvant tamoxifen or letrozole for five years in the Breast International Group (BIG) 1-98 trial.

Inclusion criteria

postmenopausal women with hormone receptor-positive breast cancer

Exclusion criteria

Population

2,463 to letrozole group

2,459 to tamoxifen group

Interventions

Women were randomly assigned in a phase III, double-blind trial to one of the four following treatment regimens:

1. tamoxifen for 5 years,
 2. letrozole for 5 years,
 3. tamoxifen for 2 years followed by letrozole for 3 years,
 4. letrozole for 2 years followed by tamoxifen for 3 years.
- The current analysis focuses on the 4,922 patients randomly assigned to the two monotherapy arms.
 - The median follow-up was 40.4 months.

Outcomes

- disease-free survival (DFS): defined as the time from random assignment to the first of the following events ending DFS
- recurrence: at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, non-breast cancer; or death without a prior cancer event.
- Subpopulation Treatment Effect Pattern Plot (STEPP) analysis was used to investigate the pattern of difference in 4-year DFS between treatment arms according to patient age at study entry.
- AEs were limited to the safety population (n=4,895) which excluded 27 patients who did not receive any trial treatment and included: any non-fracture AE, bone fractures, thromboembolic AEs, any cardiac AE, and ischemic cardiac events.

Results

DFS:

In the overall population, letrozole was more efficacious than tamoxifen (P =0.006), and this superiority was similar across the age spectrum and not significantly influenced by age (interaction of age and treatment, P=0.84).

Adverse Events:

The incidence of bone fractures, observed more often in the letrozole group, did not differ by age. In elderly patients, letrozole had a significantly higher incidence of any grade 3 to 5 protocol-specified non-fracture AE compared with tamoxifen ($P = 0.002$), but differences were not significant for thromboembolic or cardiac AEs.

- There were no statistically significant differences between the two treatment groups for any of the risk factor categories.
- When the cumulative incidence of first non-fracture grade 3 to 5 adverse event with DFS as competing events, was evaluated it was found that there was a significantly earlier occurrence of grade 3 to 5 non-fracture AE in elderly patients (75 years and older) receiving letrozole ($P = 0.002$).

Fracture Rate:

- Incidence of bone fractures was higher among patients treated with letrozole (8.0% let. group v 5.4% receiving tamoxifen; $P < 0.001$).
- Risk factors for bone fractures (grade 1 to 5) during treatment were statistically significant for: smoking history ($P = 0.006$) and prior bone fracture ($P < 0.0001$).

Cardiovascular AEs:

- In the total population, thromboembolic events of any grade were less frequently reported in women treated with letrozole (2.0% in let. group v 3.8% receiving tamoxifen; $P < 0.0001$).
- After adjusting for risk factors, the treatment difference in time to first thromboembolic event observed for the two younger age groups was less pronounced in the elderly groups
- Risk factors that were statistically significant for thromboembolic events during treatment were: higher Baseline BMI ($P = 0.008$ for grade 1 to 5; $P = 0.0005$ for grade 3 to 5) and prior thromboembolic events ($P < 0.0001$ for grade 1 to 5 and for grade 3 to 5).

- The overall incidence of cardiac events (grade 1 to 5) was similar in the two treatment groups (letrozole 5.7% v tamoxifen 5.2%; $P = 0.45$).
- After adjusting for risk factors, a significant difference favouring tamoxifen was observed in the older age group (65 to 74 years) but not in the elderly group (≥ 75 yrs).
- A statistically significant difference was reported for risk factors for cardiac events during treatment included history of hypertension ($P = 0.02$ for grade 3 to 5), and prior cardiac events ($P < 0.0001$ for grade 1 to 5; $P < 0.0001$ for grade 3 to 5).

- The overall incidence of ischemic heart events (grade 1 to 5) was similar in the two groups (letrozole, [2.2%] v tamoxifen, [1.8%]; $P = 0.42$).

- After adjusting for risk factors, a significant difference in time to first grade 3 to 5 ischemic heart event favouring tamoxifen was observed in the older age group (65 to 74 years) but not in the younger cohort (< 65 years) or elderly group.
- Statistically significant risk factors for ischemic heart events during treatment included history of hypertension ($P = 0.04$ for grade 1 to 5; $P = 0.001$ for grade 3 to 5), and prior ischemic heart events ($P < 0.0001$ for grade 1 to 5; $P < 0.0001$ for grade 3 to 5)

Muss HB., Tu D., Ingle JN., Martino S., Robert NJ., Pater JL., Whelan TJ., Palmer MJ., Piccart MJ., Shepherd LE., Pritchard KI., He Z and Goss PE (2008) Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG inter group trial MA.17. *J Clin Oncol* 26: 1956-1964

Design: RCT subset study, Evidence Level 1+

Country: Canada

Aim: To determine whether there were age-dependent differences in DFS, DDFS, and OS toxicity, or QOL among older and younger patients in the MA.17 RCT which tested the efficacy of letrozole compared to placebo in postmenopausal patients who were disease free after 5 years of tamoxifen.

Inclusion criteria

See original report of trial

Exclusion criteria

Population

5,169 randomly assigned patients were divided into three age groups:

1. younger than 60 years (n = 2,152)
2. 60 to 69 years (n = 1,694)
3. 70 years (n ≥ 1,323)

Interventions

letrozole (2.5 mg oral) or placebo for 5 years and stratified by hormone-receptor status, nodal involvement, and chemotherapy use.

Outcomes

- DFS
- distant-disease-free survival: DDFS
- OS
- Toxicity: QOL: Medical Outcomes Short Form 36-item general health questionnaire (SF-36), a multipurpose QOL measure.

Results

Age outcomes:

- There was no significant difference in DFS and DDFS between the three age groups.
- OS was significantly different between these three age groups due to an increased risk of non-breast cancer-related death with increasing age (with results remain the same after adjusting for other potential prognostic factors such as letrozole or placebo treatment, duration of prior tamoxifen, nodal status, and prior chemotherapy).

Treatment outcomes:

- Letrozole significantly improved both DFS and DDFS but only in women younger than 60 years of age (HR = 0.46; P = 0.0004)
- The interaction between age and treatment was not statistically significant for any of the outcomes (DFS, P =0.36; DDFS, 0.77, and OS, 0.98), indicating no evidence of a heterogeneous effect of letrozole among age groups (or a similar effect of letrozole among all age groups).
- Letrozole stats. significantly improved DFS compared with placebo for both node-negative and node-positive patients younger than 60 years (p=0.024) and for patients with negative

nodes ≥ 70 years old ($p=0.021$).

- In node-positive patients: letrozole compared with placebo led to a significant improvement in DDFS in those age 60 to 69 years (HR = 0.39, $P=0.009$) and a significant improvement in OS for those age ≥ 70 years (HR= 0.50, $P= 0.038$)

QoL:

- Women ≥ 70 years of age had significantly higher incidences of oedema, hypertension, fatigue, anorexia, constipation, diarrhoea, arthritis, dizziness, and dyspnoea but lower incidences of hot flushes, sweating, vaginal bleeding, high cholesterol, insomnia, headache, and vaginal dryness compared with younger women.
- Compared with placebo, women receiving letrozole who were younger than 60 years had a significantly lower incidence of vaginal bleeding ($P=0.007$) and higher incidence of arthralgia ($P<0.001$)
- Women on letrozole 60 to 69 years had a statistically significantly higher incidence of hot flushes($P=0.003$), insomnia ($P=0.14$), arthralgia ($P=0.005$), and alopecia ($P=0.03$).
- Women ≥ 70 years had no significant difference in toxicities between the letrozole and placebo groups.
- There was no difference in toxicity or QOL at 24 months in the letrozole group and placebo group for patients ≥ 70 years age.

Author's recommend that "healthy patients age 70 years and older completing 5 years of tamoxifen should be considered for extended adjuvant therapy with letrozole."

Eisen, A., Trudeau, M., Shelley, W., Messersmith, H., Pritchard, K. (2008) Aromatase Inhibitors in adjuvant therapy for hormone receptor positive breast cancer: A systematic review. <i>Cancer Treatment Reviews</i> 34; 157-174
Design: Systematic Review
Country: Canada
Aim: To review the evidence for the use of third generation AI's as adjuvant therapy for post-menopausal women with early stage, hormone receptor-positive breast cancer.
Inclusion criteria Randomised trials or meta-analyses evaluating third generation aromatase inhibitors (AI's) as adjuvant therapy and including the primary outcomes disease/event/relapse-free survival and/or overall survival.
Exclusion criteria <ul style="list-style-type: none"> • Non English language trials • Trials with no efficacy outcomes
Population Nine randomised trials One systematic review
Interventions: AI's compared with Tamoxifen, placebo or Tamoxifen + AI's in sequence.
Outcomes <ul style="list-style-type: none"> • AI's compared with Tamoxifen for five years in relation to clinical outcomes such as disease free or overall survival. • AI's in sequence with Tamoxifen for a total of five years compared with Tamoxifen alone outcomes such as disease free or overall survival. • AI's following five years Tamoxifen compared with placebo outcomes such as disease free or overall survival. • The harms associated with AI's compared with Tamoxifen or placebo • Do the relative efficacies of AI's compared with Tamoxifen depend on HER2/neu status?
Results <u>Summary</u> Aromatase Inhibitors are consistently associated with longer disease free survival than treatment with Tamoxifen alone with only one of nine trials reviewed not reporting significantly longer disease free survival, an effect that appears to be independent of the way in which the aromatase inhibitor is administered (i.e. alone or in sequence with Tamoxifen). There is inconsistency in the effects of aromatase inhibitors on overall survival however with

some studies reporting a significant effect in favour of aromatase inhibitors and others reporting no differences. This may be due to a number of factors such as follow-up durations or possibly the trials do not have sufficient power to detect difference in overall survival. Across the majority of trials similar effects on lipid profile were observed with Tamoxifen associated with decreased total cholesterol and LDL cholesterol and increased triglycerides while upfront therapy with aromatase inhibitors was associated with no or minimum lipid changes.

Treatment with Tamoxifen is consistently associated with an increased rate of thromboembolic events and a greater incidence of endometrial cancer.

Aromatase Inhibitors alone versus Tamoxifen alone

Two trials reported on 5 year AI's versus Tamoxifen alone; **the ATAC trial** (anastrozole) and **the BIG 1-98 trial** (letrozole).

In the **ATAC trial** at 68 months follow-up intention-to-treat analysis showed significantly improved disease free survival (HR: 0.87; 95% CI: 0.78-0.97) , time to recurrence (HR: 0.79; 95% CI: 0.7-0.9) and time to distant recurrence (HR: 0.86; 95% CI: 0.74-0.99) for anastrozole over Tamoxifen. Overall survival was similar for both groups.

In the **BIG 1-98 trial** at 51 months follow-up disease free survival favoured letrozole over Tamoxifen (HR: 0.82; 95% CI: 0.71-0.95) but no significant benefit for overall survival. Time to recurrence (HR: 0.78; 95% CI: 0.66-0.93) and time to distant recurrence (HR: 0.81; 95% CI: 0.67-0.98) both favoured letrozole over Tamoxifen.

Aromatase Inhibitors after Tamoxifen versus Tamoxifen alone

In the **IES** study, women who have completed two or three years Tamoxifen were randomised to receive exemestane or further Tamoxifen for a total of five years. At 55.7 months follow-up there was an improvement in disease free survival (HR: 0.76; 95% CI: 0.66-0.88) but not in overall survival. Time to contralateral breast cancer (HR: 0.57; 95% CI: 0.33-0.98), time to recurrence (HR: 0.70; 95% CI: 0.58-0.83) and time to distant recurrence (HR: 0.83; 95% CI: 0.71-0.99) were significantly improved with exemestane.

In the **ITA trial**, women who had received two or more years of Tamoxifen were randomised to receive anastrozole or to continue Tamoxifen for a total of five years treatment. At 64 months median follow-up there were significant improvements in disease free survival (HR: 0.57; 95% CI: 0.38-0.85) in favour of anastrozole but no difference in overall survival.

The interim results of the **ABCSG-8** and **ARNO-95** trials were combined with survival analysis conducted beginning at completion of two years Tamoxifen. At 28 months median follow-up disease free survival was significantly better in women switching to anastrozole (HR: 0.60; 95% CI: 0.44-0.81) but again there was no difference in overall survival between the two groups.

Analysis of the **ARNO-95** trial data only at 30.1 months median follow-up reported that both disease free survival (HR: 0.66; 95% CI: 0.44-1.00, p=0.049) and overall survival (HR: 0.53; 95% CI: 0.28-0.99, p=0.045) were significantly improved in the Tamoxifen followed by anastrozole arm.

A meta analysis of three trials (**ITA, ABCSG-8 & ARNO-95**) found significant improvement in

disease free survival (HR: 0.59; 95% CI 0.48-0.74, $p < 0.0001$), distant recurrence free survival (HR: 0.61; 95% CI: 0.45-0.83, $p = 0.002$) and overall survival (HR: 0.71; 95% CI 0.52-0.98, $p = 0.04$).

Aromatase Inhibitors after five years Tamoxifen

Three trials provided data on the effect of AI's versus placebo following five years Tamoxifen, the National Cancer Institute of Canada **MA 17 trial**, the **NSABP B-33 trial** and the **ABCSG 6a trial**.

In the **MA 17 trial** patients who had completed five years Tamoxifen were randomised to either five years letrozole or placebo. At 30 months median follow up, women in the letrozole arm reported significantly better disease free survival (HR: 0.58; 95% CI: 0.45-0.75) but not overall survival. In further analyzing the data, there was a significant trend in disease free survival ($p < 0.0001$) and distant disease free survival ($p < 0.0013$) out to 48 months duration in favour of letrozole.

Subgroup analysis showed that there was a significant improvement in overall survival for node-positive patients in the letrozole group (HR: 0.61; 95% CI: 0.38-0.98, $p < 0.04$) at 30 months median follow-up. At 48 months a significant trend for increasing benefit of letrozole was observed for node-positive patients for disease free survival ($p < 0.0004$), distant disease free survival ($p = 0.0005$) and overall survival ($p = 0.038$). In node-negative patients only disease free survival showed a significant trend towards improvement ($p = 0.027$).

The **NSABP B-33 trial** originally intended to randomise women who had received five years Tamoxifen to two years of either exemestane or placebo but was later amended to five years exemestane or placebo. This trial was unblinded and placebo patients were offered exemestane; at 30 months median follow-up no significant difference was observed between the two groups in relation to disease free survival or overall survival, significantly longer relapse-free survival was reported in patients receiving exemestane (HR: 0.50, $p = 0.03$).

The **ABCSG-6a trial** extended the ABCSG-6 trial from five years Tamoxifen versus five year Tamoxifen + aminoglutethimide to anastrozole versus no further treatment following five years Tamoxifen. At 60 months median follow-up the trial found a significant improvement in disease free survival in patients treated with anastrozole after five years Tamoxifen, with or without aminoglutethimide. The results were reported in abstract form and no p-values or point estimates were reported.

Harms associated with aromatase inhibitors

In the **ATAC trial** serious adverse events were defined as death, life threatening event, event causing extended hospitalisation, event causing disability or event needing intervention to prevent permanent impairment. Serious adverse events more frequently occurred with Tamoxifen (36%) than with anastrozole (33%, $p = 0.03$). Treatment related adverse events were also more frequent in the Tamoxifen group (9% versus 5%, $p < 0.0001$).

Three trials and two Tamoxifen and Exemestane Adjuvant Multi-centre (TEAM) sub studies provided data on changes to lipid metabolism associated with aromatase inhibitors.

In the **BIG 1-98 trial** patients receiving Tamoxifen had lower total cholesterol levels from

baseline while those in the letrozole arm had unchanged levels. 43.6% of the letrozole group had hypercholesterolemia reported at least once during the study as compared with 19.2% of the Tamoxifen group.

The rate of lipid metabolism disorders in the **ITA trial** was significantly lower in the Tamoxifen only group compared with the Tamoxifen followed by anastrozole group ($p=0.04$).

A companion study to the **MA. 17 trial** found no significant difference in a number of lipid parameters between patients receiving letrozole and patients receiving placebo following Tamoxifen.

A lipid sub-study of the **TEAM trial** (currently still open to accrual) measured and compared baseline, three month and six month levels of total cholesterol, HDL cholesterol and LDL cholesterol and showed that at 12 months patients receiving exemestane experienced significantly less change in baseline cholesterol level from baseline than did patients receiving Tamoxifen (median percentage change -1.9% vs. -9.9% $p=0.039$).

No significant differences were observed in HDL cholesterol at any time point for either group. There were significant differences in LDL cholesterol at three months (+4.8% vs. 9.2%, $p=0.014$) and at six months (+8% vs. -9.1% $p=0.001$) with those receiving exemestane having increased levels of LDL while those receiving Tamoxifen had decreased levels from baseline. Triglycerides were lower or unchanged in those receiving exemestane and higher in those receiving Tamoxifen at three months (+0.8% vs. +22.1%, $p=0.018$), six months (-16% vs. +10% $p=0.008$) and nine months (-7.9% vs. +32.6% $p=0.009$); there was no significant difference at 12 months.

A separate **TEAM** sub study included five years anastrozole in addition to the main TEAM five year exemestane and Tamoxifen arms and observed that triglycerides were consistently increased above baseline with Tamoxifen, decreased with exemestane and remained unchanged with anastrozole.

Bone-related toxicity

Significantly higher fracture rates were observed for aromatase inhibitors compared with Tamoxifen in the **ATAC, BIG 1-98, IES and ABCSG-8/ARNO-95** studies.

Trial	Treatment	Fractures
ATAC	Anastrozole vs. Tamoxifen	11.0% vs. 7.7%, $p<0.0001$
BIG 1-98	Letrozole vs. Tamoxifen	8.6% vs. 5.8%, $p<0.001$
IES	Tamoxifen followed by exemestane vs. Tamoxifen	7.0% vs. 4.9%, $p=0.003$
ITA	Tamoxifen followed by Anastrozole vs. Tamoxifen	1.0% vs. 1.3%, $p=0.06$
ABCSG-8/ARNO-95	Tamoxifen followed by Anastrozole vs. Tamoxifen	2.0% vs. 1%, $p=0.015$
MA. 17	Tamoxifen followed by Letrozole vs. Tamoxifen followed by placebo	5.3% vs. 4.6%, $p=0.25$

NSABP-33	Tamoxifen followed by Exemestane vs. Tamoxifen followed by placebo	28 fractures vs. 20 fractures, p=0.33
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The **ATAC** study compared rate of fracture by site for anastrozole vs. Tamoxifen finding no significant difference in fracture rates for hip (1.2% vs. 1.0% p=0.5) or wrist/Colles (2.3% vs. 2.0% p=0.4) and significant differences in fracture rates for spine (1.5% vs. 0.9% p=0.03) and all other fractures (7.1% vs. 4.6% p<0.0001).

Two sub-studies from the **ATAC trial** reported in abstract form. The first sub study examined patterns of time to fracture between anastrozole and Tamoxifen in the ATAC trial up to five years and found that time to fracture was worse for women taking anastrozole compared with Tamoxifen.

The second study examined the impact of anastrozole vs. Tamoxifen on bone mineral density. Lumbar spine and total hip bone mineral density were measured and anastrozole was associated with decreases in both lumbar spine (percentage decrease in bone mineral density on anastrozole compared with Tamoxifen; -8.1% [95% CI -10.1% to -6.1%, p<0.0001]) and total hip (percentage decrease in bone mineral density on anastrozole compared with Tamoxifen; -7.4% [95% CI -9.6% to -5.3%, p<0.0001) bone mineral density loss at five years. No patient with normal baseline bone mineral density had osteoporosis at five years.

A sub-study associated with the MA.17 trial observed changes in baseline bone mineral density in patients treated with letrozole vs. placebo. Patients on letrozole had significantly greater decrease in total hip bone mineral density (-3.6% vs. -0.71%, p=0.008) and in lumbar spine bone mineral density (-5.35% vs. -0.70%, p=0.044) compared with those on placebo. No significant difference in the rate of osteoporosis was observed in lumbar spine or total hip. Post unblinding, more patients that crossed over to letrozole experienced new osteoporosis than those that did not cross over (~4.0% vs. ~1.5% p=0.007).

Gynaecological Toxicity

Trial	Treatment	Gynaecological toxicity (including endometrial cancer)
ATAC	Anastrozole vs. Tamoxifen	<ul style="list-style-type: none"> Vaginal bleeding: 5.4 vs. 10.2%, p<0.0001 Vaginal discharge: 3.5% vs. 13.2%, p<0.0001 Endometrial cancer: 0.2% vs. 0.8%, p=0.02
BIG 1-98	Letrozole vs. Tamoxifen	<ul style="list-style-type: none"> Vaginal bleeding: 3.8% vs. 8.3%, p<0.001 Endometrial biopsies: 2.3% vs. 9.1%, p<0.001 Invasive endometrial cancer: 0.1% vs. 0.3%, p=0.18
IES	Tamoxifen followed by exemestane vs. Tamoxifen	<ul style="list-style-type: none"> Serious gynaecological events: 7.0% vs. 10.6%, p=0.0001 Vaginal bleeding: 5.2% vs. 7.6%, p=0.002

		<ul style="list-style-type: none"> • Vaginal discharge: 3.1% vs. 4.1%, p=0.06 • Endometrial hyperplasia: 0.2% vs. 1.2% , p=0.0002 • Uterine polyps/fibroids: 1.6% vs. 4.6%, p<0.0001 • Endometrial cancer: No significant difference
ITA	Tamoxifen followed by Anastrozole vs. Tamoxifen	<ul style="list-style-type: none"> • Gynaecological symptoms: 7.4% vs. 8.0%, p=0.5 • Gynaecological changes (including endometrial carcinoma): 1.0% vs. 11.3%, p=0.0002
ABCSG-8/ARNO-95	Tamoxifen followed by Anastrozole vs. Tamoxifen	<ul style="list-style-type: none"> • Endometrial cancer: <1% vs. <1%, p=0.069 • Vaginal bleeding/discharge (ABCSG-8 only): 18% vs. 17%, p=0.9348
MA. 17	Tamoxifen followed by Letrozole vs. Tamoxifen followed by placebo	<ul style="list-style-type: none"> • Vaginal bleeding: 6% vs. 8%, p=0.005 • Endometrial cancer: 4 pts vs. 11 pts, p=0.12

A sub-study of the ATAC trial (n=271), reporting in abstract form, observed that abnormalities in the anastrozole and Tamoxifen groups at six years were 27% and 44% respectively (OR: 0.52, 95% CI 0.20-1.32, p=0.17).

Median endometrial thickness was unchanged from baseline in the anastrozole group but had increased in the Tamoxifen group.

A second sub-study of the ATAC trial observed rates of endometrial cancer were lower than expected in the anastrozole group (standardised incidence rate ratio 0.73, 95% CI: 0.15-2.12) while in the Tamoxifen group they were higher than expected (standardised incidence rate ratio 2.68, 95% CI: 1.34-4.8).

Menopausal symptoms

A number of menopausal symptoms were assessed across the trials; the table outlines the significant results from the different trials.

Trial	Treatment	Menopausal Symptoms
ATAC	Anastrozole vs. Tamoxifen	<ul style="list-style-type: none"> • Hot flashes: 35.7% vs. 40.9%, p<0.0001 • Arthralgia: 35.6% vs. 29.4%, p<0.0001
BIG 1-98	Letrozole vs. Tamoxifen	<ul style="list-style-type: none"> • Hot flashes: 32.8% vs. 37.4%, p<0.001 • Arthralgia: 20% vs. 13.5%, p<0.001
IES	Tamoxifen followed by exemestane vs. Tamoxifen	<ul style="list-style-type: none"> • Insomnia: 20.8% vs. 18.2%, p<0.03 • Arthralgia: 20.8% vs. 15.1%, p<0.0001 • Arthritis: 17.5% vs. 14.6%, p=0.008 • Muscle pain: 25.7% vs. 20.3%, p<0.0001
MA. 17	Tamoxifen followed by Letrozole vs. Tamoxifen followed by placebo	<ul style="list-style-type: none"> • Hot flashes: 58% vs. 54%, p=0.003 • Arthralgia: 25% vs. 21%, p<0.001 • Muscle pain: 15% vs. 12%, p=0.004

In the **TEAM trial** menopausal symptoms were assessed during the first year of exemestane of Tamoxifen in 997 patients. Vaginal dryness ($p=0.0004$), impaired word finding ($p=0.0057$), bone/muscle aches ($p<0.0001$), decreased libido ($p=0.0343$) and difficulty sleeping ($p=0.0346$) were worse in the exemestane group while vaginal discharge ($p<0.0001$) and hot flashes ($p=0.0253$) were worse in the Tamoxifen group.

Quality of Life

The **ATAC, MA.17, IES and NSAS BC 03 trials** and the **TEAM trial NSAS BC 04 sub study** reported on quality of life issues

In the **ATAC trial** 1021 patients were evaluated with quality of life measurements made at baseline, three months, six months and every six months thereafter. There was no significant difference in the Treatment Outcomes Score between anastrozole and Tamoxifen. All groups showed an improvement in the TOI scores at baseline and three months.

In the **MA.17 trial** 3582 patients were evaluated with measurements made at baseline, six months, twelve months and every twelve months thereafter. There was no significant difference in mean change scores between the letrozole and placebo groups.

No clinically meaningful differences were found between treatment arms in the **IES trial**.

The **NSAS BC 03** patients receiving Tamoxifen reported significantly better quality of life compared with those receiving anastrozole ($p=0.012$).

The **TEAM sub study NSAS BC 04** showed no significant difference in quality of life issues between the three arms.

Effect of HER2/neu status

There was no evidence identified regarding the relative efficacy of any aromatase inhibitor compared with Tamoxifen when analysed by HER2/neu status.

General comments

All major trials under review were multi-centre trials with all but two reporting appropriate methods of randomisation.

All major trials, with the exception of three, reported double blinding; two trials were open label and one trial did not report on blinding.

All trials were sufficiently powered

Details of Coombes 2007

Coombes, L S Kilburn, C F Snowdon, R Paridaens, R E Coleman, S E Jones, J Jassem, C J H Van de Velde, T Delozier, I Alvarez, L Del Mastro, O Ortmann, K Diedrich, A S Coates, E Bajetta, S B Holmberg, D Dodwell, E Mickiewicz, J Andersen, P E Lønning, G Cocconi, J Forbes, M Castiglione, N Stuart, A Stewart, L J Fallowfield, G Bertelli, E Hall, R G Bogle, M Carpentieri, E Colajori, M Subar, E Ireland, J M Bliss, on behalf of the Intergroup Exemestane Study* (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet*; 369: 559–70

Disease-Free Survival

Overall in the ITT group:

- unadjusted hazard ratio (HR) for disease-free survival = 0.76 (95% CI 0.66–0.88; $p=0.0001$) - in favour of exemestane. Translating to a 3.3% (95% CI 1.6–4.9) absolute improvement in

disease-free survival at 2.5 years after randomisation, and a 3.4% (0.1–6.8) improvement 5 years after randomisation.

- Both node positive and node negative were in favour of exemestane with respect to improved disease-free survival
- ER+ and ER+PgR+ were in favour of exemestane
- ER+PgR– and ER unknown both did not have a significant difference b/n exe and tamoxifen
- Age 60–69 years favoured exemestane

In the oestrogen-receptor-positive and oestrogen-receptor-unknown group, very similar results were obtained, with a HR = 0.75 (95% CI 0.65–0.87; p=0.0001). For the oestrogen-receptor-positive and oestrogen-receptor unknown group, the absolute improvement at 2.5 years = 3.5% (95% CI 1.8–5.1) and at 5 years = 3.5% (0.1–6.9).

Overall survival

Adjusting for potential confounders:

- ITT analysis: HR= 0.85 95% CI 0.71–1.01); p=0.07;
- Oestrogen-receptor-positive and oestrogen-receptor-unknown group: HR= 0.83, 0.69–0.99; p=0.04

Overall conclusions:

Findings suggest that early improvements in disease-free survival noted in patients who switch to exemestane after 2–3 years on tamoxifen persist after treatment, and translate into a modest improvement in overall survival.

5.3 Is there an indication for the use of tamoxifen after excision of pure DCIS?

Short Summary

There is evidence from one placebo controlled RCT that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, adjuvant tamoxifen reduces the risk of ipsilateral local recurrence by 30% and contralateral breast cancer by 50%. The risk at 5 years of any breast cancer event in the tamoxifen arm was 8% and in the placebo arm, 13% (NSABP B-24 trial-Fisher *et al.* 1999). One subsequent RCT with a less rigorous design found no similar benefit arising from Tamoxifen (UKCCCR trial-Houghton *et al.* 2003).

The NSABP B-24 trial found that tamoxifen and radiotherapy improved disease free survival at 5 years (87%), compared to placebo and radiotherapy (83%), but with no difference between groups for overall survival.

The UKCCCR trial examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS (without radiotherapy) and found no benefit arising from Tamoxifen, except in terms of subsequent DCIS in either breast, this risk was reduced by 30%. The risk of any breast event in the Tamoxifen arm at 56 months was 12% (UKCCCR) and in the control arm, 15%.

PICO

Population	Intervention	Comparison	Outcome
Women who have had complete surgical excision of pure DCIS	Tamoxifen	No Tamoxifen Radiotherapy	<ul style="list-style-type: none">• Local Control• Reduction in contralateral primary tumors/recurrence

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The body of evidence for this question comes from high quality systematic reviews and RCTs, however they have limited applicability; a small number of observational studies were included but add little to the RCTs.

There is some variation in the study design of the RCTs though the studies are consistent with regard to their results: For outcomes where data exists from both studies, the confidence intervals overlap and the overall estimate of effect tends to favour Tamoxifen, although this finding is not always statistically significant.

There is evidence from one placebo controlled RCT that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, adjuvant Tamoxifen reduces the risk of ipsilateral local recurrence by 30% and contralateral breast cancer by 50%. The risk at 5 years of any breast cancer event in the tamoxifen arm was 8% and in the placebo arm, 13% (NSABP B-24). One subsequent RCT with a less rigorous design found no similar benefit arising from Tamoxifen (UKCCCR).

The NSABP B-24 trial found that tamoxifen and radiotherapy improved disease free survival at 5 years (87%), compared to placebo and radiotherapy (83%), but with no difference between groups for overall survival.

The UKCCCR trial examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS (without radiotherapy) and found no benefit arising from tamoxifen, except in terms of subsequent DCIS in either breast: this risk was reduced by 30%. The risk of any breast event in the Tamoxifen arm at 56 months was 12% (UKCCCR) and in the control arm, 15%.

1. Adjuvant Tamoxifen versus no adjuvant therapy

(Note: this data was also reported for Question 4)

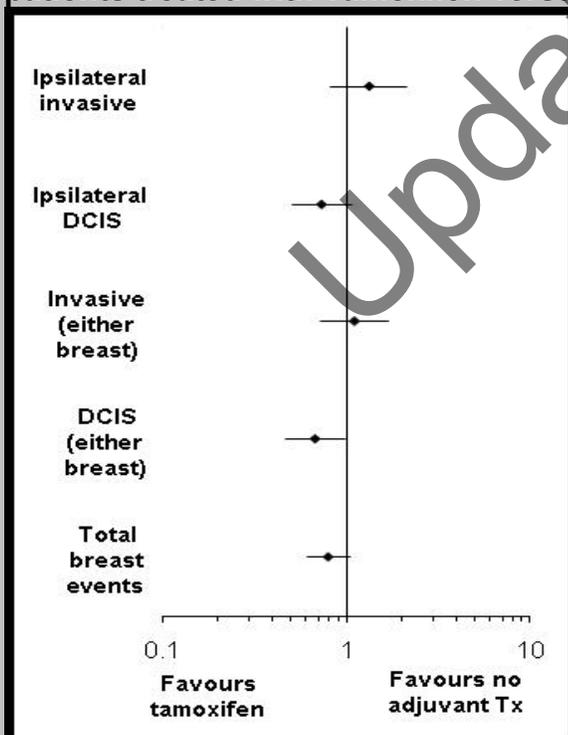
Local recurrence

One RCT provided a subgroup analysis of the effect of adjuvant Tamoxifen versus no adjuvant therapy in 1053 patients treated for DCIS with primary complete local excision, who did not receive radiotherapy (Houghton *et al.* 2003). Within this subgroup there was no difference between randomised arms in the incidence of ipsilateral invasive recurrence or ipsilateral DCIS (Figure 1).

Contralateral breast cancer

This study did not analyse the rate of contralateral breast events alone in this subgroup. Analysing events in either breast together, there was no difference in the incidence of total breast tumours (invasive plus DCIS) or invasive tumours alone. However there were statistically significantly fewer recurrent DCIS tumours in the Tamoxifen arm compared to the control arm (Figure 1). This study did not analyse survival.

Figure 1: Data from UKCCCR trial subgroup analysis (n=1053): Breast recurrence in patients treated with Tamoxifen versus no adjuvant therapy (Fisher *et al.* 1999)



Notes:

1. Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com

2. Follow-up: 4.7 years

Breast event	Rate of breast event (%)		Hazard ratio: Tamoxifen:Control (95% CI)	p value
	Tamoxifen n	No adjuvant Tx		
Ipsilateral invasive recurrence	5	4	1.32 (0.81-2.14)	0.26
Ipsilateral DCIS	6	9	0.73 (0.51-1.06)	0.10
Total invasive tumours (either breast)	5	5	1.11 (0.72-1.72)	0.64
Total DCIS tumours (either breast)	6	10	0.68 (0.47-0.97)	0.03
Total breast events	12	15	0.80 (0.61-1.05)	0.11

2. Adjuvant Tamoxifen and radiotherapy

Two RCTs investigated disease related events in patients treated for DCIS with breast conserving surgery, who then received combinations of adjuvant Tamoxifen and radiotherapy (Fisher *et al.* 1999; Houghton *et al.* 2003);

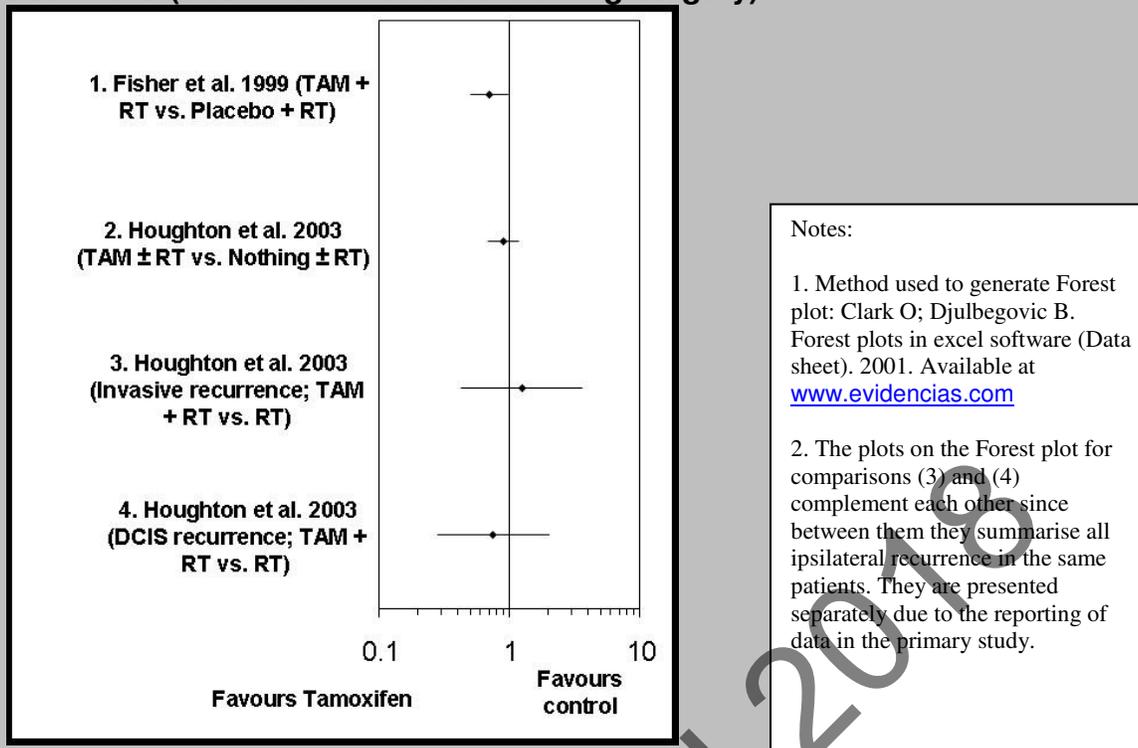
Local recurrence

The NSABP-B24 trial randomised patients treated by lumpectomy for DCIS to radiotherapy plus Tamoxifen or radiotherapy plus placebo (Fisher *et al.* 1999). The rate of ipsilateral (invasive plus non-invasive) local recurrence at 5 years was statistically significantly lower in the Tamoxifen arm than in the control arm (Figure 2). This difference was also statistically significant for invasive recurrence alone but not for non-invasive recurrence alone. An update of the NSABP B-24 trial reporting data at 7 years follow-up reported a similar result (Fisher *et al.* 2001).

The UKCCCR trial used a 2x2 factorial design to examine the individual effects of Tamoxifen and radiotherapy following complete local excision of DCIS (Houghton *et al.* 2003). In the analysis of patients randomised to Tamoxifen or control, a proportion of patients received radiotherapy in addition (34.3% and 32.1% respectively). There was little difference in the rate of ipsilateral (invasive plus DCIS) local recurrence at a median follow-up period of 4.7 years between randomised arms (Figure 2), and also when considering only invasive recurrence or DCIS recurrence.

This study provided also a sub-group analysis for 523 patients randomised with regard to Tamoxifen, all of whom received radiotherapy. Data were presented for invasive recurrence and DCIS recurrence separately, and there was little difference in risk of ipsilateral recurrence between randomised arms (Figure 2).

Figure 2: Ipsilateral local recurrence following adjuvant Tamoxifen and radiotherapy to treat DCIS (after initial breast conserving surgery)



No.	Study	Ipsilateral event	Treatment in Tamoxifen arm	Treatment in control arm	Follow-up	Ratio	Value: Tamoxifen:Control (95% CI)
1	NSABP B-24 (Fisher <i>et al.</i> 1999)	Recurrence	Tamoxifen + RT	Placebo + RT	5 years	Rate ratio	0.70 (0.50-0.98)
2	UKCCCR (Houghton <i>et al.</i> 2003)	Recurrence	Tamoxifen (+ RT in 34.3% of patients)	No Tamoxifen (+ RT in 32.1% of patients)	4.7 years	Hazard ratio	0.90 (0.69-1.17)
3	UKCCCR (Houghton <i>et al.</i> 2003)	Invasive recurrence	Tamoxifen + RT	RT	4.7 years	Hazard ratio	1.25 (0.43-3.61)
4	UKCCCR (Houghton <i>et al.</i> 2003)	DCIS recurrence	Tamoxifen + RT	RT	4.7 years	Hazard ratio	0.75 (0.28-2.02)

Contralateral breast cancer

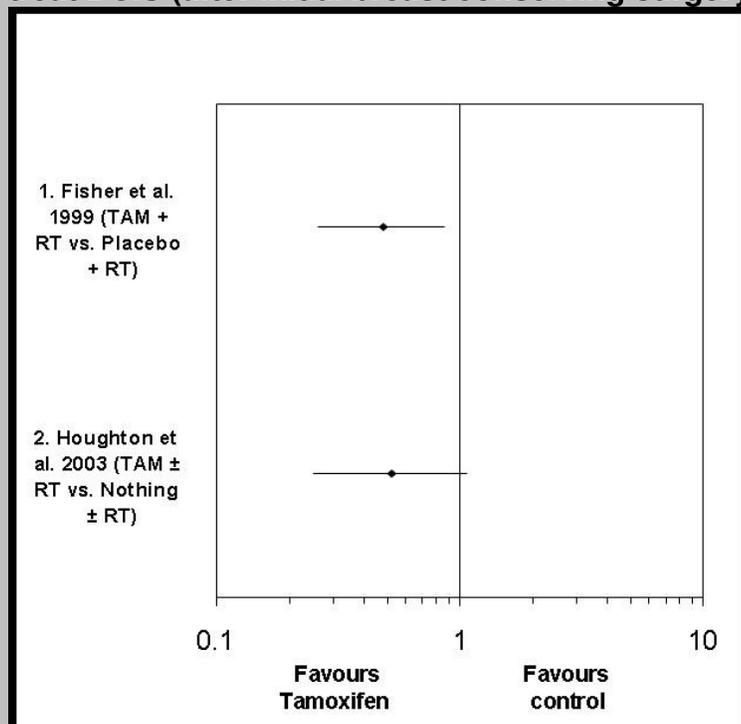
Data from the NSABP B-24 RCT demonstrates that tamoxifen reduces the occurrence of tumours in the contralateral breast in patients treated with lumpectomy and adjuvant radiotherapy (Fisher *et al.* 1999).

This trial randomised patients treated initially for DCIS with lumpectomy to either radiotherapy plus tamoxifen or radiotherapy plus placebo. At a median follow-up duration of 6.2 years there was a statistically significantly lower rate of contralateral (invasive + non-invasive) breast cancer events in the Tamoxifen arm compared to the control arm (Figure 3). A similar, statistically significant effect was observed for non-invasive contralateral breast events alone, but a similar trend for invasive contralateral breast events alone did not achieve statistical significance. Updated data at 7 years follow-up maintained these results with no marked changes (Fisher *et al.* 2001).

The UKCCCR trial (Houghton *et al.* 2003) provided within a 2X2 factorial design, a randomised comparison of tamoxifen versus control (no tamoxifen), where a proportion of patients in each arm received radiotherapy in addition (34.3% and 32.1% respectively). There was no statistically significant difference between tamoxifen and control for the incidence of contralateral (DCIS plus invasive) breast events (Figure 3). There was also no statistically significant difference in incidence of contralateral invasive events alone, and the study did not analyse contralateral DCIS events alone. This study did not analyse contralateral breast events in the subgroup of patients randomised with regard to tamoxifen who received in addition radiotherapy. Although statistical significance was not always reached, in both of these RCTs the direction of the effect for all analyses of contralateral breast events was in favour of tamoxifen over control.

Updated 2018

Figure 3: Contralateral breast events following adjuvant Tamoxifen and radiotherapy to treat DCIS (after initial breast conserving surgery)



Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com

No.	Study	Treatment in Tamoxifen arm	Treatment in control arm	Follow-up	Ratio	Value: Tamoxifen:Control (95% CI)
1	NSABP B-24 (Fisher <i>et al.</i> 1999)	Tamoxifen + RT	Placebo + RT	5 years	Rate ratio	0.48 (0.26-0.87)
2	UKCCCR (Houghton <i>et al.</i> 2003)	Tamoxifen (+ RT in 34.3% of patients)	No Tamoxifen (+ RT in 32.1% of patients)	4.7 years	Hazard ratio	0.52 (0.25-1.07)

Disease-free survival

The NSABP B-24 trial randomised patients treated by lumpectomy for DCIS to radiotherapy plus Tamoxifen or radiotherapy plus placebo (Fisher *et al.* 1999). Estimated 5-year event-free survival (breast cancer and non breast cancer events) was statistically significantly higher in the Tamoxifen arm than in the control arm. The estimated 5-year cumulative incidence of all breast cancer events was statistically significantly lower in the Tamoxifen group compared to the control group. Updated disease-free survival data at 7 years follow-up was similar to that reported after 5 years (Fisher *et al.* 2001).

In the update study a comparative analysis of the NSABP B-24 and NSABP B-17 (lumpectomy alone vs. lumpectomy with radiation therapy) trials suggested that the use of Tamoxifen plus RT reduced the cumulative incidence of all breast cancer events (including regional and distant metastases) from that arising from lumpectomy alone by 66% at 7 years follow-up. For invasive cancer recurrence events the cumulative incidence reduction was 84% and for non-invasive events, 62% (Fisher *et al.* 2001). This finding rests on the assumption that the study samples are similar.

Overall survival

The NSABP-B24 trial also analysed overall survival between randomised arms and found no difference in estimated 5-year overall survival between patients treated with Tamoxifen compared to those treated with placebo (Fisher *et al.* 1999). At 7 years follow-up there was also no difference in overall survival between the two groups (Fisher *et al.* 2001).

Observational studies

Four small to moderate sized retrospective case series were identified and included in the evidence review (Freedman *et al.* 2005; Roka *et al.* 2004; Jha *et al.* 2001; Stallard *et al.* 2001). These studies are of very little value in the light of the RCTs. One retrospective case series reported that patients given adjuvant Tamoxifen therapy after breast conserving surgery in the absence of radiotherapy had significantly greater local recurrence (type not specified) compared to those who received RT in addition to Tamoxifen (Jha *et al.* 2001). The observational studies demonstrated no statistically significant effect of Tamoxifen in terms of recurrence.

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Further details

1. Randomised Studies

(i) NSABP B-24

The NSABP-B24 trial randomised 1804 patients treated by lumpectomy for DCIS to 50 Gy radiotherapy plus Tamoxifen for 5 years or 50 Gy radiotherapy plus placebo for 5 years (Fisher *et al.* 1999). The rate of ipsilateral (invasive plus non-invasive) local recurrence at 5 years was statistically significantly lower in the Tamoxifen arm than in the control arm: 13.75 per 1000 patients per year versus 19.62 per 1000 patients per year in the control arm; rate ratio Tamoxifen:control): 0.70 [95% CI 0.50-0.98], $p=0.04$. This difference was also statistically significant for invasive recurrence alone but not for non-invasive recurrence alone.

The estimated 5-year cumulative incidence of ipsilateral, invasive breast cancer events was 2.1% in the Tamoxifen arm versus 4.2% in the control arm, with respective rates per 1000 patients per year of 5.02 and 9.02; rate ratio (Tamoxifen:control): 0.56 [95% CI 0.32-0.95], $p=0.03$. The estimated 5-year cumulative incidence of ipsilateral, non-invasive breast cancer events was 3.9% in the Tamoxifen arm versus 5.1% in the control arm, with respective rates per 1000 patients per year of 8.73 and 10.60; rate ratio (Tamoxifen:control): 0.82 [95% CI 0.53-1.28], $p=0.43$.

Data from this trial also suggest that Tamoxifen has an effect in reducing the occurrence of tumours in the contralateral breast in patients treated with lumpectomy and adjuvant radiotherapy. At a median follow-up duration of 6.2 years there was a statistically significantly lower rate of contralateral (invasive + non-invasive) breast cancer events in the Tamoxifen arm (rate per 1000 patients per year = 3.93) compared to the control arm (rate per 1000 patients per year = 8.12); rate ratio (Tamoxifen:control): 0.48 [95% CI 0.26-0.87], $p=0.01$. A similar, statistically significant effect was observed for non-invasive contralateral breast events alone, but not for invasive contralateral breast events alone. The estimated 5-year cumulative incidence of non-invasive contralateral breast cancer events was 0.2% in the Tamoxifen arm versus 1.1% in the control arm, with respective rates per 1000 patients per year of 0.66 and 2.93; rate ratio (Tamoxifen:control): 0.22 [95% CI 0.04-0.81], $p=0.02$. The estimated 5-year cumulative incidence of invasive contralateral breast cancer events was 1.8% in the Tamoxifen arm versus 2.3% in the control arm, with respective rates per 1000 patients per year of 3.27 and 5.19; rate ratio (Tamoxifen:control): 0.63 [95% CI 0.31-1.26], $p=0.22$.

This trial provided evidence for an advantage arising from Tamoxifen in terms of event-free survival, but with little difference between randomised arms for overall survival. The estimated 5-year event-free survival (breast cancer and non breast cancer events) was statistically significantly higher in the Tamoxifen arm (87.4%) than in the control arm (83.3%): rate ratio (tamoxifen:control) 0.72 [95% CI 0.57-0.91], $p=0.006$. The estimated 5-year cumulative incidence of all breast cancer events was statistically significantly lower in the Tamoxifen group (8.2%) compared to the control group (13.4%): rate ratio (tamoxifen:control): 0.63 [95% CI 0.47-0.83], $p=0.0009$. Estimated 5-year overall survival in both randomised arms (Tamoxifen versus placebo) was 97%; $p=0.74$.

A subsequent comparative analysis of the NSABP B-24 and NSABP B-17 (lumpectomy alone vs. lumpectomy with radiation therapy) trials demonstrated that the cumulative incidence of all breast cancer events (including regional and distant metastases) in the lumpectomy only arm of the B-17 trial was 30% after 7 years (Fisher *et al.* 2001). In the lumpectomy plus RT arm of the B-17 trial the cumulative incidence was 18% and the corresponding value in the B-24 trial was 17%. When Tamoxifen was given in the B-24 trial the cumulative incidence of all breast cancer events was further reduced to 10%, the benefit being attributed to reduced rates of local, contralateral and invasive cancer at regional and distant sites. Therefore Tamoxifen

therapy in combination with RT reduced the risk of any breast cancer event at 7 years by two thirds compared to no post-operative therapy. Similarly for invasive cancer recurrence events, the risk was reduced by 84% and for non-invasive events, 62%.

Updated disease-free survival data at 7 years follow-up was similar to that reported after 5 years (Fisher *et al.* 2001): in the Tamoxifen treatment arm the 7 year estimated event-free survival was 83%, compared to 77% in the control arm (RR = 0.72, P = 0.002). Covariate RR analysis revealed a significantly higher rate of ipsilateral recurrence in women younger than 49 years of age than women over 50 years. The reduction in IBT in women >50 yrs given Tamoxifen was 33% and in women <49 yrs the reduction was 30%.

(ii) UKCCCR

The UKCCCR trial aimed to examine the individual effects of adjuvant RT and adjuvant Tamoxifen in 1694 patients with predominantly screen-detected DCIS, all of whom were treated initially with complete local excision (Houghton *et al.* 2003). The study analysed breast events but not survival.

The study had a 2X2 factorial design by which 912 patients chose to enter randomisation to one of four treatment combinations of RT, Tamoxifen, or neither, or both. A further 664 patients made a choice whether to undergo RT or forego RT and accepted randomisation to either Tamoxifen or no Tamoxifen. A further 118 patients made a choice whether to receive Tamoxifen or forego Tamoxifen and accepted randomisation to either RT or no RT.

a) Tamoxifen versus control

In the analysis of patients randomised to Tamoxifen or control, a proportion of patients received radiotherapy in addition (34.3% and 32.1% respectively). The rate of ipsilateral (invasive plus DCIS) local recurrence at a median follow-up period of 4.7 years was not statistically significantly different between randomised arms, nor when considering only invasive recurrence or DCIS recurrence. The rate of all ipsilateral (DCIS + invasive) events was 13% in the Tamoxifen arm versus 15% in the control arm; hazard ratio 0.90 [95% CI 0.69-1.17], p=0.42, stratified log-rank test. The rate of new ipsilateral invasive events was 6% in the Tamoxifen arm versus 4% in the control arm; hazard ratio 1.31 [95% CI 0.84-2.03], p=0.23, stratified log-rank test. The rate of new ipsilateral DCIS events was 7% in the Tamoxifen arm versus 10% in the control arm; hazard ratio 0.74 [95% CI 0.52-1.04], p=0.08, stratified log-rank test.

In the same analysis there was no statistically significant difference between Tamoxifen and control for the incidence of contralateral breast events. The rate of all contralateral (DCIS + invasive) breast events was 1% in the Tamoxifen arm versus 3% in the control arm; hazard ratio 0.52 [95% CI 0.25-1.07], p=0.07, stratified log-rank test. There was also no statistically significant difference in incidence of contralateral invasive events alone, which was 1% in the Tamoxifen arm and 2% in the control arm; hazard ratio 0.66 [95% CI 0.30-1.46], p=0.30, stratified log-rank test. The study did not analyse contralateral DCIS events alone.

b) Tamoxifen in the patient subgroup that received radiotherapy

This study provided also a sub-group analysis for 523 patients randomised with regard to Tamoxifen, all of whom received radiotherapy. Data were presented for invasive recurrence and DCIS recurrence separately, and there was no statistically significant difference in rates of ipsilateral recurrence for either outcome between randomised arms. The rate of ipsilateral invasive tumours was 1% in the Tamoxifen arm versus 1% in the control arm; hazard ratio 1.25 [95% CI 0.43-3.61], p=0.68, stratified log-rank test. The rate of ipsilateral DCIS was 1% in the Tamoxifen arm versus 1% in the control arm; hazard ratio 0.75 [95% CI 0.28-2.02], p=0.57, stratified log-rank test.

This study did not analyse contralateral breast events in the subgroup of patients randomised with regard to Tamoxifen who received in addition radiotherapy.

c) Tamoxifen in the patient subgroup that did not receive radiotherapy

This trial also provided a subgroup analysis of new breast events in patients randomised to Tamoxifen or control, stratified by whether or not they received RT. In the subgroup of patients who did not receive RT there was no statistically significant difference between randomised arms in the incidence of ipsilateral invasive recurrence or ipsilateral DCIS. The rate of ipsilateral invasive breast events was 5% in the Tamoxifen arm versus 4% in the control arm; HR 1.32 [95% CI 0.81-2.14], $p=0.26$, stratified log-rank test. The rate of ipsilateral DCIS events was 6% in the Tamoxifen arm versus 9% in the control arm; HR 0.73 [95% CI 0.51-1.06], $p=0.10$, stratified log-rank test.

This study did not analyse the rate of contralateral breast events alone in the subgroup of patients who did not receive RT, but did analyse new breast events that occurred in either breast together in this subgroup: there was no statistically significant difference in the incidence of total breast tumours (invasive plus DCIS) or invasive tumours alone. The rate of total breast events (invasive + DCIS; ipsilateral + contralateral tumours) was 12 % in the Tamoxifen arm versus 15% in the control arm; HR 0.80 [95% CI 0.61-1.05], $p=0.11$, stratified log-rank test. The rate of total invasive (ipsilateral + contralateral tumours) was 5% in the Tamoxifen arm versus 5% in the control arm; HR 1.11 [95% CI 0.72-1.72], $p=0.64$, stratified log-rank test. However there were statistically significantly fewer recurrent DCIS tumours in the Tamoxifen arm compared to the control arm: respective rates were 6% versus 10%; HR 0.68 [95% CI 0.47-0.97], $p=0.03$, stratified log-rank test.

Method used to generate Forest plots:

Clark O; Djulbegovic B. Forest plots in excel software(Data sheet). 2001. Available at www.evidencias.com

2. Systematic reviews

One high quality systematic review (Shelley *et al.* 2006) included articles required to meet the following criteria:

- i. Study designs for the management of DCIS were randomised control trials, or meta-analyses on non-randomised and/or randomised trials.
- ii. Outcomes included overall or disease-free survival, local recurrence (invasive or non-invasive), breast conservation, distant recurrence, toxicity, or quality of life.
- iii. Clinical trials results reported in full papers or abstracts.
- iv. Evidence-based clinical practice guidelines addressing the management of DCIS.

An additional section - intended as an aid to practitioners and outside the guideline recommendations - was included in which issues for the management of DCIS that were not covered by included RCTs were reviewed through appraisal of expert opinion and non-randomised evidence identified from a non-systematic search of the literature. Of relevance to the evaluation of adjuvant Tamoxifen therapy in the management of DCIS, important outcome measurements addressed in this review included:

- i. Local and distant disease recurrence for non-invasive and invasive events
- ii. Overall and disease-free survival
- iii. Effect of Tamoxifen in patients by age at randomisation (comparison between UKCCCR and NSABP B-24 trials)
- iv. Toxicity of Tamoxifen vs. placebo (data obtained from NSABP P-1 trial)

Data concerning these outcomes were reviewed from the two RCTs covered in this evidence summary (Fisher *et al.* 1999; Houghton *et al.* 2003).

In addition to the key findings of the two randomised control studies presented in this summary, this systematic review highlights a number of other issues for the management of DCIS

Influence on recurrence of positive vs. negative resected margins:

In NSABP B-24, sixteen percent of the patients had positive resected margins and 10% had unknown margins for DCIS, and others were known to have residual suspicious micro-calcifications. The absolute risk reduction was larger in Tamoxifen plus RT treated patients with positive margins (3.5%) than in those with negative margins (1.8%) but no statistical test of this finding was reported in the review.

Influence of tumour estrogen receptor status on recurrence:

Of the 1798 eligible patients estrogen receptor (ER) status of tumours was known in 628 (35%) (327 placebo, 301 Tamoxifen). Seventy seven percent of tumours were ER positive and the risk ratio (RR) of recurrent or new breast pathology in patients receiving Tamoxifen was 0.41 in the ER positive group (95% CI, 0.25-0.65, P=0.0002). In the ER-negative group the RR was 0.8 (P=0.5) although the number of events (n=36) was too small to exclude a clinically meaningful benefit (95% CI for RR, 0.41-1.56).

Effect of Tamoxifen in patients by age at randomisation:

In this study only 9.5% of recruited patients were under 50 years of age, compared with 33.5% of those in the NSABP B-24 study. This may have been due to the nature of patient recruitment in the former study in that they were recruited through the UK national breast screening program. Age-related data comparison between studies was possible only for local (IBT) recurrence; the benefit of Tamoxifen in both studies was more apparent in women \leq 50 years of age although this failed to achieve statistical significance.

Other considerations for the use of Tamoxifen in the management of DCIS

Tamoxifen toxicity:

Both RCT studies included some data on toxicity associated with Tamoxifen treatment, but the NSABP P-1 study (Tamoxifen in the prevention of breast cancer in 13,388 women at increased risk) included a detailed analysis stratified by patient age. Significant toxicity events were; endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. The largest difference in serious adverse events appears to be in women $>$ 50 years of age, however the absolute number of adverse events is low as is the incremental risk.

Contraindications for breast conserving surgery (BCS):

The authors state that as with invasive breast cancer, there are also contraindications for performing BCS in the management of DCIS: large tumour size and small breasts may not yield satisfactory cosmetic results and may be better served by mastectomy coupled with the option of reconstructive surgery. As with other studies, only a small proportion (4%) of patients recruited to the NSABP B-24 trial had lesions $>$ 2 cm. Therefore local control rates reported may not be applicable to patients with larger lesions. Also, the detection of multiple tumours or extensive micro-calcifications are relative contraindications of BCS.

3. Observational studies

For further information on the four observational studies included in the evidence, refer to the evidence table.

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Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com

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Stallard, S., Hole, D. A., Purushotham, A. D., Hiew, L. Y., Mehanna, H., Cordiner, C., Dobson, H., Mallon, E. A. & George, W. D. (2001) Ductal carcinoma in situ of the breast -- among factors predicting for recurrence, distance from the nipple is important. *Eur J Surg Oncol*, 27: 373-377.

Evidence Tables

Fisher, Dignam, Wolmark, Wickerham, Fisher, Mamounas, Smith, Begovic, Dimitrov, Margolese, Kardinal, Kavanah, Fehrenbacher & Oishi . Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353[9169], 1993-2000. 1999.

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: United States, setting: Secondary care

Inclusion criteria Women with DCIS with a life expectancy of ≥ 10 years including:

- those with DCIS + LCIS;
- those with one or more masses or clusters of masses that could be completely excised;
- those with microscopic margin involvement;
- those with scattered calcifications on mammograms that were indeterminate

16% of patients had positive resected margins after surgery.

33.5% of patients were under 50 years of age

Exclusion criteria Time from surgery to randomisation >56 days;

Previous diagnosis of cancer, excluding squamous cell carcinoma of the skin or carcinoma in situ of the cervix

Population number of patients = 1804.

Interventions Aim: to examine the effect of tamoxifen when given to patients with DCIS after treatment by lumpectomy and RT.

Tamoxifen group (n=902): received lumpectomy, 50 Gy breast RT and 10 mg BD tamoxifen for 5 years.

Control group (n=902): received lumpectomy, 50 Gy breast RT and placebo for 5 years.

Outcomes Occurrence of tumour in the ipsilateral or contralateral breast;
Regional and distant metastases;
Survival.

Follow up Physical examination every 6 months and mammography once a year.

Median duration 74 months (range 57-93 months).

Results Estimated 5-year overall survival:

Tamoxifen: 97% [95% CI 96%-98%]

Control: 97% [95% CI 96%-98%]; p=0.74

Estimated 5-year event-free survival (breast cancer and non breast cancer events):

Tamoxifen: 87.4% [95% CI 85.1%-89.6%]

Control: 83.3% [95% CI 80.8%-85.8%]
Rate of all events per 1000 patients per year (breast cancer and non breast cancer events):
Tamoxifen: 27.50
Control: 38.12
Rate ratio (tamoxifen:control): 0.72 [95% CI 0.57-0.91], p=0.006.

Estimated 5-year cumulative incidence of all breast cancer events:
Tamoxifen: 8.2%
Control: 13.4%
Rate per 1000 patients per year:
Tamoxifen: 18.33
Control: 29.32
Rate ratio (Tamoxifen:control): 0.63 [95% CI 0.47-0.83], p=0.0009.

All ipsilateral (invasive + non-invasive) local recurrence (rate per 1000 patients per year):
Tamoxifen: 13.75
Control: 19.62
Rate ratio (Tamoxifen:control): 0.70 [95% CI 0.50-0.98], p=0.04

Estimated 5-year cumulative incidence of ipsilateral, invasive breast cancer events:
Tamoxifen: 2.1%
Control: 4.2%
Rate per 1000 patients per year:
Tamoxifen: 5.02
Control: 9.02
Rate ratio (Tamoxifen:control): 0.56 [95% CI 0.32-0.95], p=0.03

Estimated 5-year cumulative incidence of ipsilateral, non-invasive breast cancer events:
Tamoxifen: 3.9%
Control: 5.1%
Rate per 1000 patients per year:
Tamoxifen: 8.73
Control: 10.60
Rate ratio (Tamoxifen:control): 0.82 [95% CI 0.53-1.28], p=0.43

All contralateral (invasive + non-invasive) breast cancer events (rate per 1000 patients per year):
Tamoxifen: 3.93
Control: 8.12
Rate ratio (Tamoxifen:control): 0.48 [95% CI 0.26-0.87], p=0.01

Estimated 5-year cumulative incidence of invasive contralateral breast cancer events:
Tamoxifen: 1.8%
Control: 2.3%
Rate per 1000 patients per year:
Tamoxifen: 3.27
Control: 5.19
Rate ratio (Tamoxifen:control): 0.63 [95% CI 0.31-1.26], p=0.22

Estimated 5-year cumulative incidence of non-invasive contralateral breast cancer events:

Tamoxifen: 0.2%

Control: 1.1%

Rate per 1000 patients per year:

Tamoxifen: 0.66

Control: 2.93

Rate ratio (Tamoxifen:control): 0.22 [95% CI 0.04-0.81], p=0.02

Combined regional and distant metastasis (rate per 1000 patients per year):

Tamoxifen: 0.66

Control: 1.58

Rate ratio (Tamoxifen:control): 0.42 [95% CI 0.07-1.82], p=0.32

Adverse events:

Proportion of patients with no recorded overall toxicity (duration of follow-up: different for each patient):

Tamoxifen: 57.1%

Control: 62.8%

Endometrial cancer (rate per 1000 patients per year):

Tamoxifen: 1.53

Control: 0.45

Rate ratio (tamoxifen:control): 3.39 [95% CI 0.64-33.42]; p=0.20

General comments Randomisation was stratified by age (≤ 49 or > 49 years) tumour type (DCIS or DCIS + LCIS) and method of detection (screening or symptomatic or both).

Power calculation performed.

29 patients became ineligible after randomisation (11: control, 18: tamoxifen). Of 1804 randomised patients 14 (0.8%) did not start randomised therapy. 564 (31.3%) patients did not complete randomised therapy (269: control; 295: tamoxifen). 6 patients were lost to follow-up (3: tamoxifen; 3: control). All randomised patients with follow-up data were included in the intention-to-treat analysis.

No analysis is made of adverse events between randomised groups. Reported 'overall toxicity' excludes alopecia, irregular menses, hot flushes, fluid retention, vaginal discharge, nadir grades and weight change.

Reporting of results is inconsistent; many instances of 'data not shown' in text.

Fisher, Land, Mamounas, Dignam, Fisher & Wolmark . Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. *Seminars in oncology* 28[4], 400-418. 2001.

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: United States, setting: Secondary care

Inclusion criteria 1798/1804 eligible and followed-up patients with pure DCIS. In addition to the NSABP B-17 trial (RT vs nothing) women with positive tumour specimen margins or with mammogram indicating an unlikely presence of invasive cancer were eligible for inclusion.

Exclusion criteria See Fisher et al *Lancet* 353, 1993-2000. 1999

Population number of patients = 1804.

Interventions Lumpectomy + XRT (50 Gy) + Tamoxifen n = 899
Lumpectomy + XRT (50 Gy) + Placebo n = 899

Outcomes Event-free survival after 7 years

Overall survival after 7 years

Site, rate, RR, 95% CI and cumulative incidence of first events

Covariate RR (95% CI) for selected patient and tumour characteristics

Follow up Mean follow-up 82 months

Median follow-up 83 months

Results Ipsilateral breast cancer recurrence (IBT):

The rates of recurrence at 7 years follow-up for ipsilateral invasive plus non-invasive, invasive only, and non-invasive are reported to have maintained trends reported after 5 years follow-up. No significant changes in rate ratios (RR) are reported.

Contralateral breast cancer recurrence (CBT):

The rates of occurrence at 7 years follow-up for ipsilateral invasive plus non-invasive, invasive only, and non-invasive are reported to have maintained trends reported after 5 years follow-up. No significant changes in RRs are reported.

Survival:

Event-Free Survival after 7 years follow-up was similar to that reported after 5 years: in the Tamoxifen treatment arm the 7 year estimated event-free survival was 83.0% and 77.1% in the control arm of the trial, RR = 0.72 (95% CI, 0.59 - 0.89, P = 0.002).

There was no significant difference in Overall Survival between the 2 arms of the trial after 7 years, RR = 0.94 (95% CI, 0.62 - 1.44, P = 0.78)

Covariate RR analysis revealed a significantly higher rate of IBT in women younger than 49 years than women over 50 years. The reduction in IBT in women >50 yrs given Tamox was 32.7% and in women <49 yrs the reduction was 30.1%

This article reported updates for the NSABP B-17 and NSABP B-24 trials. The authors go on to examine the relationship between the two trials.

The cumulative incidence of all breast cancer events (IBT and CBT) in the lumpectomy only arm of the B-17 trial was 30.3% after 7 years. In the lumpectomy + RT arm of this trial the cumulative incidence was 18.0% and 16.9% in the B-24 trial. When Tamoxifen was given this was further reduced to 10.3%, the benefit being due to reduced rates of IBT, CBT and invasive cancer at regional and distant sites. Therefore Tamoxifen therapy in combination with RT led to a 66% lower cumulative incidence all breast cancer events at 7 years compared to women who had lumpectomy alone. For invasive cancer recurrence events the cumulative incidence reduction was 84% and 62% for non-invasive events.

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General comments Update on results emerging from the NSABP B-24 RCT, Fisher et al Lancet 353, 1993-2000 (1999).

Extended survival and recurrence data plus analysis of the relationship between this trial and the earlier NSABP B-17 (BCS +/- RT) trial.

The calculation of reduction in cumulative incidence of all breast cancer events in the NSABP B-24 and NSABP B-17 (lumpectomy alone vs. lumpectomy with radiation therapy) trials crucially assumes that the two studies are similar; the NSABP B-24 trial included patients with positive surgical margins, which would serve to attenuate the difference.

Updated 2018

Houghton, George, Cuzick, Duggan, Fentiman, Spittle, UK Coordinating Committee on Cancer Research, Ductal Carcinoma in situ Working Party, DCIS trialists in the UK, Australia & and . Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 362[9378], 95-102. 2003.

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United Kingdom, Australia, New Zealand, setting: Secondary care

Inclusion criteria 1694 patients with unilateral or bilateral screen-detected or DCIS who were candidates for breast conserving surgery; including:
-Symptomatic patients in whom DCIS was confirmed in the same way as in screening clinics;
-Patients with microinvasion <1mm in diameter, provided histologically clear margins were obtained. This group comprised 59 patients (3%).

Age distribution largely reflects screened population: modal age group 50-54 years; 90% of patients were of age >50 years i.e. older than the other RCT populations

Exclusion criteria LCIS or atypical ductal hyperplasia;
Doubtful histological margins;
Paget's disease of the nipple;
Patients with reduced life expectancy due to concomitant illness or malignancy;
Patients considered unsuitable for any of the treatment options.

A total of 7 patients were excluded (from an original study size of 1701) after randomisation.

Population number of patients = 1694.

Interventions Aim: to investigate the individual effects of radiotherapy and tamoxifen as adjuvant treatment for DCIS following complete local excision.

All patients underwent complete local excision.

2X2 factorial design:

912 patients chose to enter randomisation to one of four treatments:

RT + tamoxifen:	242
Tamoxifen alone:	224
RT alone:	220
No treatment:	226

782 patients chose 2-way randomisation:

664 patients made a choice re: RT and were randomised to either tamoxifen or no tamoxifen:

RT + Tamoxifen:	30
Tamoxifen alone:	298
RT alone:	31
No treatment:	305

118 patients made a choice re: tamoxifen and were randomised to either RT or no RT:

RT + Tamoxifen: 44
Tamoxifen alone: 45
RT alone: 16
No treatment: 13

Tamoxifen comprised 20mg daily for 5 years.
RT comprised 50 Gy in 25 fractions over 5 weeks.

Outcomes Ipsilateral breast recurrence;
Contralateral breast cancer;
New cancer (non-breast);
Death; breast cancer related or not.

Time-to-event analysis was by the life table method and the stratified log-rank test.

Follow up Yearly bilateral mammography for the first 7 years and every 2 years thereafter.

Median duration 56.2 months (range 2.4-118.3 months).

Results 1. Effect of tamoxifen (1576 patients in the randomised tamoxifen comparison)

New ipsilateral invasive events:

Tamoxifen: 45 (6%)

Control: 35 (4%)

HR 1.31 [95% CI 0.84-2.03], p=0.23, stratified log-rank test.

New ipsilateral DCIS events:

Tamoxifen: 57 (7%)

Control: 77 (10%)

HR 0.74 [95% CI 0.52-1.04], p=0.08, stratified log-rank test.

All ipsilateral (DCIS + invasive) events:

Tamoxifen: 102 (13%)

Control: 114 (15%)

HR 0.90 [95% CI 0.69-1.17], p=0.42, stratified log-rank test.

New contralateral invasive events:

Tamoxifen: 10 (1%)

Control: 15 (2%)

HR 0.66 [95% CI 0.30-1.46], p=0.30, stratified log-rank test.

New contralateral DCIS events: no data

All contralateral (DCIS + invasive) breast events:

Tamoxifen: 11 (1%)

Control: 21 (3%)

HR 0.52 [95% CI 0.25-1.07], p=0.07, stratified log-rank test.

All invasive (ipsilateral + contralateral) events:

Tamoxifen: 55 (7%)

Control: 50 (6%)

HR 1.11 [95% CI 0.76-1.63], p=0.59, stratified log-rank test.

All DCIS (ipsilateral + contralateral) events:

Tamoxifen: 58 (7%)

Control: 84 (11%)

HR 0.68 [95% CI 0.49-0.96], p=0.03, stratified log-rank test.

All events (invasive + DCIS; ipsilateral +contralateral):

Tamoxifen: 114 (14%)

Control: 137 (18%)

HR 0.83 [95% CI 0.64-1.06], p=0.13, stratified log-rank test.

2. Effect of RT (1030 patients in the randomised RT comparison)

New ipsilateral invasive events:

RT: 15 (3%)

Control: 30 (6%)

HR 0.45 [95% CI 0.24-0.85], p=0.01, stratified log-rank test.

New ipsilateral DCIS events:

RT: 14 (3%)

Control: 38 (7%)

HR 0.36 [95% CI 0.19-0.66], p=0.0004, stratified log-rank test.

All ipsilateral (DCIS + invasive) breast events:

RT: 29 (6%)

Control: 69 (14%)

HR 0.38 [95% CI 0.25-0.59], p<0.0001, stratified log-rank test.

New contralateral invasive events:

RT: 9 (2%)

Control: 6 (1%)

HR 1.50 [95% CI 0.53-4.22], p=0.44, stratified log-rank test.

New contralateral DCIS events: no data.

All contralateral (DCIS + invasive) breast events in patients in the RT comparison:

RT: 9 (2%)

Control: 11 (2%)

HR 0.82 [95% CI 0.34-1.18], p=0.65, stratified log-rank test.

All invasive (ipsilateral + contralateral) events:

RT: 24 (5%)

Control: 36 (7%)

HR 0.62 [95% CI 0.37-1.04], p=0.07, stratified log-rank test.

All DCIS (ipsilateral + contralateral) events:

RT: 14 (3%)

Control: 44 (9%)

HR 0.31 [95% CI 0.17-0.56], p<0.0001, stratified log-rank test.

All events (ipsilateral + contralateral; invasive + DCIS):

RT: 38 (7%)

Control: 82 (16%)

HR 0.43 [95% CI 0.29-0.63], p<0.0001, stratified log-rank test.

3. Subgroup analysis: New breast events in patients randomised to tamoxifen or control, stratified by whether or not they had RT

a) Patients not receiving RT (n=1053)

Ipsilateral invasive:

Tamoxifen: 37 (5%)

Control: 29 (4%)

HR 1.32 [95% CI 0.81-2.14], p=0.26, stratified log-rank test.

Ipsilateral DCIS:

Tamoxifen: 20 (6%)

Control: 68 (9%)

HR 0.73 [95% CI 0.51-1.06], p=0.10, stratified log-rank test.

Total invasive (ipsilateral + contralateral tumours):

Tamoxifen: 42 (5%)

Control: 39 (5%)

HR 1.11 [95% CI 0.72-1.72], p=0.64, stratified log-rank test.

Total DCIS (ipsilateral + contralateral tumours):

Tamoxifen: 51 (6%)

Control: 75 (10%)

HR 0.68 [95% CI 0.47-0.97], p=0.03, stratified log-rank test.

Total breast events (invasive + DCIS; ipsilateral + contralateral tumours):

Tamoxifen: 94 (12%)

Control: 117 (15%)

HR 0.80 [95% CI 0.61-1.05], p=0.11, stratified log-rank test.

b) Patients receiving RT (n=523)

Ipsilateral invasive tumours:

Tamoxifen: 8 (1%)

Control: 6 (1%)

HR 1.25 [95% CI 0.43-3.61], p=0.68, stratified log-rank test.

Ipsilateral DCIS:

Tamoxifen: 7 (1%)

Control: 9 (1%)

HR 0.75 [95% CI 0.28-2.02], p=0.57, stratified log-rank test.

Total invasive (ipsilateral + contralateral tumours):

Tamoxifen: 13 (2%)

Control: 11 (1%)

HR 1.11 [95% CI 0.50-2.48], p=0.80, stratified log-rank test.

Total DCIS (ipsilateral + contralateral tumours):

Tamoxifen: 7 (1%)

Control: 9 (1%)

HR 0.75 [95% CI 0.28-2.02], p=0.57, stratified log-rank test.

Total breast events (invasive + DCIS; ipsilateral + contralateral tumours):

Tamoxifen: 20 (3%)

Control: 20 (3%)

HR 0.95 [95% CI 0.51-1.77], p=0.88, stratified log-rank test.

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General comments 'Complete excision': defined by radiology of the surgical specimen and free margins on histological examination. Re-excision was performed where necessary.

Randomisation was performed by each contributing centre, blocked in groups of four and stratified for screening assessment centre.

Power calculation performed; additional patients were recruited because patients/clinicians favoured the 2-way randomisation.

Analysis of the individual effect of tamoxifen included only patients randomised to tamoxifen (not those who chose tamoxifen). The analysis was repeated, stratified by whether RT was given in addition.

Analysis of the individual effect of RT included only patients randomised to RT (not those who chose RT). The analysis was repeated, stratified by whether tamoxifen was given in addition.

Of 794 patients randomised to tamoxifen, 86 (11%) did not fully comply with the regimen. Study does not measure adverse effects of tamoxifen or RT.

Survival was not analysed as there were few deaths (45 in total).

Study may be underpowered where sub groups are small; the largest subgroup arising through choice of treatment is patients who chose with their clinicians to not be randomised to radiotherapy or control (n=664).

Retrospective case series

Freedman, Anderson, Hanlon, Eisenberg & Nicolaou . Pattern of local recurrence after conservative surgery and whole-breast irradiation. Int J Radiat.Oncol Biol.Phys. 61[5], 1328-1336. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

1990 women with stage T0 (DCIS), T1, or T2 breast cancer treated by breast conserving surgery and breast irradiation.
237/1990 (12%) were stage T0, DCIS.

Exclusion criteria

None specified

Population

number of patients = 237, age range 22 to 93 years, median age = 57 years.

Interventions

Breast conserving surgery
All recieved post-operative whole breast RT

DCIS patients given Tamoxifen treatment = 16/237 (6.8%)
Systemic chemotherapy (492, 25%)

Outcomes

Ipsilateral breast cancer recurrence (Kaplan-Meier) - all cancers
Crude local and regional/distant recurrence rates for DCIS +/- tamox (provided by personal communication, see results)

Follow up

Median 81 months (range, 1 to 245 months)

Results

16/237 (6.8%) received RT + Tamox
221/237 (93.2%) received RT alone

True local (ipsilateral) events (all DCIS): 13/237 (5.5%)
Contralateral events: 37/237 (15.6%)

Available results stratified by +/- Tamox treatment:

Local recurrence events:

DCIS +RT/-Tamox = 14/221 (6.3%)

DCIS +RT/+Tam = 1/16 (6.3%)

Contralateral recurrence events:

DCIS +RT/-Tamox = 30/221 (13.6%)

DCIS +RT/+Tam = 7/16 (43.8%) (see comments)

Comments from corresponding author (G. Freedman):

Only 16 patients had tamoxifen, apparently we were not using it very much in that time period before results of the NSABP B-24 became available.

There were 13 local only breast recurrences, 15 any local recurrence (perhaps with a regional), and 37 contralateral breast cancers reported in that paper. 1 of the patients out of the 15 total local failures had been on tamoxifen, she had a local and subsequent distant failure! (very rare for DCIS). And 7 of the 37 contralateral breast cancer patients had received tamoxifen, so 7 out of the 16 patients receiving tamoxifen had a contralateral breast cancer!

There must be some unusual bias against these women who had had tamoxifen. It was a retrospective study after all. My impression would be that if it was not our usual policy to give tamoxifen back in those years, there probably was something that worried the physicians about these 16 women to give them tamoxifen like a strong family history or LCIS or something.

General comments

Moderate retrospective case series study.

Corresponding author (G. Freedman) contacted and provided additional data for DCIS patients, specifically how many received Tamox and recurrence data for +/- Tamox in this treatment group.

The author made additional comments regarding the unexpectedly high rate of recurrence in the tamoxifen treatment group (see results).

Jha, Avlonitis, Griffith, Lennard, Wilson, McLean, Dawes & Shrimankar . Aggressive local treatment for screen-detected DCIS results in very low rates of recurrence. Eur J Surg Oncol 27[5], 454-458. 2001.

Design: Retrospective case series (therapy), evidence level: 3
Country: United Kingdom, setting: Primary care

Inclusion criteria 304 women with mammographically-detected DCIS, confirmed by FNAC or FNAB. 12/304 not included in analysis

Exclusion criteria None stated but 12/304 (4%) originally treated but excluded from further analysis due to: (i) evidence of invasive disease (4/304); (ii) lost to follow-up (6/304); (iii) bilateral disease (2/304).

Population number of patients = 304, age range 51 to 65 years, median age = 59 years.

Interventions Simple mastectomy, 104/304 Patey's mastectomy, 72/304 (24%)
Wide local excision + RT, 97 (32%)
Wide local excision alone, 31 (10%)

RT was 50 Gy fractioned over 5 weeks.

Adjuvant Tamoxifen therapy given to 304/304 patients.
5/304 (1.6%) withdrew from Tamoxifen treatment due to intolerable side-effects.

Outcomes Estimated local recurrence, Kaplan-Meier method (recurrence-free survival)

Follow up 88 months (range, 62 - 126 months)

Results Local Recurrence:
Mastectomy (all): 0/176
WLE + RT: 1/93 (1%)
WLE - RT: 5/30 (16.7%) P = 0.0008 (log-rank test)

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General comments Moderate sized retrospective case series. All patients received Tamoxifen and therefore this study really compares the added protective effect of receiving RT in addition to Tamoxifen following WLE. There were no recurrences in the mastectomy group.

Roka, Rudas, Taucher, Dubsky, Bachleitner-Hofmann, Kandioler, Gnant & Jakesz . High nuclear grade and negative estrogen receptor are significant risk factors for recurrence in DCIS. Eur J Surg Oncol 30[3], 243-247. 2004.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Austria, setting: Secondary care

Inclusion criteria

132 patients with DCIS treated surgically between 198 and 2001

Exclusion criteria

History of breast cancer or any other cancer
DCIS and histologically positive axillary lymph nodes

Population

number of patients = 132, age range 32 to 85 years, median age = 56 years.

Interventions

Breast conserving surgery, wide excision 132/190 (70%)
Mastectomy 58/190 (30%)
Post-operative RT, 50 Gy + 15 Gy to tumour bed

BCS alone	20/132
BCS +RT/-Tam	61/132
BCS +RT/+Tam	40/132
BCS -RT/+Tam	11/132

Outcomes

Ipsilateral breast cancer recurrence after breast conserving surgery only
statistical analysis used log-rank test for significance ($P < 0.05$)

Follow up

median 61.6 months (range, 11.2 to 244.9 months)

Results

Crude ipsilateral breast cancer recurrence rates:

BSC alone	3/20	15%
BCS +RT/-Tam, or BCS -RT/+Tam	6/72	8.3%
BCS +RT/+Tam	0/40	0%
All BCS +Tam	1/51	1.9%

$P = ns$

All BCS -Tam	8/81	9.9%	$P = ns$
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Overall local recurrence rate = 6.1%

General comments

Small retrospective study in which the primary aim was to investigate the nuclear grade and estrogen receptor status as possible risk markers for recurrence following breast conserving surgery for DCIS. No significant differences found between interventions (+RT +/- Tamoxifen) but the small numbers included make the results susceptible to errors.

Updated 2018

Stallard, Hole, Purushotham, Hiew, Mehanna, Cordiner, Dobson, Mallon & George . Ductal carcinoma in situ of the breast -- among factors predicting for recurrence, distance from the nipple is important. Eur J Surg Oncol 27[4], 373-377. 2001.

Design: Retrospective case series (therapy), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria 220 patients with pure DCIS treated between 1986 and 1997
Included patients with Paget's disease of the nipple, diffuse microcalcification on mammography, multifocal disease or involved margins with extensive DCIS, but these patients tended to be treated by mastectomy

Exclusion criteria None specified

Population number of patients = 220, age range 30 to 86 years, mean age = 58 years.

Interventions Breast conserving surgery 153/220 (70%): 99/153 (65%) had one procedure, 54/153 (35%) had a re-excision

Mastectomy 67/220 (30%)

BSC alone, 56/153 (37%)

BCS + Tamox, 54/153 (35%)

BCS + RT, 22/153 (14%)

BCS + Tamox + RT, 21/153 (14%)

22/78 (28%) of patients who did not have adjuvant Tamoxifen therapy received post-op RT

21/75 (28%) of patients who had adjuvant tamoxifen therapy received post-op RT

overall BCS patients given RT = 110/153

overall BCS patients not given RT = 43/153

52/153 were entered into the UK DCIS trial (est. 1991) and randomised to one of the 4 treatment modalities.

Outcomes Local recurrence following BCS:

Estimated 5 year freedom from local recurrence (Kaplan-Meier method)

Multivariate analysis of time to first recurrence (Cox's proportional hazards model) including factors either significant on univariate analysis or produced a large absolute difference in survival rates and were biologically plausible.

Follow up 60 months (60 month freedom from local recurrence estimate)

Results

Recurrence rates

<u>Intervention</u>	<u>No. events</u>	<u>Rate (%)</u>	<u>Type</u>
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Mastectomy	2/67	3	axillary
BCS - Tamoxifen	12/78	15.4	local
BCS + Tamoxifen	8/75	10.7	local
BCS - RT	18/110	16.4	local
BCS + RT	2/43	4.5	local

5 year actuarial recurrence-free survival

Intervention	% disease-free	Univariate <i>P</i> value (log-rank test)
BCS - Tamoxifen	75.4	
BCS + Tamoxifen	82.2	0.22
BCS - RT	75.4	
BCS + RT	94.2	0.14

Of all univariate analyses performed only two reached statistical significance: mammographically-measured nipple to lesion distance <40 mm vs >40 mm ($P=0.007$), and nuclear grade ($P=0.02$)

Multivariate analysis included 3 factors from the univariate analysis and Relative Hazard Ratios were determined: (i) nipple to lesion distance RHR = 0.33 (95% CI, 0.11-0.95); (ii) nuclear grade (per unit change) RHR = 0.45 (95% CI, 0.21-0.98); and (iii) adjuvant RT (yes vs no) RHR = 0.43 (95% CI, 0.10-1.92)

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General comments Moderate sized retrospective study. A proportion of patients in both the adjuvant Tamox group and the no adjuvant Tamox group received RT, 28% in each group. NO recurrence data for adjuvant Tamox alone or adjuvant RT alone.

Systematic review of combined study designs

Shelley, McCready & Holloway . Management of ductal carcinoma in situ of the breast: A clinical practice guideline. Cancer Care Ontario . 2006.

Design: Systematic review of combined study designs (therapy), evidence level: 2+
Country: Canada (federal state, Commonwealth Realm), setting: Secondary care

Inclusion criteria Included articles were required to meet the following criteria:

1. Study designs for the management of DCIS were randomised control trials, or meta-analyses on non-randomised and/or randomised trials.
2. Outcomes included overall or disease-free survival, local recurrence (invasive or non-invasive), breast conservation, distant recurrence, toxicity, or quality of life.
3. Clinical trials results reported in full papers or abstracts.
4. Evidence-based clinical practice guidelines addressing the management of DCIS.

An additional section - intended as an aid to practitioners and outside the guideline recommendations - was included in which issues for the management of DCIS that were not covered by included RCTs were reviewed through appraisal of expert opinion and non-randomised evidence identified from a non-systematic search of the literature.

Exclusion criteria Non English language publications
Publications occurring before 1983

Population -

Interventions Development of clinical practice guidelines for the management of ductal carcinoma in situ (DCIS) by Cancer Care Ontario's Program in Evidence-based care using the methods of the Practice Guidelines Development Cycle.

Literature search strategy:

MEDLINE search to March 2006 using a disease-specific MeSH terms ("carcinoma, intraductal, non-infiltrating") and treatment-specific Mesh terms (radiotherapy, mastectomy, Tamoxifen).

EMBASE searched to March 2006 using a disease-specific Excerpta Medica Tree (EMTREE) term("intraductal carcinoma") and the same treatment-specific EMTREE term as for MEDLINE.

Cochrane Library issue 5 (2004), the Physician Data Query database (http://www.cancer.gov/search/clinical_trials/)

Conference proceedings from the American Society of Clinical Oncology (1998 to 2005), American Society for Therapeutic Radiology and Oncology (1998 to 2005), San Antonio Breast Cancer Symposium (2001 to 2005).

Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the

National Guidelines Clearinghouse (<http://www.guideline.gov/>) were searched for evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Outcomes Of relevance to the evaluation of adjuvant Tamoxifen therapy in the management of DCIS, important outcome measurements addressed in this review included:

1. Local and distant disease recurrence for non-invasive and invasive events
2. Overall and disease-free survival
3. Effect of Tamoxifen in patients by age at randomisation (comparison between UKCCCR and NSABP B-24 trials)
4. Toxicity of Tamoxifen vs. placebo (data obtained from NSABP P-1 trial)

Data concerning these outcomes were reviewed from the two RCTs covered in this evidence summary, NSABP B-24 and UKCCCR, and the NSABP P-1 study of Tamoxifen therapy in women of increased risk of developing breast cancer

Follow up Variable across included studies

Results

In addition to the key findings of the two randomised control studies presented in this summary, this systematic review highlights a number of other issues for the management of DCIS

Influence on recurrence of positive vs. negative resected margins (NSABP B-24 trial):

Sixteen percent of the patients had positive resected margins and 10% had unknown margins for DCIS, and others were known to have residual suspicious micro-calcifications. The recurrence rate for those with negative margins was lower and the effect of Tamoxifen was less. The absolute recurrence risk for ipsilateral breast recurrence was 7.0% (Tamoxifen arm) vs. 8.8% (placebo arm) in the margin-negative group and 10.6% (Tamoxifen arm) vs. 14.1% (placebo arm) in the unknown/margin-positive group.

Influence of tumour estrogen receptor status on recurrence (NSABP B-24 trial):

Of the 1798 eligible patients estrogen receptor (ER) status of tumours was known in 628 (35%) (327 placebo, 301 Tamoxifen). Seventy seven percent of tumours were ER positive and the risk ratio (RR) of recurrent or new breast pathology in patients receiving Tamoxifen was 0.41 in the ER positive group (95% CI, 0.25-0.65, P=0.0002). In the ER-negative group the RR was 0.8 (P=0.5) although the number of events (n=36) was too small to exclude a clinically meaningful benefit (95% CI for RR, 0.41-1.56).

Effect of Tamoxifen in patients by age at randomisation:

In this study only 9.5% of recruited patients were under 50 years of age, compared with 33.5% of those in the NSABP B-24 study. This may have been due to the nature of patient recruitment in the former study in that they were recruited through the UK national breast screening programme. Age-related data comparison between studies was possible only for local (IBT) recurrence; the benefit of Tamoxifen in both studies was more apparent in

women \leq 50 years of age although this failed to achieve statistical significance.

Other considerations for the use of Tamoxifen in the management of DCIS

Tamoxifen toxicity:

Both RCT studies included some data on toxicity associated with Tamoxifen treatment, but the NSABP P-1 study (Tamoxifen in the prevention of breast cancer in 13,388 women at increased risk) included a detailed analysis stratified by patient age. Significant toxicity events were; endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. The largest difference in serious adverse events appears to be in women $>$ 50 years of age, however the absolute number of adverse events is low as is the incremental risk.

Contraindications for breast conserving surgery (BCS):

The authors state that as with invasive breast cancer, there are also contraindications for performing BCS in the management of DCIS: large tumour size and small breasts may not yield satisfactory cosmetic results and may be better served by mastectomy coupled with the option of reconstructive surgery. As with other studies, only a small proportion (4%) of patients recruited to the NSABP B-24 trial had lesions $>$ 2 cm. Therefore local control rates reported may not be applicable to patients with larger lesions. Also, the detection of multiple tumours or extensive micro-calcifications are relative contraindications of BCS.

Overall, for the purposes of developing a clinical guideline for DCIS management in Canada, the reviewers highlight data from the NSABP B-24 study which suggests that most of the benefit of receiving Tamoxifen is with younger women ($<$ 50 years) and those with positive or unknown resection margins. No significant benefit was shown in the UKCCCR study although this was possibly confounded by the fact that most of the women recruited were older than 50 years of age and with clear resection margins. The authors conclude that Tamoxifen may be an option in women less than 50 years with positive margins who refuse further surgery, and also to those who refused or are unable to undergo radiotherapy but wish to avoid mastectomy. It is also recommended that physicians and patients give due consideration to the potential toxicities of Tamoxifen as well as their possible benefits.

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General comments Canadian systematic review of literature concerning the management of DCIS and development of an evidence-based care clinical guideline.

Systematic review of randomised studies of the efficacy of adjuvant tamoxifen therapy following breast conserving surgery with or without post-operative radiotherapy.

Non-systematic review of non-randomised observational studies concerning aspects of DCIS management that fell outside the scope of randomised studies.

The key points of six existing clinical practice guidelines are tabulated as part of this review. The authors point out the fact that tamoxifen recommendations/statements were made prior to the publication of the UKCCCR study is important to note.

5.4.1 Update of NICE Technology Appraisal 109 – Docetaxel for the Adjuvant Treatment of Early Node-Positive Breast Cancer.

5.4.2 Update of NICE Technology Appraisal 108 – Paclitaxel for the Adjuvant Treatment of Early-Positive Breast Cancer

Short Summary

There is a considerable volume of high quality evidence that evaluates the clinical and cost effectiveness of docetaxel and paclitaxel for the adjuvant treatment of early breast cancer. The evidence includes a Cochrane review (Ferguson *et al.* 2007); an HTA report (Ward *et al.* 2007); a meta-analysis (De Laurentiis *et al.* 2008); a pooled analysis (Bria *et al.* 2006); 2 RCTs (Kummel *et al.* 2006; Piedbois *et al.* 2007) and 1 RCT from an abstract (Ellis *et al.* 2007).

The studies which reported overall survival (Ferguson *et al.* 2007; Ward *et al.* 2007) showed improved overall survival with use of the taxanes. The meta-analysis and pooled analysis (De Laurentiis *et al.* 2008; Bria *et al.* 2006) also showed significant improvements in overall survival with the taxanes compared with the control treatments. The TACT (taxotere as adjuvant chemotherapy) abstract (Ellis *et al.* 2007) showed a non significant difference between those given docetaxel and the control chemotherapy arm.

Disease-free survival showed improvement with the taxanes (Ferguson *et al.* 2007; Ward *et al.* 2007). The meta-analysis and pooled analysis (De Laurentiis *et al.* 2008; Bria *et al.* 2006) also showed significant differences with the taxanes compared with the control treatments in disease-free survival. The TACT study (Ellis *et al.* 2007) found a non significant difference in disease-free survival with those in the docetaxel group and those in the control group.

Neutropenia and febrile neutropenia were identified as occurring more frequently in those in the docetaxel groups than in the control groups. Where quality of life was reported the reductions in QoL associated with treatment were higher with docetaxel than in the control groups, with paclitaxel there was no significant difference compared with controls.

The HTA report (Ward *et al.* 2007) noted that the comparators used in most trials restrict the generalisability of results as they do not conform to current standards of care in the UK for reasons such as too few cycles of chemotherapy or using doxorubicin instead of the more widely used epirubicin. One further study has been published which compared the efficacy of paclitaxel and docetaxel given weekly or every 3 weeks in the adjuvant treatment of breast cancer (Sparano *et al.* 2008). All received 4 cycles of IV doxorubicin and cyclophosphamide, with each of 4 groups then followed this with paclitaxel or docetaxel (175mg/m²) at 3-week intervals for 4 cycles, or at 1-week intervals for 12 cycles (80mg/m²). For disease-free survival, compared with those receiving paclitaxel every 3 weeks there was significantly

higher survival with weekly paclitaxel and with docetaxel every 3 weeks and no significant difference with weekly docetaxel.¹¹ For overall survival, compared with those receiving paclitaxel every 3 weeks there was significantly higher survival with weekly paclitaxel and no significant difference with weekly docetaxel or 3-weekly docetaxel. Those with HER2 negative disease who had weekly paclitaxel had improved disease-free survival and overall survival. No significant difference was seen with other groups.

PICO

Patient	Intervention	Comparison	Outcomes
Patients with early node-positive breast cancer following initial surgery	Docetaxel given as part of a cytotoxic chemotherapy regimen for the adjuvant treatment of breast cancer	Other adjuvant chemotherapy regimens	<ul style="list-style-type: none"> •Disease-free survival •Overall survival •Contralateral breast cancer •Quality of life •Adverse events •Drug interactions Cost effectiveness
Patients with early node-positive breast cancer following initial surgery	Paclitaxel given as part of a cytotoxic chemotherapy regimen for the adjuvant treatment of breast cancer	Other adjuvant chemotherapy regimens	<ul style="list-style-type: none"> •Disease-free survival •Overall survival •Contralateral breast cancer •Quality of life •Adverse events •Drug interactions •Cost effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence statement

The Cochrane review considered taxanes (paclitaxel or docetaxel) for adjuvant treatment of early breast cancer (Ferguson *et al.* 2007). This included any chemotherapy regimen that contained a taxane, compared with any chemotherapy regimen without a taxane. This review included 12 studies with 21,191 participants; docetaxel was included as a treatment in 7 studies and paclitaxel in 5 studies. Analysis was completed for taxanes as a combined group in this review with only disease-free survival and overall survival being analysed for the individual agents.

¹¹ Results were similar where the definition of end point did not include contralateral breast cancer or contralateral breast cancer and second nonbreast cancer

The HTA report considered the clinical and cost effectiveness of docetaxel and paclitaxel compared with non-taxane containing chemotherapy regimens including anthracycline agent, for the adjuvant treatment of women with early stage breast cancer (Ward *et al.* 2007). This report included 18 trials which comprised 11 trials including docetaxel and 7 including paclitaxel. Information on the outcomes included were reported for individual trials as the authors considered that the heterogeneity of interventions, comparators and populations precluded meta-analysis.

De Laurentiis *et al.* (2008) completed a meta-analysis of randomised trials on taxane-based combinations as adjuvant chemotherapy of early breast cancer. This included trials containing a taxane-anthracycline based regimen with an anthracycline based regimen. There were 13 trials included with 22,903 participants. Seven studies used docetaxel (N=13,001) and six studies used paclitaxel (N=9,902).¹²

Bria *et al.* (2005) completed a pooled analysis of 15,500 patients which included those who were randomised to receive chemotherapy either with or without sequential or concomitant taxanes, all trials were specifically designed to assess if chemotherapy with taxanes improved survival. There were 9 trials with 15,598 participants, 4 trials used docetaxel (N=7,395) and 5 trials used paclitaxel (N=8,203).

One RCT considered dose-dense chemotherapy in node-positive breast cancer with T/EC or EC/T vs. standard dose TEC with the aim of selecting a dose-dense regimen for further assessment in phase III studies (Peidbois *et al.* 2007). This study had a primary end point of grade 4 toxicity. The second RCT considered the survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer using a dose-dense regimen including paclitaxel (epirubicin and paclitaxel, then CMF) compared with a conventional schedule (epirubicin and cyclophosphamide, then CMF) (Kummel *et al.* 2006).

The TACT study considered N=2073 participants who were randomised to 4 cycles of FEC followed by 4 cycles of docetaxel, these were compared with N=2089 who randomised to either 8 cycles of FEC or 4 cycles of E-CMF, designed so that all participants would have eight cycles of treatment (Ellis *et al.* 2007).

Overall survival

In the Cochrane review (Ferguson *et al.* 2007) overall survival for the taxanes was reported in 11 studies (18,304 participants), this identified a hazard ratio (HR) for taxane containing regimens vs. non-taxane containing regimens: 0.81 (0.75 to 0.88), $p < 0.00001$. Overall survival in the docetaxel studies (N=9377) identified a HR 0.76 (0.67 to 0.86), $p < 0.0001$ and in the paclitaxel studies (N=8927), HR 0.85 (0.76 to 0.94), $p < 0.001$.

In the HTA report (Ward *et al.* 2007) overall survival with docetaxel (reported in 4 studies) identified:

- significant improvement with DAC6 vs. FAC6, HR 0.69 (0.52 to 0.90)

¹² This study reported both fixed effects and random effects, the fixed effects values are used in this evidence statement, there were no values reported which were significant for random effects that were not also significant for fixed effects

- improvement with FEC3-D3 vs. FEC6 (which had a 4% lower survival rate)
- NS difference with DC4 vs. AC4 and with DA4 vs. AC4

Overall survival paclitaxel (reported in 5 studies) identified:

- significant improvement with AC4-P4 vs. AC4, HR 0.82 (0.71 to 0.95)
- 3% higher survival rate with E3-P3-CMF4 vs. E4-CMF4
- NS difference with PA4-CMF4 vs. A4-CMF4; AC4-P4 vs. AC4; FEC4-P8 vs. FEC6

The meta-analysis (De Laurentiis *et al.* 2008), twelve studies (N=22,379 participants, N=3,329 deaths) showed a significant reduction in the risk of death for taxane-based treatment total HR 0.85 (0.79 to 0.91), $p < 0.00001$, with docetaxel this was a HR 0.87 (0.79 to 0.95), $p = 0.003$, and with paclitaxel this was a HR 0.83 (0.75 to 0.92), $p = 0.0004$.

The pooled analysis (Bria *et al.* 2006) showed significant differences in favour of the taxanes in overall survival for the:

- total (8 trials, N=15,074) with RR 0.87 (0.81 to 0.93), $p < 0.0001$, NNT 49
- docetaxel (4 trials, N=7,395) with RR 0.78 (0.68 to 0.90), $p = 0.001$, NNT 42
- paclitaxel (4 trials, N=7,679) with RR 0.90 (0.83 to 0.98), $p = 0.013$, NNT 50

This significant difference in favour of the taxanes was also seen with the node-positive group, sequential taxane and concomitant taxane administration.

One RCT considered overall survival as a secondary endpoint and at a median follow-up of 38.4 months 17% of participants had died, 14% in the dose-dense group and 20% in the conventional schedule group.

The TACT study reported overall survival of 82% in the docetaxel arm and 81.8% with FEC only, the HR of 0.98 was NS, there were N=291 breast cancer deaths with docetaxel and N=301 with FEC only (Ellis *et al.* 2007).

Disease-free survival

In the Cochrane report (Ferguson *et al.* 2007) disease-free survival for the taxanes was also reported in 11 studies (19,943 participants), this identified a hazard ratio (HR) for taxane containing regimens vs. controls: 0.81 (0.77 to 0.86), $p < 0.00001$. Disease-free survival in the docetaxel studies (N=12,264) identified a HR 0.80 (0.74 to 0.87), $p < 0.00001$ and in the paclitaxel studies (N=7679), HR 0.82 (0.76 to 0.89), $p < 0.00001$.

In the HTA report (Ward *et al.* 2007) disease-free survival with docetaxel (reported in 6 studies) identified significantly better disease-free survival for:

- DAC6 vs. FAC6, HR 0.71 (0.58 to 0.87), $p < 0.001$
- DC4 vs. AC4, HR 0.67 (0.50 to 0.94), $p = 0.015$
- FEC3-D3 vs. FEC3, HR 0.83 (0.69 to 0.99), $p = 0.041$
- A3-D3-CMF3 vs. A4-CMF4 (for sequential docetaxel administration), HR 0.79 (0.64 to 0.98), $p = 0.035$

There was NS difference in disease-free survival between: DA4 vs. AC4; DA4-CMF3 vs. A4-CMF3 (for concurrent docetaxel administration); E4-D4-CMF4 vs. E4-CMF4.

In the HTA report (Ward *et al.* 2007) disease-free survival with paclitaxel (reported in 5 studies) identified significant improvement with disease-free survival for:

- AC4-P4 vs. AC4, RR paclitaxel compared with control 0.83 (0.72 to 0.95), $p = 0.006$
- FEC4-P8 vs. FEC6, HR 0.63, $p = 0.0008$

There was NS difference in disease-free survival between: E3-P3-CMF3 vs. E4-CMF4.

In the meta-analysis (De Laurentiis *et al.* 2008) disease-free survival was reported in thirteen studies. The reduction in risk of recurrence was significant for those receiving taxane-based treatments, the total for taxanes was a HR 0.83 (0.79 to 0.87), $p < 0.00001$, with docetaxel this was a HR 0.86 (0.80 to 0.92), $p < 0.00001$ and with paclitaxel HR 0.80 (0.74 to 0.86), $p < 0.00001$.

The pooled analysis (Bria *et al.* 2006) showed significant differences in favour of the taxanes in disease-free survival for the:

- total (9 trials, N=15,598) with RR 0.86 (0.81 to 0.93), $p < 0.0001$, NNT 30
- docetaxel (4 trials, N=7,395) with RR 0.83 (0.75 to 0.91), $p < 0.0001$, NNT 31
- paclitaxel (5 trials, N=8,203) with RR 0.87 (0.81 to 0.93), $p < 0.001$, NNT 28

This significant difference in favour of the taxanes was also seen with the node-positive group, sequential taxane and concomitant taxane administration.

One RCT considered overall survival as a secondary endpoint and at a median follow-up of 38.4 months 33% of participants had experienced a first event of relapse or death, 31% in the dose-dense group and 35% in the conventional schedule group (Kummel *et al.* 2006).

The TACT study reported disease-free survival of 74.7% with docetaxel and 73.9% with FEC only, a NS HR of 0.97 (Ellis *et al.* 2007).

Locoregional or distant recurrence or contralateral breast cancer

The HTA report reported on recurrence and the two docetaxel studies that reported on recurrence identified NS difference for DAC6 vs. FAC 6 for locoregional, distant or contralateral recurrence, while for FEC3-D3 vs. FEC6 distant recurrence was 17.7% vs. 21.8%, $p=0.023$ (NS difference for locoregional or contralateral recurrence)(Ward et al 2007).

In the HTA report two paclitaxel studies reported on recurrence, one study found contralateral recurrence for AC4-P4 vs. AC4 of 1.1% vs. 1.9% ($p=0.039$) with NS difference for locoregional recurrence; for E3-P3-CMF3 vs. E4-CMF4 there was NS difference with contralateral recurrence (Ward et al 2007).

Adverse events

In the Cochrane review (Ferguson *et al.* 2007), ten of the twelve studies provided data on toxicity (there was heterogeneity between studies with the use of different control regimens and varying doses and schedules of the taxane)

- febrile neutropenia; reported in 7 studies, identified an increase in the taxane arms OR 2.51 (1.11 to 5.66), the risk was highest with taxane and anthracycline concurrent administration OR 6.80(1.91 to 24.15).
- nausea; reported in 5 studies, identified a lower risk with the taxane arms OR 0.55 (0.39 to 0.77)
- cardiotoxicity (reported in 6 studies), fatigue (4 studies), stomatitis (5 studies); showed no difference between taxane and non-taxane containing regimens
- secondary malignancy (reported in 7 studies) showed N=48 cases of secondary leukaemia or myelodysplasia, there was NS difference in secondary malignancy between taxane and non-taxane regimens
- treatment related deaths (reported in 6 studies) showed N=14 deaths, there was NS difference between taxane and non-taxane regimens

In the HTA report (Ward *et al.* 2007) there were seventeen (total N=8829) treatment-related deaths in the taxane containing arms and eleven (total N=8819) in the control arms.

In the docetaxel studies, the docetaxel arm showed:

- significantly more febrile neutropenia/neutropenic fever for; DAC6 vs. FAC6; FEC3-D3 vs. FEC6; DC4 vs. AC4; DE6 vs. FEC6
- significantly less nausea and vomiting or high-grade nausea/vomiting for; DAC6 vs. FAC6; FEC3-D3 vs. FEC6; DC4 vs. AC4; DA4 vs. AC4; DE6 vs. FEC6
- significantly more stomatitis for; DAC6 vs. FAC6; FEC3-D3 vs. FEC6

- significantly more mucositis or high-grade mucositis for; DAC6 (without G-CSF) vs. FAC6; DA4 vs. AC4
- significantly more diarrhoea or high-grade diarrhoea for: DAC6 vs. FAC6; DAC6 (without G-CSF) vs. FAC6; DA4 vs. AC4

In the paclitaxel studies there were few significant values for reported adverse events, though there was significantly more peripheral neuropathy and hypersensitivity reactions with E3-P3-CMF4 vs. E4-CMF4.

The two RCTs reported primarily on adverse events. The RCT which compared two dose dense regimens (T/EC and EC/T) with a standard regimen TEC identified that neutropenia to be the most frequent toxicity; 34% with TEC, 63% with EC/T and 53% with T/EC, with NS between the groups (Piedbois et al 2007). The dose dense regimens had significantly more incidence of skin and nail disorders and hand-foot syndrome. Any grade 4 event showed NS difference between the groups (26% TEC; 40% EC/T; 18% T/EC), with any grade 3-4 event there was a significantly higher occurrence with EC/T (73%) vs. TEC (46%), $p=0.043$, T/EC (68%) vs. TEC was NS. There were higher levels of having at least one cycle delayed with the dose dense regimens (11% TEC; 53% EC/T; 38% T/EC).

The RCT which compared a dose-dense paclitaxel containing regimen with a conventional schedule identified that for haematological toxicity leukopenia and neutropenia occurred in both treatment groups at similar rates and that rate of discontinuation at 4% was the same in both groups (Kummel et al 2006). For nonhaematological toxicity events that occurred more in the dose-dense group compared with the conventional schedule group were; peripheral nervous system toxicity (47 vs. 11%), bone pain (44% vs. 23%), arthralgia/myalgia (22% vs. 15%).

With the TACT study neutropenia and febrile neutropenia were significantly higher in the docetaxel arm ($p=0.001$ for both), severe nonhaematological side effects were also significantly higher in the docetaxel arm ($p=0.001$), including neuropathy and lethargy (Ellis et al 2007).

Quality of life

In the Cochrane review (Ferguson *et al.* 2007) quality of life (QoL) was reported in N=2 studies, with one showing a transient reduction in both regimens which was greater with the taxane containing regimen, the second showed no difference between the types of treatment groups

In the HTA report (Ward *et al.* 2007) in the docetaxel studies the QoL score worsened during treatment and recovered 3-4 weeks after the last cycle of treatment for both arms in DAC6 vs. FAC6, with NS difference between the groups. The docetaxel arm showed significantly worse global QoL score with FEC4-D4 vs. FEC8 vs. E4-CMF4 ($p=0.002$), this was also found for DAC6 (without G-CSF) vs. FAC6 ($p=0.008$). With paclitaxel E3-P3-CMF4 showed NS difference vs. E4-CMF4 at baseline or at the end of treatment.

Post-hoc analysis for the taxanes

The Cochrane review (Ferguson *et al.* 2007) included a post-hoc analysis and this identified that:

- sequential or concurrent taxane and anthracycline identified a significantly lower HR with taxane vs. sequential anthracycline and also for taxane and anthracycline concurrently in the experimental arm for both overall survival and disease-free survival;
- lymph node status identified a HR favouring taxane for both overall survival and disease-free survival for both studies which included those with positive axillary node metastasis and studies which allowed the inclusion of those without lymph node metastases;
- duration of chemotherapy identified a HR favouring taxane for both overall survival and disease-free survival for both studies which had a taxane containing arm of longer duration than the control arm and studies which had taxane and control arms of the same duration'
- number of cycles of taxane containing chemotherapy identified a HR favouring taxane for both overall survival and disease-free survival for both studies which had 3 cycles of taxane in the experimental arm and those which had 4 or more cycles of chemotherapy in the experimental arm.

Subgroup analysis

HTA report – disease-free survival

Subgroup analysis was completed in the HTA report (Ward *et al.* 2007) and in the docetaxel studies identified:

- a significant benefit with DAC6 vs. FAC6; for those with 1-3 nodes, for those with a HR+ve and those with HR-ve hormone receptor status, for those with a HER2 +ve status and for those who were HER2-ve, and for those who were premenopausal
- a significant benefit with FEC3-D3 vs. FEC6; for those with 1-3 nodes, and for those aged 50+ years
- a significant benefit with DC4 vs. AC4 for those who were node positive
- a significant benefit with DA4 vs. AC4 for those with ER-PR+ve hormone receptor status

While subgroup analysis in the paclitaxel studies identified:

- a significant benefit with FEC4-P8 vs. FEC6; for those with ≥ 4 +ve nodes, for both those who were HR+ve and those who were HR-ve, for both HER2-ve and HER2+ve, and for those who were post menopausal
- a significant benefit with AC4-P4 vs. AC4 for those with HR+ve hormone receptor status

Meta-analysis

Subgroup analysis was completed, for oestrogen receptor status, taxanes significantly reduced the risk of recurrence for both ER-positive and ER-negative whether docetaxel or paclitaxel was administered. The pooled HR for disease-free survival was similar for patients with 1-3 and for 4 or more positive lymph nodes. Taxanes also showed a significant risk reduction for both ≤ 50 years/premenopausal and > 50 years/postmenopausal (De Laurentiis et al 2008).

One further study has been published which compared the efficacy of paclitaxel and docetaxel given weekly or every 3 weeks in the adjuvant treatment of breast cancer (Sparano *et al.*, 2008), with disease-free survival and overall survival as outcomes, with N=4950 participants. All received 4 cycles of IV doxorubicin and cyclophosphamide, with each of 4 groups then followed this with paclitaxel or docetaxel ($175\text{mg}/\text{m}^2$) at 3-week intervals for 4 cycles, or at 1-week intervals for 12 cycles ($80\text{mg}/\text{m}^2$).

With disease-free survival, compared with those receiving paclitaxel every 3 weeks there was significantly higher survival with weekly paclitaxel (OR 1.27, $p=0.006$, 95% CI 1.03 to 1.57) and with docetaxel every 3 weeks (OR 1.23, $p=0.02$, 95% CI 1.00 to 1.52), NS difference with weekly docetaxel.¹³

With overall survival, compared with those receiving paclitaxel every 3 weeks there was significantly higher survival with weekly paclitaxel (OR 1.32, $p=0.01$, 95% CI 1.02 to 1.72), NS difference with weekly docetaxel or 3-weekly docetaxel.

Those with HER2 negative disease who had weekly paclitaxel had improved disease-free survival (OR 1.33, $p=0.009$, 95% CI 1.07 to 1.64) and overall survival (OR 1.34, $p=0.03$, 95% CI 1.02 to 1.76). NS difference was seen with other groups.

28% of those in the weekly paclitaxel group had grade 3 or 4 toxic effects compared with 30% with 3-weekly paclitaxel (NS), 71% with 3-weekly docetaxel ($p<0.001$) and 45% with weekly docetaxel ($p<0.001$). 3-weekly docetaxel had a neutropenia rate of 46%, this was 4% or less in the other treatment groups. 20% grade 2, 3 or 4 neuropathy (paclitaxel 3-weekly), 27% (paclitaxel weekly), 16% (docetaxel 3-weekly and with docetaxel weekly), weekly paclitaxel was significantly higher than the other groups ($p<0.001$).

¹³ Results were similar where the definition of end point did not include contralateral breast cancer or contralateral breast cancer and second nonbreast cancer

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Sparano JA., Wang M., Martino S., Jones V., Perez EA., Saphner T., Wolff AC., Sledge GW, Jr., Wood WC and Davidson NE (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer.[see comment][erratum appears in N Engl J Med. 2008 Apr 3;359(1):106]. *N Engl J Med* **358**: 1663-1671

Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)* 2007;**11**:1-144.

Evidence Tables

Citation
Sparano JA., Wang M., Martino S., Jones V., Perez EA., Saphner T., Wolff AC., Sledge GW, Jr., Wood WC and Davidson NE (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer.[see comment][erratum appears in N Engl J Med. 2008 Apr 3;359(1):106]. <i>N Engl J Med</i> 358 : 1663-1671
Design
Design: RCT, Country: USA
Inclusion criteria
Inclusion: axillary lymph node-positive (tumour stage T1, T2, or T3 and nodal stage N1 or N2) or high-risk, lymph node-negative (T2 or T3, N0) breast cancer
Exclusion criteria
Population
N=4950 (98% who were eligible from the N=5052 enrolled between October 1999 and January 2002) Median age 51yrs (range 19 to 84yrs), 12% no +ve lymph nodes, 56% 1 to 3 +ve nodes, 32% 4 or more +ve nodes Tumour +ve for estrogen receptor, progesterone receptor, or both in 70%; +ve for HER2 in 19% 60% had undergone mastectomy, 40% had undergone breast-sparing surgery
Interventions
All patients received 4 cycles of IV doxorubicin and cyclophosphamide at 3-week intervals; - then IV paclitaxel or docetaxel either 3-week intervals for 4 cycles (175mg/m ²) - or 1-week intervals for 12 cycles (80mg/m ²) Treatment groups were similar with regard to prognostic characteristics, median age 51yrs, 60% had undergone mastectomy
Outcomes
Primary: Disease-free survival; defined as the time from randomisation to disease recurrence (including death from recurrence if it was the first manifestation of recurrence), death without recurrence, or contralateral breast cancer Primary comparisons: - paclitaxel with docetaxel, regardless of dosing schedule - weekly dosing with dosing every 3 weeks, regardless of taxane administered

Follow up
Interim analysis planned to begin every 2 yrs after initiation of the study
Results (all CI 95%)
<p>Taxane type and schedule: After median follow-up of 63.8mths, N=1048 had recurrence of breast cancer or cancer in the contralateral breast, N=668 had died</p> <p>NS difference in disease-free survival between paclitaxel and docetaxel groups or between those receiving weekly treatment or treatment of every 3 weeks</p> <p>Disease-free survival:</p> <ul style="list-style-type: none"> - estimated 5-yr survival for the paclitaxel every 3wks group, 76.9% - estimated 5-yr survival for the weekly paclitaxel group, 81.5% - estimated 5-yr survival for the docetaxel every 3wks group, 81.2% - estimated 5-yr survival for the weekly docetaxel, 77.6% <p>Compared with those receiving paclitaxel every 3 wks, disease-free survival was significantly better in those with weekly paclitaxel (OR 1.27, p=0.006, 1.03 to 1.57) and with docetaxel every 3 wks (OR 1.23, p=0.02, CI 1.00 to 1.52), NS difference with weekly docetaxel</p> <p>Results were similar where the definition of end point did not include contralateral breast cancer or contralateral breast cancer and second primary nonbreast cancer</p> <p>Overall survival:</p> <ul style="list-style-type: none"> - estimated 5-yr overall survival for the paclitaxel every 3wks group, 86.5% - estimated 5-yr overall survival for the weekly paclitaxel group, 89.7% - estimated 5-yr overall survival for the docetaxel every 3wks group, 87.3% - estimated 5-yr overall survival for the weekly docetaxel, 86.2% <p>Compared with those receiving paclitaxel every 3 wks, overall survival was significantly better in those with weekly paclitaxel (OR, 1.32, p=0.01, CI 1.02 to 1.72), NS difference with weekly docetaxel or those receiving docetaxel every 3 wks</p> <p>HER2: (analysis of hormone receptor status not prespecified when the study was initiated in 1999)</p> <p>Those with HER2 –ve disease who had weekly paclitaxel had improved disease-free survival (OR, 1.33, p=0.009, CI 1.07 to 1.64) and overall survival (OR, 1.34, p=0.03, CI 1.02 to 1.76). NS difference seen with other treatment groups</p> <p>Toxicity: Doxorubicin and cyclophosphamide, 40% had grade 2 toxic effects, 13% grade 3, 39% grade 4, percentages similar in the 4 treatment groups</p>

28% those in the weekly paclitaxel group had grade 3 or 4 toxic effects compared with 30% in those getting paclitaxel every 3 wks (NS difference), 71% of those receiving docetaxel every 3 wks ($p < 0.001$) and 45% with weekly docetaxel ($p < 0.001$)

Docetaxel every 3 wks had a 46% neutropenia rate (4% or less with the other groups)

Grade 2, 3 or 4 neuropathy were 20% (paclitaxel 3 wks), 27% (paclitaxel weekly), 16% (docetaxel 3wks), 16% (docetaxel weekly); incidence with weekly paclitaxel significantly higher when compared with the other groups ($p < 0.001$ for each comparison)

General comments

The end point differs from the end point of disease-free survival used in other trials of paclitaxel sponsored by the National Cancer Institute

Power analysis completed

All those who underwent randomisation were included in efficacy analysis, all treated patients were included in AE analysis regardless of eligibility

Citation

Bria et al (2008) Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomised trials. Breast Cancer Research treatment 109:231-239

Design

Design: meta-analysis

Country: Italy

1

Inclusion criteria

All phase III prospective and randomised trials published as full papers in peer-reviewed journals or presented at the American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO), European Society for Medical Oncology (ESMO) or San Antonio Breast Cancer Symposium (SABCS) meetings until December 2006

Patients with HER2 overexpressing early breast cancer, after definitive surgery, were randomised to receive either chemotherapy (control) or chemotherapy and trastuzumab (experimental arm), regardless of the schedule of administration (weekly or 3-weekly), treatment duration or timing of chemotherapy (concomitant and/or following)

Exclusion criteria

Population

N=5 trials identified, including NSABP B-31, NCCTG N9831, HERA, BCIRG 006, FinHer, N=11,186 randomised patients. FinHer subsequently excluded due to short administration (9wks) trastuzumab given prior to chemotherapy and the small size of the trial
Interventions
All RCTs provided data for safety and efficacy end points, except FinHer and BCIRG 006 which did not report data concerning the number of brain metastases
Outcomes
<p>Safety end-point:</p> <ul style="list-style-type: none"> - the incidence of symptomatic cardiotoxicity, grade III-IV NYHA functional assessment - the incidence of non-symptomatic while significant (as defined in the trial) decline in L-FEV - the incidence of brain metastases, as first site of disease relapse <p>Efficacy end-point:</p> <ul style="list-style-type: none"> - disease-free survival event rate - distant-disease-free survival event rate - overall survival event rate
Follow up
Median follow-up ranged from 24 to 36 months
Results (all CI 95%)
<p>Safety end-point: Core analysis (N=4 trials, N=10,995 patients) Grade III-IV NYHA: Arms in which trastuzumab was given for 1yr showed a significantly increased risk of grade III-IV CHF in the trastuzumab arm; RR 7.05 (3.88 to 12.83), $p < 0.0001$. NS heterogeneity. Absolute difference (AD) 1.62% which gives a NNH of 62</p> <p>Asymptomatic L-FEV reduction: A significantly increased risk of L-FEV reduction was found in the trastuzumab arm; RR 2.18 (1.45 to 3.27), $p < 0.00015$. These studies had significant heterogeneity ($p = 0.00008$), AD 7.20% which gives a NNH of 14</p> <p>Incidence of brain metastases: Incidence as first site of relapse was significantly higher in the trastuzumab arm; RR 1.57 (1.03 to 2.37), $p = 0.033$. NS heterogeneity. AD 0.62% which gives a NNH of 161</p> <p>(Overall population (N=5 trials, N=11,186 patients) showed increased risk in the trastuzumab arm for grade III-IV CHF of 1.43% and for asymptomatic L-FEV of 5.95%, these were significantly biased by heterogeneity)</p>
<p>Efficacy end-point: Core analysis (N=4 trials, N=9,974) Disease-free survival:</p>

Significantly prolonged in the trastuzumab arm; RR 0.63 (0.51 to 0.77), $p=0.00001$.
Significant heterogeneity $p=0.038$. AD 6.0% which gives a NNT of 16

Distant disease-free survival:

Significantly prolonged in the trastuzumab arm; RR 0.61 (0.54 to 0.70), $p=0.00001$. NS
heterogeneity. AD 4.8% which gives a NNT of 21

Overall survival:

Significantly prolonged in the trastuzumab arm; RR 0.66 (0.55 to 0.78), $p<0.00001$. NS
heterogeneity. AD 1.96% which gives a NNT of 51

(Overall population (N=5 trials, N=11,186 patients) showed increases of 6.10% (disease-free
survival), 5% (distant disease-free survival) and 2% (overall survival), these were significantly
biased by heterogeneity)

General comments

All data were reviewed and separately computed by two different independent investigators

Cardiotoxicity was reported consistently in the trials using toxicity grading III-IV according to
NYHA. The definition of an asymptomatic decline in L-FEV differed, defined as a decline of
10% in some trials and 15% in others.

Author's discussion: the risk for developing brain metastases was significantly higher for
those receiving trastuzumab, but overall low with >160 patients treated to see one event (how
much as these 'confounded' by the advantage in gained deaths from trastuzumab? How
many of the dead in the control arms would have developed brain metastases?)

Citation
De Laurentiis et al (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials
Design
Meta-analysis 1++
Inclusion criteria
Inclusion: early breast cancer, adjuvant therapy, randomised trial comparing a taxane-anthracycline-based regimen with an anthracycline-based regimen
Exclusion criteria
Exclusion: if the retrieved paper was an earlier report of data updated in a subsequent article, abstract or presentation; if a taxane was used in substitution (not addition to) an anthracycline
Population
N=13 studies used in pooled analysis, N=22,903 patients N=7 studies docetaxel, N=13,001 patients N=6 studies paclitaxel, N=9,902 patients
Interventions
A meta-analysis of randomised trials to address questions about the efficacy of adjuvant taxane-based therapy, particularly in relevant subgroups of EBC patients
Outcomes
Main outcomes <ul style="list-style-type: none"> • Overall survival • Disease-free survival (DFS events included second primary breast cancers, local or distant recurrences of the original cancer, or death – unless otherwise specified)
Follow up
Results (all CI 95%)
Risk of recurrence (disease-free survival) DFS for N=13 studies, N=5,829 events Single-study HR ranged from 0.63 to 0.97, were statistically significant in N=7 studies (n=4 paclitaxel, N=3 docetaxel) The reduction of risk of recurrence was significant in those receiving taxane-based therapy: <ul style="list-style-type: none"> - paclitaxel; HR: 0.80 (0.74 to 0.86), p<0.00001 (fixed effect); HR: 0.80 (0.74 to 0.86), p<0.00001 (random effect) - docetaxel; HR: 0.86 (0.80 to 0.92), p<0.00001 (fixed effect); HR: 0.86 (0.80 to 0.92), p<0.00001 (random effect) - total for taxanes; HR: 0.83 (0.79 to 0.87), p<0.00001 (fixed effect); HR 0.83 (0.79 to 0.88), p<0.00001 (random effect)

There was no evidence of heterogeneity among trials, or publication bias. Sensitivity analysis shows that DFS was significantly improved even when the meta-analysis was restricted to trials of taxanes in combination regimens, or sequential regimens, or to studies of node-positive patients only

Risk of death (overall survival)

N

Citation
Bria et al (2008) Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomised trials. Breast Cancer Research treatment 109:231-239
Design
Design: meta-analysis Country: Italy 1
Inclusion criteria
All phase III prospective and randomised trials published as full papers in peer-reviewed journals or presented at the American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO), European Society for Medical Oncology (ESMO) or San Antonio Breast Cancer Symposium (SABCS) meetings until December 2006 Patients with HER2 overexpressing early breast cancer, after definitive surgery, were randomised to receive either chemotherapy (control) or chemotherapy and trastuzumab (experimental arm), regardless of the schedule of administration (weekly or 3-weekly), treatment duration or timing of chemotherapy (concomitant and/or following)
Exclusion criteria
Population
N=5 trials identified, including NSABP B-31, NCCTG N9831, HERA, BCIFG 006, FinHer, N=11,186 randomised patients. FinHer subsequently excluded due to short administration (9wks) trastuzumab given prior to chemotherapy and the small size of the trial
Interventions
All RCTs provided data for safety and efficacy end points, except FinHer and BCIRG 006 which did not report data concerning the number of brain metastases
Outcomes
Safety end-point: - the incidence of symptomatic cardiotoxicity, grade III-IV NYHA functional assessment - the incidence of non-symptomatic while significant (as defined in the trial) decline in L-FEV - the incidence of brain metastases, as first site of disease relapse

Efficacy end-point:

- disease-free survival event rate
- distant-disease-free survival event rate
- overall survival event rate

Follow up

Median follow-up ranged from 24 to 36 months

Results (all CI 95%)

Safety end-point:

Core analysis (N=4 trials, N=10,995 patients)

Grade III-IV NYHA:

Arms in which trastuzumab was given for 1yr showed a significantly increased risk of grade III-IV CHF in the trastuzumab arm; RR 7.05 (3.88 to 12.83), $p < 0.0001$. NS heterogeneity. Absolute difference (AD) 1.62% which gives a NNH of 62

Asymptomatic L-FEV reduction:

A significantly increased risk of L-FEV reduction was found in the trastuzumab arm; RR 2.18 (1.45 to 3.27), $p < 0.00015$. These studies had significant heterogeneity ($p = 0.00008$), AD 7.20% which gives a NNH of 14

Incidence of brain metastases:

Incidence as first site of relapse was significantly higher in the trastuzumab arm; RR 1.57 (1.03 to 2.37), $p = 0.033$. NS heterogeneity. AD 0.62% which gives a NNH of 161

(Overall population (N=5 trials, N=11,186 patients) showed increased risk in the trastuzumab arm for grade III-IV CHF of 1.43% and for asymptomatic L-FEV of 5.95%, these were significantly biased by heterogeneity)

Efficacy end-point:

Core analysis (N=4 trials, N=9,974)

Disease-free survival:

Significantly prolonged in the trastuzumab arm; RR 0.63 (0.51 to 0.77), $p = 0.00001$. Significant heterogeneity $p = 0.038$. AD 6.0% which gives a NNT of 16

Distant disease-free survival:

Significantly prolonged in the trastuzumab arm; RR 0.61 (0.54 to 0.70), $p = 0.00001$. NS heterogeneity. AD 4.8% which gives a NNT of 21

Overall survival:

Significantly prolonged in the trastuzumab arm; RR 0.66 (0.55 to 0.78), $p < 0.00001$. NS heterogeneity. AD 1.96% which gives a NNT of 51

(Overall population (N=5 trials, N=11,186 patients) showed increases of 6.10% (disease-free survival), 5% (distant disease-free survival) and 2% (overall survival), these were significantly biased by heterogeneity)

General comments

All data were reviewed and separately computed by two different independent investigators

Cardiotoxicity was reported consistently in the trials using toxicity grading III-IV according to NYHA. The definition of an asymptomatic decline in L-FEV differed, defined as a decline of 10% in some trials and 15% in others.

Author's discussion: the risk for developing brain metastases was significantly higher for those receiving trastuzumab, but overall low with >160 patients treated to see one event (how much as these 'confounded' by the advantage in gained deaths from trastuzumab? How many of the dead in the control arms would have developed brain metastases?)

=12 studies, N=22,379 patients, N=3,329 deaths

Single-study HR ranged from 0.41 to 1.03, were statistically significant in N=4 studies (N=2 paclitaxel, N=2 docetaxel)

There was a reduction in the risk of death were significant for those receiving taxane-based therapy:

- paclitaxel; HR: 0.83 (0.75 to 0.92), $p=0.0004$ (fixed effect); HR: 0.81 (0.70 to 0.94), $p=0.005$ (random effect)
- docetaxel; HR: 0.87 (0.79 to 0.95), $p=0.003$ (fixed effect); HR: 0.84 (0.73 to 0.96), $p=0.010$ (random effect)
- total for taxanes; HR: 0.85 (0.79 to 0.91), $p<0.00001$ (fixed effect); 0.83 (0.76 to 0.91), $p=0.0001$ (random effect)

There was no statistical heterogeneity among studies or evidence of publication bias

Sensitivity analysis shows that overall survival was not significantly improved when the meta-analysis was restricted to studies of combination regimens

Subgroups

Oestrogen receptor (ER+ve vs. ER-ve)

N=10 studies, N=17,324 patients

Taxanes significantly reduced the risk of recurrence for both ER-positive and ER-negative

There was no statistically significant difference between the HRs in the two patient subgroups, this was independent of whether paclitaxel or docetaxel was administered

- ER+ve; HR: 0.83 (0.76 to 0.89), $p<0.00001$ (fixed effect)
- ER-ve; HR: 0.79 (0.72 to 0.86), $p<0.00001$ (fixed effect)
- total; HR: 0.81 (0.76 to 0.86), $p<0.00001$ (fixed effect)

Nodal status (N1 to 3 vs. N4+)

N=4 studies, N=6,170 patients

The pooled HR for DFS was similar for patients with one to three positive lymph nodes and for those with four or more positive lymph nodes

- N1-3; HR: 0.71 (0.61 to 0.84), $p<0.0001$ (fixed effect)
- $N\geq 4$; HR: 0.75 (0.66 to 0.87), $p=0.0001$ (fixed effect)
- total; HR: 0.74 (0.66 to 0.82), $p<0.00001$ (fixed effect)

Age (≤ 50 vs. >50 years)

N=3 studies

<p>Menopausal status (pre vs. post) N=2 studies As postmenopausal status usually arises around the age of 50yrs, the groups were analysed together Taxanes showed a significant risk reduction for both ≤50 yrs/premenopausal and >50yrs/postmenopausal - ≤50 yrs/premenopausal; HR: 0.85 (0.76 to 0.96), p=0.006 (fixed effect) - >50yrs/postmenopausal; HR: 0.75 (0.67 to 0.87), p<0.00001 (fixed effect) - total; HR: 0.80 (0.74 to 0.87), p<0.00001 (fixed effect)</p> <p>HER-2 expression N=2 studies There was no interaction between HER-2 expression and taxane administration in terms of reduction of risk of recurrence</p>
<p>General comments</p> <p>Computerised search of PubMed (yrs 2000 to 2006) using the words; breast cancer and (paclitaxel or docetaxel); computerised search of appropriate abstracts and presentations; all review articles and cross-referenced manuscripts were screened from pertinent studies</p> <p>Data were independently extracted by two individuals who were blinded to each other. After review and comparison instances of disagreement were resolved by consultation</p> <p>All trials were based on the ITT principle, 95% CIs were calculated for each point estimate. Sensitivity analysis completed</p> <p>HR were extracted from relevant trials and performed a meta-analysis which aimed to: give the best estimate of the relative reduction of risk of recurrence and death; give the best estimate of the magnitude of benefit in terms of the risk of recurrence and death; verify whether or not such benefits remain consistent across some relevant subgroups of patients</p>
<p>Citation</p>
<p>Kummel et al (2006) Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer</p>
<p>Design</p>
<p>Multicentre, randomised, open-label Phase 3 1+</p>
<p>Inclusion criteria</p>
<p>Inclusion: primary resected, histologically confirmed breast cancer, stage I, II or III, surgical procedures performed ≤15days before randomisation (included R0 resection and axillary extirpation), patients had ≥4 positive axillary lymph nodes, no distant metastases, an Eastern Cooperative Oncology Group (ECOG) performance status <2, adequate organ function, no previous chemotherapy or radiotherapy</p>

Ag 26 to 72yrs (mean age 53yrs), 60% post-menopausal
Exclusion criteria
Exclusion: leucocytes or platelets below specified levels (one patient with an ECOG performance status of 3 was admitted to the study in violation of the protocol, this patient was included in the analysis)
Population
N=231 (N=116 top dose-dense and N=115 to a conventional schedule) 30 centres in Germany between July 1996 and December 2000
Interventions
Evaluates a dose-dense sequential chemotherapy regimen administered after mastectomy or breast-conserving surgery Dose-dense (DD): - epirubicin 90mg/m ² plus paclitaxel 175mg/m ² in four 14-day cycles, then CMF (600/40/600) in three 21-day cycles (plus filgrastim if required) Conventional schedule (CS): - epirubicin 90mg/m ² plus cyclophosphamide 600mg/m ² in four 21-day cycles, then CMF (600/40/600) in three 21-day cycles (plus filgrastim if required)
Outcomes
Primary end point <ul style="list-style-type: none"> • Rate of disease-free survival Secondary end point <ul style="list-style-type: none"> • Overall survival in the two groups • Incidence of chemotherapy postponement or dose reduction • Safety and tolerability of the regimen
Follow up
Patients were followed for up to 5yrs after inclusion in the study with regularly scheduled visits
Results (all CI 95%)
N=15 excluded due to ineligibility (N=8 DD and N=7 conventional) N=4 discontinued in the each group Disease-free survival At a median follow-up of 38.4mths N=71 (33%) experienced a first event of relapse or death; N=33 events (31%) in the DD group and N=38 events (35%) in the CS group After 2yrs DFS was 81% (74-89%) in the DD group and 72% (64-81%) in the CS group After 4yrs DFS was 64% (55-76%) in the DD group and 58% (48-70%) in the CS group

The most common site of disease relapse was bone metastasis (31% of cases)

Overall survival

At a median follow-up of 38.4mths N=37/216 (17%) had died; N=15 (14%) in the DD group and N=22 (20%) in the CS group

After 2yrs OS was 94% (89-99%) in the DD group and 92% (87-97%) in the CS group
After 4yrs OS was 85% (78-94%) in the DD group and 75% (66-85%) in the CS group

Feasibility

96% of patients in both groups received all 7 cycles of chemotherapy
Doses were reduced in N=14/1477 evaluable cycles (1%)

Safety and tolerability

Rate of discontinuation (4%) the same in both groups; N=2 (2%) DD group and N=1 (1%) CS group discontinued because of toxicity (included acute hypersensitivity reaction, febrile neutropenia, fatigue); N=3 (N=1 DD group, N=2 CS group) discontinued for other reasons (withdrawal of consent, uncontrolled diabetes, infection of a breast wound)

Haematological toxicity: leukopenia and neutropenia occurred in both treatment groups at similar rates; grade 3 leukopenia (DD group N=40, 37%; CS group N=46, 43%), grade 4 leukopenia (DD group N=8, 7%; CS group N=6, 6%), grade 3 neutropenia (DD group N=26, 34%; CS group N=23, 28%), grade 4 neutropenia (DD group N=22, 29%; CS group N=30, 37%)

Nonhaematologic toxicity:

Events that occurred more in the DD group than the CS group include peripheral nervous system toxicity (47 vs. 11%), bone pain (44 vs. 23%) and arthralgia/myalgia (22 vs. 15%)
Cardiotoxicity; grade 3, N=1 in the CS group, N=0 in the DD group; grade 4 cardiotoxicity experienced by no patients

General comments

Patients were randomised in permuted blocks, stratified by centre, using a computer-generated randomisation list

The trial was designed to detect a difference of 15% in the primary end point of DFS after 5yrs, with a risk of type-1 error of 5% (one-sided) and a power of approx 80% based on a sample size of 121 patients

Citation

Piedbois et al (2007) Dose-dense adjuvant chemotherapy in node-positive breast cancer: docetaxel followed by epirubiin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomised phase II study. Annals of Oncology

Design

Design: RCT Country: France 1+
Inclusion criteria
Female, >18yrs, Eastern Cooperative Oncology Group performance status 0-1, with histologically proven invasive breast adenocarcinoma, R0 resection of their tumour within 60days before randomisation and at least one histologically positive axillary lymph node among at least 6 resected nodes, adequate biological functions (blood counts, liver function, cardiac function) Study enrollment; 12 th December 2003 to 30 th September 2004 There were no evident imbalances in baseline characteristics
Exclusion criteria
T4, N2-3 or M1 stage, bilateral, second or inflammatory breast cancer, lymph node involvement determined by immunohistochemistry alone, ductal carcinoma in situ (DCIS), aminotransferases >1.5xUNL concomitant with ALP>2.5xUNL, sensory neuropathy of grade >2, prior history of cancer within 10yrs (except basal skin carcinoma or cervical CIS, lobular CIS or ipsilateral DCIS of the breast), previous or concomitant anticancer therapy including radiation and hormone therapy
Population
N=100 (Arm A, N=35; Arm B, N=31; Arm C, N=34), 12 th December 2003 to 30 th September 2004
Interventions
Primary objective: to select a dose-dense regimen for further assessment in phase III studies Secondary objective: a preliminary assessment of efficacy Used two sequential dose-dense regimens (EC→T and T→EC) to select one of them as the experimental arm of further phase III studies, a control arm of a 3-drug regimen with conventional doses intervals was used Arm A (TEC, docetaxel 75mg/m ² , epirubicin 75mg/m ² , cyclophosphamide 500mg/m ² , every 3wks for 6 cycles) Arm B (EC→T, epirubicin 100mg/m ² , cyclophosphamide 600mg/m ² every 2wks for 4 cycles, followed by docetaxel 100mg/m ² every 2wks for 4 cycles) Arm C (T→EC, the reverse sequence for EC→T)
Outcomes
Incidence of grade 4 toxicity Efficacy end points (OS and DFS) were only exploratory
Follow up
Results
The median number of examined nodes was 12 (range 4-24), median number of

pathologically involved nodes was 2 (range 1-20)

Grade 4 toxicity:

N=27 had grade 4 toxicity

- N=9 (26%) arm A

- N=12 (40%) arm B

- N=6 (18%) arm C

N=26/27 also had grade 4 neutropenia

- febrile neutropenia:

N=4 (arm A), N=3 (arm B), N=1 (arm C), despite G-CSF prophylaxis in N=7/8

- other:

N=2 fatigue, N=1 thrombocytopenia, N=1 nausea

Other:

Dose-dense regimens reported nail disorders, hand-foot syndrome, peripheral neuropathy and fluid retention of any grade and more grade 3 or 4 events (73% arm B and 68% arm C) compared with TEC (46%)

Overall incidence and grade 3-4 incidence showed no clear difference between the dose-dense regimens

Neutropenia and mucositis occurred more frequently with EC→T than with T→EC

One patient in arm B experienced grade 3 congestive heart failure with LVEF of 35 %

Drop outs/incomplete treatment:

N=5 patients prematurely discontinued study treatment due to toxicity:

- arm A, N=1 febrile neutropenia with grade 4 asthenia and vomiting (after 4th cycle of TEC)

- arm B, N=1 congestive heart failure (after 4th EC cycle), N=2 grade 3 peripheral neuropathy and nail disorder (N=1 at docetaxel cycle 1 and N=1 at cycle 3)

- arm C, N=1 withdrew with grade 3 hand-foot syndrome associated with nail and ocular toxicity after 3rd docetaxel cycle

- N=4 patients (N=1 arm A, N=2 arm B, N=1 arm C) refused to complete their treatment

- no toxic death occurred

Exposure to treatment

N=1 arm B did not receive treatment

N=2 (6%) TEC (arm A) did not receive the 6 planned cycles

N=5 (17%) arm B and N=3 (8%) arm C did not receive the 8 planned cycles

N=2 arm B didn't receive docetaxel, N=2 arm C didn't receive EC

N=4 (11%) TEC arm had at least one cycle delayed by >7days, compared with N=16 (53%) in the EC→T arm and N=13 (38%) in the T→EC arm

N=6 (17%) TEC arm had at least one dose reduction, compared with N=11 (37%) in the EC→T arm and N=11 (32%) in the T→EC arm

General comments

Toxicity was graded according to National Cancer Institute of Canada Common Toxicity Criteria version 3

N=33 patients per arm were considered necessary to correctly reject a toxic treatment (with >50% grade 4) and correctly accept a nontoxic treatment (with <25% grade 4) with a probability of 90%

If <11 grade 4 toxic events occurred, the treatment was to be considered tolerable; if >13 grade 4 toxic events occurred, the study was not conclusive

Trial was not powered to detect differences between treatment arms

A dose of pegfilgrastim was recommended in all patients on day 2 after each chemotherapy cycle, treatment could be resumed only when biological parameters returned to normal

Citation
Ferguson et al 2007 – Taxanes for adjuvant treatment of early breast cancer. Cochrane Database of Systematic Reviews
Design
Systematic review, meta-analysis 1++
Inclusion criteria
Unconfounded RCTs Comparison of taxane (paclitaxel or docetaxel) containing adjuvant chemotherapy regimens with adjuvant regimens not containing a taxane in the management of women with operable early breast cancer
Exclusion criteria
Women who received neoadjuvant chemotherapy
Population
N=21,191 (N=12 included studies, N=5 paclitaxel, N=7 docetaxel)
Types of participants
women of any age with histologically confirmed operable breast cancer
Interventions
Any chemotherapy regimen that contained a taxane, compared with any chemotherapy regimen without a taxane: <ul style="list-style-type: none">• Taxane containing regimen vs. the same regimen without a taxane• Any taxane containing regimen vs. any regimen without a taxane• Any taxane containing regimen vs. the same regimen with another drug or drugs that were substituted for the taxane• Endocrine therapy was allowed if the same treatment was given to all groups
Outcomes

Primary outcome

- Overall survival

Secondary outcome

- Disease-free survival

post-hoc analysis

- Type of taxane
- Longer or same duration of chemotherapy
- Node positive only or node positive and negative
- Sequential or concurrent anthracycline and taxane
- Less than 4 or more cycles of taxane

Toxicity data

Quality of life

Follow up

Median follow-up ranged from 36mths to 60mths

Weighted average mean follow-up 60.4mths

Results (all CI 95%)**Overall survival**

N=18,304 (N=11 studies)

N=2483 deaths

Hazard Ratio (HR) taxane containing regimens vs. non-taxane containing regimens: 0.81 (0.75 to 0.88), $p < 0.00001$

NS heterogeneity across trials

Disease-free survival

N=19,943 (N=11 studies)

N=4800 events reported

Taxane containing group vs. controls, HR: 0.81 (0.77 to 0.86), $p < 0.00001$

NS heterogeneity across studies

Type of Taxane

Docetaxel N=7 studies

Pacitaxel N=5 studies

Overall survival:

- docetaxel N=9377, HR: 0.76 (0.67 to 0.86), $p < 0.0001$

- pacitaxel N=8927, HR: 0.85 (0.76 to 0.94), $p < 0.001$

Disease-free survival

- docetaxel N=12,264, HR: 0.80 (0.74 to 0.87), $p < 0.00001$

- pacitaxel N=7679, HR: 0.82 (0.76 to 0.89), $p < 0.00001$

Sequential or concurrent taxane and anthracycline

Overall survival:

N=12,004 (N=7 studies; 4 paclitaxel, 3 docetaxel) taxane and anthracycline administered sequentially

Taxane vs. sequential anthracycline, HR: 0.82 (0.75 to 0.90), p<0.0001

N=5284 (N=3 studies) taxane and anthracycline concurrently in the experimental arm

Taxane and anthracycline vs. non-experimental arm, HR: 0.79 (0.66 to 0.94), p=0.007

Disease-free survival:

N=10,756 (N=6 studies; 3 paclitaxel, 3 docetaxel) taxane and anthracycline administered sequentially

Taxane vs. sequential anthracycline, HR: 0.81 (0.76 to 0.88), p<0.00001

N=5284 (N=3 studies) taxane and anthracycline concurrently in the experimental arm

Taxane and anthracycline vs. non-experimental arm, HR: 0.79 (0.70 to 0.90), p=0.0003

Lymph node status

(variations in inclusion criteria between the studies may have impacted on the risk of recurrence)

Overall survival:

N=11,890, N=1903 deaths (N=6 studies; 3 paclitaxel, 3 docetaxel) required positive axillary node metastasis for eligibility

HR, favouring taxane: 0.81 (0.74 to 0.89), p<0.00001

N=6414, N=580 deaths (N=5 studies; 2 paclitaxel, 3 docetaxel) allowed inclusion of those without lymph node metastases

HR, favouring taxane: 0.81 (0.75 to 0.88), p<0.01

Disease-free survival:

N=13,529, N=3761 events (N=6 studies; 2 paclitaxel, 4 docetaxel) required positive axillary node metastasis for eligibility

HR, favouring taxane: 0.81 (0.76 to 0.87), p<0.00001

N=6414, N=580 events (N=5 studies; 2 paclitaxel, 3 docetaxel) allowed inclusion of those without lymph node metastases

HR, favouring taxane: 0.80 (0.71 to 0.91), p=0.0004

Addition of a taxane/substitution of a taxane

Overall survival:

N=8651 (N=5 studies; 4 paclitaxel, 1 docetaxel) experimental arm, taxane in addition to control chemotherapy

HR, favouring taxane: 0.84 (0.76 to 0.93), p<0.0008

N=9653 (N=6 studies) experimental arm, taxane substituted for one or more of the drugs in the control group

HR, favouring taxane: 0.76 (0.67 to 0.87), p<0.0001

Disease-free survival:

N=8651 (N=5 studies; 4 paclitaxel, 1 docetaxel) experimental arm, taxane in addition to control chemotherapy

HR, favouring taxane: 0.82 (0.76 to 0.89), $p < 0.00001$

N=8405 (N=5 studies; all docetaxel) experimental arm, taxane substituted for one or more of the drugs in the control group

HR, favouring taxane: 0.78 (0.71 to 0.86), $p < 0.0001$

Duration of chemotherapy

Overall survival:

N=7747 (N=4 studies; 3 paclitaxel, 1 docetaxel) taxane containing experimental arm of longer duration than the control arm

HR, favouring taxane: 0.85 (0.77 to 0.94), $p = 0.002$

N=10,557 (N=7 studies; 2 paclitaxel, 5 docetaxel) taxane containing experimental arm and control arm of the same duration

HR, favouring taxane: 0.76 (0.67 to 0.86), $p < 0.0001$

Disease-free survival:

N=7747 (N=4 studies; 3 paclitaxel, 1 docetaxel) taxane containing experimental arm of longer duration than the control arm

HR, favouring taxane: 0.83 (0.77 to 0.94), $p < 0.00001$

N=9309 (N=6 studies; 1 paclitaxel, 5 docetaxel) taxane containing experimental arm and control arm of the same duration

HR, favouring taxane: 0.77 (0.70 to 0.8), $p < 0.0001$

Number of cycles of taxane containing chemotherapy

Overall survival:

N=3604 (N=3 studies; 1 paclitaxel, 2 docetaxel) 3 cycles of taxane in the experimental arm

HR, favouring taxane: 0.74 (0.61 to 0.91), $p = 0.004$

N=13,452 (N=7 studies; 3 paclitaxel, 4 docetaxel) 4 or more cycles of taxane in the experimental arm

HR, favouring taxane: 0.83 (0.76 to 0.90), $p < 0.0001$

Disease-free survival:

N=3604 (N=3 studies; 1 paclitaxel, 2 docetaxel) 3 cycles of taxane in the experimental arm

HR, favouring taxane: 0.79 (0.68 to 0.91), $p = 0.001$

N=13,452 (N=7 studies; 3 paclitaxel, 4 docetaxel) 4 or more cycles of taxane in the experimental arm

HR, favouring taxane: 0.81 (0.75 to 0.87), $p < 0.00001$

Toxicity

(there was heterogeneity between studies with the use of different control chemotherapies and varying doses and scheduling of the taxane drug)

N=10/12 provided data on toxicity

Cardiotoxicity:

N=6 studies: NS difference in the risk of developing cardiotoxicity between taxane containing

and non-taxane containing regimens

Febrile neutropenia:

N=7 studies: an increase in febrile neutropenia in the taxane containing arms: OR 2.51 (1.11 to 5.66), the risk was highest where the taxane was administered concurrently with an anthracycline: OR 6.80 (1.91 to 24.15) rather than sequentially (significant heterogeneity between the studies, chi-square=145, df=6, p<0.00001)

Nausea:

N=5 studies (grade 3 or 4 and/or vomiting): lower risk for those treated with a taxane: OR 0.55 (0.39 to 0.77)

Fatigue:

N=4 studies (grade 3 or 4 fatigue): NS increase in taxane containing regimens

Stomatitis:

N=5 studies (grade 3 or 4): no increase in taxane containing regimens

Other toxicities:

Grade 3 or 4 myalgia or arthralgia reported in N=3 studies, incidence low, more frequent in taxane containing arms (2% vs. 0.3%; 1% vs. <1%; 1.3% vs. 0.3%)

Nail changes in N=3 studies, more frequent in taxane containing arms (0.4% vs. 0.1%, 55% vs. 10%, 10.3% vs. 1%)

Grade 3 or 4 allergy reported in N=3 studies, more frequent in those receiving taxanes (3.7% vs. 0.3%, 1.3% vs. 0.1%, 2.2% vs. 0%)

Grade 3 or 4 oedema was an infrequent event

Neurotoxicity was inconsistently reported

Secondary malignancy

N=7 studies (3 paclitaxel, 4 docetaxel) reported N=48 cases of secondary leukaemia or myelodysplasia – N=25 taxane containing regimens, N=23 control regimens, NS difference between the groups (NS heterogeneity)

Treatment-related deaths

N=6 studies (3 paclitaxel, 3 docetaxel) reported N=14 treatment-related deaths, N=7 taxane containing regimens, N=7 control regimens, NS difference between the groups (NS heterogeneity)

Quality of life

N=2 studies, one study (docetaxel) showed a transient reduction in both treatment arms, the reduction was greater in the taxane containing regimen, the second study (paclitaxel) showed no difference in QoL scores between the two treatment arms

General comments

Search methods – Cochrane Breast Cancer Group Specialised Register searched between

August 2005 to January 2007, hand search included abstracts published from 1995 to 2006 for presentations at the American Society of Clinical Oncology Annual Scientific meeting and the San Antonio Breast Cancer Symposium

Selection criteria were applied to each trial publication or abstract independently by the two review authors who were masked to the study title, authors and results. Two review authors independently assessed each potential eligible trial for inclusion in the review, quality and analysis

All included studies had a time-to-event primary outcome, treatment groups were balanced in most studies, all seven full publications described ITT analysis, overall study quality was considered to be high

No studies were blinded to treatment, not considered to bias results as outcomes were uniformly measured by time to event and were not subject to observer or patient bias in interpretation

Citation
Ward et al (2007) Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. Health Technology Assessment
Design
Systematic review of RCTs 1++
Inclusion criteria
Women who have had surgery for early-stage breast cancer (stages I, II and IIIa)
Exclusion criteria
Neoadjuvant therapy, advanced-stage breast cancer, where the comparator is not anthracycline-containing chemotherapy, taxanes in both/all study arms
Population
Women who have had surgery for early-stage breast cancer (stages I, II and IIIa) Subgroups: age, nodal status, ER+ vs. ER- and PR+ vs. PR-; HER2 positivity prognostic status
Interventions
Any docetaxel and paclitaxel clinically and cost effective compared with non-taxane-containing chemotherapy regimens including anthracycline agent, for the adjuvant treatment of women with early stage breast cancer <ul style="list-style-type: none">• Sequential paclitaxel therapy (paclitaxel following anthracycline therapy) vs. anthracycline-based non-taxane therapy• Combination docetaxel therapy vs. anthracycline-based non-taxane therapy

Outcomes
<ul style="list-style-type: none"> • Overall survival (defined as the hazard of death from any cause after a given follow-up period, or time from randomisation to death from any cause) • Disease-free survival (defined as the hazard of disease recurrence, second cancer or death from any cause after a given follow-up period, or time from randomisation to first of these events) • Local and distant recurrence (contralateral breast cancer, distant recurrence or local/regional recurrence) • Adverse events (AEs)/toxicity (any reported, however defined) • Health-related quality of life (HRQoL) (measured using any validated HRQoL instrument)
Follow up
Median follow-up for studies ranged from 43 to 69 months
Results (all CI 95%)
<p>Overall survival</p> <p><i>Docetaxel</i> HR 0.69 (0.52 to 0.90), significant improvement with DAC6 compared with FAC6 (BCIRG 001) Improvement for FEC3-D3 compared with FEC6 which had a 4% lower survival rate (PAC 01) NS difference: DC4 and AC4 (USO 9735), DA4 and AC4 (ECOG), USO 9735 reported deaths from breast cancer at 36mths, docetaxel group had N=17 (3.4%) from breast cancer, control group N=15 (2.9%) – no other studies reported deaths from breast cancer</p> <p><i>Paclitaxel</i> HR 0.82 (0.71 to 0.95), significant improvement with AC4-P4 vs. AC4 (CALGB 9344) 3% higher survival rate for E3-P3-CMF4 vs. E4-CMF4 (HCOG) NS difference: PA4-CMF4 and A4-CMF4(ECTO), AC4-P4 and AC4(NSABP B28), FEC4-P4 and FEC6 (GEICAM 9906)</p> <p>Disease-free survival</p> <p><i>Docetaxel</i> Significantly better for: - DAC6 vs. FAC6; HR: 0.71 (0.58 to 0.87), p<0.001 (BCIRG 001) - DC4 vs. AC4; HR: 0.67 (0.50 to 0.94), p=0.015 (USO 9735) - FEC3-D3 vs. FEC3; HR: 0.83 (0.69 to 0.99), p=0.041 (PAC 01) A3-D3-CMF3 vs. A4-CMF3 (sequential docetaxel); HR: 0.79 (0.64 to 0.98), p=0.035 (BIG 2-98) NS difference: DA4 and AC4 (ECOG), DA4-CMF3 and A4-CMF3 (concurrent docetaxel, BIG 2-98), E4-D4-CMF4 and E4-CMF4 (Taxit 216)</p>

Paclitaxel

Significant improvement AC4-P4 vs. AC4, with a 4% lower rate (NSABP B28)
FEC4-P8 vs. FEC6; HR: 0.63, p=0.0008 (GEICAM 9906)
NS difference: E3-P3-CMF3 and E4-CMF4 (HCOG)

TTR (time to relapse or recurrence – check?) was reported in 2 paclitaxel studies:
significantly improved for AC4-P4 vs. AC4; HR: 0.83 (0.73 to 0.94) and NS difference for DA4
and AC4 (ECOG)

FFP (freedom from progression – check?) was reported in 1 paclitaxel study: significantly
improved for PA4-CMF4 vs. A4-CMF4; HR 0.65 (ECTO)

Locoregional or distant recurrence or contralateral breast cancer

Docetaxel

- DAC6 vs. FAC6 (BCIRG 001) – NS for locoregional recurrence, distant recurrence and contralateral recurrence
- FEC3-D3 vs. FEC6 (PACS 01) – NS difference locoregional recurrence and contralateral recurrence; for distant recurrence FEC3-D3 vs. FEC6, 17.7% vs. 21.8%, p=0.023

Paclitaxel

- AC4-P4 vs. AC4 (NSABP B28) – NS for locoregional recurrence and distant recurrence; for contralateral recurrence AC4-P4 vs. AC4, 1.1% vs. 1.9%, p=0.039
- E3-P3-CMF3 vs. E4-CMF4 – NS difference contralateral recurrence

Disease-free survival – subgroup analysis

Docetaxel

Nodal status

- DAC6 vs. FAC6 (BCIRG 001), 1-3nodes, HR 0.61 (0.46 to 0.82), 4+ nodes NS difference
- FEC3-D3 vs. FEC6 (PACS 01), 1-3nodes, HR 0.76 (0.58 to 1.00), 4+ nodes NS difference
- DC4 vs. AC4 (USO 9735), N+ve, HR 0.67 (0.45 to 0.98), N-ve NS difference

Hormone receptor status

- DAC6 vs. FAC6 (BCIRG 001), HR+ 0.72 (0.56 to 0.92), HR- 0.69 (0.49 to 0.97)
- DA4 vs. AC4 (ECOG 2197), ER-PR+, HR 0.30 (0.10 to 0.95), all other HR status NS difference
- DC4 vs. AC4 (USO 9735), NS difference

HER2 status

- DAC6 vs. FAC6 (BCIRG 001), HER2+ HR 0.60 (0.41 to 0.88); HER2- HR 0.76 (0.59 to 1.00); HER2 unknown, NS difference

Disease-free survival by menopausal status or age

- DAC6 vs. FAC6 (BCIRG 001), premenopausal HR 0.66 (0.50 to 0.86), post menopausal NS difference
- FEC3-D3 vs. FEC6 (PACS 01), aged 50+yrs, HR 0.67 (0.51 to 0.88), aged <50yrs NS difference
- DC4 vs. AC4 (USO 9735), aged 50+yrs and aged <50yrs, NS difference
- DA4 and AC4 (ECOG), NS difference according to age or menopausal status

Paclitaxel

Nodal status

- FEC4-P8 vs. FEC6 (GEICAM 9906), $\geq 4+$ nodes significant benefit, 1-3 nodes NS difference

Hormone receptor status

- AC4-P4 vs. AC4 (NSABP B28), HR+(ER+ and/or PR+), relative RR 0.77 (0.65 to 0.92), $p=0.004$; HR-, NS difference

- FEC4-P8 vs. FEC6 (GEICAM 9906), significant improvement for both HR+ and HR- subgroups

- E3-P3-CMF4 vs. E4-CMF4 (HCOG) stated that the treatment effect on the hazard of disease progression was not different according to hormonal receptor status

HER2 status

- FEC4-P8 vs. FEC6 (GEICAM 9906), significant improvement for both HER2 -ve to 2+, and also for HER2 3+

Disease-free survival by menopausal status

- FEC4-P8 vs. FEC6 (GEICAM 9906), significant improvement for post menopausal; pre menopausal NS difference

Time to recurrence

- AC4-P4 vs. AC4 (CALGB 9344), significant improvement for HR- (unplanned analysis)

Adverse events

Treatment-related deaths

Treatment-related deaths ranged from 0 to 0.4% (excluding the DA4 vs. AC4, RAPP 01 trial). Overall deaths from toxicity in the taxane-containing arms (N=17/8829), compared with the control arms (N=11/8819); neutropenia caused N=3 deaths in those taking docetaxel, hypersensitivity reaction to paclitaxel caused one death

Docetaxel

- Febrile neutropenia/neutropenic fever;

Docetaxel associated with significantly more: DAC6 vs. FAC6 (BCIRG 001), FEC3-D3 vs. FEC6 (PACS 01), DC4 and AC4 (USO 9735), DE6 vs. FEC6 (PACS 04) – although there was less low-grade neutropenia in the docetaxel groups in BCIRG 001 and PACS 01).

- Nausea and vomitin or high-grade nausea/vomiting;

Docetaxel associated with significantly less: DAC6 vs. FAC6 (BCIRG 001), FEC3-D3 vs. FEC6 (PACS 01), DC4 and AC4 (USO 9735), DA4 vs. AC4 (RAPP 01), DE6 vs. FEC6 (PACS 04)

- Stomatitis;

Docetaxel associated with significantly more: DAC6 vs. FAC6 (BCIRG 001), FEC3-D3 vs. FEC6 (PACS 01)

- Mucositis or high-grade mucositis;

Docetaxel associated with significantly more: DAC6 without G-CSF vs. FAC6 (GEICAM

9805), DA4 vs. AC4 (RAPP 01)

- Diarrhoea or high-grade diarrhoea

Docetaxel associated with significantly more: DAC6 vs. FAC6 (BCIRG 001), DAC6 without G-CSF vs. FAC6 (GEICAM 9805), DA4 vs. AC4 (RAPP 01)

- Other

- Significantly more neurosensory effects, significantly more mild to severe congestive heart failure more prevalent nail disorders, significantly more skin toxicity, significantly more chemotherapy-related amenorrhoea, significantly more arthralgia, myalgia or asthenia, more common oedema, significantly more allergy, infection and grade 3/4 severe non-haematological AEs - DAC6 vs. FAC6 (BCIRG 001)
- Significantly less cardiotoxicity, oedema more common, FEC3-D3 vs. FEC6 (PACS 01)
- Significantly more chemotherapy-related amenorrhoea, DA4 vs. AC4 (RAPP 01)
- Significantly more arthralgia, myalgia or asthenia, DC4 and AC4 (USO 9735), DAC6 without G-CSF vs. FAC6 (GEICAM 9805)
- Oedema more common, more total serious AEs, DA4 vs. AC4 (RAPP 01)

Paclitaxel

Few significant values were reported for AEs in the paclitaxel trials;

- Significantly more peripheral neuropathy and hypersensitivity reaction, older patients (65yrs+) had significantly higher rate of severe toxicities, E3-P3-CMF4 vs. E4-CMF4 (HCOG)

Health related QOL

Docetaxel

- DAC6 vs. FAC6 (BCIRG 001), balanced at baseline, worsened during treatment , (significantly larger decline with DAC6 on Global Health Status and Physical Functioning), NS difference between the groups with both recovering by 3-4wks after last cycle of treatment
- FEC4-D4 vs. FEC8 vs. E4-CMF4 (TACT) global QoL significantly worse (p=0.002), NS vs. E4-CMF4
- DAC6 without G-CSF vs. FAC6 (GEICAM 9805) significantly worse QoL score (p=0.008), NS difference for DAC6 with G-CSF vs. FAC

Paclitaxel

- E3-P3-CMF4 vs. E4-CMF4 (HCOG), NS difference at baseline or at the end of chemotherapy (comparison of baseline and end of chemotherapy identified - social functioning significantly worsened in the paclitaxel group, p=0.003; only the control group showed significant improvement in emotional functioning (p=0.031) and pain (p=0.007)

General comments

MEDLINE, EMBASE, CINAHL, BIOSIS, CDSR, CCTR, DARE, NHS EED, HTA, NRR, the Current Controlled Trials register, US NIH website ClinicalTrials.gov, systematic review were hand searched, searches were not restricted by language, date or publication type. Searches conducted between October 2005 and February 2006

Study selection was made by one reviewer, with involvement of a second reviewer when necessary

With one exception, all studies were Phase 3, multi-centre RCTs

None of the trials were blinded (authors note that this would be difficult for patients and clinicians however, there was no indication that outcome assessors were blinded)

Randomisation was reported and adequate in 3 docetaxel and 3 paclitaxel trials

Allocation concealment was reported and adequate in 1 docetaxel and 2 paclitaxel trials

There was a high rate of compliance with therapy and few withdrawals reported

ITT or analyses including 80% or more of the randomized population were available in all trials reporting effectiveness data

Subgroups were based on small sample size

Heterogeneity of interventions, comparators and populations precluded meta-analysis

One docetaxel (BCIRG 001) and two paclitaxel trials (CALGB 9344, Elling Phase 2) used taxanes in accordance with current UK marketing authorisation

Two additional paclitaxel trials (NSABP B28, GEICAM 9906) used paclitaxel in line with the licensed regimen but at different dose and/or frequency from those recommended in marketing authorisation.

Comparators used by most of the trials restrict the generalisability of results as they do not conform to current standards of care in the UK, either through too few cycles of chemotherapy or using doxorubicin instead of the more widely employed epirubicin

Only one trial GEICAM 9906 (FEC4-P8 vs. FEC6) could be said to have an adequate comparator for UK practice and be broadly in line with UK marketing authorisation

Health Economic Summary

Full Summary

The volume of economic evidence found since the publication of technology assessments 108 and 109 on taxanes for early breast cancer (EBC) is limited. Only 37 references were obtained from the review of the literature and of these only two were full economic evaluations. A further study published after the search was carried out was identified and included in the review. A summary table of the economic evaluations is presented in

Table 2 below. A full description of all these studies has been presented in the accompanying document containing the health economic evidence tables. Only the indirect comparison and subsequent analysis by Ward et al (2007) addressed the question of the cost-effectiveness of taxanes against UK relevant comparators. This seems to be mainly due to the lack of clinical evidence of the effectiveness of taxanes against standard UK clinical practice.

The question addressed by Limwattananon et al (2006) is similar to the analysis presented in the technology assessment on paclitaxel (TA 108) except that it was carried out in a Thai health care setting. A Markov model was constructed to estimate the incremental cost per quality adjusted life year (QALY) of paclitaxel following anthracycline regimen doxorubicin, plus cyclophosphamide (AC) versus AC alone. The authors mention that the baseline data used to populate the model was taken from Randomised Controlled Trials although only the CALGB9344 trial is mentioned. The resource utilisation and unit cost costs reflect the Thai health care setting although the reporting of resource use is limited. The authors used the CALGB9344 trial even though it is not specific to the Thai health care setting. This was justified by the reliable estimates based on the large sample size and long-term follow up. The results of the analysis concluded that subsequent use of paclitaxel is not a cost effective option according to the WHO criterion for cost effectiveness (approximate incremental cost effectiveness ratio (ICER) of 304,800 Bhat) at an ICER of 738,111 Bhat per QALY. The results of the sensitivity analysis showed that the cost effectiveness results were sensitive to changes in the relative efficacy and unit price of paclitaxel.

Ward et al (2007) was a full clinical and economic evaluation of docetaxel and paclitaxel for adjuvant treatment of EBC. Three analysis were undertaken: docetaxel, doxorubicin and cyclophosphamide (TAC) was compared with fluorouracil, doxorubicin and cyclophosphamide (FAC) based on the BCIRG 001 trial and paclitaxel following AC was compared with AC alone in two analyses based on the NSABP-B28 and CALGB9344 trials. The results of the analysis concluded that the ICER for the docetaxel containing regimen was £12,418 per QALY. The results for paclitaxel containing regimens were £39,332 based on the CALGB9344 trial and £42,672 based on the NSABP-B28 trial. This was a well conducted economic evaluation and all limitations were discussed by the authors. The extrapolation of data over time is a key issue. Restriction of the length of the analysis had a considerable effect on the ICER for both docetaxel and paclitaxel. An indirect comparison and a cost effectiveness analysis using the results of the indirect comparison were carried out by the authors. The authors state that the analysis showed considerable uncertainty in the benefits of taxane containing regimens when compared with standard regimens used in the UK.

Wolowacz et al (2008) was a full cost utility analysis examining the cost of effectiveness TAC compared with FAC based on the BCIRG 001 trial. The model in this study was used to support submissions to NICE and the SMC by the manufacturer of docetaxel. The results of the analysis concluded that the ICER was £18,188 when taking a 10 year timeframe into account. This was a well conducted economic evaluation and most of the limitations were discussed by the authors. The authors also considered the use of G-CSF as prophylaxis for febrile neutropenia which has been found to occur at a higher rate in the TAC regimen than the FAC regimen. When patients received lenograstim or filgrastim as primary prophylaxis the resulting ICER was £20,432 per QALY. If patients received pegfilgrastim the resulting ICER was £57,320. The extrapolation of disease free survival was tested in sensitivity analysis and this had the largest effect on the ICER.

Table 2: Summary of included economic evaluations (cost-utility analyses)

Summary Table of Economic Evaluations							
Study	Interventions	Quality	Applicability	Cost results (all 2005)	Effectiveness results	ICER (£/QALY)	Uncertainty
Limwattananon et al (2006)	AC* and AC->P	Minor limitations – incomplete reporting of data inputs.	Non UK data. Comparators not standard UK practice.	Incremental costs with paclitaxel 221,433 Baht.	Incremental QALYs with paclitaxel. 0.30 QALYs	Base case 738,111 Baht per QALY. Negative oestrogen receptor 393,984 Baht per QALY.	The ICER of paclitaxel varied considerably with changes in the relative efficacy and unit price of paclitaxel.
Ward et al (2007)	Docetaxel: TAC and FAC Paclitaxel: AC and AC->P	Minor limitations – mainly due to assumptions made in the absence of clinical data	Comparators are not standard UK practice, although an indirect comparison was carried out.	Incremental costs with docetaxel £6,961 Incremental costs with paclitaxel (CALGB 9344 study) £6,961 Incremental costs with paclitaxel (NSABP B28 study) £5,889	Incremental QALYs with docetaxel 0.56 QALYs Incremental QALYs with paclitaxel (based on CALGB 9344 study) 0.11 QALYs Incremental QALYs with paclitaxel (based on NSABP B28 study) 0.14 QALYs	Docetaxel base case £12,418 per QALY Paclitaxel base case (based on CALGB 9344 study) £39,332 per QALY Paclitaxel base case (based on NSABP B28 study) £42,672 per QALY	The ICER of docetaxel and paclitaxel varied considerably if risk of recurrence being the same in both arms is carried on beyond the time frame of the trial (from 5 to 10 years) Decreasing the annual rate of recurrence after the follow up period also had an effect on the cost effectiveness estimates.
Wolowacz et al (2008)	TAC and FAC	Minor limitations – mainly minor issues around the probabilistic analysis	Comparators are not standard UK practice.	Incremental costs with TAC £5,759	Incremental QALYs with TAC 0.317	Base case £18,188 per QALY Varying methods of extrapolation beyond trial follow up: Pooled loglogistic (common long-term risk) £28,782 Loglogistic (treatment specific long-term risk) £12,588 Natural history data (common long term risk) £20,483	Sensitivity analysis on the timeframe of the analysis. 5 year timeframe = £58,201/QALY 40 year timeframe = £9865/QALY. When patients received lenograstim or filgrastim as primary prophylaxis for febrile neutropenia the ICER was £20,432 per QALY. If pegfilgrastim was given as primary prophylaxis for febrile neutropenia the ICER was £57,320.

Table of regimens

Abbreviation	Regimen
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
FAC	5-Fluorouracil, Doxorubicin, Cyclophosphamide
AC	Doxorubicin, Cyclophosphamide
FEC	5-Fluorouracil, Epirubicin, Cyclophosphamide
E-CMF	Epirubicin, Cyclophosphamide, Methotrexate, Fluorouracil

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Ward, S. et al., Taxanes for the adjuvant treatment of Early Breast Cancer (EBC): systematic review and economic evaluation, 2007. *Health Technology Assessment*, 11(40): 1-144.

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Evidence Tables

Economic Evaluations

Paclitaxel

Limwattananon, S., et al., Cost effectiveness analysis of sequential paclitaxel adjuvant chemotherapy for patients with Node Positive primary breast cancer. J Med Assoc Thai 2006; 89 (5): 690-8.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model in DATA 3.5).

Clinical effectiveness:

Randomised Controlled Trials (RCTs) (CALGB9344) and published oncology literature, assumptions, estimates of utilities from a survey of oncology nurses.

Cost estimation:

Cost of adjuvant medication, cost of treatment for adverse drug events, routine follow up care, treatment for the disease recurrence, and care at the end of the patient's life. Direct health care costs only, taken from a third party payer perspective such as a health insurance scheme. Costs are from 2005 and reported in Thai Baht.

Country: Thailand, **setting:** Hospital

Inclusion criteria:

Premenopausal women with Early Breast Cancer (EBC) who had axillary lymph nodes positive

Exclusion criteria:

Not stated.

Population:

Women with EBC.

Interventions:

Paclitaxel for four cycles following completion of four cycles of anthracycline regimen, doxorubicin plus cyclophosphamide (AC) versus four cycles of AC alone.

Outcomes:

Quality adjusted life years (QALYs), Life Years (LYs), costs and incremental cost effectiveness ratios (ICERs)

Follow up:

Time horizon = 15 years

Data used to populate the model:

Assumptions:

- Disease free survival rates past 7 years were estimated using a linear trend extrapolation.
- The ratio of 1:9 was assumed to both treatment arms for dividing total relapse into localized and metastatic diseases.
- Annual risks of death when in localized and metastatic states were assumed to decline gradually over time.

Health states: no disease, localized disease, metastatic disease, and death.

Data from prospective studies:

Outcome of interest	Estimate
Rates of Disease Free Survival (DFS) in the control group	-
DFS at year 1	92%
DFS at year 2	81%
DFS at year 4	70%
DFS at year 5	65%
DFS at year 7	58%
Annual risk of initial relapse in paclitaxel arm – hazard ratio (HR)	0.83
Best clinical efficacy of paclitaxel in negative oestrogen subgroup for sensitivity analysis (HR)	0.72
Worst clinical efficacy of paclitaxel in negative oestrogen subgroup for sensitivity analysis (HR)	0.94
Disease progression from localised disease to metastatic (probabilities from year 6 onwards)	0.38
Disease progression from localised disease to death	0.08
Disease progression from metastatic disease to death	0.22

Utilities: estimated by surveying oncology nurses, further details are not given.

Health States	Utility
No disease	0.85
Localised disease	0.65
Metastatic disease	0.62
Death	0
Chemotherapy use	0.72
3 months of AC alone (using CT use utility)	0.8175
3 months of AC followed by 6 months of paclitaxel (using CT use utility)	0.785

Health care resource utilisation and costs: Details of the extraction of resource utilisation is not clear however, for adverse events and terminal stage cancer costs are available from the author on request. Chemotherapy regimens were elicited through a panel of oncology experts.

Unit costs	2005 Baht
AC	52,595
AC with Paclitaxel	277,531
Disease recurrence in the AC alone arm	549,878
Disease recurrence in the paclitaxel with AC arm	487,936
Treatment cost per event of febrile neutropenia	14,406
Incurred care at terminal stage of cancer	32,544
Follow up care for state of no disease and localised and metastatic disease (cost per year for years 1-3)	2,800
Follow up care for state of no disease and localised and metastatic disease (cost per year for years 4-15)	2,300

Results

Outcome of interest	AC	Paclitaxel with AC
15 year health care costs	134,892	356,325
Incremental cost	-	221,433
Overall survival rates	38.5%	54.0%
Life expectancy	10.14	10.61
QALYs	6.87	7.17
Incremental QALYs	-	0.3
Cost per QALY (not reported – calculated here)	19,635	49,697
Incremental cost effectiveness ratio (ICER)	-	738,111

Sensitivity analysis:

One way sensitivity analysis was carried on key uncertain parameters in the simulation model. The ICER of paclitaxel varied considerably with changes in the relative efficacy and unit price of paclitaxel. The results were robust to changes in the adverse event rates, treatment for recurrence, and cost of terminal care in this study.

When paclitaxel was assumed to reduce the disease relapse by 28% in women with negative estrogen receptors, the ICER was much lower than in the base case at 393,984 Baht per QALY. When the relative efficacy of paclitaxel was reduced to an HR of 0.94 the ICER rose to 2,426,246 Baht per QALY.

Authors' conclusions:

Overall, the additional benefit of subsequent use of paclitaxel on quality-adjusted life expectancy in all patients with axillary lymph node metastasis is not cost-effective according to the WHO criterion for cost effectiveness (approx ICER of 304,800 Bhat). The author's sensitivity analysis showed that in a subgroup of high-risk patients with estrogen receptor negative and axillary node metastasis, adjuvant paclitaxel comes close to the cost effectiveness threshold (393,984).

General comments:

There are some limitations regarding the source of clinical effectiveness data. Only the CALGB9344 trial is explicitly mentioned. There are also some limitations in the in the cost analysis due to lack of reporting the resource use required. The authors mentioned that there were no well designed trials examining paclitaxel in Thailand but that the trials used in the study provided reliable estimates based on the large sample size and long-term follow up. The impact of varying utility values was not examined in sensitivity analysis

Docetaxel

Wolowacz, S., et al., Docetaxel in combination with doxorubicin and cyclophosphamide as adjuvant treatment for early node positive breast cancer: a cost-effectiveness and cost-utility analysis. Journal of clinical oncology 2008; 26 (6): 925-933.

The model used in this publication was used to support submissions by the manufacturer of docetaxel to NICE and the SMC.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model software not specified). A decision tree

was also used to estimate the costs of adjuvant chemotherapy and QALYs lost as a consequence of adverse events.

Clinical effectiveness:

RCTs (BCIRG 001) and published oncology literature, assumptions, estimates of utilities were also taken from the BCIRG 001 trial and from published literature.

Cost estimation:

Cost of adjuvant chemotherapy and support, granulocyte colony-stimulating factor (G-CSF), adverse events, the costs of monitoring and care post-relapse were included. Costs were from 2005 and reported in GBP.

Country: UK, **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Women with node positive early breast cancer. Median age 49 years, 55% premenopausal, 76% oestrogen or progesterone receptor positive.

Interventions:

(docetaxel, doxorubicin and cyclophosphamide (TAC) versus Fluorouracil, doxorubicin and cyclophosphamide (FAC), both with and without primary prophylaxis with G-CSF.

Outcomes:

QALYs, Life Years (LYs), costs and ICERs

Follow up:

Time horizon = 10 years in the base case (up to 40 years in sensitivity analysis) with a cycle length of 1 month.

Data used to populate the model:

Assumptions:

- Survival modelling using data from the BCIRG 001 trial was performed to estimate probabilities of events beyond trial follow-up.
- The authors state that simple survival functions did not provide an accurate fit to the data therefore a partitioned function of superimposed loglogistic and exponential functions, after an event-free lag-period was used.
- Long-term disease free survival was dominated by an exponential function. The disease free survival curves merge beyond the trial end. This assumed that treatment effect does not continue in the long term.
- The extrapolation of disease free survival was tested in sensitivity analysis.
- Survival after relapse was estimated from patient level data in the BCIRG 001 trial.
- Probability of death from other causes was taken from national age specific mortality rates for women.

Health states: remission, locoregional recurrence, distant recurrence, and death.

Data from prospective studies:

Outcome of interest	Estimate
Survival postrelapse estimates (years)	-

-if first relapse is locoregional	2.49
-if first relapse is distant	1.59
Probability of receiving primary G-CSF prophylaxis (TAC)	0.070
Probability of receiving primary G-CSF prophylaxis (FAC)	0.077
Incidence of febrile neutropenia for TAC	0.367
Incidence of febrile neutropenia for FAC	0.087
Probability of discontinuing chemotherapy because of adverse events (TAC)	0.060
Probability of discontinuing chemotherapy because of adverse events (FAC)	0.011

Utilities: The estimate of utility for remission was taken from data collected during the BCIRG 001 trial which was converted into utilities using a published algorithm. Other utilities were taken from the published literature:

Health States	Utility
Remission	0.79
First locoregional recurrence, under treatment	0.70
First locoregional recurrence, after treatment (assumed equivalent to remission)	0.79
Second locoregional recurrence	0.50
Third locoregional recurrence	0.50
Distant disease	0.50
Terminal illness	0.50

Health care resource utilisation and costs: Details of drug usage was taken from the BCIRG 001 trial. Other resource use estimations were taken from the published literature and expert opinion. Full details of costs and resource use were presented.

Unit costs	2005 £
Total cost per cycle of TAC plus administration	1247
Total cost per cycle of FAC plus administration	214
Monitoring for patients in remission	732
Hospital care costs postrelapse (first relapse is locoregional)	14,137
Hospital care costs postrelapse (first relapse is distant)	13,576
Primary care costs postrelapse (cost per month)	
-stable distant disease	310
-early progressive disease	310
-late progressive disease	487
-terminal illness	692

Results

Outcome of interest	FAC	TAC
Mean total costs	£9828	£15,587
Incremental cost	-	£5759
Overall survival rates with no disease recurrence	50.3	56.2

Mean life years	6.821	7.194
Incremental life years	-	0.374
Incremental cost per life year gained	-	£15,418
QALYs	5.201	5.517
Incremental QALYs	-	0.317
Incremental cost per QALY	-	£18,188

Sensitivity analysis:

- Probabilistic sensitivity analysis was carried out. Only key model parameters were assigned distributions.
- It seems that only the mean incremental cost per QALY and per LYG with 95% confidence limits are presented (£18,247 per QALY, CI: £14,161 to £32,422).
- Results of the sensitivity analysis were that varying the timeframe of the analysis had the biggest impact on the ICER. A 5 year timeframe resulted in an ICER of £58,201 per QALY and a 40 year timeframe resulted in an ICER of £9865 per QALY.
- The extrapolation of disease free survival was tested in sensitivity analysis. The results were as follows:

Method of extraction beyond trial follow up	ICER
Pooled loglogistic (common long-term risk)	£28,782
Loglogistic (treatment specific long-term risk)	£12,588
Natural history data (common long term risk)	£20,483

- When patients received lenograstim or filgrastim as primary prophylaxis for febrile neutropenia the resulting ICER was £20,432 per QALY. If pegfilgrastim was given as primary prophylaxis for febrile neutropenia the resulting ICER was £57,320.
- Subgroup analysis suggested that TAC may be more cost effective in patients who are younger, oestrogen-receptor-negative and who have fewer positive nodes and lower tumour grades.

Authors' conclusions:

Overall, the authors conclude that adjuvant TAC is cost effective compared with FAC in the UK. The authors state that although FAC is rarely used in the UK it could be considered a reasonable surrogate for FEC (the most common regimen in the UK) and studies in the metastatic setting have also shown equivalence between the two regimens. The authors also conclude that TAC supported by primary G-CSF prophylaxis is also cost effective.

General comments:

This was a well conducted study. It would have been useful to see the results of the probabilistic analysis diagrammatically or by the conventional method of probability of cost effectiveness at various willingness to pay thresholds. The authors also conclude that TAC supported by primary G-CSF prophylaxis is also cost effective, however, it may be reasonable to suggest that this would only be cost effective if lenograstim or filgrastim were used but not pegfilgrastim.

Docetaxel and paclitaxel

Ward, S. et al., Taxanes for the adjuvant treatment of EBC: systematic review and economic evaluation, 2007. Health Technology Assessment, 11(40): 1-144.

Note that only the cost effectiveness section of this paper is reviewed here (see clinical evidence tables for review of the clinical effectiveness study).

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. probabilistic state-transition model).

Clinical effectiveness:

RCTs (BCIRG 001, NSABP-B28 and CALGB9344), assumptions, published literature, estimates of utilities from published sources.

Cost estimation:

Cost of medication, costs of diagnosis and treatment of recurrence/contralateral disease, cost of remission, cost of treatment of distant recurrence, routine follow up care, care at the end of the patient's life and cost of treatment for adverse drug events. Direct medical costs only, taken from the UK health service perspective. All costs were adjusted to 2005-6 and reported in GBP.

Country: UK, **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Women with EBC eligible to receive anthracycline based chemotherapy with or without taxanes.

Interventions:

BCIRG001 trial – six 3-weekly cycles of DAC (docetaxel, doxorubicin and cyclophosphamide), with six 3-weekly cycles of FAC (Fluorouracil, doxorubicin and cyclophosphamide).

NSABP B28 and CALGB 9344 – both trials compare four 3-weekly cycles of AC (doxorubicin and cyclophosphamide) followed by four 3-weekly cycles of P (paclitaxel) with four 3-weekly cycles of AC alone.

Outcomes:

QALYs, costs and ICERs

Follow up:

Time horizon = 35 years

Data used to populate the model:

Assumptions: (see pages 35&36 of the report for a full explanation and justification of the assumptions)

- The hazard ratio for recurrence during the duration of the trial period was assumed to be constant.
- In the base-case analysis, the risk of recurrence was assumed equal in the taxane and comparator arms after the trial period.
- Long-term risk of recurrence was extrapolated from the available trial data using a parametric survival model.
- Following contralateral disease or locoregional relapse, patients cannot experience further

locoregional relapse, they can only experience metastatic relapse.

- The survival of patients who relapse was assumed to be independent of the time of relapse.
- The survival of patients with metastatic relapse was equivalent to that of patients who are initially diagnosed with metastatic disease (i.e. patients who have not previously received adjuvant chemotherapy for early disease).
- Patients who had experienced an episode of EBC but are in remission after 15 years are assumed to be cured.
- Death from breast cancer could only occur in the metastatic state.
- Death rates for non-breast cancer causes were based on UK mortality statistics and applied across all health states.

Health states: Disease-free survival (DFS), contralateral disease, locoregional relapse, metastatic relapse, remission, death from breast cancer and death from other causes.

Data from RCTs:

Outcome of interest*	Estimate
HR for DFS	0.71
Relative risk (RR) from Cox proportional hazards model	0.82
HR for recurrence	0.83
Annual probability of metastatic disease in patients with locoregional or contralateral recurrence	-
Year 1	0.18
Year 2	0.19
Year 3	0.12
Year 4	0.09
Year 5 and beyond	0.12
Annual probability of death in patients with metastatic disease	0.37

*Type of recurrence in each arm (i.e. Local, Contralateral or Distant for taxanes and comparators) was also reported, for full details of all key clinical parameters from trials used in the economic evaluation see Appendix AA5 of the study.

Utilities: From published literature, full details given in table 34 of the study.

Health States	Utility
Chemotherapy treatment	0.74
Disease-free	0.94
Contralateral	0.74
Locoregional recurrence	0.74
Distant metastases	0.5
Remission (following contralateral recurrence and locoregional recurrence)	0.85

Health care resource utilisation and costs: All health care resource utilisation and costs were presented in detail (see tables 26-33 of the study).

Unit costs	2005-6 GBP
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BCIRG 001 – FAC	1343.04
BCIRG 001 – DAC	7450.80
NSABP B28 – AC	1267.68
NSABP B28 – AC+P	7102.08
CALGB 9344 – AC	1267.68
CALGB 9344 – AC+P	5755.68
Average for hormonal therapy assuming 50% receive tamoxifen and 50% receive Aromatase inhibitors	525.83
Total cost of diagnosis of locoregional recurrence or contralateral disease	830.77
Average cost of surgery for locoregional recurrence or contralateral disease	2811
Neutropenia – Total initial cost to manage event	2155
Neutropenia – Total cost per subsequent cycle =	1067

Results

Cost per QALY for docetaxel based on BCIRG 100 study

Outcome of interest	DAC	FAC	Incremental
Cost of adjuvant chemotherapy (£)	8,516	2,254	6,262
Cost of AEs (£)	2,396	465	1,932
Cost of recurrence and death from breast cancer (£)	12,778	14,011	-1,233
Total cost (£)	23,690	16,730	6,961
QALYs	8.36	7.80	0.56
Cost per QALY (£)			12,418

Cost per QALY for paclitaxel based on CALGB 9344 study

Outcome of interest	AC+P	AC	Incremental
Cost of adjuvant chemotherapy (£)	7,609	1,860	5,749
Cost of AEs (£)	257	215	42
Cost of recurrence and death from breast cancer (£)	13,472	14,820	-1,349
Total cost (£)	21,337	16,896	4,442
QALYs	8.35	8.24	0.11
Cost per QALY (£)			39,332

Cost per QALY for paclitaxel based on NSABP B28 study

Outcome of interest	AC+P	AC	Incremental
Cost of adjuvant chemotherapy (£)	8,973	1,860	7,113
Cost of AEs (£)	257	215	42
Cost of recurrence and death from breast cancer (£)	12,080	13,345	-1,265
Total costs (£)	21,310	15,421	5,889
QALYs	9.05	8.91	0.14

Cost per QALY (£)			42,672
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Sensitivity analysis:

- Results of the univariate sensitivity analysis were that varying utility values, costs of recurrence, costs of managing febrile neutropenia, duration of routine follow up, costs of treating metastatic disease had a minimal impact on the ICER.
- If the assumption that the trial based risk of recurrence is the same in both arms is carried on beyond the time frame of the trial (from 5 to 10 years) this lowered the ICERs to below £15,000 in all three analyses and therefore had a substantial effect on the cost effectiveness estimates. Decreasing the annual rate of recurrence after the follow up period also had a substantial effect on the cost effectiveness estimates.
- Results of the probabilistic analyses for docetaxel showed that with a cost-effectiveness threshold of £30,000 docetaxel has around 95% probability of being cost-effective when compared with non-taxane chemotherapy.
- Results of the probabilistic analysis for paclitaxel showed that with a cost effectiveness threshold of £30,000 paclitaxel containing regimens have around 30–40% probability of being cost-effective when compared with non-taxane chemotherapy.

Authors' conclusions:

Overall, the cost effectiveness of taxane containing chemotherapy regimens compared with non-taxane containing regimens varied depending on the taxane under consideration and the specific trial used to inform the analysis.

General comments:

The limitations of this study are addressed in the discussion. The length of the analysis in particular is mentioned as a key issue. Further long term clinical data is required in order to be able to address this issue. The issue of the comparators was also discussed. The trials available contained regimens which are not considered standard practice in the UK. This therefore restricts the generalisability of the results. An indirect comparison and a cost effectiveness analysis using the results of the indirect comparison were carried out by the authors. This analysis showed considerable uncertainty in the benefits of taxane containing regimens when compared with standard regimens used in the UK.

5.5 Update of Technology Appraisal 107 – Trastuzumab for the Adjuvant Treatment of Early Stage HER2- Positive Breast Cancer

Short Summary

Two papers reporting from the HERA trial (Herceptin Adjuvant) trial (Smith *et al* 2007, Suter *et al* 2007), one joint-analysis of the NSABP B-31 trial, National Surgical Adjuvant Breast and Bowel project) B-31 trial and the NCCTG N9831 trial, (North Central Cancer Treatment Group) trial (Romond *et al* 2005), two papers which considered cardiac dysfunction in the NSABP B-31 (Tan-Chiu *et al* 2005) and NCCTG N9831 (Perez *et al* 2008), a meta-analysis of cardiotoxicity and brain metastases with adjuvant trastuzumab (Bria *et al* 2008), a paper from the FinHer trial (Joensuu *et al* 2006) and an abstract from the E2198 trial (Budzar *et al* 2007) were identified which considered the adjuvant treatment of early breast cancer with trastuzumab. One small trial (Budzar *et al* 2007) was identified which considered the primary systemic treatment of early breast cancer with trastuzumab.

Sequential chemotherapy:

The HERA trial results at 1-year follow-up were included in the TA (NICE 2006a), the 2-year follow-up of those who received 1-year treatment with trastuzumab showed improved overall survival and distant recurrence event-free survival benefit for trastuzumab compared with the control group (Smith *et al* 2007). A further study considered the trastuzumab-associated cardiac adverse events from HERA, this identified a higher incidence of cardiac end points (severe congestive heart failure (CHF), symptomatic CHF and confirmed left ventricular ejection fraction (LVEF) drop) in the trastuzumab group compared with the control group.

Concurrent chemotherapy:

The joint analysis of the NSABP B-31 and NCCTG N9831 trials identified improved disease-free survival, overall survival and distant metastases as a first distant recurrence with trastuzumab compared with the control group. Cardiac dysfunction in the NSABP B-31 identified a higher relative risk of a cardiac event with trastuzumab compared with control, with no significant difference between the groups in the cumulative incidence of cardiac events (Tan-Chiu *et al* 2005).

Meta-analysis:

A safety and efficacy meta-analysis identified an increased risk of grade III-IV CHF, asymptomatic LVEF and brain metastases with trastuzumab compared with controls, along with prolonged disease-free survival, prolonged distant disease-free survival and prolonged overall survival with trastuzumab (Bria *et al* 2008).

Shorter duration:

The FinHer trial showed improvements in recurrence (or died without recurrence) and distant recurrence for the trastuzumab arm (9 week duration) compared with the control group. There was no significant difference between the groups for overall survival or in adverse events (Joensuu *et al* 2006).

The E2198 trial¹⁴ did not identify a significant advantage for prolonged trastuzumab administration (10 weeks compared with 52 weeks).

Primary Systemic Therapy

One small study identified improved disease-free survival with primary systemic 24-week chemotherapy and trastuzumab regimen compared with chemotherapy alone (Budzar *et al* 2007).

PICO

Patient	Intervention	Comparison	Outcomes
Patients with early-stage HER2 positive breast cancer prior to and following intital surgery	Trastuzumab as treatment for breast cancer either alone, in sequence with or in combination with cytotoxic chemotherapy, given for 12 months according to the locensed indications.	Regimens including trastuzumab with different doses and duration. Regimens with and without trastuzumab.	<ul style="list-style-type: none"> • Disease-free survival • Overall survival • Contralateral breast cancer • Quality of life • Adverse events (notably cardiac function changes) • Drug interactions • Cost effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Sequential chemotherapy

HERA trial

The HERA trial, an RCT, compared 1 or 2 years of trastuzumab treatment (8mg/kg trastuzumab IV 90min infusion as a loading dose followed by 6mg/kg every 3 weeks for a year, or 2 years), with observation alone after standard chemotherapy in women with HER-2 positive node positive or high-risk node negative breast cancer. The results from this study at 1-year follow-up were included in the technology appraisal, this showed 87.1% in the control arm and 92.5% in the trastuzumab arm free from disease at 1 year follow-up (equating to a 46% relative reduction in risk of recurrence)

(<http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11586>).

Overall survival was 97.6% (control arm) and 98.2% (trastuzumab) equating to a 24% relative reduction in mortality. The incidence of serious cardiac adverse events was 0.6% with trastuzumab and 0.1% in the control arm. The 2-year trastuzumab group remains blinded as the comparison of 1-year versus 2-years of trastuzumab is continuing to be monitored by the independent data monitoring committee (Untch et al 2008).

¹⁴ Not designed or powered to test the question of trastuzumab duration

2-year follow-up

Smith et al (2007) reported on a 2-year follow-up of the HERA trial of those with confirmed HER2-positive and included N=1698 in the observation group and N=1703 who received 1-year treatment with trastuzumab, with a median follow-up of 23.5 months.

Overall survival: there were N=149 deaths in the two groups, N=59/1703 in the trastuzumab group vs. N=90/1698 (5%) in the observation group, unadjusted HR 0.66 (0.45 to 0.87), $p=0.0115$.

Distant metastases: N=152/1703 (9%) trastuzumab group vs. N=233/1698 (14%), HR for time to distant recurrence 0.60 (0.49 to 0.73), $p<0.0001$. This corresponds to an absolute time to distant recurrence event-free survival benefit of 6.3% at 3 years (85.7% vs. 79.4%), $p<0.0001$.

Adverse events: N=190/1668 (11%) trastuzumab group vs. N=88/1442 (6%) observation group had one or more grade 3 or 4 adverse events, $p<0.0001$. One or more serious adverse events were N=156 (9%) with trastuzumab vs. N=97 (7%) with observation, $p=0.0103$. Fatal adverse events (N=9, 0.5% trastuzumab vs. N=3, 0.2% observation) were NS between the groups.

Trastuzumab-associated cardiac adverse events

Suter et al (2007) considered the trastuzumab-associated cardiac adverse effects with data available for N=1693 assigned to 1-year of trastuzumab and N=1693 assigned to observation.

Cardiac end points: the incidence of cardiac end points was significantly higher in the trastuzumab group vs. the observation group for; severe CHF (0.60% vs. 0%, CI for difference in incidence 0.20% to 0.99%), for symptomatic CHF (2.15% vs. 0.12%, CI for difference in incidence 1.29% to 2.77%) and for confirmed LVEF drop (3.04% vs. 0.53%, CI for difference in incidence 1.59% to 3.43%).

Recovery after a cardiac end point: of those with severe CHF N=6/10 recovered their LVEF in a median of 124 days (range 36 to 409 days), for the N=24/36 of those with symptomatic CHF it was 151 days (range 26 to 831 days) and for the N=35/51 with confirmed significant LVEF drop it was 191 days (range 13 to 831 days).

Subgroups

Untch et al (2008) considered the effect of trastuzumab within the patient subgroups defined by nodal and steroid hormone receptor status using the data included in the Smith et al (2007) analysis from the HERA trial. This analysis identified that for the relative risk reduction estimates for the overall cohort and for the subgroups results indicate consistent reductions in the risk of relapse, at 23.5 months median follow-up.

Concurrent chemotherapy

NSABP B-31 and NCCTG N9831 trials Joint analysis

A joint analysis was completed of two trials the NSABP B-31 and the NCCTG N9831¹⁵. These trials considered participants randomly assigned to 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel or the same regimen followed by 52 weeks of trastuzumab beginning on day 1 of the paclitaxel treatment (Romond et al 2005). In both studies trastuzumab began with a loading dose of 4mg/kg, followed by weekly doses of 2mg/kg for 51 weeks. N=1736/2043 in the B-31 trial had at least one follow-up evaluation, N=1615/1633 in the groups used in this analysis of N9831 had follow-up data.

Disease-free survival: HR for first event for trastuzumab vs. control was 0.48 (0.39 to 0.59), $p < 0.0001$. 87.1% of the trastuzumab group compared with 75.4% of the control group were alive and disease-free at 3 years, an absolute percentage point difference of 11.8 (8.1 to 15.4); at 4 years this was 85.3% for trastuzumab and 67.1% for the control group, an absolute percentage point difference of 18.2 (12.7 to 23.7).

Overall survival: there were N=62 deaths in the trastuzumab group compared with N=92 in the control group, HR 0.67 (0.48 to 0.93), $p = 0.015$. Absolute survival at 3 years was 94.3% with trastuzumab and 91.7% in the control arm, an absolute difference of 2.5 percentage points (0.1 to 5.0); at 4 years this was 91.4% for trastuzumab and 86.6% with control, an absolute difference of 4.8 percentage points (0.6 to 9.0)

Distant metastases: reported in N=96 trastuzumab group compared with N=193 control group, HR for a first distant recurrence 0.47 (0.37 to 0.61), $p < 0.0001$. At 3 years 90.4% trastuzumab group compared with 81.5% control group were free of distant recurrence, an absolute difference of 8.8 percentage points (5.5 to 12.1); at 4 years this was 89.7% trastuzumab compared with 73.7% control group, an absolute difference of 15.9 percentage points (11.1 to 20.8)

Brain metastases: the incidence of isolated brain metastases as first event was N=21 with trastuzumab vs. N=11 with control (NSABP B-31) and N=12 with trastuzumab vs. N=4 with control (NCCTG N9831). Further analysis in the NSABP B-31 trial identified the difference in brain metastases as first events as attributed to earlier failures at other distant sites in the control group.

Adverse cardiac events: in the NSABP B-31 trial the cumulative incidence of congestive heart failure or death from cardiac causes was N=31 (4.1%) with CHF in the trastuzumab group and N=5 (0.8%) in the control group (N=4 with CHF, N=1 death from cardiac causes). In the N9831 trial the 3-year cumulative incidence of congestive heart failure or death from cardiac causes was 2.9% in the trastuzumab group (N=20 had CHF and N=1 died of cardiomyopathy) and 0% in the control group.

¹⁶

¹⁵ This study included a further group which considered trastuzumab administered after completion of chemotherapy, this group was excluded from this joint analysis

¹⁶ Cases of interstitial pneumonitis were reported that in some cases appeared to be related to trastuzumab, N=4 in B-31 and N=5 in N9831

Cardiac dysfunction

The assessment of cardiac dysfunction in the NSABP B-31 trial was reported with N=1664 in the trastuzumab group and N=814 in the observation group analysed (Tan-Chiu et al 2005).

Cumulative incidence of cardiac events: 3 years after day 1 of cycle 5 was 4.1% (2.9% to 5.8%) with trastuzumab compared with 0.8% (0.3% to 1.9%) for control, NS difference between the groups. The RR of a cardiac event for trastuzumab compared with the control 5.9 (2.3 to 15.3), $p < 0.0001$

Recovery of cardiac function: N=26/27 of those followed for more than 6 months were without symptoms (N=18 using cardiac medications).

The cardiac safety of the NCCTG N9831 trial was reported for N=1,944 who had satisfactory or no LVEF evaluation who proceeded to post-AC therapy (Perez et al 2008), this included the arm of the trial with sequential trastuzumab administration which was excluded from the combined NSABP B-31 and NCCTG N9831 analysis (Romond et al 2005).

Clinically significant cardiac events in those who proceeded post-AC therapy: for the control group cumulative incidence at 1-year (0.0%), 2-year (0.2%) and 3-year (0.3%); for the sequential trastuzumab group cumulative incidence at 1-year (1.6%), 2-year (2.7%) and 3-year (2.8%); for the concurrent trastuzumab group cumulative incidence at 1-year (3.3%), at 2-year (3.3%) and 3-year (3.3%).

Risk factors for cardiac events: in those receiving trastuzumab univariate analysis identified factors associated with an increased risk of a cardiac event within 3-years of starting a trastuzumab-containing regimen included; age ≥ 60 years ($p = 0.003$), prior/current use of antihypertensive medication ($p = 0.005$), and registration LVEF less than 55% but above lower limit of normal ($p = 0.033$). BMI and post-AC LVEF level were NS.

Shorter duration treatment

FinHer trial

The FinHer trial, a multicentre open-label RCT, compared docetaxel with vinorelbine for the adjuvant treatment of early breast cancer, women (N=232) with tumours that overexpressed HER2/neu were also randomised to receive concomitant treatment with trastuzumab or without trastuzumab (Joensuu et al 2006). The N=116 who received trastuzumab had nine infusions at 1-week intervals, the first infusion was given on day 1 of the first docetaxel or vinorelbine cycle (the docetaxel/vinorelbine was followed by FEC, no trastuzumab was given during FEC administration). The first dose of trastuzumab was 4mg/kg, subsequent doses were 2mg/kg, the full dose of trastuzumab was administered in 99.1% of cycles.

Recurrence or died without recurrence: N=12/115 trastuzumab vs. N=27/116 in the control group, HR 0.42 (0.21 to 0.83), $p = 0.01$ (this HR remained similar when adjustment was made according to type of chemotherapy, centre, and number of positive nodes).

Distant recurrence: N=8/115 trastuzumab vs. N=26/116 control, HR 0.29 (0.13 to 0.64), $p = 0.002$.

Overall survival: N=6/115 trastuzumab vs. N=14/116 died, NS difference between the groups.

Adverse events: trastuzumab did not significantly increase the frequency of adverse events related to vinorelbine or docetaxel. LVEF were preserved in women who received trastuzumab, N=4 trastuzumab and N=7 control had one or more measurements of ejection fraction more than 15 percentage points less than pretreatment value (a decrease by more

than 10 percentage points, resulting in an ejection fraction of less than 50% occurred in N=3 none of whom had trastuzumab).

E2198 trial

The E2198 is an adjuvant RCT looking at cardiac safety endpoints, this used two arms, the short duration arm included paclitaxel followed by weekly trastuzumab for 10 weeks (loading dose 4mg/kg followed by doses of 2mg/kg), plus doxorubicin plus cyclophosphamide (AC), the long duration arm had the same regimen followed by trastuzumab for a further 52 weeks (dose 2mg/kg), this study is currently only published in abstract form (Sledge et al 2006). N=234 HER-2 positive participants were randomised between the treatments. This study was designed to consider a primary end point of evaluating the rate of clinical CHF with these treatments. The authors concluded that although this study was not designed or powered to test the question of trastuzumab duration, a significant advantage (disease-free survival or overall survival) for prolonged trastuzumab administration was not observed in E2198.

Meta-analysis

The included meta-analysis included phase III prospective and randomised trials and identified 5 trials appropriate for inclusion (NSABP B-31, NCCTG N9831, HERA, BCIFG006, FinHer) and considered safety and efficacy endpoints (Bria et al 2008). For the safety analysis it was found that for trastuzumab given for 1 year compared with the control groups (4 trials, N=10,995 patients) there was a significant increase in risk of grade III to IV CHF (RR 7.05, CI 3.88 to 12.83, $p < 0.0001$, NNH 62, NS heterogeneity) and asymptomatic L-FEV reduction (RR 2.18, CI 1.45 to 3.27, $p < 0.00015$, NNH 14, significant heterogeneity $p = 0.00008$). The incidence of brain metastases was significantly higher in the trastuzumab compared with the control arm, RR 1.57 (CI 1.03 to 2.37, $p = 0.033$, NS heterogeneity). For the efficacy analysis the trastuzumab compared with the control groups showed prolonged disease-free survival (RR 0.63, CI 0.51 to 0.77, $p = 0.00001$, NNT 16, significant heterogeneity $p = 0.038$), prolonged distant disease-free survival (RR 0.61, CI 0.54 to 0.78, $p < 0.00001$, NNT 21, NS heterogeneity) and prolonged overall survival (RR 0.66, CI 0.55 to 0.78, $p < 0.00001$, NNT 51, NS heterogeneity).

Neoadjuvant

The search identified one small study for the neoadjuvant use of trastuzumab in early breast cancer, this study considered N= 42 participants randomised to paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC) alone or the same regimen with concomitant trastuzumab (first dose 4mg/kg then 2mg/kg) weekly for 24 weeks (Budzar et al 2007). This study aimed to estimate the efficacy of the chemotherapy and trastuzumab regimen.

Safety data: median LVEF for chemotherapy alone was 65% (range 55 to 76%), for chemotherapy and trastuzumab 65% (range 50 to 71%). At 6 months this was 65% (range 55 to 70%) for chemotherapy alone and 60% (range 52 to 70%) for chemotherapy and trastuzumab. None of the patients treated with trastuzumab and chemotherapy experienced clinical cardiac dysfunction, there were no cardiac deaths in this study.

Disease-free survival: at 1-year for chemotherapy alone 94.7% (85.2 to 100%), for chemotherapy and trastuzumab 100% (85.2 to 100%); at 3-year for chemotherapy 85.3%

(67.6 to 100%), for chemotherapy and trastuzumab 100%. Chemotherapy alone vs. chemotherapy and trastuzumab, $p=0.041$.

References

Bria E. C. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: The dark side of the moon? A meta-analysis of the randomized trials. *Breast Cancer Res. Treat.* 2008;**109**:231-9.

Buzdar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, Theriault RL *et al.* Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2007;**13**:228-33.

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *The New England journal of medicine* 2006;**354**:809-20.

Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA *et al.* Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J.Clin.Oncol.* 2008;**26**:1231-8.

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *The New England journal of medicine* 2005;**353**:1673-84.

Sledge, G. W. Adjuvant trastuzumab: long term results of E2198. ASCO 2006 Poster Session II: Treatment Adjuvant Therapy. 15-12-2006. Abstract

Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;**369**:29-36.

Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C *et al.* Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. *J.Clin.Oncol.* 2007;**25**:3859-65.

Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;**23**:7811-9.

Untch M. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann.Oncol.* 2008.

Evidence Tables

Citation
Buzdar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, Theriault RL <i>et al.</i> Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. <i>Clinical cancer research : an official journal of the American Association for Cancer Research</i> 2007; 13 :228-33.
Design
Design: initial RCT (scoend cohrt data also reported in this study, not included here)
Inclusion criteria
<p>Patients with histologically confirmed stage II to IIIA invasive but non-inflammatory carcinomas of the breast, all tumours were shown to be HER2/neu-positive by immunohistochemical or fluorescence in situ hybridization methods</p> <p>Randomisation between June 2001 and October 2003</p> <p>Patient distribution in both groups was similar with respect to age, tumour size, and nodal status between the groups</p>
Exclusion criteria
Patients with a history of uncompensated heart failure or of a cardiac ejection fraction of <45% were excluded
Population
N=42
Interventions
<p>Primary objective (of the revised study, following protocol amendment to add an additional N=21 to the chemotherapy and trastuzumab arm) was to estimate the efficacy of the chemotherapy and trastuzumab regimen</p> <p>Patients were randomised to receive either chemotherapy alone (paclitaxel followed by FEC) or the same chemotherapy concurrent with trastuzumab weekly for 24weeks</p> <p>Trastuzumab is given 4mg/kg trastuzumab IV over 90min on day 1 of the first cycle of paclitaxel, patients received 2mg/kg trastuzumab weekly IV over 30min during the 24wks of chemotherapy</p>
Outcomes
Pathologic complete remission, CR (CR defined as no evidence of clinical invasive cancer in either the breast or axilla)
Follow up
Median follow-up 36.1mths (range 12.30-54.8)

Results (all CI 95%)
<p>Clinical response Clinical response assessed by physical examination of the breasts and nodes</p> <p>Safety data Median left ventricular ejection fraction chemotherapy alone 65% (range 55-76%); chemotherapy and trastuzumab 65% (50-71%). After 6mths these were 65% (range 55-70%) and 60% (range 52-70%) respectively None of the patients treated with trastuzumab and chemotherapy experienced clinical cardiac dysfunction, and there were no cardiac deaths in this study</p> <p>Disease-free survival Chemotherapy alone group DFS at 1yr 94.7% (85.2 to100%), at 3yrs 85.3% (67.6 to100%) There was no recurrent disease in the chemotherapy and trastuzumab group, DFS at 1 and 3yrs 100% (85.2 to 100%) Chemotherapy alone vs. chemotherapy and trastuzumab p=0.041</p>
General comments
At the completion of the original study, the protocol was amended to discontinue the chemotherapy alone arm and to add an additional patients to the chemotherapy and trastuzumab arm – not reporting additional cohorts here, the second cohort was treated between June 2001 and October 2003
Citation
Joensuu Heikki, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R <i>et al.</i> Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. <i>The New England journal of medicine</i> 2006; 354 :809-20.
Design
Design: phase 3, randomized, open-label, multicentre trial
Inclusion criteria
Women with axillary-node-positive or high-risk node-negative cancer; less than 66years, WHO performance status of 0 or 1, breast surgery with axillary-node dissection or sentinel-node biopsy for invasive breast carcinoma; steroid hormone-receptor status and HER2 expression by immunohistochemistry, according to the guidelines of each institution
Exclusion criteria
Distant metastases, pregnancy, severe hypertension, cardiac disease (including cardiac failure of any degree, arrhythmia requiring regular medication, and myocardial infarction within the previous 12months), serum bilirubin level, an alanine or aspartate aminotransferase level, an alkaline phosphatase , a blood leukocyte count, a neutrophil count, or a platelet count outwith specified limits
Population

N=1010 N=232 whose tumours had an amplified HER2/neu gene, N=116 received trastuzumab and N=116 did not

Baseline characteristics of the groups were balanced (axillary nodal metastases tended to be more frequent in the trastuzumab group than the no trastuzumab group)

Interventions

Docetaxel or vinorelbine treatment followed by three cycles of fluorouracil, epirubicin and cyclophosphamide (FEC), those whose tumour had an amplified HER2/neu gene were further assigned to receive or not to receive nine weekly trastuzumab infusions

Nine trastuzumab infusions at one-week intervals, the first infusion was given on day 1 of the first docetaxel or vinorelbine cycle, no trastuzumab was given during FEC administration, first dose was 4mg/kg, subsequent doses were 2mg/kg

The most common reasons for a reduction in the dose of docetaxel were neutropenia/neutropenic infections, for vinorelbine it was neutropenia. The full dose of trastuzumab was administered in 99.1% of cycles (93.6% docetaxel and 96.6% vinorelbine)

Outcomes

Primary end point: recurrence-free survival (defined as the time from the date of randomisation to the date of detection of local, distant, or contralateral invasive breast cancer or death, whichever occurred first)

Secondary end point: adverse events, the effect of the treatment on LVEF, time to distant recurrence, overall survival (defined as time from randomisation to death from any cause)

Follow up

Scheduled follow-up for a minimum of 5 years, median follow-up 37mths (trastuzumab) and 35mths (no trastuzumab) groups

Results (CI 95%)

Recurrence or died without recurrence

N=12/115 trastuzumab had a recurrence of breast cancer or died without recurrence vs.

N=27/116 in the control group

HR for trastuzumab vs. control 0.42 (0.21 to 0.83), p=0.01

The HR remained similar when adjustment was made according to the type of chemotherapy given (0.41, 0.21 to 0.82), centre (0.42, 0.21 to 0.83), number of positive nodes (0.39, 0.20 to 0.77)

Distant recurrences

N=8/115 trastuzumab had distant recurrences vs. N=26/116 in the control group

HR for trastuzumab vs. control 0.29 (0.13 to 0.64), p=0.002

Overall survival

N=6/115 trastuzumab vs. N=14/116 in the control group died, NS difference between groups

Adverse events

Trastuzumab NS increase in the frequency of adverse events related to vinorelbine
Left ventricular ejection fractions were preserved in women who received trastuzumab

General comments

Randomisation central with computer-assisted blinding, to a study group within 12 weeks after surgery, permuted blocks used to randomly assign treatments

Those with HER2-positive cancer were randomly assigned to receive or not receive trastuzumab

Trastuzumab was administered at full doses regardless of blood-cell counts, but infusions were deferred whenever vinorelbine or docetaxel infusions were postponed because of adverse events

Power analysis completed

No patient was lost to follow-up

Citation

erez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA *et al.* Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J.Clin.Oncol.* 2008;**26**:1231-8

Design

NCCTG N9831 trial – a three-armed phase III randomised study
details of design in Romond et al evidence table

Inclusion criteria**Exclusion criteria****Population**

N=3,129 began AC treatment, N=1,944 began post AC treatment either having post AC LVEF level that allowed trastuzumab to be administered (N=1876) or no LVEF evaluation (N=68)

Demographics were similar across all arms

Interventions

Control arm – AC followed by paclitaxel

Sequential arm – AC followed by paclitaxel, followed by trastuzumab (4mg/kg loading dose, then 2mg/kg for 52 weeks)

Concurrent arm – AC followed by paclitaxel plus trastuzumab followed by trastuzumab alone

Outcomes

Cardiac events or cardiac death, 3-year cumulative incidence
Follow up
LVEF was measured at 6,9 and 8 to 21 months post registration
Results
<p>Range of LVEF at each evaluation point Pre-trastuzumab 4.0 to 5.1%, during trastuzumab administration 7.8% to 10.4%, and following trastuzumab (sequential arm month 21, concurrent arm month 18) 5.4% to 5.8%</p> <p>Clinically significant cardiac events during post-AC treatment among patients not precluded from receiving trastuzumab 1-year cumulative incidence rate for cardiac events: 0.0% (control), 1.6% (sequential) and 3.3% (concurrent) 2-year cumulative incidence rate for cardiac events: 0.2% (control), 2.7% (sequential) and 3.3% (concurrent) 3-year cumulative incidence rate for cardiac events: 0.3% (control), 2.8% (sequential) and 3.3% (concurrent)</p> <p>Risk factors for cardiac events in those receiving trastuzumab Univariate factors associated with an increased risk of a cardiac event within 3 yrs of starting of post-AC treatment with a trastuzumab-containing regimen included age ≥ 60 yrs ($p=0.003$), prior/current use of antihypertensive medication ($p=0.005$), and registration LVEF less than 55% but above lower limit of normal ($p=0.033$). BMI and post-AC LVEF level were NS risk factors</p>
General comments
The accrual to the concurrent arm was suspended for 9 months of the trial due to concerns regarding cardiotoxicity, following review by an independent cardiac safety monitoring

Citation
Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Davidson NE <i>et al.</i> Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. <i>The New England journal of medicine</i> 2005; 353 :1673-84.
Design
Design: joint-analysis of two RCTs (The National Surgical Adjuvant Breast and Bowel Project Trials (NSABP) B-31 and the North Central Cancer Treatment Group Trial (NCCTG) N9831)
Inclusion criteria
Pathologic diagnosis of adenocarcinoma of the breast, both trials required patients to have histologically proven, node-positive disease (some patients with high-risk node-negative disease were eligible for N9831); adequate haemopoietic, hepatic and renal function and a LVEF that met or exceeded the lower limit of normal; complete resection of the primary tumour and axillary-node dissection were required

(In both trials those treated with lumpectomy were to receive whole-breast radiotherapy with an optimal boost to the tumour bed)

Exclusion criteria

Clinical or radiological evidence of metastatic disease; angina pectoris or arrhythmia requiring medication; clinically significant valvular disease, cardiomegaly, left ventricular hypertrophy (B-31 only), poorly controlled hypertension, clinically significant pericardial effusion (N9831 only), history of MI, congestive heart failure or cardiomyopathy

Population

N=1736/2043 of NSABP B-31 as of February 2005 had at least one follow-up evaluation

N=1614/1633 of NCCTG N9831 had follow-up data submitted by March 2005

Interventions

NSABP B-31; 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel (group I), same regimen plus 52weeks of trastuzumab beginning on day 1 of paclitaxel therapy (group II). Trastuzumab beginning with a loading dose of 4mg/kg, followed by weekly doses of 2mg/kg for 51weeks

NCCTG N9831; 4 cycles doxorubicin and cyclophosphamide followed by paclitaxel for 12weeks (group A – control group), same regimen followed by 52weeks of trastuzumab beginning on day 1 of paclitaxel therapy (group C – trastuzumab group). (this study also included a group B which was excluded from this analysis because the protocol required trastuzumab to be administered after the completion of chemotherapy)

Trastuzumab beginning with a loading dose of 4mg/kg, followed by weekly doses of 2mg/kg for 51weeks

LVEF was assessed before entry, after completion of doxorubicin and cyclophosphamide therapy, and at 6, 9 and 18months after randomisation

The groups from each study were similar

Outcomes

Primary: Disease-free survival (events determining were local, regional and distant recurrence; contralateral breast cancer including DIS; other second primary cancers; death before recurrence or a second primary cancer)

Other end points: overall survival, time to distant recurrence, death from breast cancer, contralateral breast cancer, and other second primary cancer

Follow up

The median follow-up was 2.0 years (2.4 years in B-31 and 1.5 years in N9831)

Results (95% CI)

Disease-free survival

First event trastuzumab vs. control 0.48 (0.39 to 0.59), $p < 0.0001$

Percentages of patients alive and disease-free at 3 years were 87.1% (trastuzumab group) and

75.4% (control group), absolute percentage point difference 11.8 (8.1 to 15.4); at 4 years this was 85.3% trastuzumab and 67.1% control group, absolute percentage point difference 18.2 (12.7 to 23.7)

Overall survival

N=62 deaths in the trastuzumab group, N=92 in the control group, HR 0.67 (0.48 to 0.93), p=0.015

Absolute survival rate at 3 years was 94.3% trastuzumab group vs. 91.7% control group, absolute percentage point difference 2.5 (0.1 to 5.0); at 4 years this was 91.4% trastuzumab and 86.6% control, absolute percentage point difference 4.8 (0.6 to 9.0)

Distant metastases

Reported in N=96 trastuzumab group, N=193 control group

Trastuzumab vs. control for a first distant recurrence HR 0.47 (0.37 to 0.61), p<0.0001

At 3 years 90.4% trastuzumab group were free of distant recurrence vs. 81.5% control group, absolute percentage point difference 8.8 (5.5 to 12.1); at 4 years 89.7% trastuzumab and 73.7% control, absolute percentage point difference 15.9 (11.1 to 20.8)

Brain metastases

In both trials the incidence of isolated brain metastases as first events was higher in the trastuzumab group than in the control group (21 vs. 11 in B-31 and 12 vs. 4 in N9831). Those in B-31 were followed for additional occurrences beyond the first event, brain metastases as a first or subsequent event occurred in N=28 in the trastuzumab group and N=35 in the control group, HR NS, therefore the imbalance in brain metastases as first events can be attributed to earlier failures at other sites in the control group

Adjustment for additional characteristics

Adjustment for treatment assignment, nodal status, pathologic tumour size, hormone-receptor status, age, tumour grade, histologic appearance of the tumour, and trial, minimally altered the effect of trastuzumab vs. control therapy, HR for a first time event 0.46 (0.37 to 0.46), p<0.001

The number of positive nodes, pathologic tumour size, hormone-receptor status, and tumour grade were significant predictors of disease-free survival

There was no evidence that the benefit of trastuzumab differed significantly between the two studies

Adverse cardiac events

In B-31 those who met the inclusion criteria for trastuzumab the cumulative incidence of congestive heart failure or death from cardiac causes was N=31 (4.1%) had congestive heart failure in the trastuzumab group N=5 (0.8%), (N=4 had congestive heart failure, N=1 died from cardiac causes) in the control group

In the N9831 trial the 3 year cumulative incidence of congestive heart failure or death from cardiac causes was 2.9% trastuzumab group and 0% control group

Rare cases of interstitial pneumonitis were reported that in some cases appeared to be related to trastuzumab, in B-31 N=4 had interstitial pneumonitis, in N9831 N=5 had grade 3+ pneumonitis

or pulmonary infiltrates
General comments
<p>The NCI and FDA approved the joint-analysis plan</p> <p>B-31 treatments assigned balanced according to nodal status, the planned hormonal therapy, the type of surgery, the intended radiotherapy, and the institution with the use of a biased-coin minimization algorithm</p> <p>N9831 used dynamic allocation that balanced the marginal distributions of nodal status and hormone-receptor status between groups</p> <p>Genentech provided trastuzumab and partial funding support but did not participate in the design of the studies or the collection of data</p> <p>Power analysis completed, sensitivity analysis was completed</p>

Citation
Sledge, G. W. Adjuvant trastuzumab: long term results of E2198. ASCO 2006 Poster Session II: Treatment Adjuvant Therapy. 15-12-2006.
Design
E2198, pilot adjuvant trial, RCT
Inclusion criteria
HER-2 positive patients, lymph node positive breast adenocarcinoma, no prior history of CHF or recent MI, resting LVEF >50%, adequate renal, hepatic and marrow function
Exclusion criteria
Population
N=234 HER2-positive stage II breast cancer patients
Interventions
<p>Paclitaxel IV over 3hrs immediately followed by trastuzumab IV over 30-90mins, paclitaxel every 3wks for 4 courses, trastuzumab weekly for 10 courses, 3 wks following this doxorubicin IV and cyclophosphamide over 1 hr every 3wks for 4 cycles ER and/or PR +ve receive tamoxifen for 5yrs</p> <p>As above with additional trastuzumab IV weekly beginning within 3wks following completion of chemotherapy for 1yr (tamoxifen may be concurrent with trastuzumab)</p>
Outcomes
Primary end point: to evaluate the rate of clinical CHF

<p>Secondary endpoint: to evaluate a >10% decrease in LVEF from baseline</p> <p>DFS and OS were not initial end points</p>
<p>Follow up</p>
<p>Every 3mths for 1 yr, every 6mths for 2 yrs, annually thereafter</p>
<p>Results</p>
<p>Disease-free survival At 5yrs equivalent for short duration (76%) and long duration (73%) arms</p> <p>Overall survival At 5yrs equivalent for short duration (88%) and long duration (83%) arms</p> <p>Congestive heart failure N=7 CHF events (N=3 short duration, N=4 long duration) No deaths due to CHF</p>
<p>General comments</p>
<p>Results from an abstract</p> <p>This study was not designed or powered to test the question of trastuzumab duration</p> <p>Stratified according to radiotherapy (none planned vs. planned to breast or chest wall)</p> <p>Author's conclusion: optimum adjuvant trastuzumab duration remains to be established, also CHF events early N=4/7 within the first year and overall incidence is similar to other trials (N9831 and NSABP B-31)</p>

<p>Citation</p>
<p>Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M <i>et al.</i> 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. <i>Lancet</i> 2007;369:29-36</p>
<p>Design</p>
<p>Design: international, multicentre, open-label, randomized trial (HERA trial)</p>
<p>Inclusion criteria</p>
<p>Centrally confirmed HER2-positive (immunohistochemistry score 3 or FISH positive), early stage invasive breast cancer who had completed local regional therapy and a minimum of four courses of predefined standard adjuvant or neoadjuvant chemotherapy; node-positive disease or node-negative if the pathological tumour size was larger than 1cm</p>
<p>Exclusion criteria</p>
<p>Locally advanced disease including inflammatory breast cancers; LVEF of less than 55% after completion of chemotherapy and radiotherapy; congestive cardiac failure; other major cardiac</p>

problems

Population

N=5102 recruited included N=1698 in the observation group, N=1703 who received 1 year treatment with trastuzumab

Interventions

Either observation only or 8mg/kg trastuzumab IV 90min infusion as a loading dose followed by 6mg/kg every 3wks for a year (or the same schedule for 2yrs not reported here)

Outcomes

Primary: Disease-free survival previously reported in the TA

Secondary: Overall survival reported in this paper (other secondary end points included time to recurrence, time to distant recurrence, and safety including cardiac safety)

Follow up

Median follow-up of 23.5 months (0-48 months)

Results

Overall survival

N=149 deaths occurred in the two groups

N=90/1698 (5%) observation group; N=59/1703 (3%) 1-year trastuzumab group

Unadjusted HR trastuzumab vs. observation alone 0.66 (0.45 to 0.87), p=0.0115, corresponds to an absolute overall survival benefit of 2.7% (92.4% vs. 89.7%) at 3 years

HR for OS by censored analysis 0.63 (0.45 to 0.87), p=0.0051

Distant metastases

Distant events N=233/1698 (14%) observation group; N=152 (9%) trastuzumab group

HR for time to distant recurrence trastuzumab vs. observation group 0.60 (0.49 to 0.73),

p<0.0001, corresponds to an absolute time to distant recurrence event-free survival benefit 6.3% at 3 years (85.7% vs. 79.4%), p<0.0001

Adverse events

Patients with one or more grade 3 or 4 adverse events N=88/1442 (6%) observation group vs. N=190/1668 (11%) trastuzumab group, p<0.0001

Patients with one or more serious adverse event N=97 (7%) observation group vs. N=156 (9%) trastuzumab group, p=0.0103

Fatal adverse events N=3 (0.2%) observation group vs. N=9 (0.5%) trastuzumab group, NS difference between groups

Severe congestive failure; observation vs. trastuzumab, N=0 vs. N=10 (0.6%), p<0.0001

Symptomatic congestive heart failure; observation vs. trastuzumab N=2 (0.1%) vs. N=36 (2%), p<0.0001

Confirmed significant LVEF drop; observation vs. trastuzumab N=9 (0.5%) vs. N=51 (3%), p<0.0001

General comments

Randomisation was done within 7 weeks from day 1 of the last chemotherapy cycle or 6 weeks from the end of radiotherapy or definitive surgery, whichever was last. Procedure stratified according to region of the world, age, nodal status, title of chemotherapy, and hormone receptor status together with intention to use endocrine therapy

Severe congestive heart failure, was defined as New York Heart Association grade III or IV functional class confirmed by a cardiologist and a decrease in LVEF of at least 10% below baseline and to less than 50%

Power analysis completed

Efficacy analysis done on ITT basis

Collection, analysis and interpretation of data were done entirely independently

Trial sponsored and funded by Roche

Citation
Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C <i>et al.</i> Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. <i>J.Clin.Oncol.</i> 2007; 25 :3859-65.
Design
HERA trial – details of design in Smith et al evidence table
Inclusion criteria
Exclusion criteria
Population
Data available on N=1,693 trastuzumab group and N=1,693 control group The demographic characteristics were balanced in both groups
Interventions
Outcomes
Primary end point; disease-free survival Secondary end point; cardiac safety, overall survival, time to recurrence, time to distant recurrence
Follow up

Results**Cardiac end points**

Incidence significantly higher in trastuzumab group vs. observation group, severe CHF (0.60% vs. 0%, CI for difference in incidence 0.20% to 0.99%), symptomatic CHF (2.15% vs. 0.12%, CI for difference in incidence 1.29% to 2.77%), confirmed significant LVEF drop (3.04% vs. 0.53%, CI for difference in incidence 1.59% to 3.43%)

Recovery after a cardiac end point

N=6/10 with severe CHF recovered their LVEF in a median of 124 days (range 36 to 409 days)
N=24/36 with symptomatic CHF recovered their LVEF in a median of 151 days (range 26 to 831 days)
N=35/51 with a confirmed significant LVEF drop recovered their LVEF in a median of 191 days (range 13 to 831 days)

Potential cardiac risk factors

The incidence of any type of cardiac end point among patients with the risk factor was compared with the incidence of any type of cardiac end point among patients without the risk factor for the trastuzumab group

Screening LVEF of $55\% \leq \text{LVEF} < 60\%$ had a significantly higher incidence of cardiac end points vs. screening LVEF $\geq 60\%$ (6.90% vs. 2.72%)

Screening LVEF of $60\% \leq \text{LVEF} < 65\%$ had a significantly higher incidence of cardiac end points vs. screening LVEF $\geq 65\%$ (3.89% vs. 1.88%)

High BMI (>25) significantly higher incidence of cardiac end points vs. BMI in the normal range ($20 \leq \text{BMI} \leq 25$)

General comments**Citation**

Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;**23**:7811-9.

Design

NSABP B-31 trial – details of design in Romond et al evidence table

Inclusion criteria**Exclusion criteria**

Population
Evaluable cohort for this assessment; N=1,664, N=850 trastuzumab group, N=814 observation group
Interventions
Cardiac history forms were to be submitted at entry, every 6 months for the first 5 years, and yearly hereafter. MUGA scans were required in both treatment arms before entry, after AC and at 6, 9 and 18months
Outcomes
Follow up
Results
<p>Cumulative incidence of CEs (CE=cardiac event) Cardiac events N=31/850 trastuzumab, N=5/814 Cumulative incidence of CEs 3 years after day 1 of cycle 5; trastuzumab 4.1% (2.9% to 5.8%), control 0.8% (0.3% to 1.9%), NS difference between the arms RR of a CE 5.9 trastuzumab vs. control (2.3 to 15.3), p<0.0001</p> <p>Recovery of cardiac function after CHF N=31 CHF in the trastuzumab group, none had died for reasons other than breast cancer - N=26/27 (followed for ≥6mths after CHF diagnosis) without symptoms, N=18 continued to use cardiac medications, - N=24/27 (LVEF assessments ≥6mths after CHF diagnosis), N=17 decreased LVEF to baseline N=5 CHF observation group N=3 deaths (N=1 probable cardiac death), N=1/2 left followed for ≥6mths after diagnosis) symptomatic and taking medications</p> <p>Discontinuation of trastuzumab Trastuzumab discontinued before completion of 1 year or recurrence N=197 (28%), discontinued for cardiac reasons N=133 (19%) (included N=102 asymptomatic decrease in LVEF, N=31 symptoms of CHF or other cardiac problems, N=14 other toxicity/event)</p> <p>Cardiac risk factors and incidence of CHF Baseline and post-AC LVEF of 55% or more was strongly associated with subsequent CHF (p<0.0001), as was age 50+yrs at entry (p=0.03)</p> <p>Changes in LVEF during treatment Those accrued by June 2003 have had MUGA scans at 18mths (N=?), in this group median LVEF 63%, with a median decrease of 2% after AC, NS different between the arms At 6, 9 and 18mths median decline in LVEF from baseline for trastuzumab were 5%, 6% and 4% compared with 3%, 2% and 3% with observation, significant difference at 6mths (p<0.0001) and at 18mths (p=0.01)</p>
General comments

CHF denotes NYHA class III or IV

Citation

Untch M. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann.Oncol.* 2008.

Design

HERA trial – details of design in Smith et al evidence table
This paper used the HERA dataset reported by Smith et al (2007)

Inclusion criteria

Exclusion criteria

Population

Data available on N=1,693 trastuzumab group and N=1,693 control group
The demographic characteristics were balanced in both groups

Interventions

Outcomes

Primary end point; disease-free survival (defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast cancer at any site, the development of ipsilateral or contralateral breast cancer including DCIS but not lobular carcinoma in situ, second nonbreast malignant disease other than basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, or death from any cause without documentation of a cancer related event)

Secondary end point; cardiac safety, overall survival, time to recurrence, time to distant recurrence

Follow up

23.5 months median follow-up

Results

At 23.5mths median follow-up, the relative risk reduction estimates for the overall cohort and for subgroups indicate consistent reductions in the risk of relapse

Excluding neo-adjuvant (small cohort) all groups showed an improvement in estimated 3-year DFS, though estimates of the magnitude of absolute improvement ranged widely

General comments

The 2-year trastuzumab group remains blinded as the comparison of 1-year versus 2-years of

trastuzumab is continuing to be monitored by the independent data monitoring committee

The trial was sponsored and funded by Roche

All authors had access to all the data

Health Economic Summary

Full Summary

A large volume of economic evidence was found since the publication of technology assessment 107. Of the 148 initial hits from the search, 26 were requested for further review. Of these, seven studies were economic evaluations addressing the above question from a health economics point of view. Due to the number of studies identified, those that only examined costs of early breast cancer were excluded. Three further studies were included following the update search to account for studies published after the first search was carried out. Therefore ten studies were reviewed in detail. Five of the studies identified were full cost-utility analyses (Garrison et al. 2007, Kurian et al. 2007, Lidgren et al. 2007, Liberato et al. 2007 and Millar and Millward 2007) and the remaining five studies were cost-effectiveness analyses (Dedes et al. 2007, Neyt 2006, Neyt et al. 2008, Norum et al. 2007 and Shiroiwa et al. 2008). A summary of the results of these studies can be found below and in

Table 2 and a summary of their methods can be found in Table 4. A full description of these studies has been presented in the accompanying document containing health economics evidence tables.

Summary of cost utility modelling studies

Overall

The cost utility studies identified were of good or reasonable quality. There were two US studies, two European studies and one Australian study. Four of the studies were based on the 12 month trastuzumab regimen and one study considered both the 12 month and 9 week regimens. The majority of the studies based their efficacy data on the NSABP-B31 and NCCTG N983 trials (and subsequent joint analysis) and the HERA trial. One study based its effectiveness on the BCIRG 006 trial (descriptions of the main trials are given in Appendix AA2). The main comparison was AC->P with AC->PT (abbreviated regimens are explained in Appendix AA3). The studies varied as to whether or not they considered that trastuzumab may be given to patients who had progressed to metastatic cancer who had already received trastuzumab in the adjuvant stage. Most of the studies (4 of 5) examined this aspect in some way either as their base case analysis or in their sensitivity analysis. Two of the studies included the costs of HER2 testing in the model, the others did not.

Model structures

All of the cost utility studies had similar structures and all of the models were Markov models. Three of the models were set up in TreeAge modelling software, one model was built in Excel and the other study did not specify the software used (Garrison *et al.* 2007). Each model had a well/disease free state, a recurrence state (some had more than one indicating the difference between local, contralateral and metastatic recurrence), three of five models included a cardio toxicity state and all models had a death state. All but one study had a lifetime horizon; Liberato *et al.* 2007 had a 15 year time horizon.

Risk of recurrence and survival

The benefits of trastuzumab were accounted for in all models as the relative risk of recurrence. The majority of studies derived relative risks of recurrence from clinical trials. Three of the studies assumed that there was no added or diminished benefit due to trastuzumab following the trial duration and benefits were assumed to be the same over the lifetime of the patient. Two studies (Kurian *et al.* 2007 and Millar and Millward 2007) assumed that the benefit of trastuzumab would diminish over time. Kurian *et al.*, 2007 based recurrence rates for trastuzumab for the first two years on clinical trial data. Following this they assumed that the relative risk reduction for breast cancer would be reduced by one-third in years 2 to 4 and by an additional third in years 5 to 10 after which values were held constant. Millar and Millward (2007) assumed that the relative risk reported in the trials would remain for 5 years after which this would diminish over the following 3 years (by 25%, 50% and 75% of the initial RR respectively). Examining diminished benefit from trastuzumab may reflect a conservative assumption.

Individual summaries

Garrison *et al.* (2007) was a well conducted cost-utility analysis conducted in the US on the cost effectiveness of AC->P compared with AC->PT trastuzumab with a dosing schedule for trastuzumab of 12 months. The main sources of efficacy data were taken from the NSABP-B31 and NCCTG N983 trials and the EBCTCG report. In order to extend the clinical trial data over a lifetime horizon the authors state that the first five years of distant free recurrence and survival estimates were based on empirically fitted observed distributions for the first four years of reported trial data (NSABP B-31 and NCCTG N983) and extrapolation of the trends to the fifth year. From 6 years onwards the transition probabilities to recurrence and death were assumed to be the same in both arms. All patients were assumed to have received trastuzumab treatment after distant recurrence and the efficacy of trastuzumab in this setting was included in the model. Costs were based on trials and other published literature and are likely to appropriately and accurately reflect the costs and resource use. Costs and resource use associated with HER2 testing was included in the model. The rate and cost of cardiac events were included in the model however no disutility was assumed. Some indirect costs were accounted for in a separate analysis from the (partial) societal perspective. The ICER of AC->PT compared with AC->P was reported to be US\$26,417 per QALY gained (2006 prices) and a 3% discount rate applied for costs and benefits. The analysis was also carried out for a shorter time period of 20 years, resulting in an ICER of US\$34,201 per QALY gained. In further sensitivity analysis the range of results was found to be US\$9104 to US\$69,340.

Kurian *et al.* (2007) used a Markov model to estimate the costs and efficacy associated with three adjuvant therapy options for women with HER2 positive breast cancer in the US. Conventional chemotherapy (AC->P) without trastuzumab; anthracycline-based regimens with trastuzumab (AC->PT); and a nonanthracycline regimen with trastuzumab (docetaxel plus carboplatin plus trastuzumab). The trastuzumab regimen was 12 months for each of the comparators. The main sources of efficacy were the NSABP B-31 and NCCTG N9831 trials and the HERA and BCIRG 006 trials. All patients with metastatic disease were assumed to have received trastuzumab treatment. The efficacy of trastuzumab in this setting was included in the model (the costs and efficacy of metastatic disease was varied in sensitivity analysis). Costs were based on trials and other published literature and are likely to appropriately and accurately reflect the costs and resource use. The cost of HER2 testing does not appear to have been included. Costs and utility of cardiac events was included in the model. The results showed that the ICER of AC->PT compared with AC->P was US\$39,892 per QALY gained for 2005 prices and a 3% discount rate for costs and benefits. The docetaxel, carboplatin and trastuzumab regimen was dominated by the AC->PT regimen (more costly and less effective). Recurrence rates were varied in sensitivity analysis and showed that when no benefit of trastuzumab is assumed after year 4 the ICER for AC->PT compared with AC->P was US\$142,516 per QALY gained and was US\$157,078 per QALY gained for the docetaxel regimen compared with AC->P. Probabilistic analysis was carried out however, the details of the methods used were unclear.

Lidgren *et al.* (2007) carried out a cost-utility analysis to examine strategies of testing for HER2 status and the subsequent treatment of patients with trastuzumab in the Swedish health care setting. All other studies examining testing for HER2 were excluded as they did not examine in detail how testing would affect subsequent treatment. Test and treatment strategies were compared with standard care defined as adjuvant chemotherapy with no additional adjuvant trastuzumab for all patients. Patients in the testing strategies received a 12 month course of trastuzumab dependent on the results of various testing strategies with IHC and FISH testing. All patients were assumed to have had adjuvant chemotherapy before

being tested. Estimates of the effectiveness of trastuzumab were taken from the HERA trial. The cost of trastuzumab in the metastatic setting is not included. Costs were based on trials and other published literature and are likely to appropriately and accurately reflect the costs and resource use. Indirect costs were also included. Costs and utility of cardiac events were included in the model. Results showed that standard care was the least expensive and least effective strategy. The strategy of IHC testing for all patients with FISH confirmation of 2+ and 3+ followed by 12 months adjuvant trastuzumab for FISH positive patients (strategy 4) had the lowest ICER after two strategies were ruled out by dominance. The ICER of this strategy was €36,000 per QALY gained compared with the standard care strategy in 2005 prices with a 3% discount rate. The strategy of FISH testing in all patients with 12 months adjuvant trastuzumab for FISH positive patients was the most effective strategy (strategy 5). Compared with strategy 4 the ICER for this strategy 5 was €41,500. Subgroup analysis was carried on age at the start of adjuvant trastuzumab treatment. The results of this analysis found that patients aged 35 had a lower cost per QALY, €26,700 and €30,100 for strategies 4 and 5 respectively. At age 65 the resulting ICERs were €56,200 and €64,700 for strategies 4 and 5 respectively. An increase of 30% in the hazard ratio of an event after 1 year of trastuzumab resulted in ICERs of €84,400 and €97,000 for strategies 4 and 5 respectively. Probabilistic analysis was also carried out. From the graph it can be estimated that at €40,900, the probability of strategy 4 being cost effective is approximately 65% and of strategy 5 being cost effective is approximately 50%.

Liberato *et al.* (2007) used a Markov model to estimate the cost utility of AC->P compared with AC->PT with a dosing schedule for trastuzumab of 12 months. The main sources of efficacy data were taken from the NSABP-B31 and NCCTG N983 trials and the EBCTCG report. Patients were not assumed to have received trastuzumab treatment after distant recurrence if they had already been treated with trastuzumab for early breast cancer. The efficacy of trastuzumab in this setting was included in the model, however it is unclear whether the costs are also included. Costs were estimated from the perspective of the Italian and US health care systems and appear to accurately reflect costs in these settings. The costs of HER2 testing were not included. The costs and disutility of cardiac dysfunction were taken into account. The ICER of AC->PT compared with AC->P was reported to be US\$18,970 and €14,861 for the US and Italy respectively per QALY gained with a 3% discount rate for costs and benefits. No cost year was reported. The author's probabilistic analysis showed that the ICER ranged from €11,286 to €128,780 per QALY (US\$15,165 to US\$143,064 per QALY) when the time horizon is varied from 20 to 5 years respectively. Adjuvant trastuzumab was less cost effective in older women and in higher risk patients. A multiway analysis using the main characteristics of the HERA trial was performed. The resulting ICERs were €11,228 per QALY gained in the Italian setting and US\$16,199 per QALY gained in the US setting.

Millar and Millward (2007) conducted a cost utility analysis using a Markov model in the Australian setting. This was to estimate the cost effectiveness of treatment with a 12 month or 9 week course of trastuzumab. Details of the comparator treatment were not given. The main sources of efficacy data were taken from the NSABP-B31 and NCCTG N983 trials and the HERA trial. Transition probabilities for the 12 month course were also applied to the 9 week course model except for the probability of remission to metastatic disease. The costs and efficacy of treatment with trastuzumab in metastatic disease is explored. The effect of palliative trastuzumab was also examined. Costs were based on mainly on published literature and are likely to appropriately and accurately reflect the costs and resource use.

The costs of testing for HER2 status were omitted. The costs of diagnosing and treating heart failure as well as the utility of heart failure were included in the model. The ICER for 12 months of trastuzumab compared with no trastuzumab therapy was reported to be A\$ 22,793 per QALY gained. The ICER of 9 weeks of trastuzumab compared with no trastuzumab therapy was reported to be A\$1700 in 2005 prices with a 3% discount rate for costs and benefits. Univariate analysis on duration of effect showed that the ICER ranges from \$A18,444 per QALY for 10 years duration of effect to \$A 35,353 per QALY for 2 years duration of effect. Sensitivity analysis for the 9 week course showed that when the risk reduction for distant recurrence is varied (using 95% CI) the range of cost effectiveness is from \$A 1018 to \$A 5569 per QALY.

Summary of cost effectiveness modelling studies

Overall

Five cost effectiveness studies were identified. Four studies were European (one from Sweden, two from Belgium and one from Norway) and one study was carried out in Japan. Three of the studies were based on the 12 month trastuzumab regimen and two studies considered both the 12 month and 9 week regimens. The two trials that considered the 12 month and 9 week regimens based their efficacy data on the HERA and FinHer trials. One study based its efficacy data on the 2-year follow up of the HERA trial and the other studies based efficacy data on the NSABP-B31 and NCCTG N983 trials and the BCIRG 006 trial. All of the studies considered trastuzumab in patients who had progressed to metastatic cancer. However, in some of the studies it was unclear whether the efficacy of trastuzumab in this setting was taken into account. The costs of HER2 testing were included in some way in four out of the five studies.

Model structures

Neyt *et al.* (2006) and Norum *et al.* (2007) used a treatment model and a decision analytic model respectively and a diagram of the structure of each of these models was presented. Neyt *et al.* (2008) used the same structure presented in Neyt *et al.* (2006) and therefore did not reproduce the schematic. Dedes *et al.* (2007) specifically stated that a Markov model was used but no structure was presented although the health states used were clearly outlined. Shirowa *et al.* (2008) used a Markov model and a diagram was presented. A therapeutic strategy corresponding to the Markov states was also included.

Risk of recurrence and survival

It is difficult to have a clear understanding of how risk of recurrence and survival is handled in these papers. Shirowa *et al.* (2008) explain with relative clarity that three risk reduction strategies were considered: risk reduction continuing for two years, five years and for ten years. The assumed risk of recurrence during the first five years was higher than that during the next five years. Further explanation on how this was achieved would have been a useful addition to this study. Dedes *et al.* 2007 stated that the clinical benefit of trastuzumab was assumed to last for the first 5 years in the base case, thereafter the relative risk for recurrent and metastatic disease in the trastuzumab group assumed to be the same as in the observational group. Norum *et al.* 2007 stated that 10 year survival figures for CMF were adjusted for the regimens examined. A 5% absolute improvement in overall survival was

added for the FEC regimen and a 10% and 20% increase due to trastuzumab was estimated. Neyt *et al.* (2006) appears to only include hypothetical improvements due to trastuzumab. Neyt *et al.* (2008) states that the model was mainly based on the progression (or prevention of progression) of patients to metastatic disease. Life years were then calculated from the life expectancy of patients progressing and not progressing to metastatic disease.

Individual summaries

Dedes *et al.* (2007) examined the cost effectiveness of adjuvant chemotherapy with or without trastuzumab in the Swiss health care setting using a Markov model. The 12 month and 9 week trastuzumab regimens were included. Further details of the comparator treatment were not given. Efficacy data was mainly derived from the HERA trial and the FinHer trial. In the base case analysis 50% of patients with metastatic disease were retreated with trastuzumab. Costs were mainly based on the HERA trial and published literature and are likely to accurately reflect the costs and resource use in the author's setting. The cost of HER2 testing was included. The costs and effect of cardiac toxicity was taken into account. Results were given for 5, 10 and 15 years. The cost per LYG of the 12 month trastuzumab group compared with the no trastuzumab group was €212,360, €40,505 and €19,673 for 5, 10 and 15 years respectively at 2006 prices and costs discounted at 3% (benefits not discounted). With both costs and benefits discounted at 3% the ICER was €27,094 per LYG (15 year result). With the clinical benefit of trastuzumab limited to 3 years the ICER was €37,630 (15 year result). For the 9 week regimen the trastuzumab group was more effective and less costly in each of the scenarios (5, 10 and 15 years).

The study by Neyt *et al.* (2006) was primarily a costing study from the Belgian health care perspective. The authors state they carried out a threshold analysis to examine the cost effectiveness of trastuzumab. However limited details were provided and therefore this study is difficult to review as a cost effectiveness analysis. The model aimed to examine the costs and resource use associated with two trastuzumab containing regimens, AC followed by docetaxel and trastuzumab (TH) and, docetaxel, carboplatin and trastuzumab. The efficacy of trastuzumab is primarily based on the BCIRG 006 trial and the SEER database, however, mortality and estimates of progression to metastatic disease were taken from US and Canadian databases respectively. Costs were based on trial data and published literature and seem to accurately reflect the costs and resource use in the author's setting. No cost year was reported making comparison of costs difficult. The costs of HER2 testing were included. Trastuzumab was considered for use in metastatic cancer although it is not clear if the effectiveness of trastuzumab in this setting has been included. It is likely that it has not been. The costs and effects of cardiac toxicity do not appear to have been included. The total costs for stage III breast cancer patients over 50 years were €16,787 for standard treatment, €21,523 for AC->TH and €21,827 for the docetaxel, carboplatin and trastuzumab regimen. The percentage point of cancers not becoming metastatic and the improvement in time to disease progression to metastatic cancers were plotted against an ICER. It is not clear whether this ICER is by LYG and this figure is not provided. This study cannot accurately provide cost effectiveness data for trastuzumab compared with standard treatment.

Neyt *et al.* (2008) examined the cost effectiveness of standard breast cancer treatment with and without trastuzumab in the Belgian health care setting. The comparator (standard breast cancer treatment) was not discussed in detail. The 12 month and 9 week trastuzumab regimens were included. Efficacy data were mainly derived from the HERA trial for the

12 month regimen and the FinHer trial for the 9 week regimen. National data and assumptions were also used. Metastatic treatment costs with and without trastuzumab were included. It is not clear how the efficacy of trastuzumab in this setting was taken into account. Costs were based mainly on the HERA and FinHer trials as well as published literature. Some of the cost data and efficacy data were taken from Dutch sources were no Belgian data were available. The cost of HER2 testing was included. The costs of heart failure were taken into account. Results were given for three stages of cancer. For stages I, II and III the 12 month regimen produced ICERs of €34,999, €16,026, and €5994 per LYG respectively assuming a discount rate of 3% for costs and 1.5% for benefits (no single cost year was reported). The 9 week regimen dominated standard care in all three cancer stages. Results were also given by age and showed that outcomes were better for younger patients. In probabilistic analysis (applying a threshold of €30,000 per LYG), early stage breast cancer treatment with trastuzumab for 12 months is not cost effective in 6 out of the 15 analysed groups (stage and age). For the 9 week regimen, trastuzumab is not cost effective in only 1 group.

Norum *et al.* (2007) examined the cost effectiveness of FEC followed by 12 months of trastuzumab versus FEC alone in the Norwegian health care setting. Efficacy data were mainly derived from the NSABP B-31 and NCCTG N983 trials as well as other published literature and assumptions. The authors state that survival benefit was reduced due to cardiac events and secondary malignancy. This reduction was arbitrary and therefore does not adequately take into account the effect of trastuzumab for metastatic disease and cardiac events. The costs of trastuzumab for metastatic disease and the cost of cardiac events were considered. The results in terms of costs per life year gained are unclear. The table is confusing and the numbers given do not appear to add up. The authors state that a quality of life figure of 0.8 QALYs was calculated and applied. However, the quality of life figure only refers to a previous paper. Its derivation is not fully explained in this study. The authors state that the cost per life year saved ranged between €8148 and €35,947. Withdrawing trastuzumab from use in the metastatic setting raised the upper figure to €39,383. The authors state that the cost per QALY ranged between €10,185 and €48,391 although they urge caution in the interpretation of these results. Due to the poor reporting of results, this study cannot accurately provide cost effectiveness data for trastuzumab compared with standard treatment.

Shiroiwa *et al.* (2008) examined the cost effectiveness of 1 year of adjuvant trastuzumab therapy compared with an observational group in the Japanese health care setting. Efficacy data were mainly derived from HERA trial as well as other published literature and assumptions. No cost year was reported which makes the comparison of costs difficult. The costs of trastuzumab for metastatic disease and the cost of cardiac events were considered. The cost of HER2 testing does not appear to have been taken into account. The cost and effectiveness of trastuzumab was considered for metastatic cancer in this analysis. Results were given for various weight categories of patients as this affects the amount and cost of trastuzumab used and for three risk reduction scenarios (risk reduction continuing constantly for 2, 5 and 10 years, representing conservative, standard and optimistic scenarios respectively). The authors state that the cost per life year gained in the base case (5 years efficacy and 50-60kg patient) was JPY 2,740,000 (€18,000) assuming a discount rate of 3% for both costs and benefits (no cost year was reported). In probabilistic analysis the probability of adjuvant trastuzumab therapy being below JPY 5,400,000 (€36,000) was 95%. This study is a useful addition to the review showing an evaluation that examines the 2-year

follow up data from the HERA trial where the other analyses have used the 1-year follow up data.

Table 3 Summary Table of Economic Evaluations

The following is a summary table of main results of the economic evaluations considered in the review. The table is separated into cost-utility, cost-effectiveness and regulatory body studies.

Study/ Study design	Interventions	Methodological quality	Cost results	Effectiveness results	ICER (£/QALY)	Uncertainty
Garrison et al., 2007 CUA	Trastuzumab plus adjuvant chemotherapy (AC->P+/-T)	Minor limitations	Incremental costs US\$44,923	Incremental QALYs 1.70	ICER US\$26,417	Scenarios Lifetime cost per QALY- US\$26,417 20 year horizon – US\$34,201 per QALY Societal perspective – US\$27,637 One way analysis Results sensitive to discount rate, price of trastuzumab and probability of metastases.
Kurian et al., 2007 CUA	Adjuvant chemo followed by paclitaxel plus/minus Trastuzumab (AC->P+/-T) and TCH	Minor limitations	Total costs Adjuvant chemo without trastuzumab US\$133,492 Adjuvant chemo with trastuzumab US\$190,092 Docetaxel plus chemo and trastuzumab US\$206,561	Total QALYs Adjuvant chemo without trastuzumab 9.35 Adjuvant chemo with trastuzumab 10.77 Docetaxel plus chemo and trastuzumab 10.61	ICER of AAT over NT US\$ 39,892 The AAT regimen dominated the NAT regimen. AAT regimen is less costly and more effective than the NAT regimen	Probabilistic analysis Full methods not clear One way analysis Results sensitive to the discount rate, the cost of AT, median survival after breast cancer recurrence, and the cost of treating metastatic breast cancer.
Lidgren et al. 2007 CUA of testing strategies	Trastuzumab after adjuvant chemotherapy (dependent on HER2 test) and Adjuvant chemo with no added trastuzumab	Minor limitations	Total costs ranged from €115,151 to €129,188	Total QALYs ranged from 11.020 to 11.304	5 testing strategies Strategy 1 = standard care (no testing and no trastuzumab). Strategy 2 and 3 dominated standard care (were more effective and less costly). Strategy 4 and 5 had an ICER of €35,975 and €41,471 respectively compared with Strategy 1.	One-way analysis Results were sensitive to relative risk reduction (hazard ratio) of an event arising from treatment with trastuzumab, duration of effect and inclusion of future costs were the parameters that affected the ICERs. Subgroups Increase in age of patients at start of treatment = increase in cost per QALY gained. Probabilistic analysis Only the CEAC was presented - From the graph it can estimated that at €40,900, the probability of strategy 4 being cost effective is approximately 65% and of strategy 5 being cost effective is approximately 50%.
Liberato et al., 2006 CUA	Trastuzumab plus adjuvant chemotherapy (AC->P+/-T) Trastuzumab after adjuvant chemotherapy	Minor limitations	Total costs (Italian) No adjuvant trastuzumab €36,522 Adjuvant trastuzumab €54,058 Total costs (US) No adjuvant trastuzumab US\$55,526	Total QALYs (Italian and US) No adjuvant trastuzumab 8.03 Adjuvant trastuzumab 9.22	ICER (Italian) €14,861 ICER (US) US\$18,970 No cost year reported	Scenarios Results are sensitive to the time frame of the analysis and patients' age. Adjuvant trastuzumab was less cost effective in older women. A multiway analysis using the main characteristics of the HERA trial was performed. Adjuvant trastuzumab cost €11,228 per QALY for the Italian setting and \$16,199 per QALY for the US setting.

Study/ Study design	Interventions	Methodological quality	Cost results	Effectiveness results	ICER (£/QALY)	Uncertainty
			Adjuvant trastuzumab US\$77,947			
Millar and Millward, 2007 CUA	Trastuzumab (52 or 9 weeks) or no trastuzumab plus adjuvant chemotherapy	Moderate limitations	Total costs Trastuzumab 52 weeks (per patient) A\$87,819 Trastuzumab 9 weeks (per patient) A\$31,513	No details of total QALYs or incremental QALYs were provided	ICER for 52 week regimen 22,793 ICER for 9 week regimen 1700	Scenario analysis: Univariate analysis on duration of effect showed that the ICER ranges from \$A 18,444 per QALY for 10 years duration of effect to \$A 35,353 per QALY for 2 years duration of effect. When relapse with metastatic disease is treated with trastuzumab (in the 52-week regimen model) the ICER improved Increase in age of patients at start of treatment = increase in ICER.
Dedes et al., 2007 CEA	Adjuvant chemotherapy with or without trastuzumab	Minor limitations	Total cost (15 year model) of trastuzumab group €67,682 observational group €47,791 Incremental cost €19,891	Incremental LYG = 1.01	Cost per LYG of €19,673.	Scenario analysis: Results were given for 5 years and 10 years. The longer the model duration the more favourable the ICERs One way analysis: One way sensitivity analysis showed that the cost effectiveness of the trastuzumab group was sensitive to changes in clinical efficacy of trastuzumab, discounting of the effectiveness and its price. 9 week analysis In each of the analyses (at 5, 10 and 15 years) for the FinHer trials, the trastuzumab group is more effective and cost saving compared to the observational group.
Neyt et al., 2006 CEA	Standard treatment Compared with AC->TH or TCH	Serious limitations in CEA section	Total standard costs for stage III breast cancer patients Std tx - €16,787 AC->TH - €21,523 TCH - €21,827	Not stated	Not stated	The ICER varied considerably with changes in the discount rate, price of trastuzumab and the probability of metastases.
Neyt et al., 2008 CEA	Standard treatment with or without trastuzumab (12 months or 9 weeks).	Minor limitations	Incremental costs - 12 month regimen stage I €32,320 stage II €30,608 stage III €24,202 Incremental costs - 9 week regimen stage I €668 stage II €-1045 stage III €-6869	Incremental LYG - 12 month regimen stage I - 11.99 stage II - 23.88 stage III - 49.74 Incremental LYG - 9 week regimen stage I - 20.35 stage II - 36.09 stage III - 70.33	ICER (€ per life year gained) - 12 month regimen Stage I €34,999 Stage II €16,026 Stage III €5994 ICER (€ per life year gained) - 9 week regimen Dominates std regimen for stages I, II and III.	Scenario analysis: All results were shown by stage and age - the ICERs for trastuzumab treatment are better for younger patients and in patients diagnosed with more advanced disease. Probabilistic analysis: Results are sensitive to the transition probability of progressing to MBC and the hazard ratio of distant recurrence.

Study/ Study design	Interventions	Methodological quality	Cost results	Effectiveness results	ICER (£/QALY)	Uncertainty
Norum et al., 2007 CEA	FEC alone or FEC followed by trastuzumab	Serious limitations	Two survival levels - 10% or 20% improved overall survival level was assumed Only the 20% level figures seem to add up correctly. Incremental costs societal costs €17,844	LYG for 10% survival benefit: 1.095 LYG for 20% survival benefit: 2.19	10% survival benefit LYG – 30290 QALYs – 37862 20% survival benefit LYG – 8148 QALYs – 10185	Univariate sensitivity analyses: Results were most sensitive to variations in the LYG (increases in overall survival), the price of trastuzumab, production gains and the discount rate. Scenario analysis: If trastuzumab is used in the metastatic setting, LYG was the only factor having a significant influence on the cost effectiveness.
Shiroiwa et al., 2008 CEA	Adjuvant trastuzumab compared with observational group	Moderate limitations	Reported in JPY Observational group 7,900,000 Trastuzumab Risk reduction continuing for: 2 years - 11,500,000 5 years - 11,200,000 10 years - 10,900,000	Observational group: 12.46 Trastuzumab Risk reduction continuing for: 2 years - 13.06 5 years - 13.70 10 years - 14.10	Compared with the observational group the cost per LYG in JPY for the groups is: 2 years - 6,000,000 5 years - 2,600,000 10 years - 1,800,000 In Euros: 2 years - €40,000 5 years - €17,000 10 years - €12,000	One way sensitivity analysis: Results were most sensitive to the period of trastuzumab efficacy. Cost per LYG was JPY 4,700,000, JPY 1,900,000 and JPY 1,300,000 for the period of efficacy of two, five and ten years respectively based on the 1 year follow up data. Probabilistic sensitivity analysis: The probability of 1 year of trastuzumab in the standard scenario being below JPY 5,400,000 (€36,000) was above 95%.
KCE CEA	Current breast cancer treatment with either a 12 month or 9 week regimen of trastuzumab given in addition	Moderate limitations	As for Neyt et al. (2008)	As for Neyt et al. (2008)	As for Neyt et al. (2008) 1 yr post-anthracycline trastuzumab is cost effective in 9 out of 15 patient subgroups. Pre anthracycline regimen cost effective in all but one subgroup.	In addition to the results presented by Neyt et al. 2008 tables and cost effectiveness planes are presented for each of the subgroups (based on prognostic factors) for HERA and FinHer and additional results were presented for the B31/N9831 trials (by stage and according to LVEF).
PHARMAC CUA	Trastuzumab compared with standard treatment.	Minor limitations	Not stated	Not stated	NZ\$ 70,000 – 80,000 per QALY for trastuzumab compared with standard therapy	Scenario analysis: Treatment benefit continues after cessation of therapy for the lifetime of the patient (\$24,000 per QALY). Treatment benefits last two years, then adopt comparator rates (\$127,000). Other one-way sensitivity analyses: A discount rate of 3.5% resulted in an ICER of \$46,000 per QALY and a 50% reduction in the risk of relapse in both arms resulted in an ICER of \$113,000 per QALY.
Ward et al and Roche	Trastuzumab therapy added to standard chemotherapy	Minor limitation	Total costs No trastuzumab: £73,323 Trastuzumab:	QALYs No trastuzumab: 8.78 Trastuzumab:	Manufacturer base case Cost per QALY: £5687 ERG base case	The manufacturer undertook several sensitivity analyses. The cost of trastuzumab and the relative risk reduction had the greatest impact on the ICER. A probabilistic analysis was also carried out.

Study/ Study design	Interventions	Methodological quality	Cost results	Effectiveness results	ICER (£/QALY)	Uncertainty
	compared with standard chemotherapy alone		£87,159	11.21	Cost per QALY: £18,449	The ERG carried out sensitivity analysis and revised the manufacturer's base case. They assumed that all patients received trastuzumab in the metastatic setting whether or not they had previously received it in the adjuvant setting and that there was no further benefit in risk of recurrence after five years. These assumptions gave a revised ICER of £18,449 per QALY gained. Further sensitivity analysis by the ERG gave ICERs of £16,000 to £33,000 per QALY gained, the upper estimate was from an analysis assuming that 23% of women receiving trastuzumab would experience a cardiac event.

* Also see table below on cost perspective

CUA: Cost-utility analysis

CEA: Cost-effectiveness analysis

Table 4 Summary Table of methods and assumptions presented in the economic evaluations

This table outlines the methods used by the studies, particularly with regard to the issues raised in TA 107. The table is separated into cost-utility, cost-effectiveness and regulatory body studies.

Study/ Study design	Intervention and dosing schedule (9/52 weeks)	Main sources of efficacy	HER2 testing included?	Risk of recurrence and survival	Trastuzumab considered in metastatic period? (Cost and/or efficacy?)	Cost perspective	Utilities	Cardiac toxicity included?
Garrison et al., 2007 CUA	Trastuzumab plus adjuvant chemotherapy followed by paclitaxel (AC->P+/-T) 12 months	NSABP B-31 and NCCTG N983 EBCTCG report	Yes 20-30% incidence of HER2 assumed 5 tests performed for each patient identified for trastuzumab tx	The first five years of distant free recurrence and survival estimates were based on empirically fitted observed distributions for the first four years of reported trial data (from NSABP B-31 and NCCTG N983) and extrapolation of the trends to the fifth year. From 6 years onwards the transition probabilities for entering recurrence and death states were assumed to be the same in both arms. Patients were assumed to progress to recurrence based on the rates observed in the EBCTCG report. Before progression to recurrence death rates are based on standard tables. After recurrence death rates are based on trastuzumab in MBC literature.	Yes – all patients were assumed to have received trastuzumab treatment after distant recurrence. Efficacy included.	US	Published literature – limited details provided.	Includes rate and cost of cardiac event but it seems no disutility assumed.
Kurian et al., 2007 CUA	Adjuvant chemo followed by paclitaxel plus/minus Trastuzumab (AC->P+/-T) and TCH 12 months	NSABP B-31 and NCCTG N983 HERA BCIRG 006	Not reported, assume not included.	Relative risk reduction for breast cancer in the no trastuzumab arm was estimated from the NSABP B-31 and NCCTG N983 trials and rates extrapolated beyond four years using published survival data. Relative risk reduction for breast cancer in the trastuzumab arm was assumed to decline. The first two years were taken from clinical trial data then the relative risk reduction was assumed to decrease by one-third with both trastuzumab arms in years 2 to 4, and an additional one-third decrease in years 5 to 10; values were held constant beyond year 10. Non breast cancer deaths were based on standard tables. Deaths from breast cancer were based on trastuzumab in MBC literature.	Yes – all patients received trastuzumab on diagnosis of recurrent systemic HER2neu/positive breast cancer. Patients with metastatic disease are assumed to receive 9 months of trastuzumab therapy. Efficacy included Costs and efficacy varied in SA.	US	Published literature. Life in disease free state adjusted for age – further details were limited.	Costs and utility of cardiac events included.
Lidgren et al. 2007 CUA of testing strategies	Trastuzumab after adjuvant chemotherapy. Adjuvant chemo with no added trastuzumab 12 months	HERA	Yes	A Weibull regression was used to estimate the risks and the mortality of locoregional recurrence, contralateral cancer and distant recurrence for no trastuzumab (based on data on file). The hazard ratio of disease free survival from 1 year of HERA data was used to calculate the probability of locoregional recurrence, contralateral cancer and distant recurrence for trastuzumab. The duration of treatment effect was assumed to last throughout the patient's lifetime. Survival in the no recurrence state was based on standard tables.	No	Sweden	From published literature, based on Swedish population HRQoL data, adjusted by a reduction in HRQoL that the authors derived from	Costs and utility of cardiac events included.

Study/ Study design	Intervention and dosing schedule (9/52 weeks)	Main sources of efficacy	HER2 testing included?	Risk of recurrence and survival	Trastuzumab considered in metastatic period? (Cost and/or efficacy?)	Cost perspective	Utilities	Cardiac toxicity included?
				The hazard ratio used and the duration of treatment effect was varied in sensitivity analysis.			a previous study they carried out.	
Liberato et al., 2006 CUA	Trastuzumab plus adjuvant chemotherapy (AC->P+/-T) Trastuzumab after adjuvant chemotherapy 12 months	NSABP B-31 and NCCTG N983 EBCTCG report HERA (sensitivity analysis)	No costs of HER2 testing were included	The rate of relapse for trastuzumab was taken from the NSABP B-31 and NCCTG N983 trials. No additional benefit due to trastuzumab was applied after the first 5 years of follow-up. Relapse rates for patients receiving adjuvant anthracycline based chemo were taken from the EBCTCG report. Local relapse rates taken from published literature. All reported local relapses occurred in the first 5 years of follow up. Deaths from breast cancer were based on trastuzumab in MBC literature (dependent on previous adjuvant treatment). Non breast cancer deaths were based on National mortality rates.	Yes – Patients with metastatic disease received first line therapy including chemotherapy and trastuzumab if they had not received adjuvant trastuzumab, and chemotherapy alone if they had received adjuvant trastuzumab. It is not clear if costs of trastuzumab are included. The efficacy is varied.	US and Italy.	Published literature – further details were limited.	Costs and utility of cardiac events included.
Millar and Millward, 2007 CUA	Trastuzumab compared with no trastuzumab Both 12 month and 9 week regimen	NSABP B-31 HERA	Cost of testing for HER2 status was not included as it is routine in Australia	The risk of recurrence for no trastuzumab and trastuzumab was taken from the NSABP B-31 and NCCTG N983 trials When calculating the corresponding transition probabilities for the trastuzumab group, the authors further assumed that the relative risk of trastuzumab preventing relapse (~0.5) remained for five years and then diminished progressively to zero over a further three years (by 25%, 50% and 75% respectively), after which the benefit ceased. Deaths from causes other than breast cancer were taken from National mortality rates. Deaths from breast cancer were based on trastuzumab in MBC literature.	It was assumed that no patients receive trastuzumab in the metastatic setting in the base case	Australia	From published literature in which utility weights were extracted from 40 papers on economic analysis in cancer	Costs and utility of cardiac events taken into account
Dedes et al., 2007 CEA	Trastuzumab after adjuvant chemotherapy Both 12 month and 9 week regimen	HERA FinHer	Yes	A constant yearly risk for local and distant recurrences for the first 5 years after adjuvant treatment was assumed. The risk for local and distant recurrences was then gradually reduced by 10% from year 6 to year 15 in order to reflect the flattening of recurrence curve in breast cancer patients after 5 years. The clinical benefit of trastuzumab was assumed to last for the first 5 years in the base case, thereafter the relative risk for recurrent and metastatic disease in the trastuzumab group assumed to be the same as in the observational group.	Yes, base case 50% patients were retreated with trastuzumab. Rate tested in SA.	Sweden	-	The costs and effects of cardiac toxicity was taken into account.

Study/ Study design	Intervention and dosing schedule (9/52 weeks)	Main sources of efficacy	HER2 testing included?	Risk of recurrence and survival	Trastuzumab considered in metastatic period? (Cost and/or efficacy?)	Cost perspective	Utilities	Cardiac toxicity included?
Neyt et al., 2006 CEA	Standard treatment Compared with AC->TH or TCH 12 months	Based on the BCIRG 006 trial and the SEER database	Yes	Unclear – study appeared to take only hypothetical improvements due to trastuzumab into account.	Trastuzumab was considered for use in metastatic cancer although it is not clear if the effectiveness of trastuzumab in this setting has been included.	Belgian	-	Costs and effects of cardiac toxicity were not included.
Neyt et al., 2008 CEA	Standard breast cancer treatment without trastuzumab compared with standard treatment with trastuzumab Both 12 month and 9 week regimen	HERA and FinHer	Yes	The model was mainly based on the progression (or prevention of progression) of patients to metastases. For patients progressing to metastatic disease, life expectancy data were based on a published study. The incremental percentage of patients not progressing to metastatic disease was estimated by multiplying the hazard ratios of patients surviving free of distant recurrence with the baseline risk of progressing to metastatic disease. LYG were then calculated from the life expectancy of patients progressing and not progressing to MBC.	Yes	Belgian	-	Costs of cardiac toxicity were included. The costs were taken from Dutch data as none were available for Belgium.
Norum et al., 2007 CEA	FEC compared with FEC followed by Trastuzumab 12 months	NSABP B-31 and NCCTG N983	Yes	Distant relapse free survival was used as a surrogate for future overall survival. Using published sources, 10 year survival figures for CMF were adjusted for the regimens examined. A 5% absolute improvement in overall survival was added for the FEC regimen and a 10% and 20% increase due to trastuzumab was estimated. The improved survival level was in addition to a stated level and assumed to be reached at 10 years follow up. The benefit was equally distributed over the 10 year period.	Yes – costs are taken into account.	Norwegian	-	Survival benefit was arbitrarily reduced due to cardiac events and secondary malignancy Costs of cardiac events were taken into account.
Shiroiwa et al., 2008 CEA	1 year of adjuvant trastuzumab compared with observational group (various chemotherapy)	HERA trial 2-year follow up	Not reported	Three risk reduction strategies were considered: risk reduction continuing for two years (conservative scenario), risk reduction continuing for five years (standard scenario) and for ten years (optimistic scenario). The assumed risk of recurrence during the first five years was higher than that during the next five years.	Yes	Japan	-	Costs of cardiac toxicity included.
KCE	Both 12 month and 9 week	HERA trial	Yes	Short term results were mainly translated to the long term relying on the hazard ratio of patients surviving	No trastuzumab is given to patients developing	Belgium	-	None

Study/ Study design	Intervention and dosing schedule (9/52 weeks)	Main sources of efficacy	HER2 testing included?	Risk of recurrence and survival	Trastuzumab considered in metastatic period? (Cost and/or efficacy?)	Cost perspective	Utilities	Cardiac toxicity included?
	regimen	Fin Her		free of distant recurrence. For patients progressing to metastatic disease, life expectancy was calculated by adding the time to progression by age and stage, and the respective survival of metastatic disease.	metastatic disease in the base case.			
PHARM AC	Trastuzumab after adjuvant chemotherapy Both 12 month and 9 week regimen	HERA trial for main analysis based on marketing authorisation Fin Her 9 week regimen	Costs only appeared to be reported for the 9 week analysis	Patients were assumed to have continued benefit from treatment with trastuzumab for four years. Patients who remained in remission had a reduced risk of relapse over time (of both local/regional relapse and metastatic relapse).	Of patients with metastatic disease, 20% were assumed to be HER2 positive and receive trastuzumab.	New Zealand	Taken from EQ-5D NZ weights. Values were estimated using descriptions of breast cancer states derived by oncologists. Full details were provided.	Costs and utility of cardiac events included
Ward et al and Roche	Trastuzumab therapy added to standard chemotherapy compared with standard chemotherapy alone	HERA trial	Yes	Natural disease history modelled using transition probabilities from the HERA trial – extrapolated over 45 years. Rate of recurrence for comparator taken from HERA trial – trend of recurrence taken from the ECGBCG report therefore for the first 5 years recurrence rates are assumed to be the same as in the first year (recurrence reduce by a factor of 0.64 and 0.41 years at 5 and 10 years respectively). The relative risk of recurrence from trastuzumab is taken from the HERA trial and assumed to be maintained for 10 years following the initial administration and that two thirds of the benefit is seen until year 45.	No trastuzumab was given in the metastatic setting if patients had already received trastuzumab previously, efficacy data was taken from a trial of trastuzumab in metastatic setting.	UK	From an external report using standard gamble interviews based on health states established by oncologists, breast cancer specialists and psychometric experts completed by 100 members of the public. Participants also completed the EQ-5D to assess their own current	Costs of cardiac events were taken into account.

Study/ Study design	Intervention and dosing schedule (9/52 weeks)	Main sources of efficacy	HER2 testing included?	Risk of recurrence and survival	Trastuzumab considered in metastatic period? (Cost and/or efficacy?)	Cost perspectiv e	Utilities	Cardiac toxicity included?
							health.	

Appendix 2: Description of trials

NSABP-B31 and NCCTG N983 trials – carried out separately and a joint analysis was subsequently carried out. This was an open label RCT examining AC->P with AC->PT.

HERA – open label RCT 12 months of trastuzumab following adjuvant chemotherapy, neoadjuvant chemotherapy or both (various regimens were allowed) compared with observation.

FinHer – open label RCT comparing 9 weeks of adjuvant trastuzumab following on from docetaxel or vinorelbine compared with docetaxel or vinorelbine alone.

BCIRG 006 trial – this was a phase III trial comparing 3 treatment regimens. Chemotherapy (AC) followed by docetaxel plus trastuzumab (TH), chemotherapy (docetaxel and carboplatin chemo) plus trastuzumab (TCH), and chemotherapy followed by docetaxel alone (AC->T).

Appendix 3: Regimens

Abbreviation

AC
AC->P
AC->T
AC->PT
AC->TH
DAC
FAC
FEC
CMF
E-CMF
TCH

Regimen

Doxorubicin and cyclophosphamide
Doxorubicin and cyclophosphamide followed by paclitaxel
Doxorubicin and cyclophosphamide followed by docetaxel
Doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab
Doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab
Docetaxel, Doxorubicin, Cyclophosphamide
5-Fluorouracil, Doxorubicin, Cyclophosphamide
5-Fluorouracil, Epirubicin, Cyclophosphamide
Cyclophosphamide, Methotrexate, Fluorouracil
Epirubicin, Cyclophosphamide, Methotrexate, Fluorouracil
Docetaxel, carboplatin with concurrent trastuzumab

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Economic Evaluations

Cost-utility analyses

Garrison, L., et al., Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. *Cancer* 2007; 110:489-98.

Design:Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model – software not specified).

Clinical effectiveness:

Based on the joint analysis of randomised controlled trials (RCTs) NSABP B-31 and NCCTG N983, the early breast cancer trialists' collaborative group (EBCTCG) report, published literature, conference abstracts, assumptions, estimates of utilities from published literature.

Cost estimation:

Direct costs included cost of therapy and administration, diagnostic tests, cardiotoxicity events, recurrence costs (distant metastases) and costs associated with death. Some indirect costs were included – value of patient time per hour and travel costs per infusion. The payer and (partial) societal perspective was taken. Costs are reported for 2006 and in US dollars. Cost and benefits were discounted at 3%.

Country: US, **setting:** Hospital

Inclusion criteria:

Not reported

Exclusion criteria:

Not reported

Population:

Women with early stage HER2-positive Breast Cancer aged 50 years.

Interventions:

Based on NCCTG N9831 and NSABP B-31.

NCCTG N983:

Doxorubicin and cyclophosphamide (AC) given every 3 weeks for 4 cycles. Followed by: weekly paclitaxel for 12 weeks (Arm A - AC->T); 12 weeks of weekly paclitaxel followed by weekly trastuzumab for 52 weeks (Arm B); or weekly paclitaxel plus trastuzumab for 12 weeks, followed by weekly trastuzumab alone for 40 weeks (Arm C) (AC->TH).

NSABP B-31:

AC; followed by: 3 weekly or weekly paclitaxel for 12 weeks (Arm 1 - AC->T); or 3 weekly or weekly paclitaxel for 12 weeks plus trastuzumab for 12 weeks, followed by weekly trastuzumab alone for 40 weeks (Arm 2) (AC->TH).

The cost effectiveness analysis was based on a comparison of Arm 1 in NSABP B-31 and Arm A in NCCTG N9831 with Arm 2 in NSABP B-31 and Arm C in NCCTG N9831.

Outcomes:

Quality adjusted life years (QALYs), Life Years (LYs), costs and incremental cost effectiveness ratios (ICERs)

Follow up:

Time horizon = lifetime and 20 years

Data used to populate the model:Assumptions:

- All patients received treatment during the first year while they were still disease-free.
- All patients were assumed to have received trastuzumab treatment after distant recurrence.
- Cardiac dysfunction associated with the addition of trastuzumab was assumed to be reversible and to have no direct mortality effect beyond that reflected in the 4-year trial period.
- The first five years of distant free recurrence and survival estimates were based on empirically fitted observed distributions for the first four years of reported trial data (from the joint analysis of NSABP B-31

- and NCCTG N983) and extrapolation of the trends to the fifth year.
- From 6 years onwards the transition probabilities to recurrence and death were assumed to be the same in both arms.
- Progression to recurrence was based on the rates observed in the EBCTCG report.
- Mortality due to metastatic breast cancer was taken from a conference abstract on the cost effectiveness of trastuzumab in metastatic breast cancer.
- Mortality due to other causes was based on standard US life tables.

Health states: treatment, disease-free, distant recurrence, and death

Data from studies:

Outcome of interest	Estimate
Cumulative probability, year 4	-
Control arm (AC->T)	-
Recurrence free survival	0.719
Overall survival	0.870
Trastuzumab arm	-
Recurrence free survival	0.856
Overall survival	0.911
Annual rate of recurrence after 5 years	-
AC->T (years 6-9)	0.048
AC->TH (years 6 to 9)	0.048
AC->T (years 10+)	0.033
AC->TH (years 10+)	0.033
Annual probability of death following distant metastases	-
Control arm (AC->T)	0.323
Trastuzumab arm	0.323

Utilities: from published literature, further details are limited.

Input parameter	Utility
Year 1 AC->T including treatment	0.770
Year 1 AC->TH treatment	0.710
Year 2+ stable disease utility	0.900
Year 2+ recurrence utility	0.600

Health care resource utilisation and costs: Resource utilisation is taken mainly from published sources and the clinical trial data. Costs were based on Medicare reimbursement rates and published data. Costs of comparator therapies do not seem to have been included.

Unit costs	2006 US\$
Diagnostic tests	-
Immunohistochemical (IHC) tests	89
Fluorescence in situ Hybridisation (FISH)	482
Proportion of HER2 tests by FISH method	30%
Trastuzumab infusion (per vial)	2987
Administration of trastuzumab	172.81
Left ventricular ejection fraction (LVEF) exam	367
Mean cost per cardiotoxicity event	1979
Recurrence cost (distant metastases)	40,000
Costs associated with death	10,000
Indirect costs	-
Value of patient time per hour	25.57
Travel cost per infusion	14.55

Results

Outcome of interest	AC->T	AC->TH
Lifetime health care costs (payer) (US\$)	28,749	73,627

Incremental cost (US\$)	-	44,923
LYS	11.88	13.72
Incremental life years	-	1.84
QALYs	10.08	11.78
Incremental QALYs	-	1.70
Cost per LY (US\$)	-	24,435
Cost per QALY (US\$)	-	26,417

Results were also provided for the alternative scenarios of a 20-year horizon (US\$34,201 per QALY gained) and for the societal perspective (US\$27,637 per QALY gained). It is not clear how long the lifetime horizon is in terms of years.

Sensitivity analysis:

One way sensitivity analysis was carried on most parameters in the model. This is presented as a tornado diagram. The cost utility results range from US\$9104 to US\$69,340 per QALY. The ICER varied considerably with changes in the discount rate, price of trastuzumab and the probability of metastases. The model was most robust to changes in the costs of detecting and treating cardiac events and the costs of diagnostic testing.

Authors' conclusions:

Overall, the addition of trastuzumab to standard adjuvant therapy appears to reduce the risk of recurrence and improves survival in patients with early stage breast cancer. Over a lifetime horizon it appears that trastuzumab for the treatment of early stage breast cancer is cost effective.

General comments:

There are some limitations with regard to the detail in the explanation of the projection of recurrence free survival and overall survival. It seems that a calibration exercise has been conducted. There are some limitations regarding the calculation of cost data in that drug costs other than for trastuzumab do not seem to have been included and there is a lack of reporting the resource use required. The one way sensitivity analysis is extensive, however no probabilistic sensitivity analysis was conducted. There is a detailed section in the discussion comparing the results of this study with the results of other similar studies. Contralateral and local recurrence health states were not included in the model because of limited data available. The authors state that the effect of these states is reflected in the time to distant recurrence estimates. It is not clear how this is the case.

Kurian et al., A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer; 2007. J Clin Oncol 25:6:634-641.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model – TreeAgePro 2005)

Clinical effectiveness:

Taken from the joint analysis of RCTs: NSABP B-31, NCCTG N983 and BCIRG 006 trial, published literature, assumptions, estimates of utilities from published literature.

Cost estimation:

Cost of trastuzumab and other therapies including administration, cardiac monitoring, recurrence costs (including chemotherapy, supportive and end of life care) and cardiac toxicity. A societal perspective was stated, however the only indirect cost included was costs for time lost from work to receive trastuzumab. Costs are reported for 2005 and in US dollars. Both costs and QALYs are discounted at 3% in the base case.

Country: US, **setting:** Hospital

Inclusion criteria:

Women who have undergone surgical resection of all apparent disease, with and without involved axillary lymph nodes, comparable to the trial populations.

Exclusion criteria:

Not stated.

Population:

HER2/neu-positive early stage breast cancer with an average age at baseline of 49 years

Interventions:

Based on NCCTG N9831, NSABP B-31 and BCIRG 006 trials.

Conventional chemotherapy without trastuzumab; anthracycline based trastuzumab regimens used in NCCTG N9831 and NSABP B-31, and the non-anthracycline trastuzumab regimen used in BCIRG 006 as described below.

Two model schemas were presented, one for no trastuzumab and nonanthracycline trastuzumab and another for anthracycline- based trastuzumab.

NT arm – AC, followed by paclitaxel (based on the control arms of NSABPB-31 and NCCTG9831).

AAT arm (anthracycline-containing) – AC with trastuzumab administered weekly concurrently with paclitaxel; for a total of 1 year of trastuzumab therapy.

NAT arm (non anthracycline-containing) – docetaxel plus carboplatin. Trastuzumab weekly, concurrently with chemotherapy; after completion of chemotherapy, the authors assumed that trastuzumab is administered every 3 weeks to complete a total of 1 year of trastuzumab therapy.

Outcomes :

QALYs, LYs, costs and ICERs

Follow up:

Time horizon = not stated, although a lifetime horizon may be reasonable to assume. Markov cycle length was 1 month.

Data used to populate the model:Assumptions:

- All patients received trastuzumab on diagnosis of recurrent systemic HER2neu/positive breast cancer.
- Beyond the time horizon for the trial the relative risk reduction for breast cancer was assumed to decline.
- The authors assumed a one-third decrease in the relative risk reduction with both AT arms in years 2 to 4, and an additional one-third decrease in years 5 to 10; values were held constant beyond year 10.
- Patients with metastatic disease were assumed to receive 9 months of trastuzumab therapy.
- The rate of cardiac deaths was assumed not to increase in the AAT arm in the base case and the rate of cardiac toxicity was assumed not to be elevated in the NAT arm.
- Mortality due to causes other than breast cancer was based on national mortality rates.

Health states: Well, breast cancer recurrence, cardiac toxicity, simultaneous cardiac toxicity and breast cancer recurrence, and death.

Data from prospective studies: all the monthly probabilities were provided (see table 1 of study). Only the transition probabilities were reported.

Outcome of interest	Estimate
Median survival in metastatic disease (9 months of trastuzumab)	25 months
Percentage increase in cardiac toxicity in the ATT arm	3%
Percentage of patients who improve following cardiac toxicity in the AAT arm (becoming symptomatic with or without ongoing therapy, within 6 months).	80%

Utilities: from published literature, life in the disease free state was adjusted for age. No further details were provided.

Input parameter	Utility
Adjuvant trastuzumab	0.85
Adjuvant chemotherapy without trastuzumab	0.85
Well	1.00
Well, age 45-54 years	0.90
Well, age 55-64 years	0.87
Well, age 65-74 years	0.83
Well, age > 75 years	0.79

CTS	0.64
CTNS	1.00
Weighted average, cardiac toxicity utility	0.91
Metastatic breast cancer	0.55
Death	0.00

Health care resource utilisation and costs: All costs reported are referenced although details of resource use extraction are somewhat unclear.

Unit costs	US\$ 2005
Total trastuzumab costs†	64,185
AAT, total costs	101,192
NAT, total costs	115,208
Cardiac toxicity without symptoms per month	148
Cardiac toxicity with symptoms per month	177
Breast cancer recurrence	3816

Results

Outcome of interest	NT	AAT	NAT
Total costs (US\$)	133,429	190,092	206,561
QALYs	9.35	10.77	10.61
LYS	12.29	14.01	13.56
Incremental cost per QALY (US\$)	-	39,892	Dominated*
Incremental cost per LY (US\$)	-	32,816	Dominated*

*the AAT regimen is less costly and more effective than the NAT regimen

Sensitivity analysis:

Probabilistic sensitivity analysis was undertaken. Scatter plots of the ICERs are presented. The full methods of the probabilistic analysis are unclear; it seems that the authors have only varied the base case recurrence rates in the analysis. Results of this analysis show considerable uncertainty surrounding this variable. The distribution mean shows that the ICER for AAT versus NT was \$56,491 per QALY (at the distribution minimum: NT dominates AAT and at the distribution maximum: \$8,144,473 per QALY) and AAT dominates NAT (minimum: AAT dominates NAT and maximum: \$20,398,133 per QALY).

In a sensitivity analysis that assumed that recurrence rates were minimally improved with either AT arm after year 4 (hazard ratio 0.99), the ICER increased to \$142,516/QALY for AAT and \$157,078/QALY for NAT.

The results of the one-way sensitivity analysis show that results are most sensitive to the discount rate, the cost of AT, median survival after breast cancer recurrence, and the cost of treating metastatic breast cancer. The results are least sensitive to changes in the probability of dying as a result of or recovering from cardiac toxicity, costs of cardiac toxicity, and all utilities.

Authors' conclusions:

The authors state that in their base case analysis and in a probabilistic sensitivity analysis of recurrence rates under different treatment strategies, the anthracycline dominates the NAT arm. If the improvements in overall and disease-free survival seen in the randomised AT trials do not persist over time, then the ICER of an anthracycline-based regimen may be considerably higher than in the base case.

General comments:

There are some limitations regarding the source of clinical effectiveness data. Although the authors have referenced their input data, only the transition probabilities have been presented.

The probabilistic analysis seems to only examine one variable and is therefore not a full probabilistic exploration of the uncertainty surrounding input parameters.

Lidgren et al., Cost-effectiveness of HER2 testing and 1-year adjuvant trastuzumab therapy for early breast cancer. *Annals of oncology* 2007; published December 6, 2007.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model – DATA Pro Suite 2006).

Clinical effectiveness:

Based on the HERA trial, published literature, assumptions, data on file and estimates of utilities from published literature.

Cost estimation:

Intervention costs: trastuzumab drug costs, trastuzumab infusion costs, cost of cardiac monitoring, cost of cardiac related adverse events, and cost of HER2 testing; Direct breast cancer costs: Inpatient costs, outpatient costs, drug costs, informal care cost, and palliative care cost; Indirect costs: value of productivity loss due to breast cancer. A societal perspective was taken. Costs are reported for 2005 and in Euros. Cost and benefits were discounted at 3%.

Country: Sweden, **setting:** Hospital

Inclusion criteria:

Not stated

Exclusion criteria:

Not stated

Population:

Women with early stage breast cancer that had been completely excised and treated with at least four cycles of adjuvant chemotherapy.

Interventions:

Five testing strategies were examined

The base case strategy is: no testing followed by adjuvant chemotherapy

The four alternative strategies are: strategies of a first test followed or not followed by a second test then 1 year of adjuvant trastuzumab for subgroups of tested individuals (see study for full details of each strategy).

Estimates of the effectiveness of trastuzumab were based on HERA trial.

Outcomes:

QALYs, LYS, costs and ICERs

Follow up:

Time horizon = lifetime

Data used to populate the model:

Assumptions:

- The risk of recurrence and mortality in the model has been based on a sample of 20,624 Swedish breast cancer patients – this data is unpublished.
- A Weibull regression was used to estimate the risks and the mortality of locoregional recurrence, contralateral cancer and distant recurrence.
- The risk of distant recurrence for HER2-positive patients was assumed to be twice as high compared with HER2-negative patients.
- The mortality risk for patients in the no recurrence state was based on Swedish life tables.
- Outcome in terms of survival and QALY was calculated from the effect of 1-year adjuvant trastuzumab on the risk of having a locoregional recurrence, a contralateral recurrence, or a distant recurrence, and the absolute risk in a cohort of patients was multiplied with the hazard ratio of 0.64.
- This risk reduction was only applied for HER2-positive patients in the no recurrence state receiving 1 year of adjuvant trastuzumab. In the base case scenario, the duration of treatment effect was assumed to last throughout the lifetime of the patient.

Health states: no recurrence, locoregional recurrence, contralateral recurrence, distant recurrence, and death.

Data from studies: data on the probability of IHC test results conditional on FISH test results were provided (see table 2 of study for further details).

Outcome of interest	Estimate
Prevalence of HER2 positive breast cancer	0.25
Cumulative risk of recurrence and mortality (at 20 years – 5 and 10 year figures are also presented in the study)	-
From no recurrence to	-

Locoregional recurrence	18.0%
Contralateral recurrence	9.4%
Distant recurrence	24.9%
Dead	16.5%
From locoregional recurrence	-
Distant recurrence	61.3%
Dead	40.5%
From contralateral recurrence	-
Distant recurrence	37.8%
Dead	40.0%
From distant recurrence	-
Dead	99.7%
Patients in the trastuzumab arm suffering symptomatic congestive heart failure	2.1%

Utilities: from published literature, based on Swedish population health related quality of life (HRQoL) data, adjusted by a reduction in HRQoL (general age and sex matched population for each health state) that the authors derived from a previous study they carried out.

Input parameter	Utility
No recurrence	0.935
First year in locoregional recurrence or contralateral recurrence	0.935
Second and consequent years in locoregional recurrence or contralateral recurrence	
Distant recurrence	0.822
Congestive heart failure	Utility reduced by 50% for 6 months

Health care resource utilisation and costs: indirect costs were also included based on a previous study by the authors. The indirect costs represented the loss of productivity due to breast cancer (value of productivity loss estimated using the human capital approach). Future costs are also included and were derived from a published study.

Unit costs	2005 Euros €
Outpatient visit	171
Multiple uptake gated acquisition (MUGA) scan	195
IHC test	200
FISH test	548
Trastuzumab (each cycle)	2055
Total drug cost of trastuzumab for 1 year of adjuvant treatment (including loading dose)	36,298
Outpatient costs of administration for trastuzumab (over a year)	2899
Total additional cost of cardiac monitoring and treatment of adverse effects per patient.	1559
Additional cost of palliative care (one-time cost of patients dying from breast cancer in the distant recurrence state).	6813

Results

Outcome of interest	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
Total cost (€)	115,151	122,450	129,188	124,571	125,503
QALYs gained	11.020	11.211	11.281	11.282	11.304
ICER (€)	-	dominated	dominated	35,975	41,471

Strategy 1 = standard care – no testing and no trastuzumab.

Strategy 2 and 3 dominated (were more effective and less costly).

Strategy 4 and 5 had an ICER of €35,975 and €41,471 respectively compared with Strategy 1.

Sensitivity analysis:

Subgroup analysis was carried on age at the start of adjuvant trastuzumab treatment. The results of this analysis found that patients aged 35 had a lower cost per QALY, €26,700 and €30,100 for strategies 4 and 5 respectively. At age 65 the resulting ICERs were €56,200 and €64,700 for strategies 4 and 5 respectively. In one-way sensitivity analysis, the authors found that relative risk reduction (hazard ratio) of an event arising from treatment with trastuzumab, duration of effect and inclusion of future costs were the parameters that affected the ICERs most. An increase of 30% in the hazard ratio of an event after 1 year of trastuzumab resulted in ICERs of €84,400 and €97,000 for strategies 4 and 5 respectively.

Probabilistic analysis was carried out. Distributions were only placed around the following parameters; costs, utilities and effect of 1 year of trastuzumab. Only the cost effectiveness acceptability curve (CEAC) was presented. From the graph it can be estimated that at €40,900, the probability of strategy 4 being cost effective is approximately 65% and of strategy 5 being cost effective is approximately 50%.

Authors' conclusions:

The authors state that FISH testing for all patients with 12 months of adjuvant trastuzumab for FISH+ patients is a cost effective treatment option from a societal perspective.

General comments:

This study examines cost effectiveness of testing strategies which may be considered outside of the remit of this review. However, this study was included as it was the only study identified that examined treatment with trastuzumab following the testing strategies which makes the paper more relevant for the current review. Risk of recurrence and mortality in the model from unpublished data. This means the figures cannot be fully validated. Not all parameters were included in the probabilistic analysis and only the CEAC was presented.

Liberato et al., Cost effectiveness of adjuvant trastuzumab in human epidermal growth factor receptor 2-positive breast cancer; 2006. J Clin Oncol 25:625-633.

Design:**Type of economic evaluation:**

Cost-utility analysis using modelling (i.e. Markov model – TreeAgePro).

Clinical effectiveness:

Taken from RCTs NSABP B-31 and NCCTG N983 and the subsequent joint analysis, the EBCTCG report, published literature, assumptions, estimates of utilities from published literature.

Cost estimation:

Direct costs included cost of therapy, administration and follow up, cardiac dysfunction, local relapse and metastatic disease. No costs of HER2 testing were included. The perspective of the US and Italian health care systems was taken. Costs are reported in Euros and US dollars. No cost year is reported. A discount rate of 3% was applied to both costs and benefits.

Country: US and Italy **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Women with early stage HER2-positive Breast Cancer with a median age of 50 years.

Interventions:

Based on population in NCCTG N9831 and NSABP B-31.

Adjuvant chemotherapy and trastuzumab compared with chemotherapy alone.

In the model patients had already received AC and were then allowed to receive paclitaxel alone or in combination with trastuzumab. After 3 months (one Markov cycle) only patients assigned to the trastuzumab strategy received treatment.

Outcomes:

QALYs, LYs, costs and ICERs

Follow up:

Time horizon = 15 years, Markov cycle length was 3 months

Data used to populate the model:Assumptions:

- No additional benefit was added due to trastuzumab after the first 5 years of follow-up.
- Cardiac mortality assumed zero at baseline analysis.
- Those having cardiac events (and therefore interrupted therapy) were assumed to continue benefiting from trastuzumab and had the same relapse rate as those continuing on therapy.
- All reported local relapses occurred in the first 5 years of follow up.
- Patients with metastatic disease received first line therapy including chemotherapy and trastuzumab if they had not received adjuvant trastuzumab, and chemotherapy alone if they had received adjuvant trastuzumab.
- Mortality due to causes other than breast cancer was based on national mortality rates.

Health states: disease-free, local relapse, disease free after local relapse, metastatic disease, and death

Data from prospective studies:

Outcome of interest	Estimate
Disease free state	
Cardiac dysfunction and permanent trastuzumab discontinuation in patients receiving ongoing adjuvant trastuzumab	-
0-3 months	2%
4-6 months	7%
7-9 months	6%
10-12 months	2%
Cardiac dysfunction in patients who have never received adjuvant trastuzumab	-
0-6 months	4%
Percentage of symptomatic patients with cardiac dysfunction	-
0-12 months	23%
Any relapse in patients who have never received adjuvant trastuzumab	-
0-12 months	2%/yr
13-60 months	11%/yr
5-10 years	3.4%/yr
11-15 years	2.7%/yr
Relative risk of any relapse in patients receiving ongoing or previous adjuvant trastuzumab	-
0-5 years	0.48
5-15 years (assumption)	1.00
Percentage of local relapses	-
0-5 years	32%
6-15 years (assumption)	0%
Local relapse state	
Disease free after local relapse	-
0-12 months	90%
Disease free after local relapse	
Systemic relapse in patients with a local relapse occurring in the first year of follow-up	-
0-3 years	40%/yr
>3 years	7%/yr
Systemic relapse in patients with a local relapse occurring after the first year of follow-up	-
0-3 years	20%/yr
>3 years	7%/yr
Metastatic disease state	
Death in patients not receiving trastuzumab	59%/yr
Death in patients receiving trastuzumab	48%/yr

Utilities: from published literature, further details are not given.

Input parameter	Utility
Disease free - without symptomatic cardiac dysfunction	0.97
Disease free - with symptomatic cardiac dysfunction	0.51
Disease free after local relapse	0.92
Local relapse	0.82
Metastatic disease	0.58

Health care resource utilisation and costs: Much of the resource utilisation was extracted from clinical trials (NCCTG N9831 and NSABP B-31). All costs were derived from published sources including economic evaluations. Full descriptions of costs and references are given.

Unit costs	Italy (€)	US (\$)
Adjuvant trastuzumab treatment (overall cost)	40,100	44,881
Paclitaxel treatment (overall cost)	2716	7592
Adjuvant hormone therapy	2117 per year	2701 per year
Echo Echocardiography	62	420
Symptomatic cardiac dysfunction	375 per 3 months	1750 per 3 months
Asymptomatic cardiac dysfunction	188 per 3 months	1000 per 3 months
Early follow-up (< 5 years)	96 per year	700 per year
Late follow-up (>= 5 years)	56 per year	700 per year
Local relapse (overall cost)	3780	16,200
Metastatic disease	15,600 per year	20,280 per year

Results

Outcome of interest	Adjuvant trastuzumab	No adjuvant trastuzumab
15 year survival	0.43	0.56
Life years (discounted)	9.82	8.80
Incremental LY	-	1.02
QALYs (discounted)	9.22	8.03
Incremental QALYs	-	1.18
Italian costs	€54,058	€36,522
Incremental costs	-	€17,536
Cost per LYS	-	€17,192
Cost per QALY	-	€14,861
US costs	\$77,947	\$55,562
Incremental costs	-	\$22,385
Cost per LYS	-	\$21,946
Cost per QALY	-	\$18,970

Sensitivity analysis:

The time frame of the analysis substantially affects the result. The author's probabilistic analysis showed that the ICER ranged from €11,286 to €128,780 per QALY (US\$15,165 to US\$143,064 per QALY) when the time horizon is varied from 20 to 5 years respectively. Varying the baseline age of women in the cohort, and therefore the annual risk of death due to causes other than breast cancer, also affected the result. Adjuvant trastuzumab was less cost effective in older women.

The impact of the patients' risk of relapse was tested. Adjuvant trastuzumab cost more than €50,000/QALY (\$60,000/QALY) in very low risk patients (i.e. those with a forecasted risk of relapse lower than 15% at 10 years), whereas it cost less than €20,000/QALY (\$30,000/QALY) if the risk was higher than 40%.

The results were not sensitive to the proportion of women receiving trastuzumab either in the adjuvant or in the metastatic phase, changes in the quality of life assigned to the health states or the mortality rate of patients developing symptomatic cardiac toxicity.

Probabilistic analysis on the base case demonstrated that adjuvant trastuzumab was less than €20,000 per QALY (\$27,000 per QALY) with a probability of 91%.

A multiway analysis using the main characteristics of the HERA trial was performed. Patients received

trastuzumab after adjuvant chemotherapy, incurred a 1.27 higher risk of relapse in the first 5 years and the hazard ratio of relapse in patients receiving adjuvant trastuzumab was calculated according to the hazard ratio reported by HERA (0.54). Cardiac toxicity was decreased from 17% to 8.8% and the proportion of symptomatic patients was reduced from 23% to 20%. The results were that adjuvant trastuzumab cost €11,228 per QALY (95% confidence limits (CI): €5,895 to €28,936) for the Italian setting and \$16,199 per QALY (95% CI: \$3,059 to \$52,538) for the US setting.

Authors' conclusions:

Overall, the cost effectiveness of adjuvant trastuzumab in the Italian health care setting was €14,861 per QALY. The time frame of the analysis affects the results the most. The drug was only cost effective after 7 to 10 years because the clinical benefits of trastuzumab were gained over time. Patient age, along with the ability of trastuzumab to prevent relapses also substantially affected the result. Therefore, adjuvant treatment with trastuzumab might not be cost effective in older HER2-positive patients who have a low risk of relapse. From the US perspective adjuvant trastuzumab had an ICER of \$18,970 per QALY.

General comments:

The authors performed a probabilistic sensitivity analysis. The results of varying main parameters were presented individually as well as presenting a CEAC. There is some confusion over the combined effects of some of the parameters on the overall result. However, the CEAC seems to show that adjuvant treatment may be cost effective. The multiway analysis using the HERA trial protocol could have been presented more clearly. More detail on the generalisability of the EBCTCG report would also have been useful.

Millar and Millward, Cost effectiveness of trastuzumab in the adjuvant treatment of early breast cancer. A lifetime model, 2007. *Pharmacoeconomics*, 25(5): 429-442.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model in Microsoft Excel).

Clinical effectiveness:

RCTs including NSABP-B31 and HERA, assumptions, published literature, estimates of utilities from a published source.

Cost estimation:

Cost of trastuzumab (for both a 52-week course and a 9-week course), treatment of illnesses other than cancer, metastatic cancer after relapse, local or regional recurrence and heart failure screening. Cost of testing for HER2 status was not included as it is routine in Australia. Direct medical costs only, taken from the Australian health system perspective. All costs were reported in 2005 values and in Australian dollars (\$A). Cost and benefits were discounted at 3%.

Country: Australia, **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Women with HER2-positive breast cancer with an age at diagnosis of 50 years.

Interventions:

52-week course of trastuzumab, 9-week course of trastuzumab or no treatment. Further details were not provided.

Outcomes:

QALYs, LYS costs and ICERs

Follow up:

Time horizon = Life time (51 years). Cycle length was 1 year.

Data used to populate the model:

Health states:

Remission; relapse with local or regional recurrence; relapse with distant disease (metastases); and death

from metastatic breast cancer, or from non-cancer causes while in any of the first three disease states.

Assumptions:

- Development of new or contralateral breast cancer was not included.
- Death from breast cancer could only occur in the metastatic disease state.
- Risk of cardiac toxicity was assumed maximal at the end of trastuzumab therapy and it resolved over the next three years. No increase in cardiac mortality with trastuzumab was assumed.
- All patients survived the 52-week course of trastuzumab without relapse (or the 9-week course with the non-relapse assumption carried forward to 52 weeks).
- 70% of patients experiencing relapse with metastatic disease received trastuzumab in sensitivity analyses. It was assumed that no patients receive trastuzumab in the base case.
- Transition probabilities for the 52-week course were also applied to the 9-week course model except for the probability of remission to metastatic disease.
- Transition probabilities for remission to local recurrence and metastases over time were adjusted to correspond with the risk of relapse in breast cancer decreased progressively over time. Transition probabilities for this adjustment were taken from the published literature.
- When calculating the corresponding transition probabilities for the trastuzumab group, the authors further assumed that the relative risk of trastuzumab preventing relapse (~0.5) remained for five years and then diminished progressively to zero over a further three years (by 25%, 50% and 75% respectively), after which the benefit ceased. This three year tailing off effect was held constant throughout sensitivity analysis.
- Mortality due to causes other than breast cancer was based on standard life tables.

Data from RCTs:

Outcome of interest	Estimate
Initial annual transition probabilities	-
Remission to metastatic disease (no trastuzumab)	0.087
Relative risk of reported survivals for developing distant metastases following a year of trastuzumab	0.48
Relative risk of survival free of first distant recurrence for HER2 positive patients given or not given 9 weeks of trastuzumab.	0.29
Remission to local recurrence	One third of the probabilities for development of metastases
Local recurrence to metastases	Corresponding rate from remission, adjusted by a factor of 3 – same for both groups
Metastases to death from breast cancer	0.325 – same for both groups
Metastases to death from breast cancer – when including trastuzumab as palliative care	0.280
Remission to distant metastases	Adjusted empirically to produce disease free survival in each group at 3 years equal to the reported value in the joint analysis

Utilities: From published literature in which utility weights were extracted from 40 papers on economic analysis in cancer. These were the only details provided.

Health States	Utility
Remission	0.98
Locoregional relapse	0.80
Metastatic disease	0.55
Heart failure	Factor of 0.85 applied to each of the above weights
Remission	0.83
Locoregional relapse	0.68
Metastatic disease	0.47

Health care resource utilisation and costs: All health care resource utilisation and costs were presented in

detail. Resource use was estimated by a clinical expert.

Unit costs	2005 \$A
Trastuzumab 52-week course per patient	59,752
Trastuzumab 9-week course per patient	11,332
Trastuzumab in metastatic disease – 9 months	41,208
Treatment of illnesses other than cancer	1560
Metastatic disease	47,674
Recurrence	29,834
Heart failure screening	641
Heart failure treatment	2251

Results

Outcomes for trastuzumab for 52-week regimen

Outcome of interest	Trastuzumab	No trastuzumab
Total costs with drug acquisition costs added and discounted at 3% (\$A)	87,818,858	31,513,284
Breast cancer deaths	346	482

Outcome of interest	Trastuzumab 52-weeks	Trastuzumab 9-weeks
Cost per cancer death avoided (\$A)	414,012	30,608
Cost per LYS (\$A)	13,730	1016
Cost per QALY (\$A)	22,793	1700

Sensitivity analysis:

- When relapse with metastatic disease is treated with trastuzumab (in the 52-week regimen model) the ICER improved (\$A 20,967 per QALY).
- Results of the one way and multivariate sensitivity analysis showed that the model was most sensitive to drug acquisition costs (indicated by the 9-week model), assumption on the duration of benefit and the discount rate.
- Univariate analysis on duration of effect showed that the ICER ranges from \$A 18,444 per QALY for 10 years duration of effect to \$A 35,353 per QALY for 2 years duration of effect.
- Sensitivity analysis for the 9-week course showed that when the risk reduction for distant recurrence is varied (using 95% CI) the range of cost effectiveness is from \$A 1018 to \$A 5569 per QALY.

Authors' conclusions:

The author state that adjuvant therapy with trastuzumab may be cost effective. The overall budget impact with a 52-week course is significant while the 9-week course costs much less and is therefore economically attractive.

General comments:

This study is a useful addition to the review despite some limitations around the reporting of results. This is due to the comparison of the 9 week and 12 month treatment regimens. The difference in cost effectiveness between these regimens is an important consideration in this review. The authors do not explicitly state the comparator in the model, only that they were comparing trastuzumab versus no trastuzumab and did not seem to cost current therapy.

No details of QALYs or incremental QALY results were provided.

Cost-effectiveness analyses

Dedes K. J. et al., Cost-effectiveness analysis of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial, 2007. *Annals of Oncology* 25: 1493-1499.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (i.e. Markov model – software not specified).

Clinical effectiveness:

Taken from the clinical data from HERA and FinHer RCTs, published literature, assumptions.

Cost estimation:

Cost of trastuzumab and other therapies, cost of hospitalisation, treatment for recurrent and metastatic disease, radiotherapy, diagnostics and palliative chemotherapy, treatment of symptomatic CHF and echocardiography were estimated. Direct medical costs were calculated from the perspective of a Swiss health care provider in Euros and from the year 2006. Only costs were discounted at 3% in the base case. Effectiveness was discounted by 3% in sensitivity and scenario analysis.

Country: Switzerland, **setting:** Hospital

Inclusion criteria:

As for HERA and FinHer trial.

Exclusion criteria:

Not stated.

Population:

Women with early stage HER2-positive breast cancer with an average age of 50 years.

Interventions:

Two strategies were examined based on HERA and FinHer: adjuvant treatment after surgical therapy of early breast cancer with or without trastuzumab.

Outcomes:

LYs, costs and ICERs

Follow up:

Time horizon = 15 years (5 and 10 year scenarios were also presented). Markov cycle length was 1 year.

Data used to populate the model:

Assumptions:

- A constant yearly risk for local and distant recurrences for the first 5 years after adjuvant treatment was assumed.
- The risk for local and distant recurrences was then gradually reduced by 10% from year 6 to year 15 in order to reflect the flattening of recurrence curve in breast cancer patients after 5 years.
- The clinical benefit of trastuzumab was assumed to last for the first 5 years in the base case, thereafter the relative risk for recurrent and metastatic disease in the trastuzumab group assumed to be the same as in the observational group.
- The authors assumed that medical treatment for congestive heart failure (CHF) was carried out for 1 year (assuming trastuzumab's cardiotoxicity is reversible).
- Mortality due to side-effects was assumed to be zero.
- Mortality due to causes other than breast cancer was based on national mortality rates.

Health states: disease-free survival, local recurrence, regional recurrence, metastatic disease and death.

Data from prospective studies: Annual probabilities were provided for survival, recurrence and mortality. Only the transition probabilities were reported.

Outcome of interest	Estimate for trastuzumab – HERA data
After adjuvant treatment	-
Local recurrence	0.01
Regional recurrence	0.006
Metastatic disease	0.05
Death rate for the first year	0.017

Yearly mortality for 2nd–15th year rate	0.0018 (50 years) to 0.0067 (65 years)
Outcome after treatment of metastatic disease – treatment with trastuzumab	-
Metastatic disease	0.78
Death	0.22
Outcome after treatment of metastatic disease – treatment with trastuzumab	-
Metastatic disease	0.67
Death	0.33

Outcome of interest	Estimate for trastuzumab – FinHer data
After adjuvant treatment:	-
Local recurrence	0.003
Regional recurrence	0.003
Metastatic disease	0.023
Death rate for the first year	0.017

Utilities: no utilities were included in this study

Health care resource utilisation and costs: resource utilisation was extracted from published sources.

Unit costs	2006 €
Disease free survival	1345 / year
Local recurrence	7280 for first year
Regional recurrence	13,640 for first year
Metastatic disease	-
- first year in the control group (trastuzumab treatment rate of 80%)	41,412
- first year in the trastuzumab group (trastuzumab treatment rate of 50%)	27,219
- further years in both groups	13,025
Cost of trastuzumab administration in the HERA trial	39,245
Cost of trastuzumab administration in the FinHer trial	9248

Results

Outcome of interest	Trastuzumab	Observational group
Recurrence rates at 10 years [risk ratio (RR) = 0.70]	10.44%	15.0%
Recurrence rates at 15 years [RR = 0.71]	11.3%	15.8%
Overall survival rate at 10 years [RR = 0.87]	71.8%	62.8%
Overall survival rate at 15 years [RR = 0.84]	62.9%	52.7%

At 5 years the total cost of the trastuzumab group was €53,403 and of the observational group was €27,304. The incremental cost and LYG between the groups were €26,304 and 0.12 respectively giving a cost per LYG of €212,360. At 15 years the total cost of trastuzumab group was 67,682 and of the observational group was €47,791. The incremental cost and LYG were €19,891 and 1.01 respectively giving a cost per LYG of €19,673. Results were also given for 10 years.

Sensitivity analysis:

Scenario analyses were explored including the clinical benefit of trastuzumab limited to 3 years, varying re-treatment with trastuzumab percentages for patients with adjuvant trastuzumab, and discounting life years gained at 3% (only costs were discounted in the base case).

One way sensitivity analysis showed that the cost effectiveness of the trastuzumab group was sensitive to changes in clinical efficacy of trastuzumab, discounting of the effectiveness and its price.

For the FinHer regimen:

Outcome of interest	Trastuzumab	Observational group

Recurrence rates at 10 years [risk ratio (RR) = 0.55]	4.91%	8.77%
Recurrence rates at 15 years [RR = 0.60]	5.48%	9.19%
Overall survival rate at 10 years [RR = 0.81]	81.8%	66.1%
Overall survival rate at 15 years [RR = 0.77]	73.6%	57.0%

In each of the analyses (at 5, 10 and 15 years) for the FinHer trials the trastuzumab group is more effective and cost saving compared to the observational group. Even in sensitivity analysis all the results show that the trastuzumab group dominates (is more effective and less costly than) the observational group.

Authors' conclusions:

Based on the HERA regimen, the ICER is above €50,000 per LYG, after 10 and 15 years the ICERs improve and become lower than €50,000 per LYG. Data supplied by the FinHer trial show that the 9-week regimen may save costs compared with no adjuvant trastuzumab treatment.

General comments:

It is not clear from the study what the LYG are for each of the strategies. Some of the calculations in the results tables suggest more accurate figures could have been presented to improve clarity. A comparison of figures from other studies in this area was presented in the discussion. Further data on the clinical inputs would have been helpful. All the inputs were presented as annual probabilities. Some costs were derived from standard treatment guidelines and from a retrospective chart review for metastatic disease. The authors recognised this is a limitation of the model.

Neyt, M., et al., An economic evaluation of herceptin in adjuvant setting: the breast cancer International research group 006 trial. *Annals of oncology* 2006; 17:381-390.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (i.e. Treatment model – software not specified).

Clinical effectiveness:

Based on the BCIRG 006 trial, the SEER database, mortality rates from the US census bureau and progression from metastatic disease from the Canadian provincial cancer registry data, published literature, expert opinion and assumptions.

Cost estimation:

Direct costs included cost of therapy and administration, diagnostic tests, surgery and metastatic disease. The payer perspective was taken. Costs are reported in Euros, the cost year does not seem to have been reported. Cost and benefits were discounted at 5%.

Country: Belgium, **setting:** Hospital

Inclusion criteria:

As for the trials

Exclusion criteria:

As for the trials

Population:

Women > 50 years with stage III (node positive) diagnosed breast cancer that is HER2-positive

Interventions:

Based on the BCIRG 006 trial:

AC followed by docetaxel (standard treatment)

AC for four cycles followed by docetaxel for four courses and trastuzumab for 1 year (AC->TH).

Docetaxel and carboplatin for six courses with concurrent trastuzumab given for 1 year (TCH).

Outcomes:

Life Years (LYs), costs and ICERs

Follow up:

Time horizon = until the metastatic phase

Data used to populate the model:

Assumptions:

- The authors stated that the BCIRG 006 trial was ongoing and that there was no effectiveness data

regarding the use of trastuzumab in the adjuvant setting. Instead a threshold analysis was carried out on the number of breast cancers that become metastatic and time to disease progression.

- Cost and effectiveness data were not included in the cost model as there is a lack of treatment standard during this period.
- Life expectancy data were extracted from a study on the lifetime costs in patients with metastatic disease.
- Survival data were taken from the SEER database.
- Mortality and estimates of progression to metastatic disease were taken from US and Canadian databases respectively.

Health states: phases in the model were: diagnosis, surgery, breast reconstruction, radiotherapy, pre- and post-operative chemotherapy, hormonal treatment, and metastatic treatment.

Data from studies: It is unclear what data were used in the model in terms of the effectiveness of trastuzumab.

Outcome of interest	Estimate
Average life expectancy at diagnosis for those who progressed to the metastatic phase	6.7 years
Average life expectancy at diagnosis for those who did not progress to the metastatic phase	7.8 years

Utilities: no utilities were included in this study

Health care resource utilisation and costs: Resource utilisation was based mainly on databases of the University hospital where the study took place. Experts were used when data were unavailable. Treatments for adverse events (cardiac events) did not seem to have been costed, although cardiac monitoring was included.

Unit costs	Euros €
Hematoxylin and eosin staining and IHC	146
FISH	167
Trastuzumab	10,032
AC->TH	45,034
TCH	47,765
LVEF test	55

Results

Outcome of interest	Standard tx	AC->TH	TCH
Total costs for stage III breast cancer patient over 50 years	€16,787	€21,523	€21,827

Sensitivity analysis:

One way sensitivity analysis was carried out on most parameters in the model. Results were only shown for AC->TH (as the results were similar for AC-> TH and TCH). Parameters that had the greatest impact on costs were discount rate, number of patients with HER-2 overexpression, transition probabilities, cost of resource inputs and cost of treatment phases. The ICER varied considerably with changes in the discount rate, price of trastuzumab and the probability of metastases. The model was most robust to changes in the costs of detecting and treating cardiac events and the costs of diagnostic testing.

Only a small section of this paper deals with cost effectiveness. This was based on the number of patients who may not progress to metastatic cancer. The percentage of cancers not becoming metastatic and the improvement in time to disease progression to metastatic cancers were plotted against an ICER. It is not clear whether this ICER is by LYG and this figure is not provided. A threshold analysis was conducted showing the price discounts (of drugs) needed to meet an ICER of €50,000 per life year. Again, it has not been clearly explained how the life years are calculated and this as not been provided else where in the study.

Authors' conclusions:

According to the authors' threshold analysis, an acceptable incremental cost-effectiveness ratio can be reached if health improvements are large enough and/or price discounts are given. Authors state that cost

implications of using trastuzumab in the adjuvant setting must be calculated before use of the product becomes wide-spread.

General comments:

This study was a costing study. The study states that an ICER and threshold analysis was carried out, however details on the calculation have not been given and no reliable single estimates of cost effectiveness were stated.

Neyt, M., et al., Trastuzumab in early stage breast cancer: A cost effectiveness analysis for Belgium. Health Policy 2008. E-publication ahead of print.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (model type for main analysis is a treatment model presented previously in Neyt et al. (2006) – software reported for probabilistic modelling - @risk software.

Clinical effectiveness:

Based on RCTs; HERA, NSABP B-31 and NCCTG N983 and FinHer, published literature, expert opinion, a national survey, a small patient sample from a university hospital and assumptions. Survival data and charges for CHF were based on data collected in the Netherlands.

Cost estimation:

Direct costs included cost of therapy and administration, diagnostic tests, heart failure, metastatic breast cancer, local breast cancer and follow-up costs. The perspective was that of the health care payer. Costs are reported for various years (no single cost year is reported) and in Euros. Costs and benefits were discounted at 3% and 1.5% respectively.

Country: Belgium **setting:** Hospital

Inclusion criteria:

Not reported

Exclusion criteria:

Not reported

Population:

As for the clinical trials – women with HER2-overexpressing breast cancer.

Interventions:

Comparator is standard breast cancer treatment without trastuzumab for early stage breast cancer.

The use of trastuzumab is based on two clinical trials – HERA and FinHer to demonstrate the cost effectiveness of a long regimen (1 year) and short regimen (9 weeks).

Outcomes:

LYs, costs and ICERs

Follow up:

Time horizon = lifetime

Data used to populate the model:

Assumptions:

- The model was mainly based on the progression (or prevention of progression) of patients to metastases.
- For patients progressing to metastatic disease, life expectancy data were based on a published study. These data were clearly outlined in the study
- The incremental percentage of patients not progressing to metastatic disease is estimated by multiplying the hazard ratios of patients surviving free of distant recurrence with the baseline risk of progressing to metastatic disease.
- The difference in life expectancy between patients progressing and not progressing to metastatic breast cancer (MBC) allows for the calculation of the number of life-years gained.
- The decrease in life expectancy that may be caused by CHF was based on Dutch data.
- Mortality for causes other than breast cancer was taken from Belgian life tables (adjusted due to the increased risk of secondary cancer in breast cancer patients).

Health states: health states were not explicitly stated in the study. No schematic of the model was included.

Data from studies: the risk of progressing to MBC, the mean time of progressing to MBC, mean survival of MBC (according to age and stage) and mean life expectancy with heart failure were also provided. Some Dutch data were used where no data for Belgium existed.

Outcome of interest	Estimate
Hazard ratio of surviving free of distant recurrence HERA	0.49
Hazard ratio of surviving free of distant recurrence FinHer	0.29
Probability of local recurrence – Stage I	8%
Probability of local recurrence – Stage II	10%
Probability of local recurrence – Stage III	12%
Hazard ratio of surviving free of disease – HERA	0.54
Hazard ratio of surviving free of disease – FinHer	0.42
Reduced remaining life expectancy due to risk of second cancer (mean)	97.5%
Incremental risk of heart failure – HERA	1.67%
Incremental risk of heart failure – FinHer	-0.86%
Mean time to brain relapse	11.89 months
Probability of brain metastases	26%

Utilities: Utilities were not included. Authors state no quality of life data were available.

Health care resource utilisation and costs: Resource utilisation is taken mainly from published sources and the clinical trial data. Costs were based on the Belgian National Health Insurance. Follow up costs were also included. Resource use and costs were very clearly outlined in detail in the study.

Unit costs	Euros
FISH test	299
Trastuzumab infusion (per 150mg vial)	671
Administration of trastuzumab (per administration)	246
Mean cost of heart failure	7171
Mean metastatic treatment cost (without trastuzumab)	14,050
Mean metastatic treatment cost (with trastuzumab)	31,878
Mean cost of local recurrence	5065
MUGA scan	188

Results

Outcome of interest	HERA	FinHer
Stage I	-	-
Incremental LYG	11.99	20.35
Incremental cost €	32,320	668
ICER (€ per LYG)	34,999	Dominates std regimen
Stage II	-	-
Incremental LYG	23.88	36.09
Incremental cost €	30,608	-1045
ICER (€ per LYG)	16,026	Dominates std regimen
Stage III	-	-
Incremental LYG	49.74	70.33
Incremental cost €	24,202	-6869
ICER (€ per LYG)	5994	Dominates std regimen

Base case scenario – includes possible lack of efficacy of trastuzumab to block the development of brain metastases, no re-treatment with trastuzumab in case of disease progression to MBC is assumed and costs of wasted trastuzumab are included. The above results were also provided by age. Overall the initial treatment costs for trastuzumab were €40,657 and €8667 for HERA and FinHer respectively.

Sensitivity analysis:

- As well as treatment stage and regimen, results were provided by age and showed that there were better outcomes for younger patients.
- A probabilistic sensitivity analysis was carried out and a cost effectiveness plane was presented.
- HERA – applying a threshold of €30,000 per LYG, early stage breast cancer treatment with trastuzumab is not cost effective in 6 out of the 15 analysed groups.
- FinHer – applying a threshold of €30,000 per LYG, trastuzumab is not cost effective in only 1 group.
- Multi parameter sensitivity analysis was carried out (prices and discount rates were fixed in the first scenario) and showed that the transition probability of progressing to MBC and the hazard ratio of distant recurrence are the most important variables. The percentage of brain metastases and heart failure are also important.

Authors' conclusions:

An additional trial must be carried out examining the length of treatment regimens for trastuzumab. The authors state they found no rationale in the literature consulted for administering trastuzumab for 1 year. For each of the treatment regimens tested, the ICERs for trastuzumab treatment were better for younger patients and in patients diagnosed with more advanced disease. The results of the shorter 9-week FinHer regimen were more cost-effective compared with the 1-year HERA regimen. The FinHer treatment regimen mostly results in cost savings.

General comments:

This is the published study of the Belgian KCE report.

There are some limitations with regard to the detail in the explanation of the structure in the model and no schematic was presented. Important discussion on the hazard ratios is included and good explanation of results is provided. This study also examines various subgroups. This study provides a budget impact of the introduction of treatment with trastuzumab for patients with non-metastatic breast cancer for HERA and FinHer regimens. No utilities were included in the analysis. Although all the cost calculations are presented in detail, costs were not adjusted to reflect the same year. This would have been a useful addition to the study. A clearer explanation of the probabilistic analysis would also have been useful.

Norum et al., Trastuzumab in adjuvant breast cancer therapy. A model base cost-effectiveness analysis, 2007. Acta Oncologica, 46: 153-164.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (i.e. decision analytic model, software not specified).

Clinical effectiveness:

Taken from RCTs NSABP B-31 and NCCTG N983 and the subsequent joint analysis, assumptions, published literature, estimate of utility from a published source.

Cost estimation:

Drug costs, administration costs, cost of HER-2 analysis, cost of hospitalisation, cost of out-patient therapy. Taken from the societal perspective including indirect costs: patient/family costs (travel) and costs in other sectors (production losses). All costs were reported in 2006 values and in Euros (€). Cost and benefits were discounted at 3%.

Country: Norway, **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Women aged between 20 and 70 years with HER2-positive breast cancer.

Interventions:

Fluorouracil, epirubicin, cyclophosphamide (FEC) regimen administered for six cycles on a 3-weekly basis compared with FEC followed by trastuzumab 3-weekly administration for 17 cycles.

Outcomes:

QALYs, LYG costs and ICERs

Follow up:

Time horizon = The time horizon of the model is stated as time to death (lifetime horizon is assumed).

Data used to populate the model:

Health states:

Decision tree – schematic (see figure 1 in Norum et al.). The model has the following phases, diagnosis of breast cancer, surgical treatment, adjuvant chemotherapy, radiotherapy, hormonal therapy and treatments in the metastatic phase.

Assumptions:

- Distant relapse free survival was used as a surrogate for future overall survival.
- Using published sources, 10 year survival figures for a different chemotherapy regimen cyclophosphamide, methotrexate and fluorouracil (CMF) were adjusted for the regimens examined. A 5% absolute improvement in overall survival was added for the FEC regimen and a 10% and 20% increase due to trastuzumab was estimated.
- The improved survival level was in addition to a stated level and assumed to be reached at 10 years follow up. The benefit was equally distributed over the 10 year period.
- Life expectancy following adjuvant trastuzumab therapy was based on national mortality rates.

Data from RCTs:

Outcome of interest*	Estimate
Overall survival (hazard ratio)	0.67
Life expectancy following adjuvant trastuzumab therapy was found to be 26.53 years. This was reduced to 20 years to take death rates from long term side effects into account (heart disease and secondary malignancy)	20
Rate of congestive heart failure without trastuzumab	4%
Rate of congestive heart failure with trastuzumab	1%

Utilities: the study reported QALYs. The use of utilities is not explained in any detail. The authors state that the quality of life (Q=0.8) was based on a previous publication, a review and the Harvard database.

Health care resource utilisation and costs: All health care resource utilisation and costs were presented in detail. Resource use derived mainly from published sources. Cost of testing for HER2 status was not included as they were assumed to be equal in both groups.

Unit costs	2006 €
Mean drug cost per patient treated with trastuzumab	42,354
Cardiac check ups (5 check ups – MUGA scan)	330
Pharmacy costs for IV drugs	326
Outpatient clinic costs – trastuzumab	2192
Outpatient clinic costs – patients not receiving trastuzumab	98
Treatment of congestive heart failure – reflects numbers of patients who experience CHF	23
Traveling costs – trastuzumab	1249
Traveling costs – patients not receiving trastuzumab	157
Costs in other sectors – production losses with trastuzumab treatment	2272

Results

The results were calculated for each level of costs included (health care costs, net health care resources, travelling and production gains). They were also calculated for different levels of discounting and on whether a 10% or 20% improved overall survival level was assumed. This resulted in a lowest cost per LYG of €8148 (all resource use included, 20% improved survival level) and a highest cost per LYG of €44,284 (total costs not inclusive of any savings made, 10% improved survival level). The cost per QALY was also calculated, however, only one QALY figure was calculated. The authors state that specific quality of life figures for various treatment periods among HER-2 positive breast cancer patients undergoing adjuvant trastuzumab therapy were not available.

Outcomes for trastuzumab plus FEC compared with FEC

Outcome of interest	Result
All resource use cost	€17,844
Incremental LYG (10%)	1.095
Incremental LYG (20%)	2.19
QALYs (10 and 20%)	0.8
Cost per LYG (10%)	€30,290
Cost per LYG (20%)	€37,862
Cost per QALY (10%)	€8148
Cost per QALY (20%)	€10,185

Sensitivity analysis:

- Univariate sensitivity analyses showed that results were most sensitive to variations in the LYG (increases in overall survival), the price of trastuzumab, production gains and the discount rate.
- If trastuzumab is used in the metastatic setting, LYG was the only factor having a significant influence on the cost effectiveness.

Authors' conclusions:

Overall, the authors state that if there is a minimum of an 8% improvement in absolute 10 year overall survival then trastuzumab appears to be a cost effective option in adjuvant HER-2 positive breast cancer.

General comments:

The method used to derive the utility weight was not discussed in the paper. There were also limitations around the reporting of clinical data in the methods section. The results of the sensitivity analysis were presented in limited detail. There were major limitations and inconsistencies in the presentation of results. The authors compared their results with the findings of other studies in the discussion. The authors state that they are aware that other studies do not generally take production gains and that the net costs are likely to be considered by readers rather than the full societal costs. The authors acknowledge that further sensitivity analyses on time horizons (for clinical benefit) would be useful.

Shirowa et al, The model based cost-effectiveness analysis of 1-year adjuvant trastuzumab treatment: based on 2-year follow-up HERA trial data 2008. Breast Cancer Research and Treatment, 109:559-566.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (i.e. Markov model in TreeAge Pro 2006).

Clinical effectiveness:

RCTs (HERA), assumptions and published literature.

Cost estimation:

Cost of trastuzumab (1 year course) and other chemotherapy therapies, follow up, local and metastatic recurrence, heart monitoring and adverse events (cardiotoxicity). Direct medical costs were taken into account from the health care system perspective. Costs were reported in Japanese Yen (JPY) with costs in Euros provided using an exchange of €1 = JPY 150. The cost year does not appear to have been reported. Cost and outcomes were discounted at 3%.

Country: Japan, **setting:** Hospital

Inclusion criteria:

Not stated.

Exclusion criteria:

Not stated.

Population:

Based on the HERA trial - women with HER2-positive breast cancer who met the HERA trial entry criteria (median age of 49). Japanese and node-negative patients were also included.

Interventions:

1 year course of trastuzumab was compared with an observation group (adjuvant or neoadjuvant chemotherapy only).

Outcomes:

LYG, costs and ICERs

Follow up:

Time horizon = essentially life time (50 years). Cycle length was 1 month.

Data used to populate the model:

Health states:

The Markov model consisted mainly of four parts: without recurrence, local recurrence, metastatic recurrence and death.

Assumptions:

- Three risk reduction strategies were considered: risk reduction continuing for two years (conservative scenario), risk reduction continuing for five years (standard scenario) and for ten years (optimistic scenario).
- The assumed risk of recurrence during the first five years was higher than that during the next five years.
- Cardiac events were assumed to be reversible and therefore no increase in cardiac mortality with trastuzumab was assumed.
- Patients experiencing relapse with metastatic disease received trastuzumab even if they received it as adjuvant therapy.
- Mortality due to causes other than breast cancer was based on natural death rates in Japan.

Data from RCTs:

Outcome of interest	Estimate
Hazard ratio for the risk of recurrence in the 1 year trastuzumab group	0.64
Cardiotoxicity (severe)	0.6%
Cardiotoxicity (symptomatic)	2%
Cardiotoxicity (asymptomatic)	3%
Transition rates – Trastuzumab	-
Without recurrence to metastatic recurrence	0.004483
Without recurrence to local recurrence	0.001296
Transition rates – observation group	-
Without recurrence to metastatic recurrence	0.006916
Without recurrence to local recurrence	0.001737

Utilities: Utilities were not included.

Health care resource utilisation and costs: All health care resource utilisation and costs were presented in detail. No total costs were presented for example, overall treatment with trastuzumab. This was split into different weight categories and cost for the first cycle versus costs for the consequent cycles. Therefore not all costs have been extracted into the table below. Only relevant costs with cost per event details have been included. See table 1 of the study for further details

Unit costs	JPY
Palliative care in metastatic disease	1,100,000
Severe CHF	810,000
Symptomatic CHF	170,000
Asymptomatic CHF	40,000

Results

Results were also available for varying weight categories of patients

Outcome of interest	Costs	Effectiveness	ICER (JPY)	ICER (€)
Observation	7,900,000	12.46	-	-

Conservative	11,500,000	13.06	6,000,000	40,000
Standard	11,200,000	13.70	2,600,000	17,000
Optimistic	10,900,000	14.10	1,800,000	12,000

Sensitivity analysis:

- All the results of sensitivity analyses in the standard scenario produced ICERs of less than JPY 5,000,000 (€33,000).
- The model was most sensitive to the period of trastuzumab efficacy. Cost per LYG was JPY 4,700,000, JPY 1,900,000 and JPY 1,300,000 for the period of efficacy of two, five and ten years respectively based on the 1 year follow up data.
- The model was not sensitive to other one way analyses for discount rate, recurrence rate, cardiotoxicity costs and terminal costs showed little change. Of these, the discount rate changed the results the most.
- Probabilistic sensitivity analysis was carried out. The results showed that the probability of 1 year of trastuzumab in the standard scenario being below JPY 5,400,000 (€36,000) per LYG was above 95%.

Authors' conclusions:

The authors stated that their results showed that 1 year of adjuvant trastuzumab treatment is cost effective. Both the clinical and economic benefits were superior for the 1 year adjuvant trastuzumab group compared with the observation group.

General comments:

This study is a useful addition to the review showing an evaluation that examines the 2-year follow up data from the HERA trial. The study may not be directly applicable to the UK because the study was carried out in Japan however the authors mention in their discussion that they felt it appropriate to use NICE cost effectiveness thresholds due to the similar and medical environments in UK and Japan. The authors discussed the limitation of not including health related quality of life stating that in Japan there are no data for breast cancer patients to apply to the analyses.

Regulatory submissions

PHARMAC – Technology assessment number 75 and supplementary analysis 75b. Trastuzumab (herceptin) in HER-2 positive early stage primary breast cancer. **Part 1: 12-month sequential trastuzumab treatment, August 2006.** Part 2: 9 week concurrent trastuzumab treatment in HER-2 positive early breast cancer, April 2007.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. Markov model – software not specified).

Clinical effectiveness:

Main analysis based on the HERA trial (according to the manufacturer's application for funding for trastuzumab after completion of adjuvant chemotherapy using a one-year course), published literature, assumptions, estimates of utilities derived from published literature.

Cost estimation:

Direct costs included: cost of therapy and administration; diagnostic tests; cardiotoxicity tests, monitoring and events; costs of outpatient visits for disease free patients; cost of local relapse; cost of contralateral breast cancer; cost of distant relapse; cost of terminal care; and cost of severe infection and other serious adverse events. The perspective of the DHB (funder of hospital pharmaceuticals) was taken. The cost year does not seem to have been reported. Costs are reported in New Zealand dollars. Cost and benefits were discounted at 8%.

Country: New Zealand, **setting:** Hospital

Inclusion criteria:

Not reported.

Exclusion criteria:

The analysis is restricted to those up to and including 79 years.

Population:

Women with early breast cancer who have completed locoregional therapy (surgery and/or radiotherapy) and at least four cycles of adjuvant chemotherapy, have tested IHC (3+) or FISH-positive for HER2 overexpression.

Interventions:

Intervention is trastuzumab compared with standard treatment.

Standard treatment for women with early breast cancer following surgery and chemotherapy comprising of hormone receptor positive patients who usually receive tamoxifen or hormone receptor negative patients who do not usually receive treatment after chemotherapy.

Outcomes:

QALYs, costs and ICERs

Follow up:

Time horizon = lifetime. Markov cycle length = 6 months

Data used to populate the model:

Assumptions:

- HER2 testing, was carried out in the model. Patients randomised to trastuzumab arm were tested for HER2 status and cardiac risk.
- Those with high cardiac risk were excluded from the analysis.
- Baseline risk of cardiac events was based on the age distribution of the patients.
- Patients who developed a severe adverse event or a relapse could discontinue treatment.
- Patients were assumed to have continued benefit from treatment with trastuzumab for four years.
- All patients who developed symptomatic CHF were assumed to discontinue treatment.
- All severe adverse events are assumed to result in discontinuation of treatment.
- It was assumed that cardiac events were reversible.
- The analysis assumed that patients who remain in remission had a reduced risk of relapse over time.
- Patients having a local relapse were assumed not to have an increased risk of mortality.
- Of patients with metastatic disease, 20% were assumed to be HER2 positive and receive

trastuzumab.

- Mortality due to other causes was based on standard NZ age specific mortality rates for women.

Health states: treatment, local relapse, contralateral, distant relapse, palliative care, remission and death

Data from studies:

Outcome of interest	Estimate
Overall percentage of severe adverse events in the trastuzumab arm	7%
Percentage of severe adverse events that were due to infection (trastuzumab)	24.8%
Percentage of severe adverse events that were due to cardiac event (trastuzumab)	14.5%
Fatal adverse events (trastuzumab)	0.4%
Risk of relapse (of the baseline risk) years zero to four.	100%
Risk of relapse (of the baseline risk) years five to nine	64%
Risk of relapse (of the baseline risk) for the remainder of life	41%
Probability of local relapse in the first 6 months (trastuzumab)	1.0%
Probability of a regional relapse in the first 6 months (trastuzumab)	0.6%
Probability of a contralateral relapse (both treatment arms)	0.4%
Probability of a distant relapse (trastuzumab)	5%
Risk of death in metastatic breast cancer (weighted average mortality after 6 months)	12.1%

Utilities: taken from EQ-5D NZ weights, informed in part by further published data. Values were estimated using descriptions of breast cancer states derived by oncologists with modifications to map to EQ-5D generic health states. All details were provided.

Input parameter	Utility
Disease free/remission, >5 years	1.00
Disease free/remission, <5 years	0.85
Local/regional relapse	0.46
Contralateral primary	0.46
Metastatic cancer	0.13
Terminal phase (one month prior to death)	-0.01
Serious infection	0.78
Cardiac toxicity including severe heart failure	0.63
Other serious adverse events averaged over 6 months	0.83

Health care resource utilisation and costs: Resource utilisation was taken mainly from published sources, clinical trial data and in-house analyses. Cost of HER2 diagnostic tests was not reported.

Unit costs	NZ\$
Trastuzumab (cost per mg)	8.81
Administration of trastuzumab (per infusion)	100
LVEF exam (echocardiography)	250
Total cost of local relapse	8033
Total cost of contralateral breast cancer	12,269
Total cost of trastuzumab for distant relapse	32,213
Total cost of distant relapse	35,878
Total average cost per 6 months of terminal care	27,930
Average cost of hospitalisation for serious infection	4359
Total cost of cardiac toxicity	4181
Average one off cost attributed to other serious adverse events	4000

Results

Outcome of interest	Trastuzumab ICER
Cost per QALY (NZ\$)	70,000 – 80,000

Sensitivity analysis:

Scenario analyses were carried out:

- Treatment benefit continued after cessation of therapy for the lifetime of the patient (\$24,000 per QALY).
- Treatment benefits lasted two years, then adopted comparator rates (\$127,000).
- Patients required two years of treatment to obtain four years increased benefit (144,000).

Other one way sensitivity analyses were carried out including using a discount rate of 3.5% resulting in an ICER of \$46,000 per QALY and a 50% reduction in the risk of relapse in both arms, resulting in an ICER of \$113,000 per QALY. The price of trastuzumab also influenced the results. A 30% reduction in the price resulted in an ICER of \$46,000 per QALY.

Further analysis carried out following consultation produced the following results:

Results of additional analysis

Outcome of interest	Trastuzumab ICER (NZ\$)
Base case	73,000
Lifetime duration of breast cancer risk reduction	26,500
FinHer dose, 4 year duration of breast cancer risk reduction	12,318
FinHer dose, 2 year duration of breast cancer risk reduction	29,240
4yr duration of breast cancer risk reduction +4yr half benefit	54,302
2yr benefit and lifetime half benefit	52,649
2yr benefit and 6yr half benefit	67,507

Authors' conclusions:

Based on the available information it is not possible to determine with sufficient certainty whether or not trastuzumab is a cost effective investment without a significant reduction in cost through shorter treatment duration or trastuzumab price reduction or that the clinical benefit continues to increase beyond treatment cessation.

General comments:

There are some limitations with regard to the detail in the explanation of the projection of disease free survival. The one way sensitivity analysis is extensive however no further probabilistic sensitivity analysis was conducted. There is a detailed section in the discussion comparing the results of this study with the results of other similar studies.

A supplementary analysis was carried out and is reviewed in the next table.

PHARMAC – Technology assessment number 75 and supplementary analysis 75b. Trastuzumab (herceptin) in HER-2 positive early stage primary breast cancer. Part 1: 12-month sequential trastuzumab treatment, August 2006. **Part 2: 9 week concurrent trastuzumab treatment in HER-2 positive early breast cancer, April 2007.**

The analysis was carried out as for the 12 month regimen outlined above except for the following changes:

- The original analysis used age-adjusted cardiac risk to determine the number of HER2 positive patients who would meet the criteria for trastuzumab. The updated analysis used LVEF function for women in this age group. More patients were therefore expected to receive trastuzumab in the updated analysis; however, this did not affect the cost utility, only the budget impact.
- Prevalence of HER2 positive disease was reduced from 24% to 17% - this change transfers to a conservative assumption
- Baseline risk was lowered by 10% in order to closer align the modelled mortality with observed data for HER2 positive disease progression.
- Incidence of adverse events was reduced by half as the rates were unchanged but only one Markov cycle will have cardiac toxicity rates assigned. This may underestimate the benefits and overestimate the costs of this regimen as there is some evidence to show that a shorter duration of therapy combined with pre-anthracycline treatment could result in a reduction of adverse events in clinical practice compared to the HERA regimen.
- Costs were adjusted for the 9 week regimen and costs of testing for HER2 overexpression were added.
- Concomitant administration of docetaxel was considered (not currently funded in NZ – paclitaxel is). Under the 9 week model patients are assumed to receive concurrent treatment with docetaxel.

Results

Base case (where assumptions generally favoured standard treatment) = NZ\$ 14,500 to NZ\$ 16,500. The main assumption in this analysis was that the 9 week regimen is equally effective compared to the 52 week regimen.

Sensitivity analysis

Sensitivity analyses were carried out to determine the effect of reduced efficacy in the 9 week regimen. When the effectiveness of trastuzumab was reduced to the level of the upper confidence limit (HR 0.83 – 17% reduction in risk of recurrence of disease) and consequent worse case scenario, the ICER was increased from NZ\$ 15,900 in the base case to NZ\$ 57,000 per QALY. Probabilistic analysis was not carried due to the timeframe available. In all other scenarios results were less than NZ\$ 30,000 per QALY.

Authors' conclusions

The 9 week regimen was given high priority recommendation for funding by PTAC and CaTSOP in 2006. Compared with the current standard care (FAC chemo), the 9 week trastuzumab concurrent regimen is cost effective when compared with other investment options for pharmaceuticals.

General comments

This was a supplementary analysis and so could be considered to be less thorough than the original analysis. The supplementary analysis was based closely on the original analysis and is therefore likely to be a valid attempt to include the 9 week regimen and the necessary alterations were made. An appeal was made against PHARMAC's decision and the result has recently been made available – the Court specifically upheld PHARMAC's decision to fund the 9 week treatment regimen.

KCE Belgian Health Care Knowledge Centre 2006. Trastuzumab in early stage breast cancer. KCE reports, Vol 34C. Reviewed alongside – Neyt, M., et al., Trastuzumab in early stage breast cancer: A cost effectiveness analysis for Belgium. Health Policy 2008. E-publication ahead of print. Only additional data presented in this report has been outlined here – refer to Neyt et al. 2008 for full review of publication.

Design:

Type of economic evaluation:

Cost-effectiveness analysis using modelling (model type not specified – software: @risk).

Clinical effectiveness:

Based on the following RCTs; HERA, NSABP B-31 and NCCTG N983 and FinHer, published literature and assumptions. Survival data and charges for congestive heart failure (CHF) were based on data collected in the Netherlands.

Cost estimation:

Direct costs included cost of therapy and administration, diagnostic tests, heart failure, metastatic breast cancer, local recurrence and follow-up costs. The perspective was that of the health care payer. Costs are reported for various years (no single cost year is reported) and in Euros. Costs and benefits were discounted at 3% and 1.5% respectively in the base case.

Country: Belgium **setting:** Hospital

Inclusion criteria:

Not reported

Exclusion criteria:

Not reported

Population:

As for the clinical trials – women with HER2-overexpressing breast Cancer.

Interventions:

Based on the clinical trials – comparators are current breast cancer treatment with either a one year regimen or 9 weeks of trastuzumab given in addition respectively from the HERA and B31/N9831 trial, and the FinHer trial.

The use of trastuzumab is based on four clinical trials – HERA and FinHer to demonstrate the cost effectiveness of a long regimen (1 year) and short regimen (9 weeks) and the joint analysis of NSABP B-31 and NCCTG N983 (plus FinHer) to explore the effect of LVEF.

Outcomes:

LYs, costs and ICERs

Follow up:

Time horizon = lifetime

Data used to populate the model:

Assumptions: Assumptions presented here are in addition to those stated in Neyt, M., et al 2008.

- Short-term results were mainly translated to the long term relying on the hazard ratio of patients surviving free of distant recurrence.
- For patients not progressing to metastatic disease the life expectancy according to Belgian 2001 life tables was used.
- In the metastatic disease state, life expectancy was calculated by adding the time to progression by age and stage, and the survival of metastatic disease from published sources.
- Cost effectiveness was calculated for several subgroups defined by 5 age groups (all >50 years) and stage (I, II and III) for the HERA and FinHer trial regimens.
- For concurrent 1 year trastuzumab (NSABP B-31 and NCCTG N983 trials) cost effectiveness was calculated for subgroups defined by 3 age groups (all, <50, <=50) and by LVEF at the start of trastuzumab treatment (50-54% or >=55%) because these variables were reported as determinants of heart failure after trastuzumab.
- Two scenarios were also modelled assuming efficacy of trastuzumab as for other sites of metastasis and a second scenario (default), where trastuzumab delayed by about a year (but did not stop) the development of metastatic disease in some patients expected to develop brain metastasis without trastuzumab.
- Survival of patients with brain metastasis was assumed to be similar to survival of metastatic disease.
- The base case assumed no re-treatment with trastuzumab if the patient progresses to metastatic disease.
- The base case assumed that trastuzumab drug wastage was included.

Health states: as for Neyt et al. 2008

Data from studies: as for Neyt et al. 2008

Utilities: as for Neyt et al. 2008

Health care resource utilisation and costs: as for Neyt et al. 2008

Results

Several scenarios were modelled: whether or not trastuzumab would be re-administered in metastatic disease when it has already been given for adjuvant treatment, two scenarios of costs for metastatic treatment, wasted trastuzumab due to part use of vials and the possibility of trastuzumab not being able to prevent brain metastases.

The results of these scenarios were presented for the HERA and FinHer trials for stage II breast cancer patients (all ages). Six discount rate scenarios were also presented for the HERA trial for stage II breast cancer patients (all ages). The incremental cost effectiveness of trastuzumab compared with standard treatment is presented below. All the ICER results for the FinHer trial showed that trastuzumab dominated standard treatment.

Outcome of interest	HERA
Scenario 1 – Default Trastuzumab not re-administered in MBC if patients already received the drug in adjuvant setting MBC treatment costs were not increased, Percentage of unused trastuzumab was taken into account, The effect of trastuzumab on the development of brain metastases included.	€16,026
Scenario 2 – Cost of re-administering trastuzumab in MBC included	€19,226
Scenario 3 – Cost of MBC increased	€15,672
Scenario 4 – Didn't take into account the percentage of waste (affecting costs)	€13,516
Scenario 5 – Didn't take into account that trastuzumab may have no effect on brain metastases	€11,620

In addition to the results presented by Neyt et al. 2008 tables and cost effectiveness planes are presented for each

of the subgroups (based on prognostic factors) for HERA and FinHer and additional results were presented for the B31/N9831 trials (by stage and according to LVEF).

Sensitivity analysis:

Probabilistic sensitivity analysis was presented – this does not seem to be probabilistic in the conventional sense. Uncertainty in variables was tested. This is carried out using a rank correlation calculation in which correlation coefficients are calculated between the output variables and the sampled input values. This helped to determine the importance of the different parameters behind the model on the results.

The results of this analysis are outlined under multi parameter sensitivity analysis in the table for Neyt et al. 2008

Authors' conclusions:

Trastuzumab administered post anthracycline proved on average effective in most patient subgroups defined by age and stage while the pre-anthracycline regimen was on average effective in all subgroups studied. Within each modelled regimen trastuzumab was more effective in younger women and in women with a more advanced disease stage.

When the post-anthracycline regimen was modelled on patients with a borderline cardiac function (LVEF 50-54%) trastuzumab treatment reduced life expectancy in stage I-II patients older than 50.

According to the author's model, pre-anthracycline trastuzumab is more cost-effective than the post-anthracycline options, can even lead to cost-savings, and reaches 20% more women in need of treatment for their cancer. Treatment with trastuzumab as in the HERA scenario was not cost-effective in 6 of the 15 analysed subgroups whereas this is only the case in 1 of the 15 subgroups for FinHer.

General comments:

General comments are as for Neyt et al. 2008 with the following additions. As well as stating that they found no rationale in the literature consulted for administering trastuzumab for 1 year, the authors question why shorter pre-anthracycline regimens were not included in any of the phase three trials.

There are some limitations in the reporting of the probabilistic analysis. Most of the scenarios presented simply altered the costs rather than the effectiveness, this would have been a useful addition to the study.

Ward, Pilgrim and Hind, 2006. Trastuzumab for the treatment of Primary Breast Cancer in HER2 Positive Women – A single technology appraisal. University of Sheffield. School of Health and Related Research (SchARR). Report reviews submission of clinical and cost effectiveness of trastuzumab for early breast cancer by manufacture (Roche) therefore the cost effectiveness analysis described was carried out by Roche and the criticism provided is that of SchARR. Some data were marked as commercial in confidence (CiC) and has therefore been excluded from this table.

Design:

Type of economic evaluation:

Cost-utility analysis using modelling (i.e. state transition cohort model – software not specified).

Clinical effectiveness:

Effectiveness estimates (transition probabilities) taken from the HERA trial and a previous study by the manufacturer for death due to metastatic disease, estimates of utilities provided by an external report.

Cost estimation:

Direct costs included cost of therapy and administration, diagnostic tests, cardiotoxicity events, recurrence costs (distant metastases), follow up treatment and end of life care. The analysis was undertaken from the perspective of the NHS and PSS. Costs are reported for 2004/5 and in UK pounds. Cost and benefits were discounted at 3.5%.

Country: UK, **setting:** Hospital

Inclusion criteria:

Not reported

Exclusion criteria:

Not reported

Population:

Women with primary invasive breast cancer that overexpress HER2 (determined by IHC 3+ or FISH positive) who have completed (neo-) adjuvant systemic chemotherapy and radiotherapy, if applicable.

Interventions:

Addition of 1 year of adjuvant trastuzumab therapy to standard chemotherapy compared with standard chemotherapy alone based on the HERA trial.

Outcomes:

QALYs, LYs, costs and ICERs

Follow up:

Time horizon = lifetime horizon of 45 years using a 1 year cycle length

Data used to populate the model:Assumptions:

- The effect of time on the rate of recurrence was relative to that collected by the EBCTCG based on all women with breast cancer
- The same trastuzumab relative risk of recurrence collected from the HERA trial was applied until year 10 when it was increased by a third until year 45 (only two thirds of the benefit is seen until year 45).
- All-cause mortality was applied to patients in the Disease Free and Recurrence Health State as well as in the Cardiac Adverse Event State.
- Only 1 loco-regional/contralateral breast cancer recurrence was experienced per patient.
- After a single year in the locoregional/contralateral recurrence state, the patients returned to a health state with a similar utility and cost as the DFS state. Patients remained there until they died or experienced metastases.
- IHC and FISH testing was used to determine HER2 status. FISH testing was carried out on around 10% of patients who receive borderline (2+) IHC results.
- Cardiac monitoring was carried out at baseline, 3, 6 and 9 months.
- Occurrence of a cardiac event did not increase mortality.

Health states: Disease-free survival, metastatic recurrence, local/contralateral recurrence, cardiac events and death

Data from studies: The majority of data taken from the studies was marked commercial in confidence. Data were taken from the HERA trial database.

Utilities: Taken from an external report using standard gamble interviews based on health states established by oncologists, breast cancer specialists and psychometric experts and completed by 100 members of the public. The participants also completed the EQ-5D to assess their own current health. The health utility scores used were marked CiC however, the SchARR state that the values compare favourably with other values used in other recent breast cancer models. Two values taken from public sources were provided.

Input parameter	Utility
Disutility of local recurrence	0.24
Contralateral breast cancer event	0.24

Health care resource utilisation and costs: Most costs were marked CiC in the manufacturer's submission. Costs available are presented below. Costs associated with the administration of trastuzumab were omitted from the manufacturer's model.

Unit costs	2004/5 £
Cost of trastuzumab (one year as adjuvant treatment)	21,185
Cost per trastuzumab vial	407
Cost per HER-2 Test	47
Cost of heart monitoring per year	475
Cost of other cardiac event NYHA Grade II	1395
Cost chronic cardiac event long- term treatment	316
Cost of severe cardiac events grade NYHA 3 and 4	6727

Results

Outcome of interest	No trastuzumab	Trastuzumab
Costs (£)	73,323	87,159
Incremental cost (£)	-	13,835
LYS	11.69	14.11
Incremental life years	-	2.43
QALYs	8.78	11.21
Incremental QALYs	-	2.43
Cost per LY (£)	-	5702
Cost per QALY (£)		5687

Sensitivity analysis:

The manufacturer undertook several sensitivity analyses. Following one way sensitivity analysis the manufacturer stated that the cost of trastuzumab and the relative risk reduction have the greatest impact on the ICER. A probabilistic sensitivity analysis was also carried out.

SchHARR carried out some sensitivity analysis and revised the manufacturer's base case. They assumed that all patients received trastuzumab in the metastatic setting whether or not they had previously received it in the adjuvant setting and that there was no further benefit in risk of recurrence after five years. Combining these assumptions gave a base case ICER of £18,449 per QALY gained.

SchHARR combined the above assumption with further sensitivity analyses and this resulted in ICERs of £16,000 to £33,000 per QALY gained, the upper estimate coming from an analysis that assumed that 23% of women receiving trastuzumab would experience a cardiac event (as is known to occur with anthracycline-including chemotherapy regimens).

Authors' conclusions:

The manufacturer stated that robust and extensive economic modelling confirms that trastuzumab can be regarded as a highly cost effective treatment from the perspective of the UK NHS.

Commenting on their revised base case estimate of £18,449, SchHARR stated that variations in the comparator arm to allow for different chemotherapy regimens including taxanes, did not affect the ICER by more than £3,000 per QALY gained. SchHARR stated that the cost effectiveness of trastuzumab could be improved if it were provided for 9 weekly transfusions instead of 12 month 3-weekly infusions. However, further research is required to ensure that the two regimens are equally effective.

General comments:

This was a well conducted economic evaluation with a very thorough critique of the issues including some additional sensitivity analyses to evaluate the impact of various assumptions made in the manufacturer model. It appears that when the assumptions are made more conservative by SchHARR, trastuzumab remains to represent a cost effective adjuvant treatment option for women with early breast cancer.

5.6 What are the indication for the measurement of bone mineral density in patients with invasive breast cancer who are on adjuvant hormonal therapy?

Short Summary

The following evidence based guideline was used to inform the recommendation for management of bone loss after breast cancer treatment; Guidance for the management of breast cancer treatment induced bone loss: A consensus position statement from a UK Expert Group. Cancer Treatment Reviews (2008). This guideline was appraised using the AGREE Instrument (2001) and was rated as high quality. The evidence based approach was clearly conducted.

Evidence Summary

AGREE Instrument Appraisal (2001)- Summary of findings: Overall, this guideline was of high quality;

The following areas had strong agreement with appraisal check points:

Scope & purpose: 3. *The patients to whom the guideline is meant to apply were specifically described.*

Stakeholder involvement: 6. *The target users of the guideline were clearly defined.*

Editorial Independence: 23. *Conflicts of interest of guideline development members were recorded. (Fully stated)*

The following areas had agreement with appraisal check points:

Scope & purpose

1. *The overall objective(s) of the guideline was specifically described.*

2. *The clinical question(s) covered by the guideline was specifically described.*

Stakeholder involvement

4. *The guideline development group did include individuals from all the relevant professional groups.*

11. *The health benefits, side effects and risks were considered in formulating the recommendations.*

Rigour of development

8. *Systematic methods were used to search for evidence. (Details of the strategy used to search for evidence were not provided, however, some information about databases used was included.)*

12. *There was an explicit link between the recommendations and the supporting evidence.*

13. *The guideline was externally reviewed by experts prior to publication. (The guideline was reviewed externally before it was published. Reviewers included some experts in the clinical area and possibly some methodological experts. Patients' representatives were not included. A description of the methodology used to conduct the external review was not presented.)*

Clarity and presentation

15. *The recommendations were specific and unambiguous.*

16. *The different options for diagnosis and/or treatment of the condition were clearly presented.*

17. *Key recommendations were easily identifiable.*

18. *The guideline was supported with tools for application.* (While there are clearly produced algorithms and a quick reference guide associated with this guideline, there is no information about dissemination and implementation provided with the guideline.)

Applicability

19. *The potential organizational barriers in applying the recommendations were discussed.* (This was addressed in a very brief manner in the guideline.)

20. *The potential cost implications of applying the recommendations were considered briefly.* (Addressed in this guideline)

21. *The guideline did present key review criteria for monitoring and audit purposes* (Addressed in this guideline)

Editorial Independence

22. *The guideline was editorially independent from the funding body.* (The role of the funding body was acknowledged and no influence on content was included by guideline producers .

The following areas had no agreement with appraisal check points:

Stakeholder involvement

5. *The patients' views and preferences were not sought.* (Information about patients' experiences and expectations of health care were not described in the guideline document and so therefore it is expected that this did not inform the development of clinical guidelines.)

The following areas had strong disagreement with appraisal check points:

Stakeholder involvement

7. *The guideline was not piloted among end users.* (There was no indication that the guideline was pre-tested for further validation amongst its intended end users prior to publication.)

9. *The criteria for selecting the evidence was not clearly described.* (Criteria for including /excluding evidence identified by the search were not provided.)

10. *The methods used for formulating the recommendations should be clearly described.* (There was no description of the methods used to formulate the recommendations and how final decisions were arrived at.)

14. *A procedure for updating the guideline was not provided.* (There was no clear statement about the procedure for updating the guideline)

References

The AGREE collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) instrument. 2001 [cited 2007 July 10]: Available from AGREE Collaboration (2001) <http://www.agreecollaboration.org/instrument/>

Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P and Coleman RE. (2008) Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. *Cancer Treatment Reviews*. Volume 34, Supplement 1, S3-S18

Evidence Table

Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P and Coleman RE. (2008) Guidance for the management of breast cancer treatment-induced bone loss: A consensus position statement from a UK Expert Group. *Cancer Treatment Reviews*. Volume 34, Supplement 1, S3-S18

Further Details about AGREE Instrument Appraisal

Scope & purpose

1. *The overall objective(s) of the guideline should be specifically described.*

Agree -3

2. *The clinical question(s) covered by the guideline should be specifically described.*

Agree -3

3. *The patients to whom the guideline is meant to apply should be specifically described.*

Strongly agree - 4

Stakeholder involvement

4. *The guideline development group should include individuals from all the relevant professional groups.*

Agree -3

5. *The patients' views and preferences should be sought.*

Do not agree – 2

Information about patients' experiences and expectations of health care were not described in the guideline document and so therefore it is expected that this did not inform the development of clinical guidelines.

6. *The target users of the guideline should be clearly defined.*

Strongly agree - 4

7. *The guideline should be piloted among end users.*

Strongly disagree – 1

There was no indication that the guideline was pre-tested for further validation amongst its intended end users prior to publication.

Rigour of development

8. *Systematic methods should be used to search for evidence.*

Do not agree – 2

Details of the strategy used to search for evidence were not provided, however, some information about databases used was included.

9. *The criteria for selecting the evidence should be clearly described.*

Strongly disagree – 1

Criteria for including /excluding evidence identified by the search were not provided.

10. *The methods used for formulating the recommendations should be clearly described.*

Strongly disagree – 1

There was no description of the methods used to formulate the recommendations and how

final decisions were arrived at.

11. The health benefits, side effects and risks should be considered in formulating the recommendations.

Agree -3

12. There should be an explicit link between the recommendations and the supporting evidence.

Agree – 3

While there is mention of the evidence that has been used to inform the recommendation, the link is not explicit and could be clearly described.

13. The guideline should be externally reviewed by experts prior to publication.

Agree -3

A guideline was reviewed externally before it is published. Reviewers included some experts in the clinical area and possibly some methodological experts. Patients' representatives were not included. A description of the methodology used to conduct the external review was not presented.

14. A procedure for updating the guideline should be provided.

Strongly disagree – 1

There was no clear statement about the procedure for updating the guideline

Clarity and presentation

15. The recommendations should be specific and unambiguous.

Agree -3

16. The different options for diagnosis and/or treatment of the condition should be clearly presented.

Agree -3

17. Key recommendations should be easily identifiable.

Agree -3

18. The guideline should be supported with tools for application.

Agree -3

While there are clearly produced algorithms and a quick reference guide associated with this guideline, there is no information about dissemination and implementation provided with the guideline.

Applicability

19. The potential organizational barriers in applying the recommendations should be discussed.

Agree -3

This is addressed in a very brief manner in the guideline.

20. The potential cost implications of applying the recommendations should be considered.

Agree - 3

Addressed in this guideline briefly.

21. The guideline should presents key review criteria for monitoring and audit purposes
Strongly agree – 3
Addressed in this guideline

5.7 What are the indications for the use of bisphosphonates in patients with early breast cancer?

Short Summary

There is considerable, high quality evidence from systematic reviews and meta-analyses of RCTs that have indicated the effectiveness of bisphosphonates for specific groups of breast cancer patients:

Evidence from RCTs (Brufsky 2006 and Bundred *et al.* 2008) have indicated that in women who were receiving adjuvant letrozole; immediate treatment with zoledronate compared to delayed may prevent loss of bone mineral density at both lumbar spine and total hip. There is evidence that immediate treatment with zoledronic acid maintains the baseline osteopenia status of patients compared with delayed treatment at 12 months. Furthermore, Bundred *et al.* (2008) showed no evidence to suggest a difference in the occurrence of fractures in immediate versus delayed treatment with zoledronate and that there was no difference in breast cancer recurrence when comparing immediate and delayed treatment with zoledronate. There are no significant acute adverse effects with zoledronate.

A systematic review of RCTs of bisphosphonates showed no statistically significant reduction in the risk of developing skeletal metastases (Wu *et al.* 2007). Fuleihan *et al.* (2005) has shown that pamidronate prevents chemotherapy induced bone loss compared with placebo. An RCT by Greenspan *et al.* (2007) compared risedronate with placebo and showed that in postmenopausal women with breast cancer with or without aromatase inhibitors therapy, once-weekly oral risedronate was beneficial for spine and hip BMD and reduced bone turnover. There were no significant acute adverse effects with risedronate.

Saarto *et al.* 2004 showed that there was no difference in bone metastases or overall survival in women with lymph node-positive disease who were treated with chemotherapy or endocrine therapy and received clodronate or a control. Disease free survival was poorer in the clodronate group which may be attributed to visceral metastases. When IV clodronate was compared to a control during adjuvant chemotherapy there was no statistically significant difference in chemotherapy induced bone loss at 6 months or 12 months. (Vehmanen 2004)

A meta-analysis of RCTs (Ha *et al.* 2007) compared clodronate with placebo and found no statistically significant difference in overall survival skeletal metastasis or non-skeletal metastases. A Cochrane systematic review by Pavlakis *et al.* (2006) compared adjuvant oral clodronate with placebo and found no significant difference with skeletal metastases but overall survival was significantly improved with clodronate.

Gnant *et al.* (2007) conducted a four-arm trial comparing tamoxifen and goserelin +/- zoledronate versus anastrozole and goserelin +/- zoledronate for 3 years in premenopausal women with hormone-responsive breast cancer. Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin compared with patients receiving tamoxifen and goserelin. Conversely, BMD remained stable in zoledronate treated patients compared with endocrine therapy alone. Brufsky *et al.* (2006) compared letrozole with early versus delayed zoledronate and found at 12 months BMD was higher in 'early' group versus 'delayed', both in the spine and hip. Mystakidou *et al.* (2005) conducted an RCT comparing

zoledronate with a control and found that the median bone metastases-free interval for zoledronate was significantly higher than with the control. Furthermore, there was a significant difference in favour of zoledronate in the bone-metastases-free interval at the 18 month follow up.

The following evidence based guideline was also used to inform the recommendation for the role of bisphosphonates 'Guidance for the management of breast cancer treatment induced bone loss: A consensus position statement from a UK Expert Group' Cancer Treatment Reviews *et al.* (2008). This guideline was appraised using the AGREE Instrument and rated as high quality. The evidence based approach was clearly conducted.

PICO

Population	Intervention	Comparison	Outcome
Patients with invasive breast cancer	Bisphosphonate treatment: Pamidronate, clodronate, ibandronate, zoledronate, risodronate, aledronate	No Bisphosphonate treatment	Bone Health Bone Mineral Density Recurrence Disease free survival Overall survival Patient Acceptability Quality of Life Cost Effectiveness

The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence Summary

There is strong evidence that bisphosphonates (pamidronate, zoledronate, risedronate) prevent chemotherapy induced bone loss in early breast cancer patients although this evidence is inconclusive for clodronate. Some evidence from retrospective analysis of case series that alendronate favours improvement in BMD. Bone metastases were detected at the same frequency in intervention and control groups (clodronate) and some weak evidence suggest that patients administered zoledronic acid group fare better in short term. There is no evidence of improved disease free survival (pamidronate) or overall survival (with the exception of 1 trial that shows strong evidence of improved 5 year bone relapse free survival by using adjuvant clodronate for node positive patients). There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. The studies included in the review have a relatively high degree of heterogeneity, due to the inclusion criteria and the patient population), the type and administration route of bisphosphonate.

At risk of osteoporosis due to AI

There is fairly strong evidence from a randomized, double blind, placebo controlled trial comparing Pamidronate 60mg iv every 3 months with placebo that IV pamidronate prevented chemotherapy-induced bone loss in young pre-menopausal women, was well tolerated, and is an attractive alternative in preserving skeletal health in such patients. The mean difference in percentage change in BMD at 12 months between the two treatment groups was 5.1% at the lumbar spine (p=0.002) in the overall study group and 5 % at lumbar spine and 5.2% at the total hip in the amenorrhoeic sub- group (p<0.03). [Fuleihan, G, *et al*, 2005]

Similarly, RCT of adjuvant clodronate treatment in node-positive breast cancer patients receiving adjuvant chemo- or endocrine therapy ± oral clodronate 1600mg daily for 3 years showed that within 10 years bone metastases were detected at the same frequency in the

clodronate and control groups: 44(32%) vs. 42(29%), respectively, ($p=0.35$). 10 year DFS remained significantly lower in the clodronate group (45% vs. 58%, $p=0.01$, respectively). This was especially seen in oestrogen receptor negative patients (25% vs. 58%, $p = 0.004$, respectively). No significant overall survival difference was found between the groups. As previously reported 3-year adjuvant clodronate treatment did not prevent the development of bone metastases in node-positive breast cancer patients. A negative effect of clodronate on DFS by increasing the development of visceral metastases was still seen at 10 years, but this did not significantly compromise overall survival. [Saarto, T. *et al.* 2004]

There is some evidence from an RCT that zoledronic acid as adjuvant treatment might be useful for prevention of bone metastases; the percentage of patients being bone metastases free at 12 mo was 60% in the zoledronic acid and 10% in the control group ($p < 0.0005$), while the percentages at 18 mo were 20% and 5% respectively ($p = 0.0002$). [Mystakidou *et al.*, 2005]

There is strong evidence from an RCT patients starting letrozole (2.5 mg per day for 5 years) receiving upfront zoledronic acid versus delayed zoledronic acid (4 mg, IV, 6 months) that combining the anticancer efficacy of letrozole with the bone-protective effect of zoledronic acid is an effective way to prevent cancer treatment induced bone loss. Lumbar spine BMD in women receiving upfront zoledronic acid showed a mean increase of 1.55%, compared with a mean decrease of 1.78% in women receiving delayed zoledronic acid (an overall difference of 3.33% between groups). Total hip BMD in the upfront group showed a mean increase of 1.02%, whereas the delayed group showed a mean decrease of 1.40% (an overall difference of 2.42% between groups). [Brufsky, A 2006]

There is inconclusive evidence from a small RCT investigating the effect of seven cycles IV intermittent 1500mg clodronate during adjuvant chemotherapy in prevention chemotherapy induced bone loss that clodronate treatment did not seem to prevent clinically significantly the bone loss related to chemotherapy-induced ovarian failure in pre-menopausal women with early stage breast cancer. The reported mean bone loss in the lumbar spine at 6 months was -0.5% in the clodronate group and 1.4% in the control group ($p = 0.22$) and at 12 months, -3.9% and 3.6%, respectively ($p=0.62$). [Vehmanen, L. *et al.*, 2004]

There is some evidence from a retrospective case series of 48 patients treated with cyclic etidronate disodium (400mg/day for 14 days); alendronate 10mg/day) concomitant with chemotherapy that oral daily alendronate treatment was associated with significantly greater improvements in lumbar spine bone density than use of cyclic etidronate or calcium and vitamin D alone. BMD increases were significantly greater in patients with prevalent vertebral fractures (VF) compared to those without VF ($P = 0.025$). In contrast, time since diagnosis of breast cancer was significantly associated with a decrease in BMD ($P = 0.002$). [Sawka, A. M. *et al.*, 2005]

There is fair evidence from an unsystematic review of trials of clodronate and zoledronic acid in the prevention of bone loss of localized breast cancer patients with chemotherapy-induced ovarian failure that clodronate was compatible with adjuvant chemotherapy. The main toxicity with this bisphosphonate was diarrhoea, experienced by 27% of patients in the clodronate group and 8% in the placebo group ($P \leq 0.001$). Zoledronic acid, a third-generation bisphosphonate, is a more potent inhibitor of osteoclasts than first- and second-generation agents, and does not have a strong impact of bone mineralization. This agent has been shown to be effective in the treatment of tumour-induced hypercalcemia at doses of 0.5-3.0 mg. [Anon, 2005]

A further unsystematic review shows that oral clodronate (1,600 mg/d) is effective for treatment of patients with chemotherapy-induced bone loss. When used as adjuvant therapy,

given to patients with operable breast cancer for 2 years, clodronate has been reported to reduce the risk of bone metastases during the 2-year study period [19 clodronate patients versus 35 placebo patients; hazard ratio (HR), 0.546; P = 0.03] and 5-year study period (51 clodronate patients versus 73 placebo patients; HR. 0.692; P = 0.04) with a significant reduction in mortality (HR. 0.768; P = 0.048). This benefit, together with the low toxicity and safety of clodronate, supports its use as additional adjuvant therapy for patients with primary breast cancer. [Powles, T. et al., 2006 (2)]

Made menopausal by treatment for BC

There is strong evidence from a systematic review that bisphosphonates are useful for preventing bone loss resulting from cancer or its therapy. The efficacy of bisphosphonates for early-stage breast cancers remains controversial. Significant risks of bisphosphonate therapy include nephrotoxicity, electrolyte abnormalities, and osteonecrosis of the jaw. Bisphosphonate therapy has a clear role in the management of skeletal metastases. However, significant side effects require ongoing monitoring and treatment.[Wu, S. et al, 2007]

This is confirmed by further evidence from a fairly large RCT set up to determine whether risedronate, 35 mg/wk is efficacious and safe in preventing bone loss associated with chemotherapy-induced menopause. Risedronate 35 mg/wk prevented bone loss and reduced bone turnover in women with breast cancer treated with chemotherapy. Early measures to prevent bone loss should be considered in this cohort of breast cancer survivors [Greenspan SL, et al, 2007]

There is fair evidence from the ASCO 2003 guidelines on the role of bisphosphonates in bone health issues in women with breast cancer that bisphosphonates provide a supportive, albeit expensive and non-life-prolonging, benefit to many patients with bone metastases. For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended. The presence or absence of bone pain should not be a factor in initiating bisphosphonates. [Hillner, B. E., et al. 2003]

Treatment in itself for BC

A meta-analysis of randomised clinical trials that investigating overall, bone metastasis-free or non-skeletal metastasis free survival among breast cancer patients receiving oral clodronate 1600mg/day given for either 2 or 3 years compared with an identical placebo or no treatment, found no evidence of any statistically significant difference in overall survival or non-skeletal metastasis-free survival in early breast cancer patients receiving adjuvant clodronate treatment compared with those who did not receive any active treatment. Potential limitations exist because of the availability, quality and heterogeneity of the published data.[Ha, T. & Li, H., 2007]

There is some evidence from a systematic review of the use of bisphosphonates in treatment for breast cancer that clodronate does not significantly reduce the risk of developing skeletal metastases and there is inconclusive evidence that bisphosphonates affect survival rates. [Pavlakis, N., et al., 2006]

There is strong evidence from an RCT study of bone loss associated with adjuvant endocrine therapy in pre-menopausal women, comparing goserelin (3.6 mg every 28 days, SC) plus tamoxifen (20mg/d, orally) ± zoledronic acid (4mg every 6 months, IV) versus goserelin (3.6 mg every 28 days, SC) plus anastrozole (1mg/d, orally) ± zoledronic acid (4mg every 6 months, IV) in 401 breast cancer patients (grade 1-3) that regular BMD measurements and initiation of concomitant bisphosphonate therapy on evidence of bone loss should be considered for patients undergoing endocrine therapy. Endocrine therapy caused significant bone loss that increased with treatment duration in pre-menopausal women with breast cancer. Zoledronic acid (4mg/6months) effectively inhibited bone loss. [Gnant, M.F, *et al*, 2007]

There is strong evidence from an RCT in which patients received letrozole 2.5mg orally daily for 5 years or until disease progression and were randomly assigned to upfront or delayed zoledronic acid 4 mg IV over 15 minutes every 6 months for 5 years that upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer. At month 12, LS BMD was 4.4% higher in the upfront group than in the delayed group (95% CI, 3.7% to 5.0%; P<.0001), and TH BMD was 3.3% higher (95%CL, 2.8% to 3.8%; P<.0001). [Brufsky, A., *et.al* 2007]

There is strong evidence form an RCT designed to determine if the addition of oral clodronate 1,600 mg/day for 2 years to standard treatment for primary operable breast cancer could reduce the subsequent occurrence of bone metastases and thereby reprove overall survival, that oral clodronate will significantly improve the 5 year bone relapse free survival. Survival data also favoured the clodronate arm. Oral clodronate was well tolerated, with mild-to-moderate diarrhoea being the most frequently reported adverse event.[Powles, T. *et al*, 2006]

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Evidence Tables

Study Identification:	Anonymous report, Phase 3 Trial of Intravenous Zoledronic Acid in the Prevention of Bone Loss in Localized Breast Cancer Patients With Chemotherapy-Induced Ovarian Failure, Clinical Advanced in Haematology & Oncology, vol. 3:2, Feb. 2005
Design:	Unsystematic review of RCTs, evidence level 4
Country /Setting:	International
Population:	Breast Cancer Patients with Chemotherapy-Induced Ovarian Failure
Intervention:	RCT's randomizing to: adjuvant systemic therapy (chemotherapy and/or tamoxifen) receiving 1,600mg/day of clodronate or placebo; zoledronic acid
Outcomes:	Bone Mineral Density
Follow-up:	2 years
Results:	<p>Clodronate was compatible with adjuvant chemotherapy. The main toxicity with this bisphosphonate was diarrhoea, experienced by 27% of patients in the clodronate group and 8% in the placebo group (P≤.0001).</p> <p>Zoledronic acid, a third-generation bisphosphonate, is a more potent inhibitor of osteoclasts than first- and second-generation agents, and does not have a strong impact of bone mineralization. This agent has been shown to be effective in the treatment of tumour-induced hypercalcemia at doses of 0.5-3.0 mg.</p> <p>Bone mineral density- The mean percentage difference in bone mineral density (BMD) of the total spine and total hip for the clodronate group versus the placebo group at 1 year was +2.38% (95% confidence interval [CI] 1.36-34.1, P<.001) and +1.72% at 2 years (95% CI 0.51-3.34, P=.04). The mean percentage BMD difference in the total hip for the clodronate group versus the placebo group at 1 year was +0.74% (95% CI 0.13-1.60, P=.09) and +1.85% at 2 years (95% CI 0.51-3.20, P=.008).</p>
General comments:	-

Study Identification	Atula, S., Powles, T., Paterson, A., McCloskey, E - Extended safety profile of oral clodronate after long-term use in primary breast cancer patients, Drug Safety, 2003, 26:9, pp. 661-671
Design:	RCT; evidence level 1+
Country Setting: /	USA, hospital setting
Population:	1079 patients with histologically or cytologically confirmed operable primary breast cancer with no evidence of metastases, significant renal or hepatic impairment, or non-malignant bone disease
Intervention:	randomised, double-blind, placebo- controlled, multicentre study, patients randomised to receive oral clodronate 1600 mg/day or placebo for 2 years, (4X 400mg capsules in the morning without food or 2X 400mg capsules twice daily without food depending on the tolerability) in addition to normal therapy regimen for the primary breast cancer including local (surgery, either resection or mastectomy, and radiotherapy) and systemic (chemotherapy, endocrine therapy) treatments.
Outcomes:	AEs, SAEs.
Follow-up:	total median treatment period plus follow-up was 5.5 years.
Results:	<p>In women with early breast cancer receiving adjuvant systemic therapy, oral clodronate for 2 years is generally well tolerated with no serious long-term sequelae, providing a safe, long-term therapy in the adjuvant setting.</p> <p>Overall incidence of AE (96.5% of the patients) was the same in both treatment groups, although gastrointestinal disorders were significantly more frequent in the clodronate group during the total study period (66% vs 56.2%; 95% CI 4.0—15.6; $p < 0.05$). SAE were reported for 39.4% of the patients receiving clodronate and 44.5% of those receiving placebo; no drug-related (clodronate or placebo) SAE were identified.</p> <p>Clodronate significantly lowered mortality (98 deaths vs. 129 deaths; hazard ratio (1.77; 95% CI 0.59—1.00: $p = 0.047$) reducing the risk of death over the total study period by 23%. AEs caused 58 early discontinuations (five drug-related events) in the clodronate group and 43 discontinuations (three drug-related events) in the placebo group.</p> <p>Overall survival— A total of 227 patients died (during the study (medication period 10 vs. follow-up period 217): 98 (18.5%) in the clodronate group and 129(23.9%) in the placebo group, including 188 deaths due to the underlying malignancy (clodronate group 83 vs. placebo group 105). As regards non-breast cancer deaths (clodronate group 15 vs placebo group 24). Pneumonia, secondary neoplasms and vascular events were the most common causes, five of them occurring during the medication period (clodronate group 3 vs. placebo group 2). The mortality rate was significantly lower in the clodronate group ($p = 0.047$), with a hazard ratio of 0.77 (95% CI 0.59-1.00) indicating a 23% reduction in the overall risk of death during the total study time.</p> <p>Patient acceptability – A total of 1041 patients (96.5%) experienced AEs with a similar overall incidence in both treatment groups: AEs were reported for 519 patients (96.5%) in the clodronate group and 522 patients (96.5%) in the placebo group. Of those patients with reported AEs, severe AEs were reported for 248 patients (47.8%) in the clodronate group and 262 patients (50.2%) in the placebo group. Moderate AEs were reported for 225 patients (43.4%) in the clodronate group and for 215 patients (41.2%) in the placebo group. For the rest of the patients, AEs were either mild or their nature was not recorded (five patients).</p>

When the occurrence of AEs by System Organ Class was assessed, GI system disorders were significantly more common in the clodronate group, particularly during the medication period. In contrast, skin and appendage disorders and red blood cell disorders were significantly more frequent in the placebo group, the difference was seen both on and off medication. There were no significant differences between the treatment groups as regards any other SOCs. Interestingly, no renal toxicity was observed for clodronate based on the equal distribution of urinary tract disorders for the treatment groups during both the medication period and the off medication period.

A total of 747 SAEs (clodronate group 355 vs placebo group 392) were reported for 453 patients during the study (clodronate group 212 [39.4%] vs placebo group 241 [44.5%]). The number of patients with SAE was equally distributed between the treatment groups when evaluated by SOCs (table 111), nor was an imbalance evident when SAEs affecting the 01 system were compared. Moreover, there were statistically significant differences between the treatment groups as shown by the 95% CIs for the most frequent preferred terms.

Study Identification	Brufsky, A., Management of Cancer-Treatment-Induced Bone Loss in Postmenopausal Women Undergoing Adjuvant Breast Cancer Therapy, Seminars in Oncology 33(suppl 7):S13-S17 2006
Design:	RCT; evidence level 1+
Country Setting: /	USA, hospital setting
Population:	Post-menopausal women (n = 602) with stage 1-3a estrogen-receptor-positive and/or progesterone-receptor-positive breast cancer
Intervention:	RCT; patients starting letrozole (2.5 mg per day for 5 years) receiving upfront zoledronic acid versus delayed zoledronic acid (4 mg intravenous infusion every 6 months).
Outcomes:	BMD
Follow-up:	12 months
Results:	<p>Combining the anticancer efficacy of letrozole with the bone-protective effect of zoledronic acid is an effective way to prevent cancer treatment induced bone loss.</p> <p>Bone mineral density- BMD values were available for 415 women. Lumbar spine BMD in women receiving upfront zoledronic acid showed a mean increase of 1.55%, compared with a mean decrease of 1.78% in women receiving delayed zoledronic acid (act overall difference of 3.33% between groups). Total hip BMD in the upfront group showed a mean increase of 1.02%, whereas the delayed group showed a mean decrease of 1.40% (an overall difference of 2.42% between groups).</p>

Study Identification	Brufsky, A, Harker, W.G., Beck, J.T. - Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer, Journal of Clinical Oncology, 2007, 25, 7, pp. 829-836.																																																						
Design:	RCT; evidence level 1+																																																						
Country/ Setting:	USA, hospital setting																																																						
	<p>The study included postmenopausal women from 94 Us and Canadian community-based centres who had a history of surgically respectable stage 1, 2, or 3A, estrogen receptor-positive and/or progesterone receptor-positive breast cancer; a baseline Eastern Cooperative Oncology Group performance status of ≤ 2; and baseline lumbar spine (LS) and total hip (TH) T scores ≥ -2.0. All patients underwent tumour resection, completed chemotherapy and/or radiation therapy within 12 weeks of study entry, and had no evidence of residual disease. Patients were excluded if they had clinical or radiologic evidence of distant metastases, an existing LS or TH fracture, or a history of low-intensity fractures. Patients were also excluded if they had received: letrozole or other adjuvant hormone therapy; endocrine therapy; intravenous (IV) bisphosphonates or prolonged systemic corticosteroids within the previous 12 months; growth hormone, anabolic steroids, or tibolone within the previous 6 months; or teriparatide or systemic sodium fluoride. The use of any other drug known to affect the skeleton was prohibited 2 weeks before and throughout the study. Patients who reported receiving oral bisphosphonates or hormone replacement therapy discontinued use before study entry. Patients with renal dysfunction, other malignancies, and diseases known to influence bone metabolism were excluded.</p>																																																						
Population:	<table border="1"> <thead> <tr> <th rowspan="2">Age</th> <th>Upfront Group</th> <th>Delayed group</th> </tr> <tr> <th>n</th> <th>n</th> </tr> </thead> <tbody> <tr> <td>Median</td> <td>60</td> <td>60</td> </tr> <tr> <td>Range</td> <td>35-83</td> <td>41-89</td> </tr> <tr> <td colspan="3">Onset of menopause</td> </tr> <tr> <td>Median age</td> <td>49</td> <td>49</td> </tr> <tr> <td>Age Range</td> <td>21-61</td> <td>23-59</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th rowspan="2">BMD</th> <th>Upfront Group</th> <th>Delayed Group</th> </tr> <tr> <th>n</th> <th>n</th> </tr> </thead> <tbody> <tr> <td colspan="3">Lumbar spine</td> </tr> <tr> <td>Mean</td> <td>1.110</td> <td>1.106</td> </tr> <tr> <td>SD</td> <td>0.1652</td> <td>0.1663</td> </tr> <tr> <td>Median</td> <td>1.088</td> <td>1.082</td> </tr> <tr> <td>Range</td> <td>0.818-1.649</td> <td>0.807-1.642</td> </tr> <tr> <td colspan="3">Total hip</td> </tr> <tr> <td>Mean</td> <td>0.958</td> <td>0.955</td> </tr> <tr> <td>SD</td> <td>0.1259</td> <td>0.1322</td> </tr> <tr> <td>Median</td> <td>0.954</td> <td>0.943</td> </tr> </tbody> </table>			Age	Upfront Group	Delayed group	n	n	Median	60	60	Range	35-83	41-89	Onset of menopause			Median age	49	49	Age Range	21-61	23-59	BMD	Upfront Group	Delayed Group	n	n	Lumbar spine			Mean	1.110	1.106	SD	0.1652	0.1663	Median	1.088	1.082	Range	0.818-1.649	0.807-1.642	Total hip			Mean	0.958	0.955	SD	0.1259	0.1322	Median	0.954	0.943
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	Range	0.676-1.310	0.700-1.475		
	Characteristic	Upfront Group		Delayed group	
		n	%	n	%
	ECOG				
	0	253	84.1	248	82.4
	1	44	14.6	46	15.3
	2	1	0.3	1	0.3
	unknown	3	1.0	6	2.0
	Stratification factors				
	Prior adjuvant chemotherapy	137	4.57	143	47.7
	No prior adjuvant chemotherapy	163	54.3	157	52.3
	T score ≤-1 to ≥ 2	84	27.9	85	28.2
	T score >-1	217	72.1	216	71.8
	Osteoporotic risk factors				
	Postmenopausal status	281	99.6	284	99.6
	Lack of adequate vitamin/dairy intake as a child	102	36.2	111	38.9
	Age ≥ 65 years	93	33.0	95	33.3
	Age at onset of menopause ≤ 45 years	78	27.7	75	26.3
	Adult fracture	71	25.2	67	23.5
	Family history of osteoporosis	63	22.3	62	21.8
	Current smoker or smoking cessation within past 10 years	60	21.3	52	18.2
	Lack of mobility or exercise	51	18.1	48	16.8
	Treatment of one or more comorbidities	49	17.4	49	17.2
	Lack of adequate vitamin/dairy intake as an adult	47	16.7	61	21.4
	Irregular menstrual cycles	44	15.6	48	16.8
Intervention:	Randomised study; patients received letrozole 2.5mg orally daily for 5 years or until disease progression and were randomly assigned to upfront or delayed zoledronic acid 4 mg IV over 15 minutes every 6 months for 5 years. The upfront group received zoledronic acid after random assignment, whereas the delayed group received zoledronic acid when either post baseline LS or TH T score decreased to less than -2.0 or a nontraumatic clinical fracture occurred. Patients were instructed to take an oral calcium supplement (1,000 to 1,200mg) and a multivitamin tablet containing vitamin D (400 to 800 U) once daily during the study. Patients were stratified according to adjuvant chemotherapy (yes v no) and baseline T score (normal [T score > -1.0 and -2.0] v mild to moderate osteopenia [T score between -1.0 and -2.0]). The definitions for normal BMD, osteopenia, and osteoporosis were modelled after the WHO osteoporosis guidelines.				
Outcomes:	BMD, Fractures, Markers of bone turnover, Safety				
Follow-up:	1 year				

Results:

Upfront zoledronic acid therapy prevents bone loss in the LS in postmenopausal women receiving adjuvant letrozole for early-stage breast cancer. At month 12, LS BMD was 4.4% higher in the upfront group than in the delayed group (95% CI, 3.7% to 5.0%; $P < .0001$), and TH BMD was 3.3% higher (95%CL, 2.8% to 3.8%; $P < .0001$). In the upfront group, mean serum N-telopeptide and bone-specific alkaline phosphatase concentrations decreased by 15.1% ($P < .0001$) and 8.8% ($P = .0006$), respectively, at month 12, whereas concentration increased significantly in the delayed group by 19.9% ($P = .013$) and 24.3% ($P < .0001$), respectively.

Bone health (subsequent fractures, etc) – At month 12, no- or low-trauma fractures occurred in 1% of patients in the upfront group and 0.7% of patients in the delayed group. Traumatic fractures occurred in 2.3% and 2% of patients in the upfront and delayed groups, respectively.

Bone mineral density: At month 12, the mean percent difference in BMD between the groups was 4.4% for LS (95% CI, 3.7% to 5.0%; $P < .0001$) and 3.3% for TH (95% CI, 2.8% to 3.8%; $P < .0001$). The risk of developing severe osteopenia within the first year of A1 therapy may be significant in a small percentage of postmenopausal women. In the delayed group, 12.6% of patients with normal baseline BMD developed mild to moderate osteopenia by month 12, and 14.8% of patients with baseline mild to moderate osteopenia progressed to severe osteopenia. However, in the upfront group, only 3.4% of patients with normal baseline BMD developed osteopenia by month 12, and 1.4% of patients with baseline mild to moderate osteopenia progressed to severe osteopenia.

Baseline and Month 12 BMD	Upfront Group		Delayed group	
	n	%	n	%
Normal Baseline BMD	203		198	
Month 12 BMD				
Normal	175	86.2	152	76.8
Mild to moderate osteopenia, T score ≤ -1 to ≥ 2	7	3.4	25	12.6
Severe osteopenia, T score < -2	0	0	0	0
Invalid data	21	10.3	21	10.6
Osteopenia at baseline	70		81	
Month 12 BMD				
Normal	18	25.7	8	9.9
Mild to moderate osteopenia, T score ≤ -1 to ≥ 2	44	62.9	54	66.7
Severe osteopenia, T score < -2	1	1.4	12	14.8
Invalid data	7	10	7	8.6

Patient acceptability– The safety analysis consisted of 300 patients in both groups. The occurrence of AEs was similar between the groups with the exception of bone pain, which was higher in the upfront zoledronic acid group compared with the delayed group (11.3% v 4%, respectively), as expected. Neither group experienced grade 3 or 4 renal dysfunction; one patient in the upfront group experienced a grade 1 increase in serum creatinine level. Osteonecrosis of the jaw (ONJ) was not reported in either group. Serious AEs occurred in 16.7% and 18.7% of patients in the upfront and delayed groups, respectively. Seven percent of patients in the upfront group and 9.7% of patients in the delayed group withdrew from the study as a result of AEs; 1.3% and 1% of patients in the upfront and delayed groups, respectively, discontinued therapy because of serious AEs.

General comments:

small sample size (n=40)

Study Identification:	Dunstan, S. R., Felsenberg, D., & Seibel, M. J., Therapy Insight: the risks and benefits of bisphosphonates for the treatment of tumor-induced bone disease, Nature Clinical Practice Oncology, 2007, 4:1, p.42-55
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	patients with tumour induced bone disease
Intervention:	Trials of bisphosphonates
Outcomes:	Vertebral fractures, non-vertebral fractures
Follow-up:	Not applicable
Results:	<p>Taken together, oral bisphosphonates are highly efficacious in patients with established osteoporosis, particularly in those with existing fractures or at high risk of fracture. By contrast, patients with a low risk of fracture or those determined by the risk of falling do not seem to benefit from anti-resorptive drugs in the same way as do high risk patients.</p> <p>Bone health (subsequent fractures, etc): When alendronate and risedronate are given over a period of 3 years to women with prevalent osteoporotic fractures, a significant risk reduction of new vertebral fractures (47% and 49%, respectively) was seen compared with the placebo group. The effect on vertebral fracture risk can occur as early as 6 months into treatment and is commonly explained by the rapid action of bisphosphonates on bone remodelling and on micro-architecture.</p> <p>Newer studies indicate similar effects of oral ibandronate on vertebral fracture risk, with the advantage of wider (i.e. monthly rather than weekly) dosing intervals.</p> <p>The effect of oral bisphosphonates on non- vertebral fractures is less consistent, particularly with regard to 'hip' fractures, some studies have shown no effect, while others have revealed a significant effect on non-vertebral fractures.</p>
General comments:	

Study Identification	Fuleihan, G., Salamound, M., Mourad, Y.A. – Pamidronate in the prevention of chemotherapy-induced bone loss in pre-menopausal women with breast cancer: a randomized controlled trial, The Journal of clinical endocrinology and metabolism, 2005, 90,6, pp. 3209-3214																																																																																														
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Population:	<p>40 pre-menopausal women with newly diagnosed, nonmetastatic breast cancer awaiting treatment with adjuvant chemotherapy were randomised into a double blind placebo controlled trial comparing Pamidronate 60mg iv every 3 months with placebo. Exclusion criteria: any history of metabolic bone disease, history of having received any bisphosphonate or fluoride within a year of the start of the protocol, and history of intake of pharmacological amounts of any medications that can affect bone turnover (vitamin D, vitamin A, anabolic steroids, glucocorticoids, anticonvulsants, thiazides, or calcitonin). Also excluded were subjects with any history of allergy to bisphosphonates.</p> <table border="1"> <thead> <tr> <th>Characteristic</th> <th>Pamidronate 60mg (n=21)</th> <th>Placebo (n=19)</th> <th>P value</th> </tr> </thead> <tbody> <tr><td>Age</td><td>40</td><td>40.5</td><td>0.8</td></tr> <tr><td>Height (cm)</td><td>158</td><td>157</td><td>0.7</td></tr> <tr><td>Weight (kg)</td><td>67</td><td>67</td><td>1.0</td></tr> <tr><td>BMI</td><td>27</td><td>27</td><td>0.8</td></tr> <tr><td>% Fat mass (kg)</td><td>25</td><td>24</td><td>0.8</td></tr> <tr><td>Lean mass (kg)</td><td>40</td><td>40</td><td>0.9</td></tr> <tr><td>Total hip BMD</td><td>0.84</td><td>0.89</td><td>0.2</td></tr> <tr><td>T score</td><td>-0.81</td><td>-0.45</td><td>0.2</td></tr> <tr><td>Lumbar spine BMD</td><td>0.94</td><td>0.98</td><td>0.4</td></tr> <tr><td>T score</td><td>-1.12</td><td>-0.80</td><td>0.4</td></tr> <tr><td>25-OH vitamin D</td><td>12.0</td><td>9.6</td><td>0.4</td></tr> <tr><td>TSH mU/liter</td><td>1.6</td><td>1.7</td><td>0.9</td></tr> <tr><td>Osteocalcin</td><td>20.4</td><td>18.0</td><td>0.6</td></tr> <tr><td>Cross Laps</td><td>1.9</td><td>1.7</td><td>0.5</td></tr> <tr><td>Tamoxifen</td><td>14</td><td>14</td><td>0.6</td></tr> <tr><td>Stage</td><td></td><td></td><td></td></tr> <tr><td>1</td><td>2</td><td>2</td><td></td></tr> <tr><td>2</td><td>13</td><td>9</td><td>0.5</td></tr> <tr><td>3</td><td>6</td><td>8</td><td></td></tr> <tr><td>Chemotherapy regimen</td><td></td><td></td><td></td></tr> <tr><td>FAC</td><td>16</td><td>17</td><td></td></tr> <tr><td>FAC-like regimens</td><td>2</td><td>1</td><td>0.8</td></tr> </tbody> </table>			Characteristic	Pamidronate 60mg (n=21)	Placebo (n=19)	P value	Age	40	40.5	0.8	Height (cm)	158	157	0.7	Weight (kg)	67	67	1.0	BMI	27	27	0.8	% Fat mass (kg)	25	24	0.8	Lean mass (kg)	40	40	0.9	Total hip BMD	0.84	0.89	0.2	T score	-0.81	-0.45	0.2	Lumbar spine BMD	0.94	0.98	0.4	T score	-1.12	-0.80	0.4	25-OH vitamin D	12.0	9.6	0.4	TSH mU/liter	1.6	1.7	0.9	Osteocalcin	20.4	18.0	0.6	Cross Laps	1.9	1.7	0.5	Tamoxifen	14	14	0.6	Stage				1	2	2		2	13	9	0.5	3	6	8		Chemotherapy regimen				FAC	16	17		FAC-like regimens	2	1	0.8
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Intervention:	Randomized, double blind, placebo controlled trial comparing Pamidronate 60mg iv every 3 months with placebo. Most patients (>80%) were prescribed a 5-FU, adriamycin, cyclophosphamide (FAC) regimen, 10% a cytophosphamide, methotrexate, 5-FU (CMF) regimen, and 10-15% an anthracyclin (adriamycin or epirubicin) and cyclophosphamide (FAC0like) regimen. Over two thirds were also started on tamoxifen at completion of the chemotherapy at a dose of 20mg/d for a duration of 5 yr. This treatment was equally balanced between the two arms at study entry and by development of amenorrhea.				
Outcomes:	Bone mineral density of the spine (L1-L4) and the hip and total body BMD, content, and body composition were performed at 0, 6, and 12 months using dual-energy x-ray absorptiometry.; remodelling markers				
Follow-up:	2 ± 0.8 years in the placebo arm, 1.9 ± 0.8 years in the Pamidronate arm (p=0.8)				
Results:	<p>IV Pamidronate given at the dose of 60mg every 3 months prevented chemotherapy-induced bone loss in young pre-menopausal women, was well tolerated, and is an attractive alternative in preserving skeletal health in such patients. The mean difference in percentage change in BMD at 12 months between the two treatment groups was 5.1% at the lumbar spine (p=0.002) in the overall study group and 5 % at lumbar spine and 5.2% at the total hip in the amenorrheic sub- group (p<0.03).</p> <p>Bone mineral density:</p> <p>BMD stabilized at the lumbar spine in the Pamidronate group and decreased in the placebo group, with a significant treatment effect at both the 6- and 12-month time points. Although the trend was similar at the total hip, a significant treatment effect was not achieved. Over half of the patients became amenorrheic during the study, with no differences between the two treatment arms.</p> <p>Amenorrheic group.</p> <p>BMD stabilized at the lumbar spine in the Pamidronate group and decreased in the placebo group, with a significant treatment effect at both the 6- and 12-month time points. Similarly, at the total hip, BMD stabilized in the Pamidronate group and decreased in the placebo group, with a treatment effect noted at 12 months and an almost significant effect at 6 months.</p> <p>Non amenorrheic group.</p> <p>There were no differences in percent change in BMD at either the lumbar spine or the total hip by treatment group at either time point in the nonamenorrheic subgroup (P= 0.15 at the lumbar spine; P= 0.81 at the hip at 12 months).</p>				
	Change in BMD (%)		Treatment effect		
Site	Pamidronate	Placebo	Mean	95% CI	p
Overall study group (n=40)					
Lumbar spine					
6 months	1.8	-2.8	4.6	(2.2, 6.9)	0.000
12 months	1.9	-3.2	5.1	(-2.0,	0.002

				8.2)	
Total hip					
6 months	-0.2	-1.1	0.9	(-1.5, 3.3)	0.44
12 months	-0.3	-2.8	2.6	(-0.3, 5.5)	0.08
Amenorrheic grp.(n=22)					
Lumbar spine					
6 months	1.1	-2.8	4.0	(1.0, 6.9)	0.01
12 months	0.95	-4.0	5.0	(0.6, 9.2)	0.03
Total hip					
6 months	1.5	-.07	2.2	(-0.2, 4.6)	0.07
12 months	1.2	-4.0	5.2	(2.0, 8.3)	0.003
General comments: - small sample size (n=40)					

Study Identification	Gnant, M.F., Mlineritsch, B., Luschin-Ebengreuth, G. et al. 2007. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone responsive breast cancer: a report from the Austrian breast and colorectal cancer study group. Journal of Clinical Oncology, 25:7 pp 820-823							
Design:	RCT; evidence level 1+							
Country/Setting:	Austria, hospital setting							
Population:	401 breast cancer patients (grade 1-3) patients included in the BMD sub-protocol of a 4 arm, randomised, open-label, phase III trial							
	Characteristic		Tamoxifen + Zoledronic acid (=100)		Anastrozole alone (n=94)		Anastrozole + Zoledronic acid (=104)	
	n	%	n	%	n	%	n	%
	Age							
	Median		46.6		43.8		45.7	
	Range		31.8-54.9		28.1-54.7		25.9-56.2	
	> 40	85	83	80	80	79	84	77
	≤ 40	18	17	20	20	15	16	23
	Stage							
	T1a	1	1	0	0	0	2	2
	T1b	18	17	14	14	19	20	17
	T1c	56	54	55	55	50	53	56
	T2	25	24	30	30	23	24	23
	T3	2	2	0	0	0	0	1
	Grade							
	1	17	17	20	20	11	12	13
	2	56	54	51	51	54	57	62
	3	27	26	27	27	25	27	22
	unknown	2	2	1	1	2	2	2
	Lymph mets							
	Positive	43	42	40	40	35	37	38
	Negative	59	57	59	59	57	66	60

							1		
	ER/PR status								
	ER +	98	95	98	98	87	93	38	94
	PR +	91	88	87	87	88	94	94	90
	Baseline BMD g/cm ²								
	L1-L4	1.058		1.028		1.038		1.002	
	Trochanter	0.712		0.707		0.728		0.704	

Intervention: Study of bone loss associated with adjuvant endocrine therapy in pre-menopausal women: goserelin (3.6 mg every 28 days, SC) plus tamoxifen (20mg/d, orally) ± zoledronic acid (4mg every 6 months, IV) versus goserelin (3.6 mg every 28 days, SC) plus anastrozole (1mg/d, orally) ± zoledronic acid (4mg every 6 months, IV) for 3 years

Outcomes: Bone mineral density (does zoledronic acid prevent bone loss in the intervention group); assessed by bone densitometry of lumbar spine and trochanter by dual energy x-ray absorptiometry at baseline, 6 months, 12 months and 36 months.

Follow-up: 36 months

Results:
Endocrine therapy caused significant bone loss that increased with treatment duration in pre-menopausal women with breast cancer. Zoledronic acid (4mg/6months) effectively inhibited bone loss. Regular BMD measurements and initiation of concomitant bisphosphonate therapy on evidence of bone loss should be considered for patients undergoing endocrine therapy.

Bone mineral density:

Endocrine treatment without zoledronic acid led to significant (p<0.001) overall bone loss after 3 years of treatment (BMD – 14.4% after 36 months; mean T score reduction, - 1.4). Overall bone loss was significant more severe in patients receiving anastrozole/goserelin (BMD – 17.3%; mean T score reduction, - 2.6) compared with patients receiving tamoxifen/goserelin (BMD – 11.6%; mean T score reduction, - 1.1). In contrast BMD remained stable in zoledronic acid treated patients (p<0.0001 compared with endocrine therapy alone). No interaction with age or other risk factors were noted.

Characteristic	Tamoxifen alone (n=103)	Tamoxifen+ Zoledronic acid (=100)	Anastrozole alone (n=94)	Anastrozole + Zoledronic acid (=104)
BMD measurements	n	n	n	n
Baseline n=343	82	87	79	95
6 months n=331	80	89	75	87
12 months n=318	78	83	73	84
36 months n=114	26	26	25	37

Patient acceptability – the combination of zoledronic acid with endocrine therapy was well tolerated.

The most common AE reported were consistent with the known toxicity profiles of each drug. Specifically patients treated with tamoxifen reported a greater frequent cy of hot flashes and vaginal bleeding whereas patients treated with anastrozole reported a greater frequency of musculoskeletal

disorders. Administration of zoledronic acid was associated with the infusion-related flu-like symptoms common to all IV bisphosphonates (nausea, vomiting, fever and myalgia).

These events were mild to moderate in intensity and were primarily limited to the first infusion of the drug. Importantly, there was no evidence of additive toxicity between zoledronic acid and either goserelin/anastrozole or goserelin/tamoxifen.

No fractures or other skeletal-related events were recorded in this trial. Finally, administration of zoledronic acid was not associated with changes in renal function in this patient population. Across a total of 2,904 serum creatinine measurements over 3 years, mean serum creatinine level was 0.78 ± 0.17 mg/dL, and no patient had a serum creatinine value greater than 1.5x the upper limit of normal. No cases of jaw osteonecrosis were reported in this trial.

General comments: -

Study Identification	Greenspan, SL., Bhattacharya, R.K., Sereika, SM, et al - Prevention of Bone Loss in Survivors of Breast Cancer: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial, The Journal of Clinical Endocrinology & Metabolism 52(1):151—126, 2007
Design:	RCT; evidence level 1+
Country/ Setting:	USA, hospital setting
Population:	87 breast cancer women newly postmenopausal (up to 8 yr) after being treated with chemotherapy with or without tamoxifen or aromatase inhibitors. Exclusion criteria: stage 4 breast cancer (presence of distant metastases), a history of any illness known to affect bone and mineral metabolism (renal failure or hepatic failure), malignancy (excluding breast cancer), hyperparathyroidism, and mal absorption. Women were allowed to begin or continue with tamoxifen or an aromatase inhibitor if prescribed by their physician. Participants who had been treated with other medications known to affect bone and mineral metabolism were excluded. Women with an adult fragility fracture or with an initial BMD T-score of -2.5 or below at the hip or spine were counselled about therapy but given the option to participate in the study.
Intervention:	RCT of risedronate received 35mg/wk or placebo to establish effect on bone loss in newly post menopausal women with breast cancer treated with chemotherapy with or without concomitant use of tamoxifen or AI.
Outcomes:	BMD was measured at the spine (PA and lateral projections), hip (femoral neck, total hip, trochanter, and inter trochanter), one-third distal radius, and total body by dual-energy x-ray absorptiometry.
Follow-up:	12 months
Results:	<p>Risedronate, 35 mg/wk is efficacious and safe in preventing bone loss associated with chemotherapy-induced menopause. Risedronate 35 mg/wk prevented bone loss and reduced bone turnover in women with breast cancer treated with chemotherapy. Early measures to prevent bone loss should be considered in this cohort of breast cancer survivors.</p> <p>After 12 months, bone mineral density increased by 1.2% at the spine and 1.3% at the hip in women on risedronate vs. significant decreases for women in the placebo group of 0.9% at the spine and 0.8% at the hip ($P < 0.01$, difference between groups). N-telopeptide cross-linked collagen type I, a marker of bone resorption, decreased by 19.3%, and N-terminal propeptide of type I procollagen, a marker of bone formation, decreased by 26.6% in participants on active therapy compared with increases in the control group. Risedronate was well tolerated, and the retention rate was 95% at 1 yr.</p> <p>Bone health (subsequent fractures, etc) - Two fractures; no difference between the groups</p> <p>Bone mineral density- After 1 yr BMD in the spine increased by $1.2 \pm 0.5\%$ in participants treated with risedronate and decreased by $0.9 \pm 0.5\%$ in the placebo group ($P < 0.01$, difference between groups at 12 months)</p> <p>Total hip BMD increased $1.3 \pm 0.3\%$ in women on risedronate therapy and decreased $0.8 \pm 0.3\%$ in those who received placebo ($P < 0.001$, difference between groups at 6 and 12 months)</p> <p>Similar trends were observed in the lateral spine and trochanter.</p> <p>At the distal radius and total body, BMD remained stable in the treatment group but decreased in the placebo group (0.8 ± 0.4 and $0.8 \pm 0.3\%$, respectively, both differences between groups, $P < 0.05$).</p>

When the rates of change in BMD were adjusted for baseline bone turnover markers (individually as well as simultaneously), similar results were found.

BMD changes at the spine, hip, and all other skeletal sites for women on tamoxifen and risedronate were similar to changes for women on risedronate alone. (approximately 70% in each group were on tamoxifen at baseline and 31% at 12 months) However, in the placebo group, the rate of change for total hip BMD was $1.2 \pm 0.05\%$ greater ($P < 0.05$) in women on tamoxifen compared with those who were not .

There were no significant differences in the PA spine between those on or off tamoxifen in the placebo group.

At baseline, 18.6% of participants were on an AI in the treated group, and 13.6% of participants were on an AI in the placebo group. During the first year this increased to 39.5% of women on an aromatase inhibitor in the risedronate group and 34.1% in the placebo group. There was a marginally significant treatment effect (less improvement) at the PA spine for women on an aromatase inhibitor ($P < 0.10$); no significant effect was observed at other skeletal sites.

Recurrence – Two patients; no difference between the groups

Patient acceptability – The tolerability profile of risedronate was similar to that of placebo. There were no differences between the groups in the number of women who reported heartburn, epigastric distress, arthralgias, myalgias, or other adverse events.

General comments: -

Study Identification:	Ha, T. C. & Li, H., Meta-analysis of clodronate and breast cancer survival, British Journal of Cancer, 2007, 96:12, p.1796-1801
Design:	Meta-analysis evidence level 1+
Country/ Setting:	International
Population:	Participants were patients with histologic- or cytologic-proven breast cancer but no prior history of other malignant diseases (besides recurrent breast cancer) or bisphosphonate usage. Early breast cancer was defined as patients who were diagnosed with primary operable breast cancer.
Intervention:	Trials included randomised clinical trials that investigated overall, bone metastasis-free or non-skeletal metastasis free survival among breast cancer patients receiving oral clodronate 1600mg/day given for either 2 or 3 years compared with an identical placebo or no treatment.
Outcomes:	Outcome measures included for 5-year overall, bone metastasis-free and non-skeletal metastasis free survival.
Follow-up:	Not applicable
Results:	
<p>The meta-analysis found no evidence of any statistically significant difference in overall survival or non-skeletal metastasis-free survival in early breast cancer patients receiving adjuvant clodronate treatment compared with those who did not receive any active treatment.</p> <p>Disease-free survival – There was no evidence to suggest that clodronate therapy improves overall, non-skeletal metastasis free survival or bone metastasis-free survival significantly in either group of patients. Pooled analysis did not find any statistically significant difference in the time to appearance of bone metastasis in patients who received adjuvant clodronate treatment compared with those who did not (HR=0.60, 95% CI=0.30, 1.23). No statistically significant delay in the occurrence of non-skeletal metastases between patients receiving adjuvant clodronate therapy and those receiving no treatment (HR=0.99, 95% CI=0.40, 1.99).</p> <p>Overall survival–The pooled results demonstrated no statistically significant difference in the overall survival between patients treated with adjuvant clodronate therapy and those receiving no treatment (HR=0.75, 95% CI=0.31, 1.02).</p>	
General comments: Potential limitations exist because of the availability, quality and heterogeneity of the published data.	

Study Identification:	Hillner, B. E., Ingle, J. N., Chlebowski, R. T., Gralow, J., Gary C. Yee, G. C., Janjan, N. A., Cauley, J. A., Blumenstein, B. A., Albain, K. S., Lipton, A. and Brown, S. American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer, Journal of Clinical Oncology, 2003, 21:21, p. 4042-4057
Design:	guideline evidence level 4
Country / Setting:	USA
Population:	-
Intervention:	Update to 2000 ASCO guidelines on role of bisphosphonates in women with breast cancer and address the subject of bone health in these women.
Outcomes:	BMD
Follow-up:	n/a
<p>Results: Bisphosphonates provide a supportive, albeit expensive and non-life-prolonging, benefit to many patients with bone metastases. For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended. The presence or absence of bone pain should not be a factor in initiating bisphosphonates.</p> <p>Bone mineral density- Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in pre-menopausal women with treatment-induced (usually secondary to chemotherapy) menopause.</p> <p>General comments: the evidence level of the guideline is also compromised by the review of outdated trials which provide inconclusive evidence.</p>	

Study Identification:	Pavlakakis, N., Schmidt, R. L., & Stockler, M., Bisphosphonates for breast cancer, The Cochrane Library, 2006, (1): CD003474, 1, p. CD003474
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	Randomised studies comparing bisphosphonates and placebo, or different bisphosphonates in women with metastatic breast cancer.
Intervention:	Three RCTs examining the effect of oral bisphosphonate, clodronate, on the development of bone metastases or skeletal events in 1670 women with early breast cancer.
Outcomes:	Risk of developing skeletal metastases; survival
Follow-up:	Not applicable
<p>Results: Clodronate does not significantly reduce the risk of developing skeletal metastases and there is inconclusive evidence that bisphosphonates affect survival rates.</p> <p>Bone health (subsequent fractures, etc) - Updated fixed effects meta-analysis of three studies that included 162 events among 1653 women indicates that adjuvant oral clodronate does not significantly reduce the risk of developing skeletal metastases (RR 0.82; 95% CI 0.66 to 1.01; P = 0.07). However, there is significant heterogeneity among these three studies.</p> <p>Overall survival– Treatment with bisphosphonates does not appear to significantly affect survival in women with early breast cancer.</p> <p>General comments: This review is focusing on trials of bisphosphonates in advanced breast cancer and only three trials of early breast cancer have been included. Also, the three trials have a high degree of heterogeneity and therefore the findings are inconclusive.</p>	

Study Identification	Powles, T., Paterson, A., McCloskey, E., Schein, P. - Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer, Breast Cancer Research, 2006, vol 8:2, p.R13
Design:	RCT; evidence level 1+
Country/Setting:	UK, hospital setting
Population:	(N=1069) with histologically or cytologically confirmed primary operable breast cancer with no evidence of metastasis; Primary treatment consisted of surgery and/or radiotherapy with or without systemic endocrine therapy and/or chemotherapy. Exclusion criteria: significant renal, hepatic, or non-malignant bone disease; a history of malignant disease or prior bisphosphonate use.
Intervention:	randomized, double-blind, placebo-controlled, multi-centre trial designed to determine if the addition of oral clodronate 1,600 mg/day for 2 years to standard treatment for primary operable breast cancer could reduce the subsequent occurrence of bone metastases and thereby improve overall survival.
Outcomes:	Development of bone metastases; survival
Follow-up:	mean 5.6 years; range 5-10.5 years
Results:	<p>Oral clodronate will significantly improve the 5 year bone relapse free survival when used as a supplementary adjuvant treatment for patients receiving standard treatment for primary operable breast cancer</p> <p>Oral clodronate significantly reduced the risk of bone metastases in all patients over the 5 year study period (51 patients versus 73 patients with placebo; HR = 0.692, p=0.043); the difference was also statistically significant over the 2 year medication period (19 patients versus 35 patients with placebo; HR 0.546, P= 0.031). These differences were most pronounced in patients with stage II/III disease (39 patients versus 64 patients with placebo, HR = 0.592, P 0.009 over 5 years; 16 patients versus 32 patients with placebo, HR=0.496, P=0.020 over 2 years).</p> <p>Survival data also favoured the clodronate arm (HR for all patients = 0.768, P=0.048; HR for stage II/III disease = 0.743, P=0.041) although this was not significant due to multiple analyses. Oral clodronate was well tolerated, with mild-to-moderate diarrhoea being the most frequently reported adverse event.</p> <p>Bone health (subsequent fractures, etc) - The addition of oral clodronate to adjuvant therapy for breast cancer significantly reduced the risk of bone metastases by 31% over the 5 year study period (51 patients versus 73 patients receiving placebo, HR=0.692: P=0.043). During the 2-year treatment period patients in the clodronate arm had a 45% reduction in the risk of bone metastases (P = 0.03). Over the 5 year study period only 6% of patients with stage I disease developed bone metastases compared with 15% of patients with stage II disease and 34% of patients with stage III disease. Hazard ratios for bone metastases confirmed a similar risk reduction for bone metastases for all patient subgroups that received oral clodronate, apart from patients with relatively low risk stage I disease where the numbers of events were too small to provide any meaningful comparison. For stage II/III disease, over the 5 year study period, the clodronate treated patients had a 41% decrease in the risk of developing bone metastases (P = 0.009) during the 2 year medication period, the risk was decreased by 50% (P = 0.020).</p> <p>For the 51 of 530 clodronate patients and the 73 of 539 placebo patients who developed bone</p>

metastases, there was evidence of a reduction in the number of bone metastases related hosts events in clodronate patients (29/530; 5.5%) compared with placebo patients (53/532; 9.8%) ($p < .001$). This shows that, although there were only 51 of the clodronate patients who relapsed in bone compared to 73 of the placebo patients, they did not do worse because of previous adjacent clodronate. In fact, only 57% of these patients developed skeletal events compared to 73% of the bone relapsed placebo patients. This indicates that previous clodronate therapy does not appear to have compromised the subsequent treatment of relapsed metastatic bone disease.

Overall survival– Patients who received oral clodronate had an overall survival advantage, although this is no longer statistically significant due to multiple analyses. This was observed for all patients and for patients with stage II/III disease. There was a 23% reduction in the risk of death in all patients (HR= 0.768, 95% CI 0.591-0.999; $p=0.048$) and a 26% reduction in risk of death in the subset of patients with stage II/III disease (HR = 0.743, 95% CI 0.558-0.989; $p=0.041$), although neither of these reached statistical significance because of multiple analyses.

Patient acceptability – Overall, there were no reports of drug-related serious adverse events. Study medication was stopped early due to adverse events in 13% of patients receiving oral clodronate compared with 1% of patients receiving placebo.

Although the most frequently reported adverse events were gastrointestinal, diarrhoea was the only adverse event to demonstrate a statistically significant increase in incidence in the clodronate treatment group. Diarrhoea occurred in 19.9% of the clodronate treated patients versus 10% of the placebo-treated patients ($P < 0.05$) and was generally mild. There were no cases of oesophageal perforation or ulceration or osteonecrosis of the mandible and/or maxilla, which have been associated with the use of other bisphosphonates.

General comments: -

Study Identification:	Powles, T., McCloskey, E., Paterson, A, Oral Bisphosphonates as Adjuvant Therapy for Operable Breast Cancer, Clinical Cancer Research 2006, 12:20:2, p.6301s-6304s.
Design:	Unsystematic review of RCTs, prospective cohort studies and retrospective case series; evidence level 4
Country/ Setting:	UK, hospital setting
Population:	RCTs of patients with primary operable breast cancer
Intervention:	clodronate 1,600mg/day or placebo
Outcomes:	Metastatic bone events; spine and hip BMD; patient acceptability
Follow-up:	Up to 5 years

Results:

The oral bisphosphonate clodronate (1,600 mg/d) is effective for treatment of patients with chemotherapy-induced bone loss. When used as adjuvant therapy, given to patients with operable breast cancer for 2 years, clodronate has been reported to significantly reduce the risk of bone metastases during the 2-year study period [19 clodronate patients versus 35 placebo patients; hazard ratio (HR), 0.546; P = 0.03] and 5-year study period (51 clodronate patients versus 73 placebo patients; HR. 0.692; P = 0.04) with a significant reduction in mortality (HR. 0.768; P = 0.048). This benefit, together with the low toxicity and safety of clodronate, supports its use as additional adjuvant therapy for patients with primary breast cancer.

Bone health (subsequent fractures, etc) - Oral clodronate significantly reduced the risk of bone metastases during the 2-year study period f 19 clodronate patients versus 35 placebo patients; hazard ratio (HR), 0.546; P = 0.03] and 5-year study period (51 clodronate patients versus 73 placebo patients; HR, 0.692; P 0.04). This reduction was predominantly seen in patients with stage 11 and III disease. An analysis of the incidence of skeletal-related events in the 51 clodronate patients and 73 placebo patients who developed bone metastases was also done to estimate the clinical benefit of early treatment. Clodronate patients were less likely to have metastatic bone events (fractures, hypercalcemia, and bone irradiation) even when corrected for the fewer numbers, indicating a probable spill over benefit for these patients even if they had relapsed in bone.

A further small, randomized, open-label study with oral clodronate involving 302 women with newly diagnosed primary breast cancer has also been reported. These patients had operable breast cancer but also had micro-metastases detected in their bone marrow at the time of primary diagnosis. The patients were randomly assigned to receive oral clodronate (1,600 mg/d) or no clodronate during a 2-year treatment period. All patients received standard adjuvant therapies, including surgery, radiotherapy, endocrine therapy, and/or chemotherapy. The two arms were well balanced with respect to prognostic factors during the 3-year follow-up period; patients who received oral clodronate had an ~50% reduction in the incidence of bone metastases (8% versus 17% with placebo; P= 0.003) and a significantly longer bone metastasis-free survival (P < 0.001) compared with those receiving standard treatment. A later analysis still confirmed a significant reduction in overall survival for clodronate patients, although the significant reduction in disease-free survival no longer persisted.

Bone mineral density- Oral clodronate (1,600 mg/d) protected against cancer treatment-induced loss of spine and hip bone mineral density. After the discontinuation of use of clodronate, rates of

bone loss returned after 1 year to the rate of bone loss in placebo-treated women. The women randomized to clodronate still had a significantly greater bone mineral density at 5 years than those treated with placebo.

Overall survival– There was also a significant reduction in mortality (HR. 0.768; P = 0.048; ref. 19). Furthermore, there was an overall significant reduction in mortality (98 clodronate patients versus placebo 129 patients; P = 0.048).

Patient acceptability – In this trial, oral clodronate (1,600 mg/d) was well tolerated, with no significant toxicity apart from mild to moderate diarrhoea.

General comments: -

Study Identification:	Saarto, T., Vehmanen, L., Virkkunen, P. and Blomqvist, C, Ten-year Follow-up of a Randomized Controlled Trial of Adjuvant Clodronate Treatment in Node-positive Breast Cancer Patients Acta Oncologica Vol. 43, No. 7, pp. 650 656, 2004
Design:	RCT; evidence level 1+
Country Setting: /	Finland, hospital setting
Population:	299 pre- and postmenopausal women with primary node positive breast cancer.
Intervention:	All patients received adjuvant chemo- or endocrine therapy ± oral clodronate 1600mg daily for 3 years. Pre-menopausal patients had chemotherapy, 6 cycles of cyclophosphamide (600 mg/rn2), methotrexate (40 mg/rn2), and 5-fluorostracil (600 mg/rn2) intravenously on day 1, and at successive 3-week intervals (CMF). Postmenopausal women were randomly allocated to receive either adjuvant tamoxifen 20mg or toremifene 60 mg per day for three years.
Outcomes:	Bone metastases and morbidity, Survival analysis and non-skeletal recurrence, DFS according to oestrogen receptor and menopause status
Follow-up:	10 years
<p>Results: Within 10 years bone metastases were detected 25 the same frequency in the clodronate and control groups: 44(32%) vs. 42(29%), respectively, (p=0.35). The frequency of non-skeletal recurrences (visceral and local) was significantly higher in the clodronate group 69 (50%) as compared with the controls 51(36%) (p=0.005). 10 year DFS remained significantly lower in the clodronate group (45% vs. 58%, p=0.01, respectively). This was especially seen in oestrogen receptor negative patients (25% vs. 58%, p =0.004, respectively). No significant overall survival difference was found between the groups. As previously reported 3-year adjuvant clodronate treatment did not prevent the development of bone metastases in node-positive breast cancer patients. A negative effect of clodronate on DFS by increasing the development of visceral metastases was still seen at 10 years, but this did not significantly compromise overall survival.</p> <p>Bone health (subsequent fractures, etc) - Bone metastases were detected as often in the clodronate group as in the controls: 44 (32%) vs. 42 (29%). There were no significant differences in 10-year skeletal disease-free survival between the study groups: 68% in the clodronate group and 71% in the controls (p =0.35). Bone was the first site of relapse in 29 patients (11 in the clodronate group and 18 in the controls, p=0.03), non- skeletal metastases in 78 patients (46 and 32, respectively, p=0.40) and simultaneous skeleton and non-skeleton in 26 patients (17 and 9, respectively, p=0.28). Bone as the first site of relapse was mainly seen in ER receptor positive patients: in 22 ER positive, 4 ER negative, and 3 ER unknown patients.</p> <p>Recurrence Seventy-six patients (55%) in the clodronate group and 60 (42%) control patients developed metastatic disease. Extra-skeletal (visceral and local) metastases were detected in 69 (50%) clodronate treated patients and in 51(36%) control patients with extra-skeletal DFS of 50% vs. 64%, respectively (p=0.004).</p> <p>Disease-free survival Ten-year disease-free survival (DFS) was significantly lower in the clodronate group: 45% vs. 58%, respectively (p=0.01).</p>	

In ER-positive patients 10-year DFS was 55% in the clodronate group, and 59% in the controls with no difference between the groups ($p = 0.47$); while in ER- negative patients the DFS difference was highly significant in favour of the controls: 25% vs. 58%, respectively ($p = 0.004$).

When pre- and postmenopausal patients were analysed separately according to receptor status, the only subgroup where no negative effect of clodronate was seen was ER- positive postmenopausal women treated with 3 years' antioestrogen therapy (10 year DFS 56% in both groups). In all the other subgroups the clodronate group did worse than the controls.

Overall survival

Sixty-four (46%) clodronate treated patients and 55 (38%) control patients died. Ten-year overall survival was 54% and 62% respectively ($p = 0.13$). The number of non-breast-cancer-related deaths was 12 (4 in the clodronate and 8 in the control group).

General comments: -

Study Identification:	Sawka, A. M., Ioannidis, G., Papaioannou, A. - Are oral bisphosphonates effective in improving lumbar bone mineral density in breast cancer survivors with osteopenia or osteoporosis? Journal of Obstetrics and Gynaecology, Canada, JOGC, 2005, 27:8 pp 759-764
Design:	retrospective case series; evidence level 3
Country/ Setting:	Canada, hospital setting
Population:	70 breast cancer survivors, age >50, with at least one year of clinical follow-up identified from the prospective observational Canadian Database of Osteoporosis and Osteopenia (CAN000).
Intervention:	Patients treated with cyclic etidronate disodium (400mg/day for 14 days); alendronate 10mg/day) concomitant with chemotherapy
Outcomes:	BMD performed using dual-energy X-ray absorptiometry (DXA).
Follow-up:	1 year
Results:	<p>Oral daily alendronate treatment was associated with significantly greater improvements in lumbar spine bone density than use of cyclic etidronate or calcium and vitamin D alone. BMD increases were significantly greater in patients with prevalent vertebral fractures (VF) compared to these without VF (P = 0.025). In contrast, time since diagnosis of breast cancer was significantly associated with a decrease in BMD (P = 0.002).</p> <p>Bone mineral density- Lumbar spine bone density measurements at baseline and at one year were available for 55 patients (79%). In control patients, lumbar BMD decreased at one year by 1.4% (SD 3.8), whereas BMD increased by 2.3% (SD 4.7) in etidronate-treated patients and increased by 4.3% (SD 4.1) in alendronate-treated patients. Minimal changes in femoral neck bone mineral densities were seen over the course of one year in each treatment group; in the control group, there was a decrease of 1 .7% (SD 3.7), to the etidronate group an increase of 0.1% (SD 4.5), and in the alendronate group an increase of 0.6% (SD 5.0).</p>
General comments:	-

Study Identification	Vehmanen, L., Saarto, T., Risteli, J, Short-term intermittent intravenous clodronate in the prevention of bone loss related to chemotherapy-induced ovarian failure, Breast cancer research and treatment, 2004, 87:2, p.181-188
Design:	RCT; evidence level 1+
Country/ Setting:	Finland, hospital setting
Population:	48 pre-menopausal newly diagnosed breast cancer patients with operable T1-3 NO-2 MO breast cancer. Exclusion criteria: Karnofsky performance index < 70; S-Krea > 150 µmol/l.; peptic ulcer; hysterectomy or ovariectomy; osteoporosis; untreated hypothyreosis; bisphosphonate, calcitonin or peroral steroid therapy; pregnancy or lactation; other malignancies; and age >55 years. Pre-menopausal status was defined as ongoing menstruation during the last 6 months.
Intervention:	RCT investigating the effect of seven cycles IV intermittent 1500mg clodronate during adjuvant chemotherapy in prevention chemotherapy induced bone loss.
Outcomes:	Lumbar spine BMD
Follow-up:	12 months
Results:	<p>Short-term intermittent intravenous clodronate treatment did not seem to prevent clinically significantly the bone loss related to chemotherapy-induced ovarian failure in pre-menopausal women with early stage breast cancer. The mean bone loss in the lumbar spine at 6 months was -0.5% in the clodronate group and 1.4% in the control group (p = 0.22) and at 12 months, -3.9% and 3.6%, respectively (p=0.62).</p> <p>Bone mineral density- Four month intermittent intravenous clodronate treatment did not prevent the bone loss associated with chemotherapy-induced ovarian failure and amenorrhea. The change in lumbar spine BMD at six months was -0.5%. (CI -1.6% to + 0.7%) in the clodronate group and -1.4% (CI -2.7% to -0.2%) in the control group (p = 0.22). and in the femoral neck -0.4% (CI -2.2% to +1.4%) and 1.9% (CI -3.9% to 0%), respectively (p = 0.37). The bone loss in the lumbar spine at 12 months was -3.9% (CI -5.1% to -2.8%) in the clodronate group and 3.6% (CI 4.8% to 2.4%) in the control group (p = 0.62); in the femoral neck -1.4% (CI -3.6% to +0.8%) and -2.9% (CI -4.7% to -1.1%) (p =0.43), respectively. The effect of clodronate treatment on BMI change at 12 months was not significant (p = 0.83 for lumbar spine and p=0.54 for femoral neck) while a highly significant effect of menopausal status (amenorrhea vs. irregular or regular menstruation) was found in the lumbar spine (p = 0.003). In the femoral neck, the effect of menopausal status on BMD was not statistically significant (p = 0.31).</p>
General comments:	-

Study Identification:	Wu, S., Dahut, W. L., & Gulley, J. L., The use of bisphosphonates in cancer patients, Acta Oncologica, 2007, 46:5, p.581-591
Design:	systematic review of RCTs evidence level 1++
Country / Setting:	international
Population:	RCTs of bisphosphonates in cancer patients
Intervention:	Clodronate and zoledronic acid
Outcomes:	Bone health, metastases, overall survival
Follow-up:	Majority of studies included in the review had long-term follow-up
Results:	<p>Emerging data indicate that bisphosphonates are useful for preventing bone loss resulting from cancer or its therapy. The efficacy of bisphosphonates for early-stage breast cancers remains controversial. Significant risks of bisphosphonate therapy include nephrotoxicity, electrolyte abnormalities, and osteonecrosis of the jaw. Bisphosphonate therapy has a clear role in the management of skeletal metastases. However, significant side effects require ongoing monitoring and treatment.</p> <p>Bone health (subsequent fractures, etc) - The utility of bisphosphonates as an adjuvant treatment for breast cancer remains controversial. In 3 studies of oral clodronate that included 1,653 women with early-stage breast cancer but high risk for metastatic disease, there was no significant reduction in the risk of developing skeletal metastases (RR 0.82, p = 0.07). Early results from several large randomized trials indicate that zoledronic acid may reduce bone loss associated with aromatase inhibitors. Short-term intermittent use of clodronate has not been shown to prevent bone loss in women with chemotherapy-induced premature menopause.</p>
General comments:	

UPDATE EVIDENCE

Bundred, Campbell, Davidson, DeBoer, Eidtmann, Monnier, Neven, Minckwitz, Miller, Schenk, Coleman. Effective Inhibition of Aromatase Inhibitor-associated Bone Loss by Zoledronic Acid in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole (2008) *Cancer* 112;5:1001-1010

Design: Randomised Controlled Trial, Evidence level: 1-

Country: 28 countries

Aim: To evaluate the effect of either immediate or delayed use of 4mg zoledronic acid on the prevention of bone loss in both recently postmenopausal (due to chemotherapy or LHRH suppression) and established postmenopausal women with early stage breast cancer who had received adjuvant letrozole for 5 years.

Inclusion criteria

Postmenopausal women

ER positive early breast cancer

Baseline lumbar spine (LS) and total hip (TH) T-scores above -2.0

Eligibility criteria for this trial were similar to the previously published Z-Fast study which was included in the original evidence base (Brufsky 2007).

Exclusion criteria

None given

Similar to Brufsky et al. 2007

Population

N=1065

Interventions

Immediate or delayed zoledronic acid for 15 minutes every 6 months for 5 years.

Immediate group received zoledronic acid after randomisation; Delayed group received zoledronic acid when 1) post-baseline spine or hip T-score decreased to below -2.0, when a non-traumatic clinical fracture occurred or when asymptomatic fracture was discovered at the month 36 scheduled visit.

Outcomes

Primary: percentage change in spine bone mineral density (BMD) at 12 months in patients receiving immediate start compared with delayed zoledronic acid.

Secondary: percentage change in TH BMD, changes in serum N-telopeptide (NTX) and bone-specific alkaline phosphate (BSAP) concentrations at 12 months.

Note: BMD is a surrogate measure for fracture risk

Analyses of BMD and bone markers were based on the intent to treat (ITT) population (N=1065); analyses relating to cancer recurrence used a modified ITT (mITT), defined as all randomized patients that underwent at least 1 post-baseline assessment (N=1064) and;

analyses of adverse effects and clinical fractures used a safety population, defined as all patients who received at least 1 dose of zoledronic acid or letrozole (N=1050).

The procedure for measuring NTX concentrations was changed during the trial and the methods were not standardized against each other thus limiting the ability to interpret the magnitude of change from baseline.

Results

BMD:

In the ITT population the unadjusted mean percentage change for lumbar spine from baseline in the immediate arm was 2.1% and in the delayed arm was -3.5% (p<0.0001). In the safety population the results were similar with adjusted mean percentage change from baseline of 1.9% (p<0.0001; 95% CI: 1.6-2.2) in the immediate arm and -3.1% (p<0.0001; 95% CI: -3.5 to -2.8) in the delayed arm.

The adjusted mean percentage difference between the two groups at month 12 for the ITT and safety populations was 5.7% (p<0.0001; 95% CI: 5.2-6.1) at spine and 3.6% (p<0.0001; 95% CI: 3.3-4.0) at hip.

In the safety population, immediate zoledronic acid prevented BMD loss at both L₂-L₄ LS and TH compared with the delayed treatment population in recently post-menopausal women. Adjusted mean percentage change from baseline at 12 months was -0.2% (95% CI: -1.1 to 0.7) at LS and 0.07% (95% CI: -0.6 to 0.7) at TH. In the delayed group the change in BMD was -5.5% (95% CI: -6.3 to -4.7%) at LS and -3.4% (95% CI: -4.0 to -2.8) at TH.

In the delayed treatment arm, losses in BMD were -5.49% in the recently post-menopausal group versus -2.61% in the established post-menopausal group, suggesting more rapid bone loss in the recently post-menopausal women.

Changes to osteopenia status from baseline:

	Immediate		Delayed	
	Baseline	12 Month	Baseline	12 Month
Normal LS	69.5%		68.9%	
Mild to Moderate Osteopenia		0.9%		19.1%
Mild to Moderate Osteopenia	30.5%		31.1%	
Severe Osteopenia		0.6%		18%

The difference in distributions was statistically significant (p<0.0001).

Fractures

The incidence of fractures was similar in both groups for the first 12 months; 1.5% in the

immediate group and 1.7% in the delayed group.

Breast Cancer Recurrence

Breast cancer recurrence was similar for both groups; 2.3% recurrence and 4 deaths in the immediate group and 2.1% recurrence and 5 deaths in the delayed group.

Markers of Bone Turnover

Unadjusted mean percentage change from baseline serum BSAP concentrations decreased significantly in the immediate group (-15.5%, $p < 0.0001$) and increased significantly in the delayed group (30.1%, $p < 0.0001$).

NTX concentration was, on average, 33% higher in the delayed group compared to the immediate group ($p < 0.0001$).

Safety

The occurrence of adverse events was similar in both groups apart from bone pain which was higher in the immediate group (12.3% vs. 6.9%).

Serious adverse events occurred in 8.2% of patients in the immediate arm and in 6.7% of patients in the delayed arm.

Withdrawal as a result of adverse effects was 5.3% in the immediate group and 4.7% in the delayed group. 1.5% of patients in the immediate group and 1% in the delayed group discontinued therapy as a result of adverse events.

General comments

Greenspan, Brufsky, Lembersky, Bhattacharya, Vujevich, Perera, Sereika & Vogel. Risedronate Prevents Bone Loss in Breast Cancer Survivors: A 2-Year, Randomised, Double Blind, Placebo Controlled Clinical Trial (2008) *Journal of Clinical Oncology* 26;16:2644-2652

Design: Randomised Controlled Trial, Evidence level: 1-

Country: USA

Aim: To examine the prevention of breast cancer related bone loss.

Inclusion criteria

Newly post-menopausal (≤ 8 years, verified by gonadotrophin levels)
Stage I-III breast cancer, treated with chemotherapy
With or without tamoxifen, an antiestrogen or an AI concomitant therapy

Exclusion criteria

Women with any illness known to affect bone mineral metabolism
Women on any medications known to affect bone mineral metabolism

Population

N=87

Interventions

35mg risedronate orally once a week.

Outcomes

Changes in spine and hip bone mineral density
Biochemical markers of bone turnover
Safety

Results

Compliance for the study was 70.5% in the placebo group and 65.1% in the risedronate group ($p=0.88$).

Comparison of Treatment Groups

Bone Mineral Density (BMD) and bone turnover marker % change at 24 months:

Outcome	Placebo		Risedronate		P for difference between groups
	Mean \pm SD	P	Mean \pm SD	P	
BMD					
Spine	-1.2 \pm 0.7	0.088	0.4 \pm 0.8	0.63	0.082
Total Hip	-1.6 \pm 0.4	0.001	0.9 \pm 0.6	0.176	<0.001
Bone Turnover					
Urinary NTX	39.4 \pm 14.4	0.0097	-6.5 \pm 10.4	0.534	0.020
P1NP	37.2 \pm 13.5	0.009	2.8 \pm 16.7	0.870	0.195
Osteocalcin	13.7 \pm 9.3	0.151	-2.5 \pm 7.4	0.736	0.1850

Comparison of Treatment and Cancer Therapy Groups

Significant differences across the groups with respect to bone mineral density were observed at 2 years.

BMD of spine included a decrease of 4.8% \pm 0.8% ($p<0.01$) for placebo + AI and a decrease of 2.4% \pm 1.1% ($p<0.05$) for risedronate + AI.

There was no significant change for placebo with no AI or risedronate with no AI, although there was an increase of 2.4% \pm 0.8% ($p=0.011$) at 18 months for risedronate with no AI.

For total hip, patients on placebo + AI had the greatest loss of bone mass with a decrease of 2.8% \pm 0.5% ($p<0.001$) compared with the risedronate + AI group which maintained bone mass. Placebo with no AI showed a decrease of 1.2% \pm 0.5 ($p=0.04$) and risedronate with no AI showed an increase in BMD of 2.2% \pm 0.99% ($p<0.05$).

Comparing patients on AIs showed a difference of 2.4 \pm 1.0 percentage points in spine bone density in women on placebo and risedronate ($p=0.025$). For total hip there was a difference of 3.0 \pm 0.7 percentage points in women on placebo and risedronate.

Bone turnover was greatest in the placebo + AI group with an increase in urinary NTX of approximately 99% \pm 24% ($p<0.001$) compared with risedronate + AI and placebo with no AI, which showed no significant change. Risedronate with no AI showed a significant decrease at 12 and 18 months, but was no longer significant at 18 months.

Safety

Risedronate was well tolerated and there was no significant difference in adverse effects in women receiving risedronate compared to women receiving placebo.

General comments

If a patient had an initial bone mineral density T-score in the osteoporotic range at the hip or spine, or an adult fragility fracture, they were counseled about options for therapy versus participation in the trial.

The study was a double blind, placebo controlled, randomised clinical trial conducted over 12 months with a 12 month extension.

Compliance was defined as taking at least 80% of the medication and was assessed through pill counts.

Subgroup analyses examined the effect of treatment \pm AI and placebo \pm AI.

Author's conclusion: once weekly oral risedronate was successful at maintaining or improving bone mass in post-menopausal women with cancer related bone loss. The medication was well tolerated and proved to be effective with or without the use of an AI.

Kristensen, B., Ejlersen, B, Mouridsen, H., Jensen, M., Anderson, J., Bjerregaard, B., Cold, S., Edlund, P., Ewertz, M., Kamby, C., Lindman, H., Nordenskjold, B., Bergh, J. (2008) Bisphosphonate treatment in primary breast cancer: Results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. *Acta Oncologica* 47:740-746

Design: Randomised Controlled Trial

Evidence Level: 1-

Country: Denmark, Sweden & Iceland

Aim: To investigate whether oral pamidronate can prevent the occurrence of bone metastasis and fractures in patients with lymph node positive primary breast cancer.

Inclusion criteria

Women with resectable adenocarcinoma of the breast and without signs of distant metastases according to an initial physical examination, x-ray examination of the chest and axial x-ray examination of the skeleton or a whole body scintigraphy confirmed by x-ray examination if suspect for bone metastases.

Exclusion criteria

None given

Population

N = 953

Patients were recruited from three groups:

premenopausal women without lymph node metastases but with grade 2 or 3 malignancy

and a primary tumour ≤ 5 cm in diameter independent of hormone status premenopausal women with negative or unknown hormone receptor status and with either axillary lymph node metastases or with primary tumour > 5 cm in diameter. Postmenopausal women with hormone receptor negative tumours and with either axillary lymph node metastases or a primary tumour >5 cm in diameter.

Interventions

150mg oral pamidronate twice daily for 4 years vs. no pamidronate

Outcomes

Overall Survival
Skeletal Events
Bone Mineral Density

Results

No significant difference in overall survival was observed between the treatment groups.

Hazard ratio for recurrence in bone in the pamidronate group compared to the control group was 1.03 (95% CI 0.75-1.40; $p=0.86$).

No significant difference observed in the rate of fracture between the two groups ($p=0.17$) although there were more fractures in the pamidronate group.

There was a significant decrease in lumbar bone mineral density in the control group ($p=0.0001$).

General comments

Analysis was carried out according to both intention to treat and a per protocol analysis.

Authors Comments:

The results of the intention to treat and the adjusted per protocol analysis were identical and it is unlikely that closer adherence to the pamidronate regimen would have changed the outcomes.

Data from the trial do not support a beneficial effect of oral pamidronate on occurrence of bone metastases and fractures in patients with primary breast cancer receiving adjuvant chemotherapy.

Health Economics Summary

Overview

A systematic review was conducted to assess the cost-effectiveness of undertaking measurements of bone mineral density (BMD) in patients with invasive breast cancer who are on adjuvant hormonal therapy to assess bone health. The initial search identified 207 hits, from which 205 papers were excluded on the bases of the title and the abstract. Two papers were obtained for appraisal: 1 of them (Boyc *et al* 2004) was excluded because it was not relevant for the study question: it assessed health care resources used and costs of treatment patterns for cancer therapy induced bone loss. The other paper (Yeh *et al* 1995) was considered for further appraisal, and it was finally excluded on the grounds that it did not assess the patient population considered in the PICO question (it was not clear that patients in this study were on hormonal treatment; in addition, some patients with stage IV breast cancer were also included). Therefore, no economic evaluations were found that were relevant for this topic; uncertainty remains about the cost-effectiveness of using measurements of BMD in patients with invasive breast cancer that are on adjuvant hormonal therapy.

Chapter 6 – Adjuvant radiotherapy

6.1 What are the indications for radiotherapy after breast conserving surgery?

Short Summary

Invasive breast cancer

The strongest overview was the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Clarke *et al* 2005) who conducted a systematic review of individual patient data (IPD) from the relevant trials, and provided data up to the year 2000 with 15 years of follow-up. A heterogeneous group of studies were assessed of patients receiving breast conserving surgery (BCS) with and without radiotherapy (RT). A range of participants were included, for example patients with tumours of less than 1 cm and elderly patients. Some of the studies provided an additional boost of radiotherapy to the tumour bed. A number of associated reviews were not as strong as the EBCTCG review and these have been included where additional data was provided (Liljegren 2002, Rutqvist *et al* 2003, Vinh-Hung & Verschraegen 2004). One recent randomised controlled trial (Ford *et al* 2006) from the St George's study (with earlier IPD reported in Clarke 2005) and another retrospective cohort study from the US SEER database (Vinh-Hung *et al* 2003) were also included.

Two systematic reviews reported cosmetic outcomes (Liljegren *et al.* 2002, Mul *et al* 2007). These were also reported in one RCT (Johansen *et al* 2002) and one non-randomised study (Duetsch & Flickinger 2003). Four studies reported quality of life outcomes using five different instruments. Three were recruited from RCTs (Lee *et al* 2008, Rayan *et al* 2003, Whelan *et al* 2000) and the fourth was a survey (Back *et al* 2005).

Three reviews (one narrative, Kuerer *et al* 2004, and two systematic reviews Cuncins-Hearn *et al* 2004, Sarin 2005) of non-randomised studies assessed a range of Accelerated Partial Breast Irradiation (APBI) techniques including intra-operative and postoperative brachytherapy. Another review (Kunkler *et al* 2006) discussed whether radiotherapy could be omitted after surgery.

Four guidelines were included, two Canadian (Shelley & Trudeau 2002, Whelan *et al* 2003), one American (Morrow *et al* 2002) and one recent German DEGRO guideline (Sautter-Bihl *et al* 2007).

Most studies from RCTs and well conducted meta-analyses/systematic reviews were consistent in the finding that postoperative radiation decreased the risk of local recurrence. The EBCTCG meta-analysis of breast conserving surgery trials showed a moderate reduction in breast cancer deaths and overall mortality after 15 years. Subgroup analyses by age, tumour characteristics and nodal status in the EBCTCG revealed further treatment effects of radiotherapy. Quality of Life (QoL) was generally high among patients receiving radiotherapy. Patient satisfaction with breast conserving surgery was also high.

PICO question

POPULATION	INTERVENTION	COMPARISON	OUTCOME
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Patients with operable invasive breast cancer who have received breast conserving surgery	RT to the breast after breast conserving surgery including: <ul style="list-style-type: none"> • Electrons • Implant 	Breast conserving surgery alone	<ul style="list-style-type: none"> • Recurrence • Disease Free Survival (DFS) • Overall Survival (OS) • Quality of life • Patient acceptability • Cosmesis
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The search strategy developed from this table and used to search the literature for this question can be found in Appendix A

Evidence Summary

The literature search was limited to the last 10 years (1997-2007). The strongest overview was the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (Clarke *et al* 2005) who conducted a systematic review of Individual Patient Data (IPD) from the relevant trials, and provided data up to the year 2000 with 15 years of follow-up. A heterogeneous group of studies were assessed of patients receiving Breast Conserving Surgery (BCS) with and without radiotherapy (RT). A range of participants were included, e.g., patients with tumours of less than 1 cm, elderly patients. Some of the studies provided an additional boost of RT to the tumour bed. A number of associated reviews were not as strong as the EBCTCG review and these have been included where additional data was provided (Liljegren 2002, Rutqvist *et al* 2003, Vinh-Hung & Verschraegen 2004). One recent RCT (Ford *et al* 2006) from the St George's study (with earlier IPD reported in Clarke 2005) and another retrospective cohort study from the US SEER database (Vinh-Hung *et al* 2003) were also included.

Two systematic reviews reported cosmetic outcomes (Liljegren 2002, Mul *et al* 2007). The former used the same studies as the EBCTCG, so only cosmetic outcomes were reported in the evidence table. Cosmesis outcomes were also reported in one RCT (Johansen *et al* 2002) and one non-randomised study (Duetsch & Flickinger 2003).

Four studies reported quality of life outcomes using five different instruments. Three were recruited from RCTs (Lee *et al* 2008, Rayan *et al* 2003, Whelan *et al* 2000) and the fourth was a survey (Back *et al* 2001).

Three reviews (one narrative Kuerer *et al* 2004, and two systematic reviews Cuncins-Hearn *et al* 2004, Sarin 2005) of non-randomised studies assessed a range of Accelerated Partial Breast Irradiation (APBI) techniques including intra-operative and postoperative brachytherapy. Another review (Kunkler *et al* 2006) discussed whether RT could be omitted after surgery.

Four guidelines were included, two Canadian (Shelley & Trudeau 2002, Whelan *et al* 2003), one American (Morrow *et al* 2002) and one recent German DEGRO guideline (Sautter-Bihl *et al* 2008).

The systematic reviews of RCTs included a variety of post-operative interventions in addition to RT, the adjuvants used were boost to the scar, chemotherapy or tamoxifen. The RCTs compared BCS alone vs. BCS and RT. Wide local excision and adjuvant therapy were used in Ford *et al* (2006). In the cosmesis study (Johansen *et al* 2002), BCS patients received RT and a boost dose to the scar and tumour bed of either photons or electrons. Adjuvant chemotherapy was offered to high risk patients. Two QoL studies (Whelan *et al* 2000, Rayan *et al* 2003) included a boost dose to the tumour site. The QoL study by Lee *et al* (2008) included women after mastectomy or BCS receiving conventional or hypofractionated RT to the breast or chest wall, and a proportion with RT to the supraclavicular nodes.

Most studies from RCTs and well conducted meta-analyses/systematic reviews are consistent in the findings that post operative radiation decreases the risk of local recurrence, but has no effect on overall survival. Subgroup analyses revealed further treatment effects. QoL was generally high among patients receiving RT.

Local recurrence, breast cancer mortality and overall mortality were assessed from level 1 evidence using pooled meta-analyses of both IPD and RCT data. One retrospective cohort (level 2) from the US SEER database was also included (Vinh-Hung & Verschraegen 2003).

Local Recurrence

From a logrank analysis of IPD (Clarke *et al* 2005) of 10 randomised trials the reduction in local recurrence by allocation to RT was highly significant ($p < 0.00001$), the 5-year risk of local recurrence was 7% with radiotherapy, and 26% without radiotherapy. This corresponds to an absolute reduction of 19% in 5-year risk. Similar findings were reported by Liljegren (2002) using the most up to date trial data (not IPD) at the time (published between 1996-2001) from 5 of the studies in Clarke *et al* (2005) as well as an additional later trial (Holli 2001). They reported that the addition of postoperative radiotherapy reduced the risk of local recurrence by 2/3. The dose-intensity of radiotherapy and surgery had a positive impact on local control. Patients at low risk of local recurrence were > 55 years of age, with stage I tumours and favourable histology treated with adequate resection margins.

The meta-analysis (Vinh-Hung *et al* 2004) reported the pooled relative risk of ipsilateral breast tumour recurrence estimated from 15 trials (9422 randomised patients' data available for analysis) as 3.00 (95% CI 2.65-3.40). There was statistically significant heterogeneity between these studies.

Ford *et al* (2006) in the most recent RCT also reported a statistically significant reduction in locoregional recurrence in the RT arm [0.45 (95% CI 0.31-0.64; $P = 0.0001$), Kaplan Meier] with 26.8% of recurrences for the RT arm and 49.8% for no RT. This was independent of node status, ER status or T stage.

Node status

A subgroup analysis by node status (Clarke *et al* 2005) found the addition of radiotherapy produced a substantial absolute reduction in local recurrence risk [16.1% (SE1.0) for node-negative disease, and 30.1% (SE2.8) for node-positive disease].

Age

Most local recurrences were in the conserved (ipsilateral) breast. The absolute effects of post-BCS radiotherapy on local recurrence were greater in younger women than in older women (test for trend in absolute benefits $2p=0.00002$) (Clarke *et al* 2005).

Tumour characteristics

The 5-year local recurrence risk without radiotherapy was higher in women with tumours that were large or with direct extension to the skin or chest wall (T2/T3/T4 tumours) or poorly differentiated. The absolute reduction in this risk from radiotherapy was correspondingly greater, however, ER status did not appear to affect these risks (Clarke *et al* 2005).

Summary of local recurrence

In trials of RT after BCS radiotherapy reduced the risk of local recurrence irrespective of age, tumour grade, tumour size and Estrogen Response (ER) status (Clarke *et al* 2005). The authors suggest that the avoidance of local recurrence (mostly during the first 5 years) appears to be relevant to breast cancer mortality (after the first 5 years) using data from a further analysis of trials of post BCS radiotherapy. Another finding was that the avoidance of recurrence in the conserved breast and the avoidance of other local recurrences (e.g. in the chest wall or regional lymph nodes) were relevant to 15 year breast cancer mortality.

Breast cancer mortality

From a pooled logrank analysis there was a significant overall reduction in breast cancer mortality (breast cancer death rate ratio 0.83 SE 0.05, 95% CI 0.75–0.91, $2p=0.0002$). The absolute risk reduction of the addition of RT following BCS was 5.4% (SE 1.7) at 15 years (35.9% vs. 30.5%+ RT) (Clarke *et al* 2005).

An analysis of breast cancer deaths by Ford *et al* (2006) did not show any effect of radiation ($p=0.44$).

Overall mortality

In the post-BCS radiotherapy trials the radiotherapy regimes produced a moderate reduction in 15 year mortality (15 year gain of RT 5.3% (SE 2.3%, $2p=0.005$). The absolute reduction in 15-year overall mortality was similar in magnitude to 15-year breast cancer mortality. There is a lack of data beyond this time period as women are still being followed-up (Clarke *et al* 2005).

Ford *et al* (2006) reported no significant differences between groups for disease-free ($p=0.63$) or overall survival ($p=0.59$), with a Hazard Ratio of 0.91 (95%CI 0.64-1.28; $P=0.59$) for overall survival with RT. There were also no statistically significant differences in overall survival between groups when stratified for node positive vs. node negative; ER positive vs. ER negative; T1 vs. T2; pre-menopausal vs. post-menopausal status.

In the meta-analysis by Vinh-Hung & Verschraegen (2004) the pooled relative mortality risk of no RT vs. RT estimated from 13 trials with survival or mortality data (8206 randomised patients' data available for analysis) was 1.086 (95% CI 1.003-1.175). This equates to an 8.6% excess mortality if no RT is administered.

The weaker retrospective cohort by Vinh-Hung (2003) found the omission of radiotherapy compared to delivery of radiotherapy was associated with an overall increased mortality hazard ratio of 1.346 (95% confidence interval: 1.204-1.504) which increased with time. However, this may be an over-estimate as patients with high grade tumours were less likely to receive RT in more recent time periods. The findings were not generalizable.

Cosmesis

Four studies reported on the cosmetic effects of RT: one systematic review by Liljegren (2002) included cosmetic/QOL outcomes, one systematic review of case reports (Mul *et al* 2007), one RCT (Johansen *et al* 2002) and one prospective non-randomised study (Deutsch & Flickinger 2003).

Johansen *et al* (2002) reported that 73% of patients regarded the cosmetic result as excellent or good. A univariate analysis found that treatment with a direct anterior electron field produced more morbidity and inferior cosmetic outcomes compared with tangential photon treatment. Anterior electron fields also led to significantly more grade 2 and 3 late reactions compared to tangential photons. On multivariate analysis cosmetic outcome was significantly associated with electron therapy (OR 2.3 CI 1.4-4.1; $p=0.002$). Increasing breast size was associated with increased breast retraction and breast fibrosis after tangential RT on multivariate analysis (OR 1.73 CI 1.17-2.56, $p=0.006$). Treatment characteristics that were independently associated with a fair/poor cosmetic outcome on multivariate analysis were the use of a direct anterior electron field (OR = 2.15, CI 1.25-3.70) and adjuvant systemic therapy (OR = 2.13, CI 1.22-3.71).

The non-randomised study by Deutsch & Flickinger (2003) reported 48.3% of women had an excellent cosmetic result (no skin changes or deformity and very slight, or no, differences in size); and 41.5% had a good result (no skin changes and little difference in size between the breasts; or skin changes with no difference in size between the breasts). 10.2% of women had a fair or poor cosmesis with skin pigmentation and a difference in size or breast distortion. An excellent or good cosmetic result versus a fair or poor result was associated with white race ($p = 0.0056$), smaller separation between the tangential fields ($p = 0.01$), the use of a boost dose ($p = 0.0025$), and no use of tamoxifen ($p = 0.025$). This study was likely to be biased since the same physician treated patients and assessed cosmesis.

Mul *et al* (2007) reported the rare side effect bullous pemphigoid (a blistering below the skin) which may occur after percutaneous treatment with RT.

The systematic review of 2 earlier RCTs (Liljegren 2002) concluded that the negative effect of postoperative radiotherapy on cosmesis and quality of life was small and occurred during early follow-up but not in later follow-up two to three years after treatment.

Quality of Life

Quality of life was assessed using five different instruments in 4 studies (three RCTs Whelan *et al* 2000, Rayan *et al* 2003, Lee *et al* 2008; and one survey Back *et al* 2005). Three studies used the EORTC QLQ-30 (Back, Lee, Rayan) and two studies used the EORTC QLQ BR-23 breast cancer module (Lee, Rayan).

Whelan *et al* (2000) reported that breast irradiation therapy had an effect on quality of life during early treatment, with irradiated patients reporting increased breast symptoms compared with controls. After 2 years no differences were found between groups for rates of skin irritation, breast pain, and being upset by the appearance of the breast.

A small RCT of post-menopausal women, with node-negative breast cancer taking tamoxifen, (Rayan *et al* 2003) applied tangential field irradiation. RT did not significantly contribute to breast pain or adversely impact the QOL up to 12 months after treatment.

An update search identified a small Australian RCT (Lee *et al* 2008). The findings indicated that quality of life improves after RT treatment to reach baseline levels by 7 months of treatment. Breast symptoms and fatigue were found to be predictors of quality of life and treatment may be best targeted at these symptoms.

A short term non-randomised study by Back *et al* (2005), of women receiving tangential RT, reported a minimal impact of RT on patient functioning at 6 weeks post-treatment.

The three studies using the EORTC QLQ-30 questionnaire (Back, Lee, Rayan) and the two using the EORTC QLQ BR-23 breast cancer module (Lee, Rayan) all report that by the end of the study period QoL had reached pre-treatment levels.

Accelerated Partial Breast Irradiation

Two systematic type reviews (Cuncins-Hearn *et al* 2004, Sarin 2005) assessing studies incorporating intra-operative and post operative APBI techniques both recommend that there is not sufficient evidence at this time for optimal use of these techniques. Longer term data from RCTs are awaited. This view is supported by Kuerer *et al* (2004).

Guidelines

Four guidelines were identified (Morrow *et al* 2002, Sautter-Bihl *et al* 2007, Shelley & Trudeau 2002, Whelan *et al* 2003). All recommend post operative RT after BCS however the role of fractionation schedules and other adjuvant therapies eg, chemotherapy are less clear. Intra-operative and brachytherapy techniques are not recommended at this time.

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Evidence table
Systematic review of RCTs

Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y, Early Breast Cancer Trialists' Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.[see comment]. [Review] [33 refs]. *Lancet* **366**, 2087-2106.

Design: Systematic review of individual patient data

Level 1++

Country: Multi-national

Aim: To update previous meta-analyses of the individual patient data from randomised trials of the effects of radiotherapy and extent of surgery on local disease control and cause-specific mortality in early breast cancer. Specifically to quantitate the relationship between local control and long term mortality.

Inclusion criteria Randomised trials of Breast Conserving Surgery (BCS) with or without post surgery radiotherapy (RT). (Other studies involving mastectomy were also included in the overview).

Exclusion criteria

Trials considered to be confounded, e g., no difference in treatment groups in the use of systemic therapy.

Population 7311 women in 10 trials

Interventions

Update of individual patient data from randomised trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) with results up to the year 2000. The randomised trials compare local treatments of various types of surgery or radiotherapy (RT) or both. The intervention category relevant to this topic was RT versus no RT with the same BCS surgery (generally with axillary clearance).

Outcomes

Breast cancer recurrence (ipsilateral locoregional, contralateral or distant). Includes residual breast tissue, scar area, chest wall, ipsilateral regional lymph nodes.

Cause-specific mortality

Overall mortality

Incidence of second primary cancers before breast cancer recurrence.

Follow up –This is an ongoing systematic overview of randomised trials with an update every 5 years. The current publication (2005) used a pooled analysis of individual patient data from the included studies rather than the primary studies themselves. Findings from 15 years of follow-up were reported.

Results

Trials included in the meta-analysis are listed in the following table:

Isolated local recurrence

Trial	Year started	Events/ woman years	
		BCS+RT	BCS
RT to conserved breast only: N+ 14%			
NSABP B-06	1976	125/6862	285/4991
Upsala-Orebro	1981	10/1636	43/1511
St George's London	1982	12/1202	31/1047
Ontario COG	1984	53/3543	155/2754
INT Milan 3	1987	19/2478	60/2005
NSABP B -21	1989	6/1810	40/1729
Swedish BCCG	1991	33/3718	92/3429
Subtotal	5 yr risk	258/21249 (7.2%)	706/17466 (25.6%)
RT to conserved breast and other sites: N+ 24%			
St George's London	1982	14/620	30/380
Scottish	1985	16/2598	83/2260
West Midlands UK	1985	42/2398	104/1929
CRC UK	1986	33/1604	77/1454
Subtotal	5 yr risk	105/7220 (7.7%)	294/6023
Total	Overall 5 yr risk	363/28 469 (7.3%)	1000/23 489 (25.9%)

A number of analyses were conducted after stratification by trial, time since randomization and nodal status (positive or negative). The main outcomes of local recurrence, breast cancer mortality and overall mortality were also stratified by age at randomization (<40, 40-49, 50-59, 60-69, > 70 years).

Local recurrence

Results of a meta-analysis of 10 trials were provided as a Forest plot in the paper.

Results from 2 subgroups of trials were shown:

- a) RT to conserved breast only; 14% node positive patients
- b) RT to conserved breast and other sites; 24% node positive patients

There was a reduction in isolated local recurrences after RT compared with no RT in every trial. The difference was significant in each subgroup (RT to breast only and RT to breast and other sites) as well as overall studies.

The ratio of local recurrences between groups (RT vs. no RT) were:

RT to conserved breast only 0.31 (SE 0.04) 2p <0.00001

RT to conserved breast and other sites 0.32 (SE 0.06) 2p <0.00001
 Overall studies 0.31 (SE 0.03) 2p <0.00001

This corresponds to a proportional reduction in local recurrences of 70% in patients receiving post-operative RT. No significant heterogeneity was present between the 11 strata or subgroups analysed.

The overall 5 year risk of local recurrence was 7.3% with RT and 25.9% without post-operative RT, corresponding to an 18.6% (25.9%-7.3%) absolute reduction in 5 year risk.

Breast cancer mortality

A second Forest plot was reported in the paper of deaths from breast cancer after 15 years, with the same sub-groupings. The findings of each subgroup and overall results are reported in the following table:

	Deaths/women		Ratio of annual death rates	P value
	BCS+RT	BCS		
RT to conserved breast only: N+ 14%	499/2683	587/2662		
15 year risk	28%	33.2%	0.84 (SE 0.06)	2p=0.004
RT to conserved breast and other sites: N+ 24%	254/990	302/976		
10 year risk	28.2%	35.1%	0.81 (SE 0.08)	2p=0.02
Total events (N + 14% and N+ 24%)	753/3683	889/3638		
Overall 15 year risk	30.5%	35.9%	0.83 (SE 0.05)	2p=0.0002

There was a significant overall reduction in breast cancer mortality when studies were pooled (breast cancer death rate ratio 0.83 SE 0.05, 95% CI 0.75–0.91, 2p=0.0002).

The corresponding values between groups (RT vs no RT) for the 2 subgroups were:

RT to conserved breast only 0.84 (SE 0.06) 2p =0.004
 RT to conserved breast and other sites 0.81 (SE 0.08) 2p =0.02

The absolute risk reduction of the addition of RT following BCS was 5.4% (SE 1.7) at 15 years (35.9% vs. 30.5% + RT).

Effect of BCS and RT by node status

The results of local recurrence and breast cancer mortality were plotted (%)

isolated recurrence vs. time since randomization; and % breast cancer mortality vs. time since randomization) by node status (6097 women with BCS were node negative; and 1214 with BCS were node positive). The risk of local recurrence at 5 years was greater for women with node positive disease than node negative disease. Radiotherapy provided a larger 5 year gain in node positive than node negative women (ARR 30.1% vs. 16.1%). Data is shown in the following table. The numbers were too small to provide sufficient statistical power.

	Events by year 5		5 year risk (actuarial %)		Absolute reduction in 5 year risk (%) for addition of RT
	BCS +RT	BCS	BCS +RT	BCS	
Node negative	216/3071	637/3026	6.7	22.9	16.1% (1.0)
Node Positive	66/602	221/612	11.0	41.1	30.1% (2.8)

The authors suggest that the avoidance of a local recurrence mainly during the first 5 years influenced the breast cancer mortality rate after the first 5 years.

Subgroup analyses

These were conducted on available data from all trials by age and tumour characteristics. For women with node-negative disease, in trials of RT after BCS, radiotherapy produced similar proportional reductions in local recurrence risk irrespective of age, tumour grade, tumour size and Estrogen Response (ER) status. Data are shown in the following table which was provided in the original paper.

	5 year risk of local recurrence (%) in RCTs of RT after BCS (node negative)	
Subgroup	RT vs. control	Absolute reduction (SE)
Age (years)		
<50	11 vs 33	22 (2)
50-59	7 vs 23	16 (2)
60-69	4 vs 16	12 (1)
≥ 70	3 vs 13	11 (2)
Tumour grade		
Well differentiated	4 vs 14	
Moderately differentiated	9 vs 26	
Poorly differentiated	12 vs 34	
Tumour size (T)		

category)	5 vs 20	15 (1)
1-20mm (T1)	14 vs 35	21 (3)
21-50mm (T2)	-	-
> 50mm (T3 or T4)		
ER status		
ER poor	12 vs 30	18 (3)
ER positive	6 vs 25	19 (2)
All women	7 vs 23	16 (1)

Age

The 5-year local recurrence risks of different subgroups of patients with node-negative disease are shown in the Table. Most local recurrences were in the conserved (ipsilateral) breast. The absolute effects of post-BCS radiotherapy on local recurrence were greater in younger women than in older women. The 5-year risk reductions by age group are shown below:

<i>Age</i>	<i>5-year risk reduction</i>
< 50 years	22%
50-59	16%
60-69	12%
> 70	11%

Test for trend in absolute benefits $2p=0.00002$.

Tumour characteristics

The 5-year local recurrence risk without radiotherapy was higher in women with tumours that were large or with direct extension to the skin or chest wall (T2/T3/T4 tumours) or poorly differentiated. The absolute reduction in this risk from radiotherapy was correspondingly greater, however, ER status did not appear to affect these risks.

Overall mortality

The radiotherapy regimes produced a moderate reduction in 15 year mortality (15 year gain of RT 5.3% (SE 2.3%, $2p=0.005$). In the post-BCS radiotherapy trials the absolute reduction in 15-year overall mortality were similar in magnitude to 15-year breast cancer mortality. However there is little follow-up beyond year 15 and many women have not yet been followed to year 15.

Author conclusions

Avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (e.g., the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

General comments –

Included studies:
(Listed as Trial names)

NSABP B-06
Uppsala-Orebro
St George's
Ontario COG
Scottish
West Midlands
CRC UK
INT Milan 3
NSABP B-21
Swedish BCCG

Updated 2018

Vinh-Hung V, Verschraegen C (2004) Breast-conserving surgery with or without radiotherapy: Pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *Journal of the National Cancer Institute* **96**, 115-121.

Design: Systematic review and pooled analysis Level 1++

Country: Belgium

Aim: The objective of the study was to investigate whether radiotherapy or its omission after breast-conserving surgery has measurable consequences on local tumour growth and patient survival.

Inclusion criteria Randomized clinical trials of invasive breast cancer that compared radiotherapy versus no radiotherapy after breast-conserving surgery (lumpectomy or local excision) with or without systemic treatment.

Exclusion criteria None

Population 18 randomised trials identified. Eleven were published as full articles, most of these were included in Clarke (2005) as individual patient data to 2000. Four were abstracts and 3 were unavailable since they were ongoing.

Interventions

Breast-conserving surgery (lumpectomy or local excision) with or without postoperative radiotherapy

Outcomes

Ipsilateral breast tumour recurrence as a first event
Survival analysis from death by any cause

Follow up -

Results

Mortality

The pooled relative mortality risk of no RT vs. RT estimated from 13 trials with survival or mortality data (8206 randomised patients' data available for analysis) was 1.086 (95% CI 1.003-1.175). This equates to an 8.6% excess mortality if no RT is administered. A re-analysis of a subset of 9 trials, that excluded the studies reported as abstracts only, found a relative mortality risk of 1.083 (95% CI 0.993-1.180).

Local recurrence

The pooled relative risk of ipsilateral breast tumour recurrence estimated from 15 trials (9422 randomised patients' data available for analysis) was 3.00 (95% CI 2.65-3.40). There was statistically significant heterogeneity across these studies. Relative risks from individual studies ranged from 2.32 (95% CI 1.56-3.45) to 4.89 (95% CI 2.45-9.76). A re-analysis of a subset of 9 trials that excluded the studies reported as abstracts only found a relative risk of ipsilateral breast tumour recurrence of 3.09 (95% CI 2.69-3.56).

Data are shown in the following table:

Outcome	BCS + RT	BCS no RT	Relative risk
Relative mortality risk (13 trials)	755/4109 (deaths)	824/4097 (deaths)	1.086 (95% CI 1.003-1.175)
Relative risk of ipsilateral breast tumour recurrence (15 trials)	279/4691	875/4731	3.00 (95% CI 2.65-3.40)

Author conclusions

Omission of RT after BCS was associated with a 3 fold increase of ipsilateral breast tumour recurrence and a marginally statistically significant excess mortality risk of 8.6% (95% CI 0.3%-17.5%) relative to the delivery of RT alone.

General comments –

Included studies (4 were abstracts)

Blamey RW, Chetty U, Mitchell A, British Association of Surgical Oncology (BASO) Breast Group. The BASO II trial of adjuvant radiotherapy versus none and tamoxifen versus none in small, node negative, grade I tumours [abstract]. *Eur J Cancer* 2001;37(Suppl 5):2 *Data used from abstract in 2001.*

Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst* 1996;88:1659-64.

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233-41.

Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 2002;2002 Oct 15; 20(20):4141-9.

Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. *Lancet* 1996;348:708-13.

Fyles AW MDMLTMM. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *The New England journal of medicine* 2004 Sep;351(10):963-70. *Data used from abstract in 2001.*

Holli K, Saaristo R, Isola J, Joensuu H, Hakama M. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results from a randomized study. *Br J Cancer* 2001; 84: 164-9.

Houghton J, Potyka I, Tobias J, Baum M, Odling-Smee W. Prophylactic radiotherapy following surgery for early breast cancer- Is the benefit mainly to patients with involved margins? Results from a Cancer Research Campaign trial. *Proc ASCO* 2001;20:31a. *Data used from abstract in 2001.*

Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351(10):971-7. *Data used from abstract in 2001.*

Inoue M, Tanaka II, Masuda R, Furuhashi Y. Local control and cosmetic outcome after sector resection with or without radiation therapy for early breast cancer. *Breast Cancer* 1996; 3: 39-46.

Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: A randomized trial. *J Clin Oncol* 1999;17(8):2326-33.

Malmstrom P, Holmberg L, Anderson H, Mattsson J, Jonsson P-E, Tennvall-Nittby L, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: A randomised clinical trial in a population with access to public mammography screening. *Eur J Cancer* 2003;39(12):1690-7.

Renton SC, Gazet JC, Ford HT, Corbishley C, Sutcliffe R. The importance of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol* 1996; 22: 17-22.

Semiglazov VF, Kanaev SV, Bugrova IL. [Preliminary results of the randomized trial "The role of adjuvant radiotherapy in organ-preserving treatment of breast cancer"]. *Vopr Onkol* 1998; 44: 414-21. Russian.

Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long term results of a randomized trial. *Ann Oncol* 2001; 12: 997-1003.

Liljegren G (2002) Is postoperative radiotherapy after breast conserving surgery always mandatory? A review of randomised controlled trials. [Review] [15 refs]. *Scandinavian Journal of Surgery: SJS* **91**, 251-254.

Aim: The aim of this review was to synthesise the results from randomised trials to define a subgroup of patients in whom postoperative radiotherapy could be omitted.

Design: Systematic review

Level

1+

Country: Sweden

Inclusion criteria Studies comparing BCS alone vs. BCS followed by radiotherapy. Literature search from 1966 to 2002.

Exclusion criteria None reported

Population 12 trials were identified

Interventions

6 trials compared different types of BCS alone with BCS followed by radiotherapy. All these studies were included in the EBCTCG (2005) overview with individual patient data to 2000.

Two trials evaluated different types of radiotherapy to the breast after BCS (Bartelink 2001 evaluated additional boost to the tumour bed; Ribeiro 1993 evaluated tumour bed RT vs. wide field RT).

One trial compared different types of surgery followed by the same type of RT (Mariani 1998).

One trial compared quality of life (Whelan 2000). (This is included in the evidence table).

Two trials compared cosmetic results (Liljegren 1993, Sacchini 1995).

Outcomes

Cosmetic results only are reported here.

Follow up -

Results

In the Uppsala-Orebro trial (Liljegren 1993) the cosmetic result was evaluated yearly up to 3 years post-operatively. Good to excellent results were reported in 91-94% of patients after surgery alone, and in 84-90% in the radiotherapy arm. These findings were based on self-reports.

In the Milan III trial (Sacchini 1995) a subset of 61/101 patients had radiotherapy. No overall differences in cosmesis were reported.

Author conclusions (cosmesis):

The negative effect of postoperative radiotherapy on cosmesis and quality of life is small and only observed in the early period of follow up but not later than two to three years after treatment.

Other findings:

Addition of postoperative radiotherapy reduced the risk of local recurrence by

2/3. The dose-intensity of radiotherapy and surgery had a positive impact on local control. Patients at low risk of local recurrence were aged > 55 years, with stage I tumours and favourable histology treated with adequate resection margins. No trial showed any positive effect of radiotherapy on survival. Author conclusion: In most patients postoperative radiotherapy is an integral part of breast-conservation. Radiotherapy can be omitted in selected low risk patients.

References for cosmesis studies:

1) Liljegren G, Holmberg L, Westman G and the Uppsala-Orebro Breast Cancer Study Group: The cosmetic outcome in early breast cancer treated with sector resection with or without radiotherapy. Eur J Cancer 1993; 29A: 2083-2089.

2) Sacchini V, Luini A, Agresti R, Manzari A, Mariani L, Zucali R, McCormick B: The influence of radiotherapy on cosmetic outcome after breast conservative surgery. Int J Radiat Oncol Biol Phys 1995; 33: 59-64.

General comments –

Updated 2018

Mul VE, van Geest AJ, Pijls-Johannesma MC, Theys J, Verschueren TA, Jager JJ, Lambin P, Baumert BG (2007) Radiation-induced bullous pemphigoid: a systematic review of an unusual radiation side effect.[see comment]. [Review] [41 refs]. *Radiotherapy & Oncology* **82**, 5-9.

Design: Systematic review of case reports

Level 1-

Country: Holland

Inclusion criteria Studies reporting histologically confirmed bullous pemphigoid (BP) and treatment with radiotherapy (RT). Languages: Dutch, English, French, Italian, German. Searches to April 2006.

Exclusion criteria Pemphigus vulgaris and other forms of pemphigus. Bullous diseases with no histopathology diagnosis.

Population 21 references identified of BP and breast cancer from 289 potentially relevant articles.

Interventions

Percutaneous radiotherapy to the breast

Outcomes

Bullous pemphigoid described as a severe pruritis in combination with a bullous eruption (blistering below the skin surface)

Follow up -

Results

An association between RT and BP was reported in 27 patients. The majority developed BP after RT and a median dose of 50 Gy. Four patients developed BP during RT after a minimal dose of 20 Gy.

Conclusions

In all reported cases, there is a clear relationship of BP with RT. Therefore, BP may be considered as an RT-induced side effect. RT can induce a BP following a minimal dose of 20 Gy.

General comments –Very rare event caused by RT to the breast affecting the appearance.

Accelerated Partial Breast Irradiation

Kuerer HM, Julian TB, Strom EA, Lyerly HK, Giuliano AE, Mamounas EP, Vicini FA (2004) Accelerated partial breast irradiation after conservative surgery for breast cancer.[see comment]. [Review] [57 refs]. *Annals of Surgery* **239**, 338-351.

Design: Review of recent selected studies

Level 4

Country: USA

Aim: APBI has very recently come to the forefront as a potential local treatment option for women with breast cancer. This review aims to give an overview of the biologic rationale for APBI techniques, and benefits and limitations of APBI techniques.

Inclusion criteria Breast-conserving surgery with and without postoperative irradiation; all studies involving partial breast irradiation, including brachytherapy, for breast cancer; and currently accruing and planned APBI trials

Exclusion criteria None reported

Population

Interventions

APBI techniques after BCS

Outcomes

Early results of treatment in terms of toxicity, complications, cosmesis, and local control.

Follow up -

Results

Local recurrence

There is some overlap with studies in the Sarin review. Of the eight studies reported excluding Fentiman (1996) where 56% of patients had involved margins, local recurrence rates were 0-4.4%.

Approximately 3% of patients treated with breast-conserving surgery experience an ipsilateral breast local recurrence away from the site of the lumpectomy in groups with or without postoperative standard whole-breast irradiation. Results of phase I-II studies involving approximately 500 patients treated with APBI after breast-conserving surgery have been published. Many of the studies have limited long-term follow-up and potential selection biases, but early results suggest that toxicity, cosmesis, and local control are comparable to outcomes seen after breast-conserving surgery followed by standard whole-breast irradiation.

Author conclusions

Recent advances in radiation delivery and published series of partial breast irradiation support large randomized trials comparing APBI with standard whole-breast irradiation after breast-conserving surgery.

Cuncins-Hearn A, Saunders C, Walsh D, Borg M, Buckingham J, Frizelle F, Maddern G (2004) A systematic review of intraoperative radiotherapy in early breast cancer. [Review] [34 refs]. *Breast Cancer Research & Treatment* **85**, 271-280.

Design: Systematic review

Level 1-

Country: Australia

Aim: To assess safety and efficacy of IORT in EBC

Inclusion criteria All studies of any form of BC surgery (local excision, lumpectomy, segmentectomy, quadrantectomy) and any form of IORT.

Mastectomy was also included.

Exclusion criteria high dose IORT

Population 7 studies (incl 1 RCT, five of the seven were Level IV evidence)

Interventions

Any IORT study including boost.

Outcomes

Safety, efficacy

DFS

Overall survival

Cosmesis

Follow up -

Results

Local recurrence

From 5 studies local recurrence ranged from 0-29% (However the upper limit (29%) was from a study with only 7 patients).

Overall survival

From 3 studies: 86-100%

DFS

Not reported in IORT studies

Cosmesis

Cosmesis was measured differently across the studies and long-term IORT data is not available. Preliminary data suggest that IORT gives a similar short-term cosmetic outcome to BCT.

Author conclusions

Further research is required to clarify several issues such as identification of the most appropriate subgroups of patients for IORT, a comparison of the currently available mobile IORT technologies, establishing whether IORT is most appropriate as a boost replacement dose or replacement for all postoperative radiotherapy, the examination of how biological repair processes may differ between the two treatment modalities and determining

precisely where local recurrences originate with respect to the original tumour site.

General comments –

There was little overlap between this review and the Sarin (2005) review since the inclusion criteria were broader and older studies were used.

Updated 2018

Sarin R (2005) Partial-breast treatment for early breast cancer: emergence of a new paradigm. [Review] [51 refs]. *Nature Clinical Practice Oncology* **2**, 40-47.

Design: Critical Review

Level 1-

Country: India

Aim: To review the clinical, biologic and technical aspects of an emerging paradigm of partial-breast irradiation with BCS

Inclusion criteria Studies of surgery and radiotherapy techniques for Accelerated Partial Breast Irradiation (APBI)

Exclusion criteria None reported

Population Studies using the techniques listed below in the next section. Case selection is critical for good clinical outcomes since the location of tumour, size of tumour, proximity to the skin, and breast size determine the type of technique used for optimum outcomes. The American Brachytherapy Society (ABS) and American Society of Breast Surgeons (ASBS) recently defined conservative patient selection criteria and treatment guidelines in 2003.

Interventions

APBI techniques including intra-operative or postoperative implantation of needles or catheters for continuous low dose rate (LDR), pulsed low dose rate (PDR) or fractionated high dose rate brachytherapy. Techniques include the inflatable balloon device known as Mammosite, external beam 3D conformal RT (3DCRT), external electron beam. Intra-operative RT (IORT) with a large single radiation dose to the tumour bed is being evaluated in Milan with the ELIOT trial using electrons from a mobile linear accelerator. In the TARGIT trial an Xray device, Intrabeam, is used.

Outcomes

Ipsilateral recurrence
 Contralateral incidence
 Cosmesis

Follow up –Long term results from RCTs are not yet available. Several prospective and retrospective studies are available with median follow-up from 4 to 12 years. The best results have been achieved with careful case selection.

Results

Only studies post 2000 were included in the tables.

Ipsilateral recurrence and contralateral incidence

Five year APBI results from quality assured LDR or HDR interstitial implants in optimally selected patients:

Institution	N of patients	Median follow-	5 year actuarial ipsilateral breast	Contralateral breast
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		up (years)	recurrence rates. Anywhere in Outside the breast tumour bed		cancer incidence
Ochsner Clinic (2 studies)	160	7	2.5%	1.2%	NA
NIO Budapest phase I/II (1 study)	45	6 7	4.4%	4.4%	0
William Beaumont (2 studies)	199	5.4	1.2%	0.6%	1%
Virginia Commonwealth University (2 studies)	59	4.2	5.1%	2.6%	0
Orebro (1 study)	49	4.6	4%	2%	NA
RTOG 9517 phase II (1 study)	99	3.7	3% (4 yr)	NA	3%
All studies	611	4-7	1-5%	0.6-4.4%	0-3%

Cosmesis

With a radiobiologically optimal dose most APBI studies report good to excellent cosmesis in 85-100% of women.

Fat necrosis occurred in 0-25% of women at 3-5 years follow-up.

Severe late radiation sequelae have occurred with radiobiologically unacceptable schedules.

Long term cosmetic outcome and complications with Mammosite and single fraction IORT are awaited. Adverse cosmetic outcome is associated with higher implant volume and doxorubicin-based adjuvant chemotherapy.

Author conclusions

There is enough evidence against the use of APBI for inappropriately selected women or with suboptimal techniques, which may lead to unacceptable breast recurrences and late sequelae. Long term clinical outcome data in appropriately selected women (ABS guidelines) is ongoing and, along with RCT clinical evidence, together can establish the role of APBI in breast cancer treatment.

Additional information from systematic reviews or analyses by other authors who have further examined some of the EBCTCG included randomised trials and other studies:

Kunkler IH, Prescott RJ, Williams LJ, King CC (2006) When may adjuvant radiotherapy be avoided in operable breast cancer?. [Review] [57 refs]. *Clinical Oncology (Royal College of Radiologists)* **18**, 191-199.

Randomised trials in which the omission of radiotherapy has been tested after breast-conserving surgery, with or without adjuvant systemic therapy, show a significant four- to five-

fold reduction in local recurrence. No subgroup of women, managed by breast-conserving surgery, has been identified where radiotherapy may be omitted.

The PRIME trial which evaluates the role of radiotherapy in a population of low risk, older women is ongoing. Adjuvant radiotherapy after breast-conserving surgery or mastectomy significantly reduces the incidence of local recurrence. Adjuvant radiotherapy improves survival after mastectomy in women at high risk of recurrence (> 20% risk of recurrence at 10 years), when combined with adjuvant systemic therapy. Postoperative radiotherapy is the standard of care among women with T3 tumours, and those with four or more involved axillary nodes treated by mastectomy. The role of radiotherapy is unclear in women at intermediate risk of recurrence (i.e. <15% 10-year risk of recurrence after surgery and systemic therapy alone), with one to three involved nodes or node negative with other risk factors. Clinical trials to assess the role of postmastectomy radiotherapy (PMRT) in this setting are needed. There is no evidence presently that PMRT is needed for women with pT1-2, pNO tumours without other risk factors.

Rutqvist LE, Rose C, Cavallin-Stahl E (2003) A systematic overview of radiation therapy effects in breast cancer. *Acta Oncologica* **42**, 532-545. Level 1-

Abstract: A systematic review of radiation therapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The synthesis of literature on radiation therapy for breast cancer was based on data from 29 randomized trials, 6 meta-analyses and 5 retrospective studies. Forty articles were included and involved 41 204 patients. The conclusions reached for breast conserving surgery can be summarized as follows:

- There are conflicting data whether breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy on local recurrence rates.
- There is strong evidence that breast conservation surgery plus radiotherapy is comparable to modified radical mastectomy alone for disease-free survival and overall survival.
- There is strong evidence that postoperative radiotherapy to the breast following breast conservation surgery statistically significantly reduces ipsilateral breast recurrences and diminishes the need for salvage mastectomies.
- There is strong evidence that the omission of postoperative radiotherapy to the breast following breast conservation surgery has no impact on overall survival. One meta-analysis using Bayesian statistics, which included three randomized studies, found a survival advantage.
- There is strong evidence that the addition of a radiation boost to the tumour bed after breast conservation surgery and conventional radiotherapy significantly decreases the risk of ipsilateral breast recurrences but has no impact on overall survival after short follow-up.

Randomized controlled trial

Ford HT, Coombes RC, Gazet JC, Gray R, McConkey CC, Sutcliffe R, Quilliam J, Lowndes S (2006) Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. *Annals of Oncology* **17**, 401-408

Design: RCT Level 1++
Country:UK (St George's Hospital), setting: Single hospital
Update of RCT included in EBCTCG (2005) and Vinh-Hung (2004) reviews

Inclusion criteria

Exclusion criteria

Population number of patients: Post-operative RT (n=208); no post-operative RT (n=192)
Age < 70 years at recruitment
T1 or T2 breast cancer

Interventions

Wide local excision and adjuvant therapy [oestrogen receptor (ER) positive: tamoxifen; ER negative: CMF chemotherapy].

Outcomes

Local recurrence
Distant recurrence
Deaths

Follow up up to 20 years (median 13.7 years)

Results

Local recurrence

Statistically significant reduction in recurrence in ipsilateral breast in RT arm (p=0.0001). Kaplan-Meier rates for each arm are shown in the table below. A Forest plot stratified by subgroups for node status, ER status, T stage (1 or 2) and pre or post menopausal status found no significant differences between groups for local recurrence.

Distant disease-free survival

110 (27.5%) patients developed distant metastases, which was not related to treatment with or without RT. Kaplan-Meier rates for each arm are shown in the table below. There was no significant difference between groups for occurrence of distant metastases (HR = 0.91 95%CI 0.64-1.33; p=0.63). When stratified in a Forest plot by node status, ER status and T stage there were no significant differences between groups. There was a significant difference between pre-menopausal and post-menopausal status (P=0.02) suggesting that RT had a greater effect in post-menopausal women.

Overall survival

There was no significant difference in overall survival between groups (p=0.59). The hazard ratio for deaths in women is shown in the table below.

The authors reported a strong association of local recurrence in the breast with distant metastases:

119 patients had a local recurrence, and 51 (42.8%) of these also had a distant recurrence;

281 patients had no local recurrence, and 59 (21%) of these also had a distant recurrence.

The authors suggested that patients with a local recurrence were more likely to develop distant metastases. This was tested with Cox regression analysis with local recurrence as a time-dependent variable and showed a risk ratio of 5.28 ($P < 0.0001$). This strong relationship is dependent on the intensity of post-treatment follow-up and investigation.

Outcome	BCS + RT	BCS no RT	Result
Local recurrence (20 year Kaplan-Meier)	28.6% (95%CI 19.6 – 37.6%)	49.8% (95%CI 40.8 – 58.9%)	Reduction in locoregional recurrence: 0.45 (0.31-0.64; P=0.0001)
Deaths (Hazard ratio at 20 years)	39.5%	43.3%	HR for RT vs no RT: 0.91 (95%CI 0.64-1.28; P=0.59)
Overall survival	60.5% (SE 4.7%)	56.7% (SE 6.1%)	
Development of metastases (20 year Kaplan-Meier)	33.8% (95%CI 25.1 – 42.5%)	32.2% (95%CI 24.7 – 39.7%)	HR for RT vs no RT: 0.91 (95%CI 0.64-1.33; P=0.63)

Conclusions

Post-operative radiotherapy produced a reduction in locoregional recurrence, but did not influence the incidence of distant metastases or time of death.

General comments -

Observational Studies (eg. Prospective Cohort or Retrospective Cohort or Case Series):

BCS ± RT

Vinh-Hung V, Voordeckers M, Van de SJ, Soete G, Lamote J, Storme G (2003) Omission of radiotherapy after breast-conserving surgery: survival impact and time trends. *Radiotherapy & Oncology* **67**, 147-158.

Design: Retrospective cohort (SEER)

Level 2 +

Country: USA, setting: Multi-centre

Aim: To evaluate the survival impact of omission of radiotherapy after breast-conserving surgery and changes over time.

Inclusion criteria

Women diagnosed between 1988-1998;

Ages 40-69 years;

Primary non-inflammatory, histologically confirmed invasive carcinoma confined to breast;

Tumour diameter < 50 mm;

No previous cancer, no known internal mammary node involvement or distant metastases.

Exclusion criteria

Non hospital or non clinic based record, unknown race, unknown month of diagnosis, size of primary tumour not specified, discrepancy between nodal status and reported nodal involvement.

Population number of patients = 27491 patient records

Interventions

Treatment was breast-conserving surgery (partial mastectomy, lumpectomy, wedge resection, quadrantectomy, segmental resection, tylectomy), with axillary dissection, with or without post-surgery radiation.

No details provided about how RT was delivered.

Outcomes

Survival

Death from any event was recorded.

Follow up 10 years

Results

Radiation therapy was omitted in 3586 patients (13%).

Patients with histologically high grade tumours were less likely to be omitted from RT than patients with low grade tumours in 1988 than in 1997, i.e., in more recent years a higher proportion of patients with grade 3-4 tumours did not receive RT.

There was an increased overall mortality hazard ratio associated with the omission of radiotherapy compared to delivery of radiotherapy:

Hazard ratio = 1.346 (95% CI 1.204-1.504).

The time profile suggested an increase in mortality over time associated with the omission of radiotherapy. The baseline mortality hazard ratio of 1.14-1.17 (14-17% excess relative mortality risk), increased to a projected hazard ratio of 2.26 (more than doubling the relative mortality risk) for omission of radiotherapy.

Author conclusions

In the selected population of patients aged 40–69 years with complete treatment records available, and who also had extensive axillary dissection, the omission of radiotherapy was independently associated with increased mortality. The most conservative estimate of a baseline effect yields a hazard ratio of 1.14–1.17, corresponding to a 14–17% increase of relative mortality. The time trend indicated an exponential increase associated with the omission of radiotherapy in patients who presented more unfavourable factors. Even by discarding the latest registration year, the estimation still yields a hazard ratio of 2.16; more than doubling the relative mortality of no-radiotherapy as compared to radiotherapy. The data do not give support to omitting radiation or give rationale to clinical trials that would omit radiation.

General comments –

There was an increasing trend from 1988 to 1998 to omit radiotherapy for patients with tumours of histological grade 3–4, in comparison to patients receiving radiotherapy. Patients meeting the inclusion criteria were selected from the database, and there was a significant difference between the trial arms for patients with grade 3-4 tumours receiving RT (28.3%) and those not receiving RT (34.7%). The odds of not receiving RT for a high grade tumour increased with time. This may lead to an overestimate of the hazard ratio for this population.

Since only 15% of the database records were selected, the findings are not generalizable.

COSMESIS

Johansen J, Overgaard J, Rose C, Engelholm SA, Gadeberg CC, Kjaer M, Kamby C, Juul-Christensen J, Blichert-Toft M, Overgaard M, Danish Breast Cancer Cooperative Group (DBCG) and the DBCG Radiotherapy Committee. (2002) Cosmetic outcome and breast morbidity in breast-conserving treatment--results from the Danish DBCG-82TM national randomized trial in breast cancer. *Acta Oncologica* **41**, 369-380.

Design: RCT (1982-1990)

Level 1++

Country: Denmark, setting: Multi-centre

Aim: To assess factors that may impact on late effects after BCS.

Inclusion criteria Recurrence free and alive

Exclusion criteria

Population number of patients = 266/343 (78%) recurrence free patients from the BCS arm

Interventions

Breast conservation compared with mastectomy. BCS is the focus of this paper. BCS patients received RT (50 Gy in 25 fractions over 5 weeks) and a boost dose (10Gy) to the scar and tumour bed of either photons or electrons. Adjuvant chemotherapy was offered to high risk patients.

Outcomes

Cosmesis, assessment made by patients and clinician.

Includes: asymmetry and contour, dyspigmentation, telangiectasia, fibrosis, oedema, pain, sensibility, body image, need to change clothing habits, plastic surgery

Follow up Median 6.6 years (3.5-10.5)

Results

194/266 (73%) of patients regarded the cosmetic result as excellent or good. This compared with 125/266 (47%) when assessed by oncologists.

Cosmesis

Morbidity assessments showed that breast fibrosis, skin telangiectasia, and breast retraction were significantly associated with a less satisfactory cosmetic result.

On univariate analysis, treatment with a direct anterior electron field produced more morbidity and inferior cosmetic outcomes compared with tangential photon treatment.

Photons 78% excellent/good outcome

Electrons 66% excellent/good outcome

P=0.04 (patient outcomes)

55% vs. 35% for physician assessment (p=0.002)

Anterior electron fields also led to significantly more grade 2 and 3 late reactions compared to tangential photons:

Grade ≥ 2 dyspigmentation 32% vs 9% ($p < 0.001$)

Grade ≥ 2 telangiectasia 42% vs 3% ($p < 0.001$)

Grade ≥ 2 breast fibrosis 29% vs 18% ($p < 0.05$)

On multivariate analysis cosmetic outcome remained significantly associated with electron therapy (OR 2.3 CI 1.4-4.1; $p = 0.002$).

Increasing breast size was associated with increased breast retraction and breast fibrosis after tangential RT on multivariate analysis (OR 1.73 CI 1.17-2.56, $p = 0.006$).

Treatment characteristics that were independently associated with a fair/poor cosmetic outcome on multivariate analysis were the use of a direct anterior electron field (OR = 2.15, CI 1.25-3.70) and adjuvant systemic therapy (OR = 2.13, CI 1.22-3.71).

Author conclusions

Patient satisfaction with BCS was high despite a high frequency of observed breast changes related to treatment with electrons, resected breast volume, and adjuvant systemic therapy. The prevalence of breast morbidity reported by patients was low.

General comments -

Updated 2018

Deutsch M, Flickinger JC (2003) Patient characteristics and treatment factors affecting cosmesis following lumpectomy and breast irradiation. *American Journal of Clinical Oncology-Cancer Clinical Trials* **26**, 350-353.

Design: Prospective Cohort (June to Nov 1999)

Level 2 -

Country: USA, setting: Single University centre

Aim: To evaluate factors influencing cosmetic outcome in women following lumpectomy and breast irradiation.

Inclusion criteria All women previously treated by one physician who were followed-up in a 6 month period (June-Nov 1999).

Exclusion criteria Bilateral breast cancer and loco-regional recurrence. Patients with previous or subsequent cosmetic surgery.

Population number of patients = 265 women with a unilateral breast cancer. Median age 61 years (28-85)

Interventions

Women treated with lumpectomy with or without axillary dissection (84 lumpectomy alone; 181 lumpectomy and AXD) and post-operative breast irradiation. Irradiation with two tangential fields. A boost to operative area given in 217/265 (81.9%). Majority treated with X-rays, but Cobalt-60 was used in 83 patients. Systemic therapy administered to 188 patients [127 (47.9%) tamoxifen alone; 32 had tamoxifen and chemotherapy]. Sixty (22.6%) patients were treated with chemotherapy with or without tamoxifen. Seventy seven (29.1%) had no adjuvant systemic therapy. Cosmetic outcome assessed by the same physician who treated the patients.

Outcomes

Cosmetic outcome factors including skin pigmentation changes, distortion of the breast, asymmetry, and differences in size between the two breasts.

Follow up 3-249 months (median 61)

Results

On multivariate analysis:

- Skin pigmentation changes were significantly associated with axillary dissection ($p = 0.0049$) and black race ($p = 0.001$).
- An increased interval from surgery was associated with a decreased incidence of pigmentation changes ($p = 0.0058$).
- Smaller size of the treated breast was associated with a longer interval from surgery ($p < 0.0001$) and an increased separation between opposed tangential fields ($P < 0.0001$).

128/265 (48.3%) women had an excellent cosmetic result (no skin changes or deformity and very slight or no differences in size).

110/265 (41.5%) patients had a good result (no skin changes and little difference in size between the breasts, or skin changes with no difference in size between the breasts).

27/265 (10.2%) had a fair or poor cosmesis with skin pigmentation and a difference in size or breast distortion.

An excellent or good cosmetic result versus a fair or poor result was associated with white race ($p = 0.0056$), smaller separation between the tangential fields ($p = 0.01$), the use of a boost dose ($p = 0.0025$), and no use of tamoxifen ($p = 0.025$).

Author conclusions

The majority of women treated with lumpectomy and breast irradiation will have a good or excellent cosmetic outcome.

General comments –

There does not appear to be a description of the instrument used to rate cosmetic outcome as excellent, good, fair or poor. The same physician who treated the patients also assessed cosmesis, likely to be very biased.

Updated 2019

QUALITY OF LIFE

Whelan TJ, Levine M, Julian J, Kirkbride P, Skingley P (2000) The effects of radiation therapy on quality of life of women with breast carcinoma: Results of a randomized trial. *Cancer* **88**, 2260-2266.

Design: RCT (1984-1989)

Level 1++

Country: Canada, setting: Multi-centre

Aim: To evaluate the effect of breast irradiation after lumpectomy on quality of life, including cosmetic outcome, of patients in a clinical trial.

Inclusion criteria Breast carcinoma treated by lumpectomy and axillary lymph node dissection, tumour <4 cm diameter, local excision microscopically complete, and no evidence of histological involvement of axillary lymph nodes.

Exclusion criteria

Population number of patients = 837 randomized

416 received RT

421 no RT

Interventions

BCS and radiation therapy with Cobalt -60 to a dose of 40 Gy in 16 daily fractions to the whole breast over 3 weeks.

A boost dose of 12.5 Gy in 5 daily fractions was also given to the primary site.

A modified version of the Breast Cancer Chemotherapy Questionnaire (BCQ) containing 17 items (questions) was administered by a nurse.

Outcomes

Breast Cancer Chemotherapy Questionnaire (BCQ) scores (modified version).

Irritation of the skin of the breast, breast pain, and appearance of the breast to the patient were assessed 3 monthly for the first 2 years of the study.

Follow up

BCQ administered at baseline, 1 month and 2 months after randomisation.

Data available for 91% of patients after 2 years.

Results

Short term QOL

Effect on individual domains

Mean change scores from baseline to 1 month and from baseline to 2 months were measured for each domain.

At 1 month the differences in mean change scores between RT and control groups were statistically significant for the fatigue, physical symptoms, and inconvenience domains. No statistically significant differences were reported for the emotional dysfunction, social, and attractiveness domains. The overall difference in score between groups was significant favouring no RT (RT = -0.07; no RT +0.21; p=0.0001). A similar pattern was observed for the overall change scores between baseline and 2 months after randomization ((RT = -0.05; no RT +0.30; p=0.0001).

A comparison of patients with a mean score reduction of ≥ 0.5 at 2 months was made between the 2 arms:

93/344 (27%) in the RT group experienced a reduction in scores

60/376 (16%) in the control group experienced a reduction in scores.

The difference was statistically significant ($P = 0.0003$).

Long term QOL

Approximately 75% of patients responded to the 3 items (fatigue, physical symptoms, and inconvenience domains) over the 2 years since randomization.

The 3-month (12 week) assessment was performed at a median of 7 weeks after the last radiation treatment (25–75%, range 5.3– 8.7 weeks).

Skin irritation

Radiation increased the occurrence of skin irritation.

At 3 months 28% in the radiation group and 14% in the control group ($P = 0.0001$) were affected. The number of patients reporting skin irritation decreased over time in both groups ($P = 0.0001$ for trend). At 24 months 7% in each group reported this symptom.

Breast pain

A similar pattern was observed for breast pain. Radiation therapy increased the occurrence of breast pain. At 6 months after randomization 33% of patients in the radiation group and 20% in the control group reported this symptom ($P = 0.0002$). Breast pain also decreased over time ($P = 0.0001$ for trend) with approximately 15% of patients in each group reporting breast pain at 24 months.

Appearance

Dissatisfaction with the appearance of the breast was reported less frequently, with no difference between groups.

4.8% of patients in each group reported being dissatisfied at 2 years ($P = 0.62$).

Author conclusions

Breast irradiation therapy had an effect on quality of life during treatment. After treatment, irradiated patients reported increased breast symptoms compared with controls. However, no difference was detected between groups at 2 years in the rates of skin irritation, breast pain, and being upset by the appearance of the breast.

General comments -

Rayan G, Dawson LA, Bezjak A, Lau A, Fyles AW, Yi Q-L, Merante P, Vallis KA (2003) Prospective comparison of breast pain in patients participating in a randomized trial of breast-conserving surgery and tamoxifen with or without radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* **55**, 154-161.

Design: RCT (1992-2000; Companion study over last 2 years of trial)
Level 1++

Country: Canada, setting: Single hospital

Aim: To determine whether breast pain affects quality of life (QOL) after breast-conserving surgery and tamoxifen (TAM) with or without adjuvant breast radiotherapy (RT).

Inclusion criteria

Women aged ≥ 50 years treated with breast-conserving surgery (BCS) with negative excision margins and stage T1-T2 N0 breast cancer.

Exclusion criteria

Previous diagnosis of breast cancer and disease free for < 10 years

A diagnosis of another malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix)

Disease free for < 5 years

Bilateral breast cancer.

Population number of patients = 86 patients
(41 received RT plus TAM and 45 received TAM alone)
Median age was 70 years (range 51-80).

Interventions

RT protocol consisted of 40 Gy in 16 fractions over 3 weeks to the whole breast and a tumour site boost of 12.5 Gy in 5 fractions over 1 week OR

A dose of 50 Gy in 25 fractions to the whole breast and no boost dose.

A coplanar pair of opposed tangential fields using 6-MV photons or Cobalt-60 radiation was administered to the whole breast. The boost was delivered with a mixed beam of photons and electrons.

Questionnaires were completed by participants within 1 week of randomization in the randomized clinical trial (baseline) and at 3, 6, and 12 months.

Outcomes

The short-form McGill Pain Questionnaire (SF-MPQ)

European Organization for Research and Treatment of Cancer (EORTC) QOL (QLQ-C30)

EORTC breast cancer module (QLQ-BR23)

Follow up

Compliance

The compliance rates for QLQ-C30 and QLQ-BR23 (physical function scale, pain symptom scale, global health status/ QOL, and breast symptom scale) were high (88–100%) at baseline and subsequent time points.

Compliance rates were similar for the other functional and symptom scales of the QLQ-C30 and QLQBR23 (88–100%), an exception was the sexual function scale of the QLQ-BR23. Compliance rates for the five items of the sexual function scale ranged from 69% to 88%.

Compliance with the SF-MPQ was lower - rates ranging from 58% to 100%.

Results

QLQ-C30 scores

Mean scores for each function and symptom measured by the scale were compared for each treatment group. There were no statistically significant differences in mean scores at baseline or follow-up at 3, 6 or 12 months with the exception of one parameter, role function, which was higher in the RT group than the group without RT ($p=0.02$). The most commonly reported symptoms were fatigue and sleep disturbance. The scores for dyspnea, appetite and financial impact improved over time on both groups.

QLQ-BR23 scores

Mean scores for each function and symptom measured by the scale were compared for each treatment group. There were no statistically significant differences in mean scores at baseline or follow-up at 3, 6 or 12 months. Arm and breast symptoms improved in both groups over the year. Women were not concerned about body image, with high scores during the study period. The scores for sexual functioning were low, however this was an older group of women (median age 70 years).

There was no statistically significant difference in pain or breast symptoms between groups. By 12 months breast and arm symptoms improved in both groups compared to baseline, and there was again no statistically significant difference between groups.

SF-MPQ scores

At 3 months the RT group reported more breast pain than the tamoxifen only group, but the difference was not significant ($p=0.47$). At 12 months breast pain scores had decreased in both groups but the difference was not significant ($p=0.71$)

Scores for acute RT toxicity did not correlate with breast pain or QOL scores at 12 months.

Author conclusions

These results suggest that breast RT does not significantly contribute to breast pain or adversely impact the QOL up to 12 months after treatment in postmenopausal patients with node-negative breast cancer who take TAM.

General comments -

Back M, Ahern V, Delaney G, Graham P, Steigler A, Wratten C (2005)
Absence of adverse early quality of life outcomes of radiation therapy in breast conservation therapy for early breast cancer. *Australasian Radiology* 49, 39-43.

Design: Prospective longitudinal cohort (Nov 1998- Mar 2001) Level 3

Country: NSW, Australia, setting: Multi-centre

Aim: To assess the impact of RT on acute toxicity and quality of life (QOL).

Inclusion criteria

Women with EBC or DCIS treated with BCS (wide excision) followed by adjuvant tangential RT.

Exclusion criteria Women receiving systemic cytotoxic chemotherapy

Population number of patients = 195 women

Mean age 56 years (range 36-81)

Node dissection 71%

Postoperative complication 15%

Postoperative oedema 21%

Cosmesis (good/excellent) 76%

Interventions

European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) and Perceived Adjustment to Chronic Illness Scale (PACIS) QoL instruments.

Eight formal assessments over a 14-month period from the commencement of adjuvant RT (weeks 0, 2, 4, 6 during RT; weeks +2, +6, +26 and +52 post-RT). Assessments included physician review, clinical examination, QoL survey, patient symptom diary and cosmesis grid photography.

Outcomes

EORTC QLQ-30 and PACIS questionnaires

Lethargy

Global QoL.

Follow up

Lethargy and global QoL at baseline and week 6 after RT treatment.

175 women had completed follow-up at the time of the analysis.

Results

15% received RT to the nodes

77% received a tumour site boost of RT

Lethargy

Of 175 women, 34.3% described lethargy as a significant disruption to normal activity during RT. At 6 weeks 7.5% reported significant lethargy.

Univariate analysis found breast discomfort to be associated with lethargy (p=0.027)

QoL

Scores were compared at baseline and 6 weeks.

- No negative effects on QoL were noted over the time period of RT.
- EORTC demonstrated no difference in scores between baseline and 6 weeks ($P = 0.79$)
- PACIS demonstrated a significant improvement in functioning ($P < 0.001$) from baseline to week 6.
- On univariate analysis older patient age ($p=0.02$), breast discomfort ($p=0.01$), nodal dissection ($p=0.02$) and lethargy ($p<0.001$) were associated with higher than mean PACIS scores at 6 weeks

Author conclusions

This study confirms the minimal impact of RT on patient functioning at 6 weeks post-treatment.

General comments –

Study includes women with invasive breast cancer and ductal carcinoma in situ. Short term study.

Updated 2018

An update search identified a further study on quality of life after treatment with radiotherapy (Lee *et al* 2008)

Lee TS, Kilbreath SL, Refshauge KM, Pendlebury SC, Beith JM, Lee MJ. Quality of life of women treated with radiotherapy for breast cancer. Support Care Cancer 2008;16(4):399-405.

Design: RCT

Level 1+

Country: Australia, setting: Single centre

Aim: To describe the quality of life of women undergoing radiotherapy for breast cancer.

Inclusion criteria Women post breast cancer surgery and receiving RT to the breast or chest wall

Exclusion criteria

Women receiving RT to the axilla

Population number of patients =64 consecutive sample

Mean age 54 ± 12 years

T I-II n=44

T III n=7

No axillary surgery n=16

Full AXD n=24

Mastectomy n=13

Lumpectomy n=48

Interventions

Women received BCS or mastectomy

RT to breast or chest wall

Doses 50 Gy in 25 fractions or 42.5 Gy in 16 fractions in 2 fields OR

50 Gy in 25 fractions and a supraclavicular fossa field (3 fields)

In this study women were randomized to a control and stretch group throughout the RT period.

Outcomes

EORTC QLQ-C30

QLQ-BR23

Follow up

Baseline, post RT and 7 months

Results

- There were no differences in scores over all time points on the EORTC QLQ-C30 and QLQ-BR23 questionnaires between the control and stretch groups.
- Global health status scores were high
- Trend towards an improvement in QoL between completion of RT and 7 month follow-up
- Fatigue increased during RT but returned to baseline at 7 months
- Breast symptoms increased from baseline to completion of RT, then

returned to baseline at 7 months

- A higher dose of RT (50 Gy vs 42.5 Gy) and more fractions (25 vs. 16) were associated with lower QoL (2 way analysis of variance)
- Fatigue after completion of RT and at 7 months was predictive of lower quality of life at the same time point (linear regression)

Author conclusions

Women retain a high quality of life and return to baseline function by 7 months after radiotherapy. Treatment may best be targeted to alleviate fatigue and breast symptoms during radiotherapy.

General comments

Updated 2018

GUIDELINES

Whelan T, Olivotto I, Levine M, Health Canada 's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. (2003) Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update). *CMAJ Canadian Medical Association Journal* **168**, 437-439.

Design: Guideline

Level 4

Country: Canada

Inclusion criteria

A literature search was conducted using MEDLINE from 1966 to October 2001 and CANCELIT from 1983 to September 2001 for a systematic review of English Language articles. A nonsystematic review of the literature was continued through to April 2002.

Exclusion criteria Non-English language articles

Population

Interventions

Breast radiotherapy after BCS

Outcomes

Local control, survival, quality of life, adverse effects of irradiation and cosmetic results.

Follow up

Results

Recommendations (taken from section 6 of the clinical practice guidelines):

- Women who undergo BCS should be advised to have postoperative breast irradiation. Omission of radiation therapy after BCS increases the risk of local recurrence.
- Contraindications to breast irradiation include pregnancy, previous breast irradiation (including mantle irradiation for Hodgkin's disease) and inability to lie flat or to abduct the arm. Scleroderma and systemic lupus erythematosus are relative contraindications.
- A number of different fractionation schedules for breast irradiation have been used. Although the most common fractionation schedule in Canada to date has been 50 Gy in 25 fractions, recent data from a Canadian trial demonstrate that 42.5 Gy in 16 fractions is as good as this more traditional schedule.
- Irradiation to the whole breast rather than partial breast irradiation is recommended.
- There is insufficient evidence to recommend breast irradiation with brachytherapy implants

or intraoperative radiation therapy. Further evaluation of these treatments in randomized trials is required.

- Additional irradiation to the lumpectomy site (boost irradiation) reduces local recurrence but can be associated with worse cosmesis compared with no boost. A boost following breast irradiation may be considered in women at high risk of local recurrence.
- Physicians should adhere to standard treatment regimens to minimize the adverse effects of breast irradiation.
- When choices are being made between different treatment options, patients must be made aware of the acute and late complications that can result from radiation therapy.
- Breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiation therapy is preceded by chemotherapy. However, the optimal interval between BCS and the start of irradiation has not been defined.
- The optimal sequencing of chemotherapy and breast irradiation is not clearly defined for patients who are also candidates for chemotherapy. Most centres favour the administration of chemotherapy before radiation therapy. Selected chemotherapy regimens are sometimes used concurrently with radiation therapy. There is no evidence that concurrent treatment results in a better outcome, and there is an increased chance of toxic effects, especially with anthracycline-containing regimens.
- Patients should be offered the opportunity to participate in clinical trials whenever possible.

Shelley W, Trudeau M (2002) Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. Practice Guideline Report #1-2. Cancer Care Ontario.

Design: Guideline

Level 4

Country: Canada

Inclusion criteria

MEDLINE and CANCELIT were searched for the years 1966-1999. Bibliographies of articles identified by the searches, recent reviews, relevant articles and personal files were reviewed. For the update entries to MEDLINE (through to December 2001), the Cochrane Library (through to Issue 4, 2001) and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society of Radiation Oncology were searched for evidence relevant to this practice guideline. The most recent literature search was performed in January 2002.

Exclusion criteria

Population

Adult patients with early-stage (stages I and II) invasive breast cancer who have had breast-conserving surgery.

Interventions

Outcomes

Follow up

Results (taken from the published guideline)

Breast irradiation versus no breast irradiation: Four randomized controlled trials and one meta-analysis compared breast irradiation versus no breast irradiation following breast-conserving surgery. Results indicated a significant decrease in local recurrence rates for patients receiving radiotherapy. In the four trials with a median follow-up of five years or longer, the relative risk reduction with breast irradiation ranged from 73 to 89%. The absolute differences ranged from 16% ($p < 0.001$) to 29% ($p < 0.0001$). Despite the effect on local recurrence, no difference in survival was detected in any of the five trials. Most of the patients with breast recurrence in these trials underwent mastectomy. Additional evidence from two randomized trials that examined the efficacy of breast irradiation following breast-conserving surgery, and from a meta-analysis and randomized trial that examined adverse effects of irradiation were identified and reviewed by the Breast Cancer DSG for the update. No changes were made to the recommendations at that time.

Recommendations (from the published guideline)

- Women with early stage (stages I and II) breast cancer who have undergone breast-conserving surgery (defined as excision of the tumour with clear resection margins) should be offered postoperative

breast irradiation.

- The optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. Outside of a clinical trial, two commonly used fractionation schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions. Shorter schedules (e.g., 40 or 44 Gy in 16 fractions) have also been used routinely in some centres. The enrolment of patients in ongoing clinical trials is encouraged.
- Women who have undergone breast-conserving surgery should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery.
- For women who are candidates for chemotherapy, the optimal sequencing of chemotherapy and radiotherapy is unknown. It is reasonable to start radiotherapy after the completion of chemotherapy, or concurrently if anthracycline-containing regimens are not used.

Updated 2018

Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowble B, Giuliano A, Harris JR, O'Malley F, Schnitt SJ, Singletary SE, Winchester DP, American College of Radiology, American College of Surgeons, Society of Surgical Oncology, College of American Pathology. (2002) Standard for breast conservation therapy in the management of invasive breast carcinoma.[see comment]. [Review] [100 refs]. *CA: A Cancer Journal for Clinicians* **52**, 277-300.

Design: Guideline

Level

4

Country: USA

Review and literature summary

Inclusion criteria

9 RCTs comparing breast conserving surgery (BCS) alone with BCS and radiotherapy (RT).

Exclusion criteria

Population

Interventions The trials are varied in patient selection criteria, the extent of surgery and radiotherapy, and use of adjuvant systemic therapy. All were included in the EBCTCG overview (Clarke 2005).

Outcomes

Follow up

Results

RCTs:

- Older women, (>55 years of age) with small primary infiltrating ductal tumours (< 1-2 cm) and negative axillary nodes without an extensive intraductal component (EIC) or lymphatic invasion, had the lowest risk of breast recurrence when radiation was omitted in a subset analysis.
- A further analysis suggested that tamoxifen could not replace radiation therapy even in women with the most favourable tumors.
- Radiation therapy appeared to benefit all women with early-stage invasive breast cancer (including primary tumours < 2cm, histological Grade 1 and negative axillary nodes), although the magnitude of the benefit varied depending on patient selection.

An update search identified another guideline (Sautter-Bihl *et al* 2007).

Sautter-Bihl ML, Budach W, Dunst J, Feyer P, Haase W, Harms W, et al. DEGRO practical guidelines for radiotherapy of breast cancer I: breast-conserving therapy. *Strahlenther Onkol* 2007 Dec;183(12):661-6.

Design: Guideline (March 2007) Level 4
Country: Germany (DEGRO)

Inclusion criteria

Guideline compiled by an expert panel of the German Society of Radiation Oncology

Results

Recommendations (from the published article)

- For invasive carcinoma postoperative RT of the breast is indicated after BCS (Level 1a evidence)
- External beam RT improves local control and increased survival (1a evidence)
- Accelerated partial-breast irradiation as a sole intraoperative or postoperative procedure instead of whole-breast RT is experimental and should not be performed except in studies (Level 3 evidence)

Updated 2018

References

Systematic reviews or overviews

Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y, Early Breast Cancer Trialists' Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.[see comment]. [Review] [33 refs]. *Lancet* **366**, 2087-2106.

Clarke M (2006) Meta-analyses of adjuvant therapies for women with early breast cancer: the Early Breast Cancer Trialists' Collaborative Group overview. *Annals of Oncology* **17 Suppl 10**, x59-x62.

Liljegren G (2002) Is postoperative radiotherapy after breast conserving surgery always mandatory? A review of randomised controlled trials. [Review] [15 refs]. *Scandinavian Journal of Surgery: SJS* **91**, 251-254.

Mul VE, van Geest AJ, Pijls-Johannesma MC, Theys J, Verschueren TA, Jager JJ, Lambin P, Baumert BG (2007) Radiation-induced bullous pemphigoid: a systematic review of an unusual radiation side effect.[see comment]. [Review] [41 refs]. *Radiotherapy & Oncology* **82**, 5-9.

Rutqvist LE, Rose C, Cavallin-Stahl E (2003) A systematic overview of radiation therapy effects in breast cancer. *Acta Oncologica* **42**, 532-545.

Vinh-Hung V, Verschraegen C (2004) Breast-conserving surgery with or without radiotherapy: Pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *Journal of the National Cancer Institute* **96**, 115-121.

Brachytherapy, IORT, APBI

Cuncins-Hearn A, Saunders C, Walsh D, Borg M, Buckingham J, Frizelle F, Maddern G (2004) A systematic review of intraoperative radiotherapy in early breast cancer. [Review] [34 refs]. *Breast Cancer Research & Treatment* **85**, 271-280.

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Sarin R (2005) Partial-breast treatment for early breast cancer: emergence of a new paradigm. [Review] [51 refs]. *Nature Clinical Practice Oncology* **2**, 40-47.

Other primary studies

Back M, Ahern V, Delaney G, Graham P, Steigler A, Wratten C (2005) Absence of adverse early quality of life outcomes of radiation therapy in breast conservation therapy for early breast cancer. *Australasian Radiology* **49**, 39-43.

Deutsch M, Flickinger JC (2003) Patient characteristics and treatment factors affecting cosmesis following lumpectomy and breast irradiation. *American Journal of Clinical Oncology-Cancer Clinical Trials* **26**, 350-353.

Ford HT, Coombes RC, Gazet JC, Gray R, McConkey CC, Sutcliffe R, Quilliam J, Lowndes S (2006) Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. *Annals of Oncology* **17**, 401-408

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Lee TS, Kilbreath SL, Refshauge KM, Pendlebury SC, Beith JM, Lee MJ. Quality of life of women treated with radiotherapy for breast cancer. *Support Care Cancer* 2008;**16**(4):399-405.

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Whelan TJ, Levine M, Julian J, Kirkbride P, Skingley P (2000) The effects of radiation therapy on quality of life of women with breast carcinoma: Results of a randomized trial. *Cancer* **88**, 2260-2266.

Guidelines

Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowble B, Giuliano A, Harris JR, O'Malley F, Schnitt SJ, Singletary SE, Winchester DP, American College of Radiology, American College of Surgeons, Society of Surgical Oncology, College of American Pathology. (2002) Standard for breast conservation therapy in the management of invasive breast carcinoma.[see comment]. [Review] [100 refs]. *CA: A Cancer Journal for Clinicians* **52**, 277-300.

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Ongoing RCTs

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Cuttino LW, Arthur DW, Keisch M, Jenrette JM, Prestidge BR, Quiet CA, et al. Multi-institutional experience using the MammoSite radiation therapy system (RTS) in the treatment of early-stage breast cancer: 2 year results. *International Journal of Radiation Oncology Biology Physics* 2006;66(3):S30-S31.

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Health Economics Summary

The only economic evaluation conducted in the UK (Prescott *et al.* 2007) was based on an RTC performed in Scotland and England, with a follow-up of 15 months, which assessed whether omission of RT after BCS improved quality of life (QoL) and was more cost-effective than administering RT after BCS. The study focused on EBC women aged 65 or older, at low risk of local recurrence. The RCT appeared to be appropriately conducted, with study groups being comparable at baseline and analyses conducted using an intention-to-treat approach. The follow-up period was 15 months. The type of economic evaluation was a cost-utility analysis (i.e. cost savings per QALY lost with non-RT vs RT were estimated). The study was conducted from the UK NHS perspective. The cost analysis appeared to be appropriate and reflected UK clinical practice. The results showed that no-RT for EBC patients aged 65 or older at low risk of local recurrence is likely to be cost-effective compared to RT after BCS, with a 94% of probability at a £30,000 threshold, given that omitting RT would not result in a significant loss of QALYs. In total, £215,160 could be saved per QALY lost with no-RT compared to the RT option. The authors highlighted that longer-term follow-up data still needs to be collected.

Hayman *et al.* (2000) conducted a cost-utility analysis to assess the incremental cost-effectiveness of adding RT following BCS compared to BCS alone for EBC patients aged 60, diagnosed with clinical stage I or II BC and who underwent lumpectomy and axillary dissection, from a societal perspective. They used a Markov model with 1 year cycles and a 10 year time horizon. The clinical parameters were derived from one of the identified RCTs (the National Surgical Adjuvant Breast and Bowel Project: NSABP) for being this the RTC representing best USA clinical practice and population. Utilities for the estimation of QALYs were obtained from a survey conducted on 97 BC patients treated with lumpectomy+RT using the standard gamble technique. In sensitivity analysis, utilities derived from a sample of 20 medical oncology nurses were used. Expert judgement was used to estimate the utilities of BC patients in metastatic states. The cost analysis appeared to be appropriately conducted, although health care resources used were not reported separately from the unit costs. The authors concluded that adjuvant RT after BCS for EBC patients seemed to be cost-effective, since the ICER obtained was \$28,000 per QALY, much lower than the commonly accepted threshold for USA studies (i.e. \$50,000 per QALY). The cost-effectiveness seemed to be minimally affected by changes in most of the parameters; the most influential parameters were the costs of RT and the utility scores associated with a reduction in the fear of local recurrence.

Liljegren *et al.* (1997) conducted a cost-utility analysis to assess the cost-effectiveness of routine post-operative RT compared to BCS alone in women < 80 with a unifocal BC, with stage I cancer, from a societal perspective and considering a 5-year time horizon. A decision tree was developed, which may not have been the most appropriate choice since usually Markov models are used in EBC to take account of the recurrent nature of local relapse and survival related to EBC. The clinical effectiveness was obtained from a RCT with a median of 5-year follow-up (range: 3 to 10 years), which reported recurrences and survival, although the authors did not report whether patient groups were comparable at analysis; therefore, although the RCT seemed to be appropriate in terms of randomisation and analysis (an intention-to-treat analysis was conducted), there may be potential biases that cannot be assessed due to the lack of information in the paper. Expert judgement was used to obtain the utility scores for the QALY estimation; the instrument used for that was not reported. The

cost analysis appeared to be appropriately conducted, although health care resources used were not reported separately from the unit costs.

The authors concluded that the costs per avoided recurrence and per QALY gained with postoperative RT after sector resection and axillary dissection for EBC patients with stage I tumour are high and vary considerably depending on the utility values considered. Moreover, they highlight the need to identify risk factors for local recurrence and quality of life for these patients, since cost-effectiveness of postoperative RT depends on these factors.

The last economic evaluation was published as two congress abstracts, by Alvegard *et al* (2005) and by Persson *et al* (2005), therefore limited information was available as to confidently assess the methodological quality of this study. A cost-utility analysis was conducted to assess the cost-effectiveness of post-operative RT after BCS in stage I-II BC patients considering a 10 year time horizon. A stochastic decision analytic model was developed and the clinical effectiveness was derived from the RCT SweBCG 91-RT. Time horizons of 5, 15 and 20 years seemed to have been considered. The authors concluded that postoperative RT is cost-effective in pre- and post-menopausal BC women with stage I and II undergoing BCS in Sweden only as an adjunct to no medical adjuvant treatment. As an adjunct to novel adjuvant medical treatment, RT is cost-effective in high-risk groups only.

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Updated 2018

Health Economics Evidence Tables

Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, Goh TT, Lindley R and Cairns J. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technology Assessment 2007; Vol 11(31)

Design:

Type of economic evaluation:

Cost-utility analysis. Discounting of health benefits and costs over 1 year was conducted, using a 3.5% discount rate. Incremental cost-effectiveness ratios were estimated and uncertainty was assessed by means of bootstrapping the differences in costs and benefits, and by presenting cost-effectiveness acceptability curves (CEACs), in addition to one-way sensitivity analyses.

Clinical effectiveness:

RCT, with randomisation balanced by participating centre, to assess whether omission of radiotherapy (RT) after breast conserving surgery (BCS) improved quality of life (QoL) and was more cost-effective. Patients in the RCT seemed to be comparable at baseline. The follow-up period was 15 months. QALYs were estimated based on the EuroQol 5-D questionnaire.

Cost estimation:

NHS perspective. Cost categories included were: RT treatment, NHS transport, treatment of recurrence, medication, endocrine therapy, primary and secondary care. Cost of follow-up visits excluded since they were common to both treatment arms. Cost data sources were identified; forms and patient diaries were mainly used to collect cost data. Health care resource utilisation was reported separately from unit costs. The price year was £2004-05

Country: Scotland and England (UK), **setting:** NHS

Inclusion criteria

EBC patients aged ≥ 65 , receiving endocrine therapy; medically suitable for treatment and follow up; histologically confirmed unilateral breast cancer of tumour, node, metastasis (TNM) stages T0-2, N0, M0 and with no axillary node involvement on histological assessment (i.e. at low risk of local recurrence); who had BCS with complete excision on histological assessment; able and willing to give informed consent.

Exclusion criteria

Past history of pure in situ carcinoma of either breast or previous or concurrent malignancy within the past 5 years other than non-melanomatous skin cancer or carcinoma in situ of cervix; grade III cancer with lymphatic/vascular invasion.

Population

255 patients were randomised to either BCS alone (128 patients) or BCS + RT (127 patients), although only 253 patients had complete baseline data.

Interventions

BCS and adjuvant endocrine therapy without RT

BCS and adjuvant endocrine therapy with RT (normally 45-50Gy over 4-5 weeks, with or without a boost of 10-15 Gy, although the type of RT depended on local practice).

Results –

Based on the results of the cancer-specific quality of life questionnaires (EORT QLQ-C30 and EORT QLQ-BR23), overall, there were not significant differences in outcomes in either treatment group, but for significantly higher mean levels of insomnia in the non-RT group ($p = 0.01$), besides a higher level of sexual functioning ($p = 0.05$) and small but higher systemic therapy side effects on this group ($p = 0.03$). There were not significant differences between treatment groups in terms of anxiety levels and depression. In terms of the functional status (mobility, housework and self-care) as measured by the Clackmannan Scale, there was no evidence of a treatment effect. In terms of acute morbidity, scores related to acute skin reactions were significantly worse for patients receiving RT ($p < 0.0001$); no significant differences were found in terms of the scores recorded for lung reactions; fibrosis was significantly higher among RT patients (44% versus 6% at 1 year after surgery; $p < 0.0001$); RT patients presented a significantly higher level of pain at 8 months ($p = 0.03$), although at 12 months the levels of pain were similar between the two groups. No loco-regional recurrences were reported for any of the groups at 15 months. The number of deaths in the RT and the no RT groups were 4 and 1, respectively, at 15 months.

OUTCOME OF INTEREST	RT group	Non-RT group
Total costs (£2004-05): mean (95% CI)	3,500 (3066, 3934)	1,893 (759, 3027)
Cost difference (£2004-05): mean (95% CI)	-	-1,607 (2741, 474)
Unadjusted QALYs	0.95 (0.90, 0.99)	0.92 (0.88, 0.95)
Difference in unadjusted QALYs	-	-0.03 (-0.09, 0.03)
Difference in adjusted QALYs	-	-0.01 (-0.05, 0.04)
ICER (£ saved per QALY lost)	-	215,160

A threshold analysis conducted to identify the critical value for the recurrence rate at which RT would become cost-effective considering a 15 month time horizon (and assuming that diagnostic and treatment for recurrence would cost £20,000 and that recurrence decreases QoL by 9% and has no impact in life expectancy), it was estimated that an increase of at least 5.5% in local recurrences would be required in order to make RT cost-effective at a £30,000 threshold.

Authors' conclusions –

The authors concluded that no RT for this patient population is likely to be cost-effective compared to RT after BCS, with a 94% of probability at a £30,000 threshold, given that omitting RT would not result in a significant loss of QALYs. As the authors reported, the

costs differences would have been even larger, and therefore no RT would have been even more cost-effective, if a societal perspective would have been taken into account, since patients incur in substantial costs (travel and accommodation) when attending RT sessions. However, they highlighted the fact that the evidence for the longer term has yet to be determined.

General comments –

The RCT seemed to have been appropriate, although the sample size was not very large and several protocol changes occurred during the development of the clinical studies. It was reported that the treatment groups were comparable at baseline. The follow-up period was considerably short and did not allow for enough time to observe differences in terms of local recurrences between the treatment arms. The cost analysis seemed to have been appropriate. Bootstrapping was conducted, which allowed the assessment of uncertainty surrounding cost-effectiveness results. The patient population considered at analysis is very specific and therefore the results here obtained should not be generalised outside similar patient populations.

Non-UK Economic Evaluations: full studies

Hayman JA, Hillner BE, Harris JR and Weeks JC. Cost-effectiveness of routine radiation therapy following conservative surgery for early-stage breast cancer. *Journal of Clinical Oncology* 1998; 16(3):1022-1029.

Design:

Type of economic evaluation:

Cost-utility analysis. A Markov model was used, with cycles of 1 year and a 10 year time horizon, to assess the incremental cost-effectiveness of adding RT following BCS compared to BCS alone for EBC patients. Discounting of health benefits and costs was conducted using a 3% discount rate. A societal perspective was adopted. Sensitivity analyses were conducted on all the model parameters.

Clinical effectiveness:

A review of the literature seemed to have been conducted, although it was not stated whether it was systematic or not; the clinical parameters were derived from one of the identified RCTs (the National Surgical Adjuvant Breast and Bowel Project: NSABP) for being this the RTC representing best USA clinical practice and population, according to the authors.

Utilities for the estimation of QALYs were obtained from a survey conducted on 97 BC patients treated with lumpectomy+RT using the standard gamble technique. In sensitivity analysis, utilities derived from a sample of 20 medical oncology nurses were used. Expert judgement was used to estimate the utilities of BC patients in metastatic states.

Cost estimation:

The costs included were direct medical costs (i.e. consultation and follow-up visits, RT, salvage surgery and salvage chemotherapy administration), and patients' costs (i.e. time and transportation). BCS costs were not included since they were assumed to be the same across groups. The sources of costs and the unit costs used in the model were clearly identified; however, health care resource utilisation was not reported separately. The price year was 1995.

Country: USA, **setting:** societal

Inclusion criteria

Patients aged 60, diagnosed with clinical stage I or II BC, having already chosen to undergo BCS and having undergone a lumpectomy and axillary dissection.

Exclusion criteria

None stated

Population

A hypothetical cohort of 60-year old women with EBC

Interventions

BCS alone (i.e. lumpectomy plus axillary dissection) versus BCS followed by RT

Results –

OUTCOME OF INTEREST	BCS + RT	BCS alone
Years of life	7.81	7.81
Δ Years of life	0	-
QALYs	7.19	6.84
Δ QALYs	0.35	-
Total costs per patient (\$1995)	27,200	17,400
Δ cost per patient	9,800	-
ICER (\$1995 per QALY)	28,000	-

The ICER was insensitive to: small changes in survival associated with RT and changes in the assumption regarding the percentage of patients undergoing mastectomy followed by reconstruction versus BCS + RT as salvage treatment after local recurrence. The results were sensitive to: changes in the utility values (if anxiety derived from fear to local recurrence without RT was not considered in the analysis, the ICER increased to \$149,100 per QALY gained); changes in the costs of RT (between \$20,600 and \$35,600 per QALY when the cost of RT was decreased and increased, respectively, by 20%). If the provider's perspective was undertaken (i.e. costs of time and transportation were excluded), the ICER obtained was \$25,800 per QALY gained.

Authors' conclusions –

The authors concluded that adjuvant RT after BCS for EBC patients seems to be cost-effective, since the ICER obtained was \$28,000 per QALY, much lower than the commonly accepted threshold for USA studies (i.e. \$50,000 per QALY). The cost-effectiveness seemed to be minimally affected by changes in the parameters, with modifications in the costs of RT and in the health benefit derived from a reduction in the fear of local recurrence being the most influential parameters.

General comments –

The applicability of this study to the EBC guideline is limited since the study was conducted in USA, and the patient population and clinical practice seemed to be representative of USA, which may differ substantially from a UK context (specially in terms of clinical practice). Additionally, only women aged 60 were included, which limits the generalisability of the results to patients with different ages. The cost results may be biased in favour of RT since it was assumed that patients with local recurrence would undergo mastectomy followed by immediate reconstruction, which would lead to higher costs for the non-RT option. On the other hand, quality of life would have been biased in

favour of the non-RT group due to this assumption. The authors highlighted the limitations of the utility values used in the analysis (obtained from patients that had not experience recurrence; therefore, they may be biased, although the bias was reported to be minor after comparing the utilities with those obtained from the nurses); in addition, the limitation of considering only 60 year-old patients.

Liljegren, G., et al., The cost-effectiveness of routine postoperative radiotherapy after sector resection and axillary dissection for breast cancer stage I. Results from a randomized trial. *Annals of oncology* 1997; 8(8): p. 757-763.

Design:

Type of economic evaluation:

Cost-utility analysis. A decision tree was constructed to assess the cost-effectiveness of routine post-operative RT compared to BCS alone considering a 5-year time horizon. Local recurrences and QALYs were used as measures of health benefit, and a societal perspective was adopted. Costs and health benefits were discounting using a 5% discount rate.

Clinical effectiveness:

The clinical effectiveness was obtained from a RCT with a median of 5-year follow-up (range: 3 to 10 years), which reported recurrences and survival. Expert judgement was used to obtain the utility scores for the QALY estimation; the instrument used for that was not reported.

Cost estimation:

The cost categories included were: medical costs, including cost of primary treatment and of local recurrence (i.e. surgery, anaesthesia, hospital stay, radiotherapy, laboratory tests and X-ray investigations) and follow-up (i.e. mammograms, X-ray investigation, laboratory tests, cytology tests and outpatient visits); travel expenses and productivity losses due to absence from work. The cost data sources appeared to be appropriate. Resource quantities were not reported separately from the costs. The price year was 1993.

Country: Sweden, **setting:** societal

Inclusion criteria

Women < 80 with a unifocal BC, with stage I cancer: specimen histopathologically free from multifocal in situ and a maximum tumour diameter of 20mm on the preoperative mammogram; axillary nodes histopatologically free from metastases.

Exclusion criteria

None stated

Population

381 patients: 184 randomised to the RT group and 197 randomised to the non-RT group.

Interventions

Sector resection of the tumour bearing part of the breast, including the underlying pectoral fascia and axillary dissection, with or without postoperative RT to the breast only.

RT was administered as 54Gy in 27 fractions, five fractions a week, with no boost to the tumour bed.

Perioperative X-ray was conducted to ensure complete tumour excision, and axillary was dissected a levels I and II.

Results –

Only results with QALYs and costs discounted at a 5% rate are presented below; the study also reported QALYs with 0% discount rate.

OUTCOME OF INTEREST	BCS + RT	BCS alone
Local recurrences developed during follow up	6	37
Local recurrence rate	0.023	0.184
All patients:		
QALYs	4.231	4.184
Total costs in SEK 1993 (£)	SEK 120,633 (£9,651)	SEK 66,187 (£5,295)
ICER: SEK (£) per avoided local recurrence in all patients	SEK 337,727 (£27,018)	-
ICER: SEK (£) per avoided local recurrence in intermediate/high risk patients	SEK 209,666 (£16,773)	-
ICER: SEK (£) per avoided local recurrence) in low risk patients	SEK 1,229,780 (£98,382)	-
ICER: SEK (£) per QALY all patients	SEK 1,125,721 (£90,058)	-
ICER: SEK (£) per QALY intermediate/high risk patients	SEK 532,609 (£42,609)	-
ICER: SEK (£) per QALY low risk patients	Dominated	-

The results of the sensitivity analysis showed the results were sensitive to modifications in the cost of RT

Authors' conclusions –

The authors concluded that the costs per avoided recurrence and per QALY gained with postoperative RT after sector resection and axillary dissection for EBC patients with stage I tumour are high and vary considerably depending on the utility values used. Moreover, they highlight the need to identify risk factors for local recurrence and quality of life for these patients, since cost-effectiveness of postoperative RT depends on these factors.

General comments –

A decision tree may not have been the most appropriate type of model to use within the context of EBC. A more appropriate approach may have been to use a Markov model, which is the type model usually considered when recurrences and survival are taken into account in EBC interventions. It was not reported whether patient groups were comparable at analysis; therefore, although the RCT seemed to be appropriate in terms of randomisation and analysis (an intention-to-treat analysis was conducted), there may be potential biases that cannot be assessed due to the lack of information in the paper. Utility scores may not represent actual

preferences since these were obtained from the judgement of health professionals in the BC context. The time horizon for the decision tree may not be long enough to capture all the health benefits related to RT if local recurrences for the non-RT group happen in the long term.

Non-UK Economic Evaluations: congress abstracts

Alvegard TA, Borg S, Ferras-Nunez J, Franzen S, Genell A, Malstrom PO, Persson U, Wallgren A, Ostlund A. The cost-effectiveness of post-operative radiotherapy after breast conservation surgery in stage I-II breast cancer in Sweden. *Journal of Clinical Oncology*, 2005. 23(16): p. 79S-79S.*

Persson U, Borg S, Ferras-Nunez J, Franzen S, Genell A, Malmstrom P, Wallgren A, Ostlund A, Alvegard T. The cost-effectiveness of post-operative radiotherapy after breast conservation surgery in stage I-II breast cancer in Sweden. *Value in Health*, 2005. 8(6): p. A36-A36.*

*Note: These two congress abstracts correspond to the same study.

Design:

Type of economic evaluation:

Cost—utility analysis. A stochastic decision analytic model was used to assess the cost-effectiveness of post-operative RT after BCS in stage I-II BC patients considering a 10 year time horizon.

Clinical effectiveness:

Obtained from the RCT SweBCG 91-RT

Cost estimation:

Costs included health care costs, pharmaceuticals, hospice and home care. Some sources were identified and seemed appropriate, but limited information was provided in the abstract. The price year was not reported.

Country: Sweden, **setting:** health service, although unclear

Inclusion criteria

Women aged 75 or younger who had received BCS and axillary dissection in Sweden between 1991 and 1997 with a median follow up of 5 years.

Exclusion criteria

None stated

Population

1187 women in the RCT, although the population used for the model may have been hypothetical and it was not identified within the abstract.

Interventions

BCS alone versus BCS followed by RT

Results –

OUTCOME OF INTEREST	BCS + RT	BCS alone
10 year risk of local and regional recurrence	8.4	24.1
QALYs	7.73	7.60

Δ QALYs	0.13	-
Treatment costs (SEK)	101,453	97,467
Treatment costs (€)	11,300	10,800
ICER (SEK per QALY)	32,000	-
ICER (€ per QALY)	3,600	-

Consideration of longer time horizons (15 and 20 years) resulted in RT being a cost-saving strategy for preventing relapses.

Authors' conclusions –

The authors concluded that postoperative RT is cost-effective in pre- and post-menopausal BC women with stage I and II undergoing BCS in Sweden only as an adjunct to no medical adjuvant treatment. As an adjunct to novel adjuvant medical treatment, RT is cost-effective in high-risk groups.

General comments –

Little information was provided in the abstract; therefore, the limitations of the study cannot be appropriately assessed.

Updated 2018

6.2 When should patients with DCIS who have undergone complete excision or wide local excision (WLE) be given radiotherapy?

Short Summary

When radiotherapy is compared to no radiotherapy following breast conserving surgery for DCIS there are RCTs that provide strong evidence that radiotherapy after breast conserving surgery to treat patients with DCIS is associated with a lower rate of ipsilateral breast recurrence compared to breast conserving surgery alone, and reduces the risk of such recurrence by approximately half (Bijker *et al.* 2006; Emdin *et al.* 2006; Fisher *et al.* 1998; (Bijker *et al.* 2006; Emdin *et al.* 2006; Fisher *et al.* 1998; Houghton *et al.* 2003; Holmberg *et al.* 2008; Houghton *et al.* 2003).

Evidence from three systematic reviews of mixed primary study designs and two large retrospective analyses, (Boyages *et al.* 1999; Fonseca *et al.* 1997; Shelley *et al.* 2006; Baxter *et al.* 2005; Smith *et al.* 2006) provide evidence that the addition of radiotherapy to breast conserving surgery reduces the risk of local recurrence.

There is strong evidence that the use of radiotherapy following breast conserving surgery to treat patients with DCIS is associated with longer disease-free survival than breast conserving surgery alone (Bijker *et al.* 2006; Emdin *et al.* 2006; Fisher *et al.* 1998). Evidence from two RCTs suggest no difference in overall survival between in patients with DCIS treated with breast conserving surgery plus radiotherapy versus breast conserving surgery alone (Fisher *et al.* 1998; Bijker *et al.* 2006). One retrospective study found no statistically significant difference in 10-year overall survival between patients treated for DCIS with local excision alone, local excision plus radiotherapy and local excision plus radiotherapy plus boost (Omlin *et al.* 2006).

There is evidence that small lesion size (<2cm), widely clear surgical margins (≥ 1 cm), low nuclear grade and the absence of necrosis are favourable risk factors with a risk of breast cancer recurrence after 10 years of 4%-10% in patients with all four factors, and with a very small absolute risk reduction arising from radiotherapy. Guidelines associated with these two systematic reviews concluded that the evidence does not support identification of a group of patients with DCIS who can be treated routinely with breast conserving surgery without radiotherapy.

PICO

Population	Intervention	Comparison	Outcome
Patients with DCIS including those with microinvasive tumours who have received WLE	Radiotherapy	No Radiotherapy	<ul style="list-style-type: none">• Local Recurrence Rate• Disease Free Survival• Overall Survival• Cosmetic Result• Psychological Morbidity

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There was a good body of high quality evidence available to address the issue of when should patients with DCIS who have undergone complete excision or wide local excision be given radiotherapy, consisting of randomised trials and systematic reviews and a small number of relevant observational studies.

The four RCTs have good applicability to this question, but do not assess cosmetic outcomes, psychological morbidity or cost-effectiveness. The non RCT studies have in general, reasonable applicability to this question and do assess quality of life outcomes, though as none were UK based studies these may be influenced by subtle cultural factors.

There is very little variability in radiotherapy regimens across the RCTs, with 50 Gy in 25 fractions being the commonest regimen but the exact type of breast conserving operation performed varies somewhat between RCTs.

There is consistency in the RCTs in relation to their direction of effect, favouring the use of RT, adjuvant to breast conserving surgery. The strength of the effect of RT from the RCTs is largely similar to that summarised in the systematic reviews.

1. Radiotherapy versus no radiotherapy following breast conserving surgery for DCIS:

Local recurrence

Four RCTs provide strong evidence that radiotherapy after breast conserving surgery to treat patients with DCIS is associated with a lower rate of ipsilateral breast recurrence compared to breast conserving surgery alone, and reduces the risk of such recurrence by approximately half (Bijker *et al.* 2006; Emdin *et al.* 2006; Fisher *et al.* 1998; Houghton *et al.* 2003) (Figure 1). In addition three of these trials observed lower rates of ipsilateral recurrence in the radiotherapy arm when considering either invasive ipsilateral recurrence or non-invasive ipsilateral recurrence (Bijker *et al.* 2006; Fisher *et al.* 1998; Houghton *et al.* 2003) whereas the SweDCIS trial found no statistically significant difference for these subtypes of recurrent tumours (Emdin *et al.* 2006).

Three systematic reviews of mixed primary study designs, summarise the risk of local recurrence in patients with DCIS treated either with breast conserving surgery alone or breast conserving surgery plus RT (Table 1) and support the finding of the RCTs: that the addition of RT to breast conserving surgery reduces the risk of local recurrence.

Two recent, large retrospective analyses also found that breast conserving surgery plus radiotherapy is superior to breast conserving surgery alone in reducing local recurrence (Baxter *et al.* 2005; Rakovitch *et al.* 2007; Schouten van der Velden *et al.* 2007; Smith *et al.* 2006). A smaller observational study provided a similar result and suggested also that radiotherapy plus boost confers a further benefit in reducing local recurrence to that of conventional radiotherapy (Omlin *et al.* 2006).

Table 1: Systematic reviews: rates of local recurrence following treatment for DCIS

Study	Size	Follow-up	Rate of local recurrence	
			BCS alone	BCS + RT
(Shelley <i>et al.</i> 2006) (cites a previous meta-analysis by Yin <i>et al.</i> 1997)	24 studies; 2407 patients	5 years	No data	10.6% (95% CI 5.6%-16.9%)
(Boyages <i>et al.</i> 1999)	36 studies; 2600 patients	5 years*	22.5% (95% CI 16.9%-28.2%)	8.9% (95% CI 6.8%-11.0%)
(Fonseca <i>et al.</i> 1997)	16 studies; 794 patients	5 years*	23% (range 8%-63%)	9% (range 4%-21%)

* Approximated by reported mean follow-up periods

Disease-free survival

Three RCTs provide strong evidence that the use of radiotherapy following breast conserving surgery to treat patients with DCIS is associated with longer disease-free survival than breast conserving surgery alone (Bijker *et al.* 2006; Emdin *et al.* 2006; Fisher *et al.* 1998) (Figure 2). The UKCCCR trial did not analyse survival due to low event rates (Houghton *et al.* 2003). (Houghton *et al.* 2003). An update of the original RCT (Emdin *et al.* 2006) reported no statistically significant difference in distant metastasis-free survival (Holmberg *et al.* 2008); where a total of 18 events of metastatic breast disease and breast cancer deaths occurred in the RT arm and a total of 15 in the control group (RR=1.2; 95% CI, 0.60 to 2.4).

Overall survival

Two RCTs analysed overall survival in patients with DCIS treated with breast conserving surgery plus radiotherapy versus breast conserving surgery alone (Fisher *et al.* 1998; Bijker *et al.* 2006). Both trials found no difference in overall survival between the randomised arms (Figure 3).

One retrospective study found no statistically significant difference in 10-year overall survival between patients treated for DCIS with local excision alone, local excision plus RT and local excision plus RT plus boost (Omlin *et al.* 2006).

Cosmesis and quality of life

Evidence from two observational studies suggests that in patients treated with breast conserving surgery plus radiotherapy, a good cosmetic result is achievable (Mills *et al.* 1997;

Claus *et al.* 2006). Clinicians rated the cosmetic result as good or excellent in 97% of cases in one series (Mills *et al.* 1997) whereas in another larger series 50% of patients perceived a good or excellent result (Claus *et al.* 2006).

Evidence from one case-control study and one observational study suggests that patients treated for DCIS with breast conserving surgery, with or without adjuvant radiotherapy have good physical health at 4-5 years follow-up (Amichetti *et al.* 1999; Claus *et al.* 2006). The same studies suggest also that in this patient group, breast conserving surgery plus radiotherapy has an adverse impact on emotional, psychological and sexual outcomes, but with uncertainty around the clinical significance of this effect (Amichetti *et al.* 1999; Claus *et al.* 2006).

Factors for predicting no benefit from radiotherapy

Evidence from two good quality systematic reviews does not define clearly and consistently a low risk group of patients in whom adjuvant radiotherapy has no benefit after breast conserving surgery.

The reviews, both undertaken to inform Canadian guidelines, report on primary studies (of predominantly observational design) that examined factors which may have potential to identify patients with an acceptably low risk of recurrence when treated with breast conserving surgery without RT (Olivotto 1998; Shelley *et al.* 2006).

Olivotto (1998) identified small lesion size (<2cm), widely clear surgical margins (≥1cm), low nuclear grade and the absence of necrosis as favourable risk factors; reporting a risk of breast cancer recurrence after 10 years of 4%-10% in patients with all four factors, and with a very small absolute risk reduction arising from RT.

A second systematic review cited studies that developed the Van Yuys Prognostic Index (VNPI), which includes the four factors reported above, and also patient age (Shelley *et al.* 2006). Using VNPI it is possible to identify a group of patients with DCIS and favourable risk factors in whom there is little benefit from RT, but further observational studies have omitted RT in highly selected patients treated only with BCS and experienced high local failure rates (Shelley *et al.* 2006).

Both guidelines associated with these two systematic reviews concluded that the evidence does not support identification of a group of patients with DCIS who can be treated routinely with breast conserving surgery without RT.

An observational study of breast conserving surgery alone or with RT (Omlin *et al.* 2006) identified, in addition to RT, younger age and positive/unknown margin status as independent risk factors for local failure (Omlin *et al.* 2006).

A large retrospective analysis (Smith *et al.* 2006) found, at a median follow-up of 5 years, that in patients of age 66 years or more, advanced age was protective with regard to breast cancer events, but large tumour size, comedo histology and high grade were predictive factors for breast cancer events. Using these factors to define groups according to risk, the absolute risk reduction arising from RT in addition to breast conserving surgery alone was statistically significant both in the low risk sub group (ARR 7%) and the high risk subgroup (ARR 10%); $p < 0.001$ in each case (Smith *et al.* 2006).

One observational study aimed to measure the utility (i.e. a measure of value, or desirability) attributed by patients and non patients for different hypothetically proposed outcomes that can

follow treatment for DCIS by either lumpectomy or lumpectomy plus RT (Hayman *et al.* 2005). Participants had strongest utility for being free of invasive recurrence. For outcomes that follow treatment with breast conserving surgery plus RT, patients had higher utility for being recurrence-free than did non-patients.

Rakovitch *et al.* (2007) evaluated the risk of local recurrence risk among women with multifocal DCIS who were treated with breast conserving surgery and to determine whether multifocality is an independent risk factor for local recurrence in a retrospective study. Among women treated with breast conserving surgery only, 21% developed local recurrence as compared with 9% of women treated with breast conserving surgery and radiotherapy. The 5 year actuarial local recurrence free survival rates were 85% for women treated with breast conserving surgery alone and 93% for those treated with BCS plus radiotherapy. Median time to local recurrence was 4.2 years (Range; 0.3-16.7 years) following BCS Alone and 3.0 years (Range; 0.6-8.7) following BCS + RT. On univariate analysis, administration of radiation (HR: 0.48 (95% CI; 0.30-0.75), P=0.002), presence of comedonecrosis (HR: 1.7 (95% CI; 1.02-2.85), P=0.04) and resection margins of 4mm or smaller (HR: 1.89 (1.20-2.98), P=0.006), were significantly associated with the development of local recurrence. Administration of radiation and positive or close resection margins (≤ 4 mm) were associated with the development of an invasive recurrence. On multivariate analysis multifocality (HR: 1.8 (95% CI; 1.2-2.8), P=0.01), radiotherapy (HR 0.46 (95% CI; 0.29-0.74), P=0.001), margin width 4mm or smaller (HR: 1.7 (95% CI; 1.0-2.9), P=0.04) and high nuclear grade (HR: 1.6 (95% CI; 1.0-2.7), P=0.04) were predictors of local recurrence. For women treated with breast conserving surgery alone, the 5 year actuarial local recurrence free survival rates were 82% for women with multifocal disease and 87% for those with unifocal disease. At ten years the recurrence-free survival rate was significantly lower; 59% for women with multifocal disease compared to 80% for women with unifocal disease (p=0.02). There was no significant impact of multifocality among women that received radiation therapy.

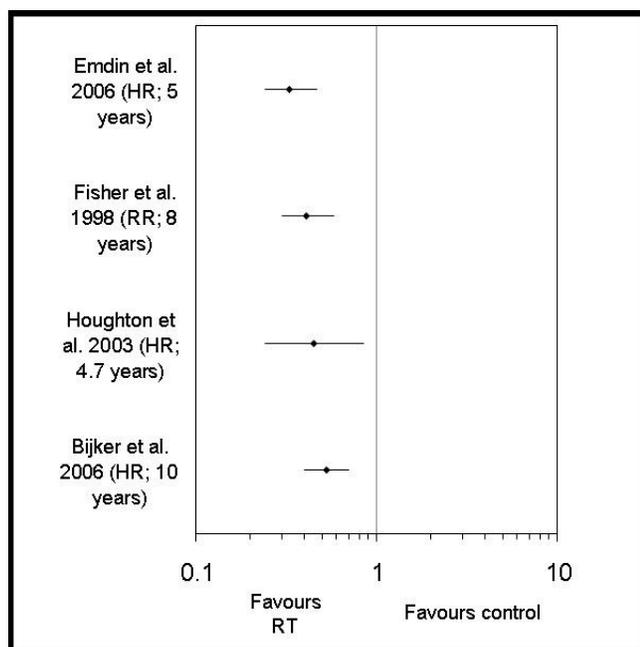
2. Adjuvant tamoxifen in patients who are not treated with radiotherapy

Local recurrence

One RCT provided a subgroup analysis of the effect of adjuvant tamoxifen versus no adjuvant therapy in 1053 patients treated for DCIS with primary complete local excision, who did not receive radiotherapy (Houghton *et al.* 2003). Within this subgroup there was no statistically significant difference between randomised arms in the incidence of ipsilateral invasive recurrence or ipsilateral DCIS (Figure 4).

This study did not analyse the rate of contralateral breast events alone in this subgroup. Analysing events in either breast together, there was no statistically significant difference in the incidence of total breast tumours (invasive plus DCIS) or invasive tumours alone. However there were statistically significantly fewer recurrent DCIS tumours in the tamoxifen arm compared to the control arm (Figure 4). This study did not analyse survival.

Figure 1: Data from RCTs: Ipsilateral local recurrence following breast conserving surgery plus radiotherapy versus breast conserving surgery alone for DCIS

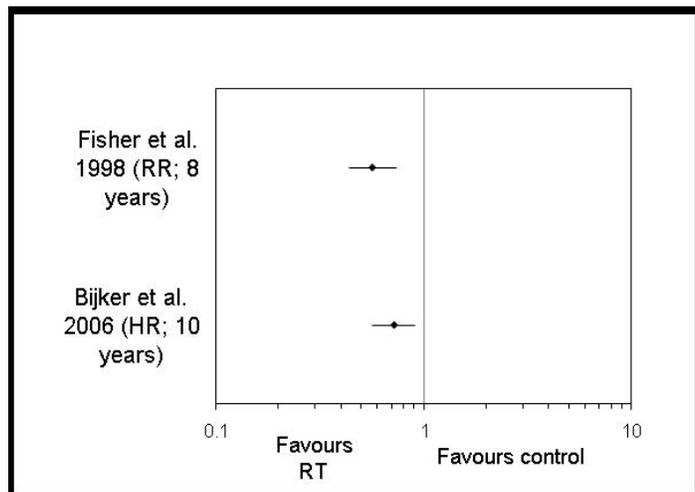


Notes:

1. Information in parentheses: (HR: Hazard ratio or RR: Relative risk; extent of follow-up)
2. Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com

RCT	Citation	Follow-up	Rate of ipsilateral local recurrence (%)		Ratio	Ratio value: RT:Control (95% CI)
			BCS + RT	BCS alone		
SweDCIS	(Emdin <i>et al.</i> 2006)	5 years	7	22	Hazard ratio	0.33 (0.24-0.47)
	(Holmberg <i>et al.</i> 2008)	8 years	64	141	Relative Risk	0.40 (0.30-0.54)
NSABP B-17	(Fisher <i>et al.</i> 1998)	8 years	12	27	Relative risk	0.41 (0.30-0.58)
UKCCCR	(Houghton <i>et al.</i> 2003)	4.7 years	3	6	Hazard ratio	0.45 (0.24-0.85)
EORTC 10853	(Bijker <i>et al.</i> 2006)	10 years	15	26	Hazard ratio	0.53 (0.40-0.70)

Figure 2: Data from RCTs: Disease-free survival following breast conserving surgery plus radiotherapy versus breast conserving surgery alone for DCIS

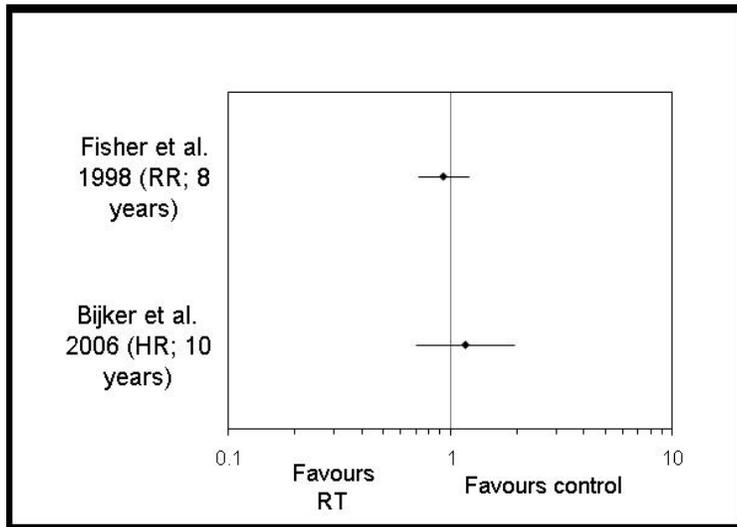


Notes:

1. Information in parentheses: (HR: Hazard ratio or RR: Relative risk; extent of follow-up).
2. Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com
3. A third RCT (Emdin *et al.* 2006) measured disease-free survival but did not report a ratio outcome; disease-free survival over the entire follow-up period (median 5.2 years) was statistically significantly longer in the RT group compared to the control group ($p < 0.001$, log-rank test); with estimated survival at 5 years: 87% in the RT group; 72% in the control group.

RCT	Citation	Follow-up	Ratio	Value: RT:Control (95% CI)
NSABP B-17	(Fisher <i>et al.</i> 1998)	8 years	Relative risk	0.57 (0.44-0.74)
EORTC 10853	(Bijker <i>et al.</i> 2006)	10 years	Hazard ratio	0.72 (0.57-0.91)

Figure 3: Data from RCTs: Overall survival following breast conserving surgery plus radiotherapy versus breast conserving surgery alone for DCIS

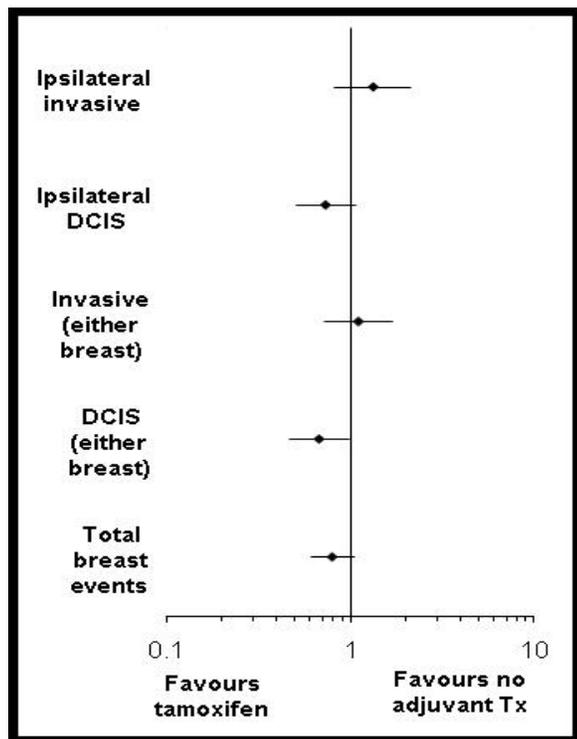


Notes:

1. Information in parentheses: (HR: Hazard ratio or RR: Relative risk; extent of follow-up)
2. Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com

RCT	Citation	Follow-up	Ratio	Value: RT:Control (95% CI)
NSABP B-17	(Fisher <i>et al.</i> 1998)	8 years	Relative risk	1.07 (0.72-1.22)
EORTC 10853	(Bijker <i>et al.</i> 2006)	10 years	Hazard ratio	1.18 (0.70-1.96)

Figure 4: Data from UKCCCR trial subgroup analysis (n=1053): Breast recurrence in patients treated with tamoxifen versus no adjuvant therapy (Fisher *et al.* 1999)



Notes:

3. Method used to generate Forest plot: Clark O; Djulbegovic B. Forest plots in excel software (Data sheet). 2001. Available at www.evidencias.com
4. Follow-up: 4.7 years

Breast event	Rate of breast event (%)		Hazard ratio: Tamoxifen:Control (95% CI)	p value
	Tamoxife n	No adjuvant Tx		
Ipsilateral invasive recurrence	5	4	1.32 (0.81-2.14)	0.26
Ipsilateral DCIS	6	9	0.73 (0.51-1.06)	0.10
Total invasive tumours (either breast)	5	5	1.11 (0.72-1.72)	0.64
Total DCIS tumours (either breast)	6	10	0.68 (0.47-0.97)	0.03
Total breast events	12	15	0.80 (0.61-1.05)	0.11

Further details from randomised trials

NB: For further details of non RCT studies, see related evidence table.

EORTC 10853

The EORTC 10853 trial randomised 1010 patients treated initially with complete local excision for DCIS to either 50 Gy RT in 25 fractions in 5 weeks or no further treatment (Bijker *et al.* 2006).

The trial reported a statistically significant advantage for patients treated with RT in terms of local recurrence-free survival, which in addition, held true when invasive recurrences or DCIS recurrences were considered individually. The 10-year estimated local recurrence-free survival rate was 85% in the RT group versus 74% in the control group; Hazard ratio (HR; RT:control) 0.53 [95% CI 0.40-0.70], $p < 0.0001$, log-rank test. The 10-year estimated local recurrence-free survival rate (DCIS recurrence only) was 93% in the RT group versus 86% in the control group; HR (RT:control) 0.52 [95% CI 0.34-0.77], $p = 0.0011$, log-rank test. The 10-year estimated local recurrence-free survival (invasive recurrence only) was 92% in the RT group versus 87% in the control group; HR (RT:control) 0.58 [95% CI 0.39-0.86], $p = 0.0065$, log-rank test.

The trial demonstrated a statistically significant advantage arising from adjuvant RT in terms of disease-free survival at 10 years' follow-up, whereas there was no difference at 10 years follow up for overall survival. The 10-year estimated rate of disease-free survival was 76% in the RT group versus 70% in the control group; HR (RT:control) 0.72 [95% CI 0.57-0.91], $p = 0.0066$, log-rank test. The 10-year estimated rate of overall survival was 95% in the RT group versus 95% in the control group; HR (RT:control) 1.18 [95% CI 0.70-1.96], $p = 0.53$, log-rank test.

NSABP B-17

The NSABP B-17 trial randomised 818 patients with DCIS detected either by physical examination or mammography to either lumpectomy (excision, with tumour free margin) plus 50 Gy RT in 2 Gy fractions or lumpectomy alone (Fisher *et al.* 1998).

The trial demonstrated an advantage in disease-free survival at 8 years' follow-up arising from adjuvant RT, but with little difference in overall survival between randomised groups. The estimated 8-year rate of disease-free survival was 75% in the RT group versus 62% in the control group; $p = 0.00003$, log-rank test; Relative risk (RR; Control:RT) 1.74 [95% CI 1.34-2.26], $p = 0.00003$, log-rank test. There was no statistically significant difference in the 8-year estimated rate of overall survival in the RT group (95%) versus the control group (94%); RR (control:RT) 1.07 [95% CI 0.82-1.39], $p = 0.84$, log-rank test.

RT also resulted in a lower rate of local recurrence. The estimated 8-year rate of all ipsilateral local recurrence as the first event was 12.1% in the RT group versus 26.8% in the control group; RR (Control: RT) 2.44 [95% CI 1.72-3.45], $p < 0.000005$, log-rank test. The estimated 8-year rate of invasive ipsilateral local recurrence as first event was 8.2% in the RT group versus 13.4% in the control group; RR (control: RT) 3.45 [95% CI 2.00-5.95], $p < 0.000005$, log-rank test. The estimated 8-year rate of non-invasive ipsilateral local recurrence as first

event was 3.9% in the RT group versus 13.4% in the control group; RR (Control: RT) 1.87 [95% CI 1.19-2.93], $p < 0.007$, log-rank test.

SweDCIS

The SweDCIS trial randomised 1067 patients treated with sector resection for histologically proven DCIS occupying one quadrant or less of the breast to either 50 Gy RT in 25 fractions over 5 weeks or no further treatment (Emdin *et al.* 2006).

At 5 years' follow up there were statistically significantly fewer cases of local recurrence in the RT group compared to the control group. The estimated 5-year rate of ipsilateral local recurrence was 7% in the RT group versus 22% in the control group; HR (RT:control) 0.33 [95% CI 0.24-0.47], $p < 0.0001$, log-rank test. There was no statistically significant difference in the proportion of ipsilateral recurrences that presented as invasive tumours: 47.7% in the RT group versus 41.0% in the control group; difference: 6.7% [95% CI -10.0% to 23.3%].

Disease-free survival over the entire follow-up period was statistically significantly longer in the RT group compared to the control group ($p < 0.001$, log-rank test). For example the estimated 5-year disease-free survival was 87% in the control group versus 72% in the control group. This study did not analyse overall survival.

An update study by Holmberg 2008 showed that there were 64 ipsilateral events in the RT arm and 141 in the control group corresponding to a risk reduction of 16.0 percentage points at 10 years (95% CI, 10.3% to 21.6%) and a relative risk of 0.40 (95% CI, 0.30 to 0.54). Out of the 64 ipsilateral events; 59.4% (in the RT arm) and 45.4% (in the control arm) were invasive. There was no statistically significant difference in distant metastasis-free survival. A total of 18 events of metastatic breast disease and breast cancer deaths occurred in the RT arm and a total of 15 in the control group (RR=1.2; 95% CI, 0.60 to 2.4). There was an effect modification by age, yielding a low effect of RT in women younger than 50, but substantial protection in women older than 60 years. The age effect was not confounded by focality, lesion size, completeness of excision, or detection mode. There was no group as defined by study stratification variables that had a low risk without radiotherapy. There were signs of increasing effect of RT by age although this was not significant ($p = 0.07$ for interaction between RT and age-group). There were no indications of effect modification on RT for any other factors examined.

UKCCCR

The UKCCCR trial aimed to examine the individual effects of adjuvant RT and adjuvant tamoxifen in 1694 patients with predominantly screen-detected DCIS, all of whom were treated initially with complete local excision (Houghton *et al.* 2003).

The study had a 2X2 factorial design by which 912 patients chose to enter randomisation to one of four treatment combinations of RT, tamoxifen, RT plus tamoxifen, or no adjuvant therapy. A further 664 patients made a choice whether to undergo RT or forego RT and accepted randomisation to either tamoxifen or no tamoxifen. A further 118 patients made a choice whether to receive tamoxifen or forego tamoxifen and accepted randomisation to either RT or no RT.

a) Radiotherapy versus control

1030 patients were randomly allocated to either RT or control, of whom a proportion received tamoxifen in addition (55% and 53% respectively). There were statistically significantly fewer ipsilateral breast cancer events in patients randomised to RT compared to those randomised to control, which held true when analysing invasive events and DCIS events individually. The rate of ipsilateral (DCIS + invasive) breast events was 6% in the RT arm versus 14% in the control arm; HR 0.38 [95% CI 0.25-0.59], $p < 0.0001$, stratified log-rank test. The rate of new ipsilateral invasive events was 3% in the RT arm versus 6% in the control arm; HR 0.45 [95% CI 0.24-0.85], $p = 0.01$, stratified log-rank test. The rate of new ipsilateral DCIS events was 3% in the RT arm versus 7% in the control arm; HR 0.36 [95% CI 0.19-0.66], $p = 0.0004$, stratified log-rank test.

b) Tamoxifen in the patient subgroup that did not receive radiotherapy

This trial also provided a subgroup analysis of new breast events in patients randomised to tamoxifen or control, stratified by whether or not they received RT. In the subgroup of patients who did not receive RT there was no statistically significant difference between randomised arms in the incidence of ipsilateral invasive recurrence or ipsilateral DCIS. The rate of ipsilateral invasive breast events was 5% in the tamoxifen arm versus 4% in the control arm; HR 1.32 [95% CI 0.81-2.14], $p = 0.26$, stratified log-rank test. The rate of ipsilateral DCIS events was 6% in the tamoxifen arm versus 9% in the control arm; HR 0.73 [95% CI 0.51-1.06], $p = 0.10$, stratified log-rank test.

This study did not analyse the rate of contralateral breast events alone in the subgroup of patients that did not receive RT, but analysed new breast events that occurred in either breast together in this subgroup: there was no statistically significant difference in the incidence of total breast tumours (invasive plus DCIS) or invasive tumours alone. The rate of total breast events (invasive + DCIS; ipsilateral + contralateral tumours) was 12% in the tamoxifen arm versus 15% in the control arm; HR 0.80 [95% CI 0.61-1.05], $p = 0.11$, stratified log-rank test. The rate of total invasive (ipsilateral + contralateral tumours) was 5% in the tamoxifen arm versus 5% in the control arm; HR 1.11 [95% CI 0.72-1.72], $p = 0.64$, stratified log-rank test. However there were statistically significantly fewer recurrent DCIS tumours in the tamoxifen arm compared to the control arm: respective rates were 6% versus 10%; HR 0.68 [95% CI 0.47-0.97], $p = 0.03$, stratified log-rank test. This study did not analyse survival.

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Design

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: USA, setting: Secondary care

Inclusion criteria

818 patients with DCIS detected either by physical examination or mammography; including those with diffuse calcifications on mammography, where excised tissue margins showed histologically no tumour.

Exclusion criteria

Positive margin of excised tissue;
Clinically or histologically involved axillary nodes;
History of previous cancer, excluding carcinoma in situ of the cervix or basal cell carcinoma of the skin

Population

number of patients = 818.

Interventions

Aim: to examine the effect of RT after lumpectomy to treat patients with DCIS.

RT group (n=413): underwent lumpectomy (excision, with tumour free margin) plus 50 Gy RT in 2 Gy fractions.

No RT group (n=405): underwent lumpectomy alone.

Outcomes

Ipsilateral local recurrence;
Second ipsilateral primary tumour;
Contralateral breast cancer;
Regional or distant metastasis;
Death.

Follow up

Clinical examination was performed every 6 months and mammography each year.

Mean duration 90 months (range 67-130 months).

Results

Survival:

Estimated 8-year rate of disease-free survival:

RT group: 75%

No RT group: 62%; p=0.00003, log-rank test.

Relative risk (RR; No RT:RT) 1.74 [95% CI 1.34-2.26], p=0.00003, log-rank test.

Estimated 8-year rate of overall survival:

RT group: 95%

No RT group: 94%

RR (No RT:RT) 1.07 [95% CI 0.82-1.39], p=0.84, log-rank test.

Local recurrence:

Estimated 8-year rate of all ipsilateral local recurrence as first event:

RT group: 12.1%

No RT group: 26.8%

RR (No RT: RT) 2.44 [95% CI 1.72-3.45], p<0.000005, log-rank test.

Estimated 8-year rate of invasive ipsilateral local recurrence as first event:

RT group: 8.2%

No RT group: 13.4%

RR (No RT: RT) 3.45 [95% CI 2.00-5.95], p<0.000005, log-rank test.

Estimated 8-year rate of non-invasive ipsilateral local recurrence as first event:

RT group: 3.9%

No RT group: 13.4%

RR (No RT: RT) 1.87 [95% CI 1.19-2.93], p<0.007, log-rank test.

Other events:

Estimated 8-year rate of all events as first event (combined) excluding ipsilateral recurrence:

RT group: 12.5%

No RT group: 11.0%

RR (No RT:RT) 0.99 [95% CI 0.64-1.52], p=0.96, log-rank test.

Individual relative risks of regional recurrence, non-breast cancer primary tumour, contralateral breast cancer tumour and distant breast cancer metastasis (RT:No RT; p values from log-rank test):

Regional recurrence: 1.81 [95% CI 0.33-9.86], p=0.79

Non-breast cancer primary: 1.26 [95% CI 0.56-2.85], p=0.72

Contralateral tumour: 1.32 [95% CI 0.65-2.67], p=0.55

Distant metastasis: 0.90 [95% CI 0.18-4.47], p=0.99

General comments

Proportion of patients with pure DCIS or microscopic invasion is not known.

Age distribution similar between randomised groups.

Randomisation was stratified for age (<=49 or >49 years), tumour type (DCIS or DCIS +

LCIS), method of detection (mammography, clinical examination or both) and axillary dissection (performed or not performed).

Axillary dissection was obligatory at study outset but became optional during the study period.

18 patients (RT: 12, No RT: 6) were ineligible but are included in the analysis. 4 patients (2 in each group) were lost to follow-up and were not included in the analyses. Study does not report whether analysis is by intention-to-treat.

Study reports its relative risk outcomes as either RT:No RT or the reciprocal, No RT:RT.

Bijker, Meijnen, Peterse, Bogaerts, Van, Julien, Gennaro, Rouanet, Avril, Fentiman, Bartelink & Rutgers . Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and. J Clin Oncol 24[21], 3381-3387. 2006.

Design

Design: Randomized controlled trial (therapy), evidence level: 1++
Country: European States, setting: Secondary care

Inclusion criteria

1010 patients treated initially with complete local excision for DCIS with no histological evidence of DCIS at the surgical margin. Other criteria:

Tumour diameter ≤ 5 cm;

No evidence of invasive disease or Paget's disease;

Exclusion criteria

Age > 70 years;

Pregnancy;

Previous/concomitant malignancy except for treated basal cell carcinoma of skin or treated carcinoma in situ of the cervix;

WHO performance status ≥ 2 ;

Mental or social condition precluding follow-up

Population

number of patients = 1010, median age = 53 years.

Interventions

Aim: to examine the effect of RT after complete local excision of DCIS.

RT group (n=507): underwent 50 Gy RT in 25 fractions in 5 weeks. No boost was advised.

No RT group (n=503): underwent no further treatment.

Outcomes

Invasive and non-invasive recurrence in the treated breast;

Regional recurrence;

Metastasis;

Death;

Contralateral breast cancer.

Follow up

Patients were followed at 6-monthly intervals until the 10th postoperative year and then at annually intervals. Bilateral mammograms were performed every year.

Median duration 10.5 years.

Results

Local recurrence:

4-year estimated local recurrence-free survival was 91% in the RT group versus 84% in the No RT group; HR (RT:No RT) 0.62 [95% CI 0.44-0.87], $p=0.005$, log-rank test.

4-year estimated local recurrence-free survival (DCIS recurrence only) was 95% in the RT group versus 92% in the No RT group; HR (RT:No RT) 0.65 [95% CI 0.41-1.03], $p=0.06$, log-rank test.

4-year estimated local recurrence-free survival (invasive recurrence only) was 96% in the RT group versus 92% in the No RT group; HR (RT:No RT) 0.60 [95% CI 0.37-0.97], $p=0.04$, log-rank test.

10-year estimated local recurrence-free survival was 85% in the RT group versus 74% in the No RT group; HR (RT:No RT) 0.53 [95% CI 0.40-0.70], $p<0.0001$, log-rank test.

10-year estimated local recurrence-free survival (DCIS recurrence only) was 93% in the RT group versus 86% in the No RT group; HR (RT:No RT) 0.52 [95% CI 0.34-0.77], $p=0.0011$, log-rank test.

10-year estimated local recurrence-free survival (invasive recurrence only) was 92% in the RT group versus 87% in the No RT group; HR (RT:No RT) 0.58 [95% CI 0.39-0.86], $p=0.0065$, log-rank test.

Regional recurrence:

10-year estimated regional recurrence free-survival was 99% in the RT group versus 97% in the No RT group; HR (RT:No RT) 0.46 [95% CI 0.20-1.07], $p=0.064$, log-rank test.

Contralateral breast cancer:

4-year estimated contralateral breast cancer-free survival was 97% in the RT group versus 99% in the No RT group; HR (RT:No RT) 2.57 [95% CI 1.24-5.33]; $p=0.01$, log-rank test.

10-year estimated contralateral breast cancer-free survival was 92% in the RT group versus 96% in the No RT group; HR (RT:No RT) 1.41 [95% CI 0.87-2.30], $p=0.16$, log-rank test.

10-year estimated contralateral (as DCIS) breast cancer-free survival was 98% in the RT group versus 98% in the No RT group; HR 1.10 (RT:No RT) [95% CI 0.47-2.59], $p=0.82$, log-rank test.

10-year estimated contralateral (as invasive tumour) breast cancer-free survival was 94% in the RT group versus 97% in the No RT group; HR (RT:No RT) 1.48 [95% CI 0.83-2.65], $p=0.18$, log-rank test.

Distant metastasis:

4-year estimated distant metastasis-free survival was 99% in the RT group versus 98% in the No RT group; HR (RT:No RT) 0.98 [95% CI 0.44-2.18]; p=0.96, log-rank test.

10-year estimated distant metastasis-free survival was 96% in the RT group versus 96% in the No RT group; HR (RT:No RT) 1.14 [95% CI 0.63-2.08]; p=0.66, log-rank test.

Overall survival:

4-year overall survival was 99% in the RT group and 99% in the No RT group; HR (RT:No RT) 0.97 [95% CI 0.44-2.16], p=0.94, log-rank test.

10-year overall survival was 95% in the RT group versus 95% in the No RT group; HR (RT:No RT) 1.18 [95% CI 0.70-1.96], p=0.53, log-rank test.

Disease-free survival:

4-year disease-free survival was 86% in the RT group versus 82% in the No RT group; HR (RT:No RT) 0.82 [95% CI 0.61-1.10], p=0.2, log-rank test.

10-year estimated disease-free survival was 76% in the RT group versus 70% in the No RT group; HR (RT:No RT) 0.72 [95% CI 0.57-0.91], p=0.0066, log-rank test.

General comments

Cited data originate in part from earlier trial publication: Julien et al. (2000).

Trial was performed in 46 centres in 13 countries.

41 patients were randomised although they did not meet the inclusion criteria; generally we would expect poorer prognosis in these patients as a result. 30 patients received treatment as per the opposite arm to their randomised arm and 5 patients received RT outside of the stipulated 12 weeks from surgery. 25 patients received a boost of RT to the site of surgery. 8 patients were lost to follow-up; 3 in the No RT group and 5 in the RT group. All analyses were by intention-to-treat.

Re: population: the trial included a central pathology review: sufficient data was available in 863 (85%) patients. Invasive tumour was found or suspected in 40 cases and benign proliferative lesions or LCIS in 48 cases; therefore an estimated 91% of randomised patients had pure DCIS.

Emdin, Granstrand, Ringberg, Sandelin, Arnesson, Nordgren, Anderson, Garmo, Holmberg & Wallgren . SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 45[5], 536-543. 2006.

Design

Design: Randomized controlled trial (therapy), evidence level: 1++
Country: Sweden, setting: Secondary care

Inclusion criteria

1067 patients treated with sector resection for histologically proven DCIS occupying one quadrant or less of the breast.

Exclusion criteria

Paget's disease of the nipple;
Invasive carcinoma or intracystic carcinoma in situ;
Pregnancy;
Previous or concurrent malignancy excluding treated basal cell skin carcinoma or carcinoma in situ of the cervix;
Doubtful surgical margin (see comment)

Population

number of patients = 1067, mean age = 56 years.

Interventions

Aim: to examine the effect of RT following breast conserving surgery for DCIS. All patients underwent breast sector resection with a 1cm macroscopic surgical margin and mandatory specimen X-ray. Following surgery patients were randomised as follows:

RT group (n=534): received 50 Gy RT in 25 fractions over 5 weeks or 54 Gy in two series with a gap of two weeks. No boost was given.

No RT group (n=533): received no further treatment.

Outcomes

Ipsilateral breast recurrence;
Ipsilateral regional recurrence;
Contralateral breast cancer;
Distant metastasis;
Death (any cause);
Death due to breast cancer.

Follow up

Biannual clinical examination plus annual mammography for five years; thereafter annual clinical examination and mammography.

Median duration 5.2 years

Results

Estimated 5-year rate of ipsilateral local recurrence:

RT group (44 events): 7%

No RT group: (117 events): 22%

HR (RT: No RT) 0.33 [95% CI 0.24-0.47], $p < 0.0001$, log-rank test.

Proportion of ipsilateral recurrences that presented as invasive tumours:

RT group: 21/44 = 47.7%

No RT group: 48/117 = 41.0%

Difference: 6.7% [95% CI -10.0% to 23.3%]

Estimated 5-year rate of contralateral breast cancer:

RT group (26 events): 3.3%

No RT group: (22 events): 3.2%

HR (RT: No RT) 1.16 [95% CI 0.62-2.14], $p = 0.64$, log-rank test.

Proportion of cases of contralateral breast cancer that presented as invasive tumours:

RT group: 23/26 = 88.5%

No RT group: 15/22 = 68.2%

Difference: 20.1% [95% CI -3.0% to 42.5%]

Estimated 5-year rate of combined distant metastasis or deaths due to breast cancer:

RT group (9 events): 1.3%

No RT group (9 events): 0.5%

HR 1.02 [95% CI 0.40-2.56], $p = 0.97$

Disease-free survival over the entire follow-up period was statistically significantly longer in the RT group compared to the No RT group ($p < 0.001$, log-rank test); e.g. estimated 5-year disease-free survival:

RT group: 87%

No RT group: 72%

General comments

Multi-centre trial with 58 contributing centres.

Completeness of surgical excision was assessed by operative findings, pathology report and specimen X-ray. Cases of doubtful margin were not randomised.

47 patients received treatment that violated the protocol for their randomised arm. No patients were lost to follow-up. 19 patients in the RT group plus 14 patients in the No RT group received systemic anti-oestrogen therapy. All analyses were by intention-to-treat.

Histological re-evaluation by three pathologists was planned for a sample of 20% ($n = 212$) of randomised patients. Of these, 93% (198) had slides available. Of these, 163 (83%) were classified as pure DCIS; the remainder were either benign, atypical ductal hyperplasia, invasive/microinvasive ductal carcinoma, LCIS or inconclusive.

Holmberg, L., Garmo, H., Granstrand, B., Ringberg, A., Arnesson, L.A., Sandelin, K., Karlsson, P., Anderson, H., Emdin, S. (2008) Absolute Risk Reductions for Local Recurrence After Postoperative Radiotherapy After Sector Resection for Ductal Carcinoma In Situ of the Breast. *Journal of Clinical Oncology* 26;8:1247-1252

Design: Randomised Controlled Trial Evidence Level: 1++ (from original RCT Emdin et al. 2006)

Country: Sweden

Aim: To evaluate the effects of radiotherapy following sector resection for DCIS in patient groups defined by age, lesion size, focality, completeness of excision and mode of detection.

Inclusion criteria:

Women who underwent breast conserving surgery for histologically proven DCIS occupying a quadrant or less of the breast and with a clinically negative examination of the axilla.

Exclusion criteria:

Paget's disease of the nipple, invasive carcinoma or intracystic carcinoma in situ, ongoing pregnancy, history of previous or concurrent malignancy (except basal cell carcinoma and treated carcinoma in situ of the uterine cervix).

Population: 1067 randomised to RT or control

21 patients excluded due to protocol violations prior to receiving RT

Interventions: Patients were randomised to receive radiotherapy or control following a sector resection where macroscopic lateral and medial margins of at least one centimetre were aimed for.

Outcomes: New ipsilateral breast events and distant metastasis-free survival. The data were analysed according to intention to treat.

The absolute risk reduction of the cumulative incidence proportion of local recurrence.

Results:

There were 64 ipsilateral events in the RT arm and 141 in the control group corresponding to a risk reduction of 16.0 percentage points at 10 years (95% CI, 10.3% to 21.6%) and a relative risk of 0.40 (95% CI, 0.30 to 0.54). Out of the 64 ipsilateral events; 59.4% (in the RT arm) and 45.4% (in the control arm) were invasive

- There was no statistically significant difference in distant metastasis-free survival. A total of 18 events of metastatic breast disease and breast cancer deaths occurred in the RT arm and a total of 15 in the control group (RR=1.2; 95% CI, 0.60 to 2.4).
- There was an effect modification by age, yielding a low effect of RT in women younger than 50, but substantial protection in women older than 60 years. The age effect was not confounded by focality, lesion size, completeness of excision, or detection mode. There was no group as defined by study stratification variables that had a low risk without radiotherapy. There were signs of increasing effect of RT by age although this was not significant ($p = 0.07$ for interaction between RT and age-group).

- There were no indications of effect modification on RT for any other factors examined.

Authors Comment:

RT substantially reduces the risk of local recurrence after a sector resection for DCIS.

General comments:

Author Comment: The findings by age were not likely to have been confounded by the use of exogenous hormones or hormone therapy. Hormone replacement therapy was considered strictly contraindicated in all women with a previous breast cancer in situ at the time in Sweden. Tamoxifen was used by less than 4% in the cohort and none of the women underwent hormone ablation.

Houghton, George, Cuzick, Duggan, Fentiman, Spittle, UK Coordinating Committee on Cancer Research, Ductal Carcinoma in situ Working Party, DCIS trialists in the UK, Australia & and . Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 362[9378], 95-102. 2003.

Design

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: UK, Australia, New Zealand, setting: Secondary care

Inclusion criteria

1694 patients with unilateral or bilateral screen-detected or DCIS who were candidates for breast conserving surgery; including:

- Symptomatic patients in whom DCIS was confirmed in the same way as in screening clinics;
- Patients with microinvasion <1mm in diameter, provided histologically clear margins were obtained. This group comprised 59 patients (3%).

Age distribution largely reflects screened population: modal age group 50-54 years; 90% of patients were of age >50 years i.e. older than the other RCT populations.

Exclusion criteria

LCIS or atypical ductal hyperplasia;
Doubtful histological margins;
Paget's disease of the nipple;
Patients with reduced life expectancy due to concomitant illness or malignancy;
Patients considered unsuitable for any of the treatment options.

A total of 7 patients were excluded (from an original study size of 1701) after randomisation.

Population

number of patients = 1694.

Interventions

Aim: to investigate the individual effects of radiotherapy and tamoxifen as adjuvant treatment for DCIS following complete local excision.

All patients underwent complete local excision.

2X2 factorial design:

912 patients chose to enter randomisation to one of four treatments:

RT + tamoxifen:	242
Tamoxifen alone:	224
RT alone:	220
No treatment:	226

782 patients chose 2-way randomisation:

664 patients made a choice re: RT and were randomised to either tamoxifen or no tamoxifen:

RT + Tamoxifen:	30
Tamoxifen alone:	298
RT alone:	31
No treatment:	305

118 patients made a choice re: tamoxifen and were randomised to either RT or no RT:

RT + Tamoxifen:	44
Tamoxifen alone:	45
RT alone:	16
No treatment:	13

Tamoxifen comprised 20mg daily for 5 years.

RT comprised 50 Gy in 25 fractions over 5 weeks.

Outcomes

Ipsilateral breast recurrence;

Contralateral breast cancer;

New cancer (non-breast);

Death; breast cancer related or not.

Time-to-event analysis was by the life table method and the stratified log-rank test.

Follow up

Yearly bilateral mammography for the first 7 years and every 2 years thereafter.

Median duration 56.2 months (range 2.4-118.3 months).

Results

1. Effect of tamoxifen (1576 patients in the randomised tamoxifen comparison)

New ipsilateral invasive events:

Tamoxifen: 45 (6%)

Control: 35 (4%)

HR 1.31 [95% CI 0.84-2.03], p=0.23, stratified log-rank test.

New ipsilateral DCIS events:

Tamoxifen: 57 (7%)

Control: 77 (10%)

HR 0.74 [95% CI 0.52-1.04], p=0.08, stratified log-rank test.

All ipsilateral (DCIS + invasive) events:

Tamoxifen: 102 (13%)

Control: 114 (15%)

HR 0.90 [95% CI 0.69-1.17], p=0.42, stratified log-rank test.

New contralateral invasive events:

Tamoxifen: 10 (1%)

Control: 15 (2%)

HR 0.66 [95% CI 0.30-1.46], p=0.30, stratified log-rank test.

New contralateral DCIS events: no data

All contralateral (DCIS + invasive) breast events:

Tamoxifen: 11 (1%)

Control: 21 (3%)

HR 0.52 [95% CI 0.25-1.07], p=0.07, stratified log-rank test.

All invasive (ipsilateral + contralateral) events:

Tamoxifen: 55 (7%)

Control: 50 (6%)

HR 1.11 [95% CI 0.76-1.63], p=0.59, stratified log-rank test.

All DCIS (ipsilateral + contralateral) events:

Tamoxifen: 58 (7%)

Control: 84 (11%)

HR 0.68 [95% CI 0.49-0.96], p=0.03, stratified log-rank test.

All events (invasive + DCIS; ipsilateral +contralateral):

Tamoxifen: 114 (14%)

Control: 137 (18%)

HR 0.83 [95% CI 0.64-1.06], p=0.13, stratified log-rank test.

2. Effect of RT (1030 patients in the randomised RT comparison)

New ipsilateral invasive events:

RT: 15 (3%)

Control: 30 (6%)

HR 0.45 [95% CI 0.24-0.85], p=0.01, stratified log-rank test.

New ipsilateral DCIS events:

RT: 14 (3%)

Control: 38 (7%)

HR 0.36 [95% CI 0.19-0.66], p=0.0004, stratified log-rank test.

All ipsilateral (DCIS + invasive) breast events:

RT: 29 (6%)

Control: 69 (14%)

HR 0.38 [95% CI 0.25-0.59], p<0.0001, stratified log-rank test.

New contralateral invasive events:

RT: 9 (2%)

Control: 6 (1%)

HR 1.50 [95% CI 0.53-4.22], p=0.44, stratified log-rank test.

New contralateral DCIS events: no data.

All contralateral (DCIS + invasive) breast events in patients in the RT comparison:

RT: 9 (2%)

Control: 11 (2%)

HR 0.82 [95% CI 0.34-1.18], p=0.65, stratified log-rank test.

All invasive (ipsilateral + contralateral) events:

RT: 24 (5%)

Control: 36 (7%)

HR 0.62 [95% CI 0.37-1.04], p=0.07, stratified log-rank test.

All DCIS (ipsilateral + contralateral) events:

RT: 14 (3%)

Control: 44 (9%)

HR 0.31 [95% CI 0.17-0.56], p<0.0001, stratified log-rank test.

All events (ipsilateral + contralateral; invasive + DCIS):

RT: 38 (7%)

Control: 82 (16%)

HR 0.43 [95% CI 0.29-0.63], p<0.0001, stratified log-rank test.

3. Subgroup analysis: New breast events in patients randomised to tamoxifen or control, stratified by whether or not they had RT

a) Patients not receiving RT (n=1053)

Ipsilateral invasive:

Tamoxifen: 37 (5%)

Control: 29 (4%)

HR 1.32 [95% CI 0.81-2.14], p=0.26, stratified log-rank test.

Ipsilateral DCIS:

Tamoxifen: 20 (6%)

Control: 68 (9%)

HR 0.73 [95% CI 0.51-1.06], p=0.10, stratified log-rank test.

Total invasive (ipsilateral + contralateral tumours):

Tamoxifen: 42 (5%)

Control: 39 (5%)

HR 1.11 [95% CI 0.72-1.72], p=0.64, stratified log-rank test.

Total DCIS (ipsilateral + contralateral tumours):

Tamoxifen: 51 (6%)

Control: 75 (10%)

HR 0.68 [95% CI 0.47-0.97], p=0.03, stratified log-rank test.

Total breast events (invasive + DCIS; ipsilateral + contralateral tumours):

Tamoxifen: 94 (12%)

Control: 117 (15%)

HR 0.80 [95% CI 0.61-1.05], p=0.11, stratified log-rank test.

b) Patients receiving RT (n=523)

Ipsilateral invasive tumours:

Tamoxifen: 8 (1%)

Control: 6 (1%)

HR 1.25 [95% CI 0.43-3.61], p=0.68, stratified log-rank test.

Ipsilateral DCIS:

Tamoxifen: 7 (1%)

Control: 9 (1%)

HR 0.75 [95% CI 0.28-2.02], p=0.57, stratified log-rank test.

Total invasive (ipsilateral + contralateral tumours):

Tamoxifen: 13 (2%)

Control: 11 (1%)

HR 1.11 [95% CI 0.50-2.48], p=0.80, stratified log-rank test.

Total DCIS (ipsilateral + contralateral tumours):

Tamoxifen: 7 (1%)

Control: 9 (1%)

HR 0.75 [95% CI 0.28-2.02], p=0.57, stratified log-rank test.

Total breast events (invasive + DCIS; ipsilateral + contralateral tumours):

Tamoxifen: 20 (3%)

Control: 20 (3%)

HR 0.95 [95% CI 0.51-1.77], p=0.88, stratified log-rank test.

General comments

'Complete excision': defined by radiology of the surgical specimen and free margins on histological examination. Re-excision was performed where necessary.

Randomisation was performed by each contributing centre, blocked in groups of four and stratified for screening assessment centre.

Power calculation performed; additional patients were recruited because patients/clinicians favoured the 2-way randomisation.

Analysis of the individual effect of tamoxifen included only patients randomised to tamoxifen (not those who chose tamoxifen). The analysis was repeated, stratified by whether RT was given in addition.

Analysis of the individual effect of RT included only patients randomised to RT (not those who chose RT). No results are provided stratified by whether tamoxifen was given in

addition. Approximately 54% of patients in either arm of the RT comparison received tamoxifen in addition.

Of 794 patients randomised to tamoxifen, 86 (11%) did not fully comply with the regimen. Study does not measure adverse effects of tamoxifen or RT.

Survival was not analysed as there were few deaths (45 in total).

Study may be underpowered where sub groups are small; the largest subgroup arising through choice of treatment is patients who chose with their clinicians to not be randomised to radiotherapy or control (n=664).

Systematic review of combined study designs

{Olivotto, 1998 8448 /id}

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2 +
Country: Canada, setting: Secondary care

Inclusion criteria

RCTs, meta-analyses, practice guidelines and literature reviews; patients with DCIS.

Exclusion criteria

Non-English language papers.

Population

-

Interventions

Aim: to systematically review evidence for management of patients with DCIS; in order to inform recommendations in a Canadian clinical guideline.

Cited data relate to selection of patients for RT, assuming primary treatment with breast conserving surgery.

Outcomes

Outcomes cited here are pathologic prognostic factors to predict local recurrence following treatment for DCIS, in the context of patient selection for the omission of RT.

Follow up

Not known; review cites data on the risk of recurrence at 10 years follow-up.

Results

Relevant findings from the systematic review:

The "Consensus conference on the classification of ductal carcinoma in situ" concluded that the most useful clinical factors to predict local recurrence in patients treated for DCIS are: nuclear grade, necrosis, margin width and lesion size.

The EORTC 10853 RCT and the NSABP B-17 RCTs demonstrated reduced risk of ipsilateral invasive and non-invasive breast cancer recurrence even for patients with clear margins of excision.

Evidence from observational studies and the pathology review of the NSABP B-17 RCT indicates that four pathological factors tend to identify patients with a lower risk of recurrence when treated with breast conserving surgery without RT:

Small lesion size (<2cm);

Widely clear margins (≥ 1 cm);

Low nuclear grade;
Absence of necrosis.

Patients with all four favourable risk factors may have a risk of breast cancer recurrence after 10 years of 4%-10%. In such cases the further absolute risk reduction arising from RT is very small. However omission of RT remains controversial (the Canadian clinical guideline recommends that breast conserving surgery for DCIS be usually followed by RT).

General comments

Literature search:

English-language literature published between 1976 and 2001, identified primarily through MEDLINE and CANCELIT databases;

Key words: "breast neoplasms," "carcinoma in situ,"

Subject headings "carcinoma, intraductal, non-infiltrating";

Text words: "duct," "dcis" and "ductal carcinoma"

The search was restricted to RCTs, meta-analyses, practice guidelines and literature reviews.

References in review articles and textbooks were also used.

Quality assessment:

The quality of the evidence was categorised into 5 levels, according to the reference cited below, but no further details are provided.

Sackett (1989) Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95(Suppl):2S-4S

Data cited here originate from 1 consensus conference, 2 RCTs (EORTC 10853 and NSABP B-17, including a paper of a related pathology review) and 3 non-randomised studies which address factors associated with local control/recurrence.

It is unclear how relevant observational studies were identified and study quality assessment is not made explicit and is rarely evident. However the review is structured according to recommendations for practice in Canada and as such is fit for purpose.

Shelley, McCready & Holloway . Management of ductal carcinoma in situ of the breast: A clinical practice guideline. Cancer Care Ontario . 2006.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2+
Country: Canada, setting: Secondary care

Inclusion criteria

1. RCT, or meta-analysis design
2. Outcomes: overall or disease-free survival, local recurrence (invasive or non-invasive), breast conservation, distant recurrence, toxicity, or quality of life.
3. Results reported in full papers or abstracts.
4. Evidence-based clinical practice guidelines

NB: The systematic review continued to include observational studies, for topics where the authors demonstrated an absence of RCT evidence.

Exclusion criteria

Non English language papers;
Publications prior to 1983.

Population

-

Interventions

Aim: to provide a clinical guideline for the management of patients with DCIS based upon a systematic review of the evidence.

Outcomes

Review reports important outcomes for the management of patients with DCIS, including survival and disease recurrence.

Information cited from the review in this report relates to 3 areas

1. A meta-analysis by Yin et al (1997) that is not otherwise included in this report: Yin XP, Li XQ, Neuhauser D, Evans JT. Assessment of surgical operations for ductal carcinoma in situ of the breast. *Int J Tech Ass Health Care*. 1997;3:420-9.
2. Additional prognostic information from RCTs (whose main results are already included) about risk of recurrence of DCIS, in the context of selecting patients in whom RT may be omitted following breast conserving surgery.
3. Observational studies aimed at deriving prognostic factors in the context of selecting patients in whom RT may be omitted following breast conserving surgery.

Follow up

Variable across included studies.

Results

1. Result of a meta-analysis of 24 published observational studies (2407 patients in total; number of patients for cited result not known):

Risk of local recurrence at 5 years follow-up in patients treated for DC IS by breast conserving surgery and RT: 10.6% [95% CI 5.6%-16.9%].

2. Additional prognostic information from RCTs

EORTC 10853

Prognostic factor analysis in a subset of 775 patients with DCIS without invasion who underwent a central pathology review.

Median follow-up 5.4 years.

Multifactorial analysis of: treatment group, age, method of detection, nuclear grade, necrosis, architecture, size, margin status, histologic grade, and Van Nuy's classification. Age \leq 40 years, clinical detection, cribriform or solid/comedo architecture, close, involved or unknown margins, and no postoperative RT were all risk factors for local recurrence.

Multivariate analysis not performed for each treatment group but, in the single factor analysis, all subgroups had an observed lower incidence of local recurrence in the RT group compared to the No RT group. Two subgroups in the RT group had local recurrence rates \geq 20% i.e. those \leq 40 years of age, a 23% recurrence rate, and those with involved, close, or unspecified resection margins, a 20% recurrence rate.

NSABP B-17

623 patients underwent central pathology review.

Analysis at 8 years follow-up.

Factors examined: comedo necrosis, histologic type, margin status, lymphoid infiltrate, nuclear grade, focality, cancerisation, stroma, and tumour size.

In a multifactorial analysis, only the presence of moderate to marked comedo necrosis was a significant predictor of breast recurrence. The average annual hazard rates for recurrence were lower for all nine pathologic characteristics in the RT group compared to the No RT group.

Subgroups according to the Van Nuys classification: recurrence rates were lower in all three groups in patients who received RT.

In these two RCTs there was no subgroup of patients identified in whom a low rate of recurrence was observed, with or without RT.

3. Prognostic information from observational studies

Four observational studies by Silverstein (1995, 1996, 1999, 2003) of patients with DCIS informed the development of the Van Nuys prognostic index:

Silverstein (1995) defined three groups (Van Nuys classification) to examine risk of local recurrence patients with DCIS as follows:

I: Nuclear grade I-II, comedo necrosis absent;
 II: Nuclear grade I-II, comedo necrosis present;
 III: Nuclear grade III.

In 425 patients treated with either mastectomy, BCS plus RT or BCS alone, 8-year disease-free survival was as follows:

I: 93%

II: 84% (I versus II, p=0.05)

III: 61% (II versus III, p=0.003).

Failure was most commonly due to local recurrence.

[i.e. higher local recurrence in the high risk group defined by the Van Nuys classification]

Silverstein (1996) derived the Van Nuys Prognostic Index (VNPI; scale range 3-9) in 333 patients treated with either BCS alone or BCS plus RT. The VNPI utilised the Van Nuys Classification (as above) and also tumour size (<1.5, 1.6-4.0, >4.1 mm) and margin width (>10, 1-9, <1 mm) and derived low risk (score 3-4), intermediate risk (score 5-7) and high risk (score 8-9) groups.

8-year risk of ipsilateral breast recurrence (invasive plus non invasive; %), by VNPI group and by treatment received:

	BCS	BCS + RT
VPNI group		
Low (3-4)	3	0
Intermediate (5-7)	32	15
High (8-9)	100	65

This finding was suggestive of little additional benefit of RT in patients in the low risk VNPI group; a benefit in the intermediate risk group; and in the high risk group benefit, but with a remaining high risk of local recurrence.

Silverstein (1999) studied the effect of BCS alone and BCS plus RT in 469 patients stratified according to surgical margin width:

Relative risk of recurrence at 8 years (RT:BCS+RT) by margin size:

>10 mm 1.14 [95% CI 0.10-12.64] p=0.92

1-10 mm 1.49 [95% CI 0.76-2.90] p=0.24

<1mm 2.54 [95% CI 1.25-5.18] p=0.01

This finding was suggestive of no benefit of RT except in patients with margins <1mm in size.

Silverstein (2003) re-defined the VNPI in 706 patients treated with either BCS alone or BCS plus RT; the index comprised tumour size, margin width, the pathological criteria described above and also age:

At 12 years follow-up there was no statistically significant difference in local recurrence-free survival in patients in the low risk VNPI group (score 4-6) in patients treated by BCS alone versus those treated with BCS plus RT; rates in both groups >90% (from graph in original paper), p=NS.

In patients with a VNPI of 7-9 RT was associated with a statistically significant reduction

in the rate of local recurrence over the 12 years of follow up, of between 12% and 15%; $p=0.02$.

In patients with a VNPI of 10-12, RT was also associated with a statistically significant reduction in the rate of local recurrence over the 12 years of follow up; $p=0.001$; although the rate of local recurrence was high, even in patients treated with RT e.g. 30% at 5 years follow-up (from graph in original paper).

These results are suggestive of no advantage of RT existing only in the low risk group, however in the highest risk group RT does not reduce the rate of local recurrence to an acceptable level.

These four studies suggest that a low risk group of patients with DCIS exists in whom there is little benefit from RT. However further observational studies have omitted RT in highly selected patients treated only with BCS and experienced high local failure rates (17% at 10 years in Lagios et al. 1989 and 12% at 3 years in Wong et al. 2006).

Based upon the evidence cited above the authors of this systematic review (undertaken for a Canadian clinical guideline) concluded that it is not possible to safely identify a group of patients with DCIS, treated with BCS, who do not require adjuvant RT.

General comments

Literature Search Strategy :

MEDLINE to March 2006, using MeSH terms ("carcinoma, intraductal, noninfiltrating") and treatment-specific MeSH terms ("radiotherapy", "mastectomy", or "tamoxifen").

Excerpta Medica database (EMBASE) up to March 2006, using a disease-specific Excerpta Medica Tree (EMTREE) term ("intraductal carcinoma") and the same treatment-specific EMTREE term as for the MEDLINE search.

Issue 5 (2004) of the Cochrane Library, the Physician Data Query database (http://www.cancer.gov/search/clinical_trials/)

Conference proceedings from the American Society of Clinical Oncology (1998 to 2005)

American Society for Therapeutic Radiology and Oncology (1998 to 2005)

San Antonio Breast Cancer Symposium (2001 to 2005).

Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/>)

Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

One original paper by Silverstein used to read values from graphs, where indicated.

Reference: Silverstein, M. J. (2003) The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. American Journal of Surgery, 186: 337-343.

Boyages, Delaney & Taylor . Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis.[see comment]. Cancer 85[3], 616-628. 1999.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 3
Country: Australia, setting: Secondary care

Inclusion criteria

Studies (no design restrictions) of treatment of patients with DCIS by:
Mastectomy;
Breast conserving surgery;
Breast conserving surgery plus RT.

Exclusion criteria

Pooled data;
Data available only in abstracts or books.

Population

number of patients = 2600.

Interventions

Aim: to examine the rate of local recurrence in patients treated for DCIS, and to analyse predictive factors for local recurrence.

Treatment groups considered:
Mastectomy (data not cited);
Breast conserving surgery;
Breast conserving surgery plus RT.

Outcomes

Local recurrence;
Risk factors for local recurrence (data not cited).

Follow up

Not reported in all primary studies.

Average follow up by treatment group:
Breast conserving surgery alone: 68 months
Breast conserving surgery plus RT: 62 months

Results

Pooled rates of local recurrence by treatment group:

Breast conserving surgery alone:
22.5% [95% CI 16.9%-28.2%]; 17 studies, n=1148

Breast conserving surgery plus RT:

8.9% [95% CI 6.8%-11.0%]; 19 studies, n=1452

Proportion of recurrent tumours presenting as invasive tumours:

Breast conserving surgery alone: 93/217=43%

Breast conserving surgery plus RT: 63/126=50%

General comments

Studies were identified by a MEDLINE search and by reference lists in papers; no further details provided.

Statistical methods are reported, including assessment of study heterogeneity.

'Average' follow-up reported since authors refer to 'median or mean'.

Some of the included studies are dated; 6 were published prior to 1983.

No details are provided for the precise type of breast conserving surgery performed in each primary study, nor the dose of RT given. Studies were known to vary in terms of design, length of follow-up and selection of participants. For these reasons, study is graded as level 3 evidence.

Fonseca, Hartmann, Petersen, Donohue, Crotty & Gisvold . Ductal carcinoma in situ of the breast (DARE structured abstract). Ann Intern.Med 127, 1013-1022. 1997.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 3
Country: Multinational, setting: Secondary care

Inclusion criteria

Women with DCIS

Exclusion criteria

Personal communications and case reports.

Population

number of patients = 794.

Interventions

Aim: to review data on the natural history of DCIS and different treatment approaches.

Cited data are of patients with DCIS who were treated with breast conserving surgery alone or breast conserving surgery plus RT.

Outcomes

Local recurrence;
Survival (no data cited).

Follow up

Breast conserving surgery alone: mean 65 months.
Breast conserving surgery plus RT: mean 64 months

Results

Characteristics of included studies:

	BCS	BCS + RT
Number of studies	10	6
Number of patients	461	333
Mean follow-up (months)	65	64

Mean rate (range) of local (invasive + non-invasive) recurrence:

BCS: 23% (8%-63%)

BCS + RT: 9% (4%-21%)

Mean rate of local invasive recurrence:

BCS: 9%

BCS + RT: 6%

General comments

The review included RCTs and retrospective case series (observational) studies. Data were presented narratively.

Literature search described in brief: used the search terms 'carcinoma in situ', 'ductal carcinoma in situ', 'intra-ductal breast cancer' and 'DCIS'; MEDLINE database only; English language papers only; papers published since 1966. The authors do not state how the data were extracted for the review, and the number of studies included is unclear. However, the authors gave details of 11 studies for lumpectomy and 7 for lumpectomy plus RT. Personal communications and case reports were excluded. Authors include a statement that papers were reviewed critically - no further details.

No details provided of the included studies re: design, age of the women. No details provided of assessment of study validity.

Data cited here excludes that of the NSABP B-17 trial, which has been included for this question as a primary study.

Degree of primary study heterogeneity not known.

Appraisal of this review cites the DARE (University of York) structured abstract, available online at:

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=11997008523>

Last accessed: 12.04.07

Case control study

Claus, Petruzella, Carter & Kasl . Quality of life for women diagnosed with breast carcinoma in situ. J Clin Oncol 24[30], 4875-4881. 2006.

Design

Design: Case control study (therapy), evidence level: 2+
Country: USA, setting: Secondary care

Inclusion criteria

795 patients with breast cancer in situ (87% of whom had DCIS; 13% LCIS) and 702 healthy controls identified in Connecticut between 1994 and 1998.

Exclusion criteria

Of 2067 patients identified for an older study, 570 were excluded in this analysis due to:
Refusal to participate;
Deceased;
Too ill;
Lost to follow-up;
New pathology rendered ineligible (i.e. invasive breast cancer or previous history of in situ breast cancer).

Population

, mean age = 55 years.

Interventions

Aim: to assess the quality of life (QOL) in patients treated for breast cancer in situ (predominantly DCIS) compared to selected healthy controls.

Analysis groups were as follows:

CASES (n=795)

Lumpectomy only (n=282)

Lumpectomy + RT (n=397)

Mastectomy only (n=111)

(5 patients reported no treatment)

CONTROLS (n=702) were randomly selected based on telephone numbers and frequency-matched for age in 5 year intervals.

Outcomes

1. Health related QOL: 36 item Medical Outcomes Study Short Form (MOS SF-36); 8 scales for physical functioning, role function-physical, bodily pain, social functioning, mental health, role function-emotional, vitality and general health perceptions; scale range 0-100; 100 representing best QOL.

Two additional summary scales:

Physical component summary scale;

Mental component summary scale.

The Medical Outcomes Sexual Problems Measure List was also added

2. Centre for Epidemiologic Studies Depression scale (CES-D): 20 item scale used to measure depressive symptoms over the last week (maximum score 60, representing highest risk of depression; score >16 generally regarded as an indicator of depression).

3. Cut Down, Annoyed, Guilty, Eye-opener (CAGE) screening questionnaire (scored 0-4); used to evaluate alcohol consumption.

Outcomes evaluated by descriptive statistics, t, Chi square, Fisher's exact, and ANOVA.

Estimates of MOS SF-36 and CES-D were adjusted for age, race, education, menstrual status, comorbidity, marital status.

Follow up

Survey performed at a mean follow-up of 5 years from diagnosis.

Results

The majority (>85% of both cases and controls reported having good, very good or excellent health at 5 years after diagnosis.

Case participants and controls did not differ in reported levels of limitations due to physical health problems, bodily pain, social functioning, or overall physical functioning (MOS Physical component summary scale). This was true for all cases together and also each individual treatment group within the cases.

With regard to alcohol consumption there was no statistically significant difference in score between cases and controls (0.23 versus 0.28 respectively; $p=0.13$).

Statistically significantly lower MOS SF-36 scores were reported for case participants for the following dimensions: general mental health, role limitations due to emotional problems, vitality and general health perceptions, as well as for the MOS mental component summary scale. CES-D score for cases was statistically significantly higher (indicating higher levels of depressive symptoms) than for controls. These differences were mainly due to poorer scores in the subset of cases who underwent lumpectomy plus RT, relative to controls. In the case of the SF-36 item: role limitations due to emotional problems; the the difference between cases and controls was due to lower scores in the lumpectomy group.

Case participants who underwent lumpectomy with radiation reported lower levels of emotional functioning, general health perceptions, vitality, sexual interest, and overall mental health, as well as more depressive symptoms than did control subjects; although, the clinical significance of these statistical differences appears to be limited.

Authors conclude that at 5 years after diagnosis, cases reported levels of physical, emotional, and mental health functioning similar with those reported in a general healthy female population.

General comments

This study represents a smaller, subsequent study arising from an original study which evaluated family history and exogenous/endogenous hormone factors and breast cancer in situ risk.

Applicability of results is likely to be affected due to possible differences in psychological/QOL traits between the Italian and British populations.

Prospective comparative study

Hayman, Kabeto, Schipper, Bennett, Vicini & Pierce . Assessing the benefit of radiation therapy after breast-conserving surgery for ductal carcinoma-in-situ. J Clin Oncol 23[22], 5171-5177. 2005.

Design

Design: Prospective comparative study (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

120 patients treated for DCIS who had undergone lumpectomy plus RT and who were free of disease, with an interval of >1 month between RT and assessment.

210 non patients, identified from an appointment list for routine health maintenance visits.

Exclusion criteria

Patients whose radiation oncologists requested no contact be made;
Patients who refused participation.

Population

-

Interventions

Aim: to measure the utilities of patients and nonpatients for relevant health states following treatment for DCIS with lumpectomy, compared to lumpectomy plus RT.

Participants were given an in-depth overview of issues attending DCIS, its treatment and necessary actions in different scenarios of recurrence e.g. the need for axillary surgery in cases of invasive recurrence.

Participants were then asked to rank 8 scenarios in order of most desirable to least desirable (see outcomes).

Outcomes

Differences within groups and between groups in the ranking of 8 scenarios according to desirability:

- A: BCS + RT without recurrence
- B: BCS + RT then noninvasive recurrence, salvaged by mastectomy
- C: BCS + RT then invasive recurrence salvaged by mastectomy
- D: BCS alone without recurrence
- E: BCS alone then noninvasive recurrence salvaged with BCS + RT
- F: BCS alone then noninvasive recurrence salvaged with mastectomy
- G: BCS alone then invasive recurrence salvaged with BCS + RT

H: BCS alone then then invasive recurrence salvaged by mastectomy

In addition, logistic regression was performed to examine whether participants' utilities for scenarios or differences in utility between any two scenarios were affected by any of the following variables:

Age, race, marital status, number of dependents, education, and income for all participants; months since completion of RT, toxicity, treatment with tamoxifen, satisfaction with local outcome, fear of recurrence, and satisfaction with treatment decision for patient participants; and 5-year and lifetime risks of breast cancer for nonpatient participants.

Follow up

Mean 39 months (range 3-175 months)

Results

1. Within-group comparisons

The results of pairwise comparisons between health states within the patient and nonpatient groups were surprisingly similar. For the health states after treatment with RT, both groups had the strongest preference for being without recurrence, followed first by a DCIS recurrence and then by an invasive recurrence (ie, $A > B > C$).

For the health states after treatment with lumpectomy alone, patient and nonpatient participants alike were indifferent to a DCIS recurrence but not to an invasive recurrence (ie, $D=E=F>G$ and H). Both groups had similar utilities for the nonrecurrent health states, whether they had or had not received initial treatment with RT (ie, $A=D$). Patients and nonpatients also had similar utilities for a DCIS recurrence requiring mastectomy whether or not they had received upfront RT (ie, $B= F$).

In contrast, patients and nonpatients not only had different utilities for an invasive recurrence requiring mastectomy after initial treatment with RT compared with no RT (ie, C vs. H), but the direction of the difference was also reversed. Patient participants preferred having received RT (ie, $C>H$), whereas nonpatient participants preferred not to have had received RT (ie, $C < H$).

The only other relevant difference between the two groups was that patient participants preferred to preserve their breast after an invasive recurrence after initial treatment with BCS alone (ie, $G > H$), whereas nonpatient participants were indifferent (ie, $G = H$). Neither group expressed a preference for breast preservation when confronted with a DCIS recurrence after initial treatment with BCS alone (ie, $E = F$).

2. Between-group comparisons

Overall, there were few differences that were statistically significant when comparing patient and nonpatient participants' utilities directly. Patients had higher utilities than nonpatients for being without recurrence after BCS and RT (A) and lower utilities for having an invasive recurrence salvaged by mastectomy after BCS alone (H).

Differences in utilities for being without recurrence after BCS alone (D) and for having had an invasive recurrence salvaged by mastectomy after BCS and RT (C) were

reportedly of borderline significance ($P = .09$ and $P = .06$, respectively).

3. Factors associated with participants' utilities

Although several of the clinical and sociodemographic factors examined were statistically associated with patient and nonpatient participants' utilities, none of the factors explained more than 5% of the variability in the utilities themselves or in the differences between health states.

Authors conclude that women, after breast conserving therapy for DCIS, fear mostly invasive recurrence, over recurrence, noninvasive recurrence and mastectomy.

General comments

The absolute reduction in risk of recurrence arising from RT following treatment with BCS presented to participants was 5% for noninvasive recurrence and 9% for invasive recurrence based on the NSABP B-17 RCT.

Results are reported using utilities, which are described as: "global measures of quality of life that represent the strength of one's preference for a particular state of health and are measured on a scale ranging from 0 to 1, where 0 is equivalent to death and 1 is equivalent to optimal health".

The reported differences in relative preference of different scenarios (e.g. $A > B$) reflect statistically significant differences in mean utility scores.

At baseline assessment, nonpatients, compared with patient participants, were younger (mean age, 50 v 61 years, respectively; $p < .001$), more likely not to be white (16% v 7%, respectively; $p < .03$), less likely to have dependents at home (mean, 0.65 v 1.1 dependent, respectively; $p < .001$), and better educated (71% v 50% college graduates, respectively; $p < .001$).

Re: the finding: *Patient participants preferred having received RT (ie, $C > H$), whereas nonpatient participants preferred not to have had received RT (ie, $C < H$); this may be affected by a bias since the patients in this study all underwent breast conserving surgery plus RT and were hence possibly more likely to view it favourably.*

Overall the study may be confounded since the patients were treated; whereas non-patients had to rely on imagination.

Retrospective case series

Baxter, Virnig, Durham & Tuttle . Radiation after lumpectomy for DCIS to reduce the risk of invasive breast cancer: A population-based study. J Clin Oncol (Meeting Abstracts) 23[16_suppl], 516. 2005.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

9960 women with DCIS of age 18-75 years treated with lumpectomy plus RT in the period 1987-1996, with details held on the SEER database.

Exclusion criteria

Patients with no information regarding treatment with RT.

Patients developing ipsilateral invasive recurrence within 3 months of treatment; as misdiagnosis assumed.

Patients followed for < 3 months (74).

Population

number of patients = 9960, median age = 56 years.

Interventions

Aim: to derive a population-based estimate of the effectiveness of RT after lumpectomy for DCIS using the SEER database.

Two patient groups were defined for analysis:
Lumpectomy alone treatment group (n=5008);
Lumpectomy + RT treatment group (n=4952).

Outcomes

Occurrence of:
Any invasive breast cancer;
Ipsilateral breast cancer;
Contralateral breast cancer;
Death.

The risk of subsequent breast cancer was modelled using a proportional hazards model to evaluate the effect of RT over time and adjusting for potential confounders (age, race, comedo status and geographic location). Tumour grade and size were poorly characterised and were not included in the model.

Follow up

Mean: 8 years

Results

Invasive breast cancer developed in 809 patients (8.1%); 428 (4.3%) cases of invasive breast cancer were in the ipsilateral breast and 379 (3.8%) in the contralateral breast (laterality was unknown in 2 cancers; 45 cases were excluded due to occurrence within 3 months of diagnosis).

All incident invasive disease

Over the follow-up period the actuarial rate of invasive (ipsilateral plus contralateral) breast cancer was statistically significantly higher in the lumpectomy alone group compared to the lumpectomy plus RT group ($p < 0.0001$; see below for cumulative rates at 8 years).

Invasive ipsilateral disease

Over the follow-up period the actuarial rate of invasive ipsilateral breast cancer was statistically significantly higher in the lumpectomy alone group compared to the lumpectomy plus RT group ($p < 0.0001$; see below for cumulative rates at 8 years).

Contralateral invasive disease

Over the follow-up period there was no statistically significant difference between the two groups in terms of contralateral invasive breast cancer-free survival ($p = 0.8$; see below for cumulative rates at 8 years).

Cumulative rates of invasive breast events at 8 years from diagnosis:

	Overall	Ipsilateral	Contralateral
Lumpectomy alone:	9.7%	6.0%	3.8%
Lumpectomy plus RT	6.3%	2.7%	3.7%

Proportional hazards model:

Lumpectomy alone was strongly associated with development of ipsilateral breast cancer over time after adjusting for potential confounders: HR (Lumpectomy + RT:Lumpectomy alone) 0.43 [95% CI 0.35-0.53]; $p < 0.0001$.

RT after lumpectomy was not associated with development of contralateral invasive cancer: HR (Lumpectomy + RT:Lumpectomy alone) 1.01 [95% CI not reported]; $p = 0.91$.

African American race was associated with development of ipsilateral breast cancer over time after adjusting for potential confounders:

	African American	Others
Cumulative risk:	7.9%	4.1%

HR (African American:other races) 1.7 [95% CI not reported]; $p = 0.0004$.

However African American race was not associated with development of contralateral breast

cancer over time:

	African American	Others
Cumulative risk:	3.8 %	3.8%

HR (African American:other races) 1.13 [95% CI not reported]; p=0.51.

General comments

Women in the lumpectomy plus RT group were, on average 2 years younger than those in the lumpectomy group.

Study potentially has high applicability to patients treated outside of RCTs; the authors comment that the rate of ipsilateral invasive breast cancer is lower than in published trials; possibly due to limitations of SEER data e.g. errors in transcribing codes or migration of patients from SEER registry areas.

Study does not report any data for non-invasive breast events subsequent to treatment e.g. DCIS.

Study does not analyse survival by the two treatment-defined patient groups.

Tumour grade and size are omitted from the proportional hazards model due to poor data quality; a possible drawback.

The age variable was associated with development of ipsilateral breast cancer over time after adjusting for potential confounders: HR (for an increment of one 5-year age group) 0.93 [95% CI not reported]; p=0.003 but not with development of contralateral breast cancer over time: HR (for an increment of one 5-year age group) 1.06 [95% CI not reported]; p=0.02. NB from these data it is not possible to determine the direction of effect i.e. older age or younger age.

Data extracted from ASCO meeting abstract and presentation audio/slides; available online at:

http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=34&index=y&abstractID=30402; last accessed: 4.04.07

Mills, Schultz & Solin . Preservation of cosmesis with low complication risk after conservative surgery and radiotherapy for ductal carcinoma in situ of the breast. Int J Radiat.Oncol Biol.Phys. 39[3], 637-641. 1997.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: USA, setting: Secondary care

Inclusion criteria

90 women treated with breast conserving surgery plus RT for DCIS between 1978 and 1991 at a single centre, who were free of disease with a minimum follow-up extent of 3 years.

28 cases (31%) were detected by palpation and 62 (69%) by routine mammography

Exclusion criteria

No cosmetic evaluation (12 patients)
Local recurrence before 3 years (4 patients)
Adjuvant tamoxifen (1 patient)
Second unrelated malignancy (1 patient)
Dead of intercurrent disease (1 patient)

Population

-

Interventions

Aim: to report on cosmetic results in patients treated with breast conserving surgery plus RT for DCIS.

All patients underwent complete gross excision. 44 patients (49%) underwent re-excision and 24 patients (27%) underwent axillary dissection.

All patients in addition received RT as follows:

50-50.4 Gy in 1.8-2.0 fractions over 5-5.5 weeks (84 patients);

46 Gy (4 patients)

48 Gy (1 patient)

42 Gy (1 patient)

Most patients received a boost to the lumpectomy site: 10-16 Gy (71 patients) or by Iridium implant (2 patients).

Outcomes

1. Physician-assessed cosmetic result at 1, 3 and 5 years follow-up, based on:

- a) Size oedema, retraction, elevation
- b) induration, fibrosis
- c) telangiectasias and pigmentary changes to the skin

- d) volume loss secondary to surgery
- e) symmetry with the untreated breast.

Result was classed as excellent, good, fair or poor accordingly.

2. Complications, including: arm oedema (mild or moderate based on circumference), cellulitis, axillary vein thrombosis, rib fracture, symptomatic pneumonia.

Follow up

Median 6 years (range 3-14 years).

Results

1. Physician-assessed cosmetic result

Proportion of patients with cosmetic result: good/excellent (where n = number evaluable):

- 1 year: 99% (n=90)
- 3 years: 98% (n=90)
- 5 years: 97% (n=64)

At 5 years follow-up the cosmetic result of 64 evaluable patients was as follows:

- Excellent: 46 (72%)
- Good: 16 (25%)
- Fair: 2 (3%)
- Poor: 0

There was a trend of reduction in the proportion of patients with excellent cosmetic result over time.

Percentage of cases with excellent cosmetic result by volume of excision:

	1 year	3 years	5 years
>70 cm ³ :	72	65	43
<=70cm ³ :	96	81	76
p value	0.014	0.076	0.036

2. Complications

14 complications were observed in 9 patients, and which were statistically significantly associated with axillary dissection (p<0.0001).

Only two patients developed complications who did not receive axillary surgery; 1 case of breast cellulitis and 1 case of arm cellulitis.

General comments

The exclusion criteria apply to subgroups in whom the outcome is relevant e.g. those treated by tamoxifen, or who experienced recurrence.

The volume of tissue excised was available for 57 patients (63%)

Although 27% of the series underwent axillary dissection (no longer favoured at the institution for DCIS), there was no statistically significant difference in cosmetic outcome by subgroup for axillary surgery at 3 or 5 years follow-up.

Study size is small, and probably does not permit a fuller analysis of outcomes, due to low power.

Omlin, Amichetti, Azria, Cole, Fournieret, Poortmans, Naehrig, Miller, Krengli, Gutierrez, Morgan, Goldberg, Scandolaro, Gastelblum, Ozsahin, Dohr, Christie, Oppitz, Abacioglu & Gruber . Boost radiotherapy in young women with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network.[see comment]. Lancet Oncology 7[8], 652-656. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: Multinational, setting: Secondary care

Inclusion criteria

373 patients treated during the period 1978-2004 in 18 institutions in Australia, Belgium, France, UK, Israel, Italy, Netherlands, Spain, Switzerland, Turkey and USA. All patients met the following criteria:

Pure DCIS (stage Tis, N0);
Age \leq 45 years at diagnosis;
Primary treatment with local excision

Exclusion criteria

See inclusion criteria.

Population

number of patients = 373, age range 23 to 45 years, median age = 41 years.

Interventions

Aim: to examine the effectiveness of boost RT in younger patients treated with local excision for DCIS. Three groups were retrospectively defined for analysis:

1. No RT group (n=57): underwent wide local excision alone;
2. RT group (n= 166): underwent wide local excision plus whole breast RT with median dose 50 Gy (range 40-60 Gy);
3. RT + boost group (n=150): underwent wide local excision plus whole breast RT plus a boost. The boost was of 10 Gy for 98 patients, $<$ 10 Gy for 11 patients and $>$ 10 Gy for 41 patients; delivered as either orthovoltage photons (41 patients), electrons (101 patients) or implants (9 patients).

Overall 26 patients (7%) received tamoxifen in addition:

No RT: $2/57 = 3.5\%$
RT: $17/166 = 10\%$
RT + Boost: $7/150 = 5\%$

Outcomes

Local recurrence (invasive or in situ breast cancer in the ipsilateral breast);

Contralateral recurrence (invasive or in situ breast cancer in the contralateral breast);

Regional recurrence (invasive breast cancer in the node bearing tissues);

Distant recurrence (invasive breast cancer in any body site excluding those listed above).

A proportional hazards model was used to examine the effect of RT (with and without boost) with adjustment for age; method of detection; tumour size; necrosis; tumour grade; margin status and ER status.

Follow up

Median 72 months (range 1-281 months).

Results

At a median follow-up of 72 months 55 (15%) patients had local recurrence; 8 (2%) had regional recurrence, 23 (6%) had contralateral recurrence and 9 (2%) had distant recurrence.

Overall survival

There was no statistically significant difference in 10-year overall survival between the three groups (p=0.96, log-rank test); 10-year overall survival was 97% overall [95% CI 95%-100%].

Local recurrence-free survival

Over the entire follow-up period, local recurrence-free survival was statistically significantly different between the three analysis groups (p<0.0001, log-rank test); e.g. 10-year local recurrence-free survival:

No RT group: 46% [95% CI 24%-67%]

RT group: 72% [95% CI 61%-83%]

RT + Boost group: 86% [95% CI 78%-93%]

Proportional hazards model

The following variables were statistically significantly associated with risk of local relapse: RT treatment group, age and margin status.

Hazard ratio for local relapse-free survival:

1. RT treatment group:

No RT group: 1.00

RT group: 0.33 [95% CI 0.16-0.71]

RT + Boost group: 0.15 [95% CI 0.06-0.36]; p<0.0001

2. Age:

<= 39 years: 1.00

40-45 years: 0.46 [95% CI 0.25-0.83]; p=0.010

3. Margin status:

Clear: 1.00

Positive: 3.53 [95% CI 1.48-8.43]

Unknown: 1.23 [95% CI 0.54-2.34]; p=0.02

The following variables were not statistically significantly associated with risk of local relapse:

method of detection, tumour size, necrosis, tumour grade and ER status.

General comments

Paper recommended for selection by GDG.

There is a wide definition of RT boost in this study (see 'interventions').

Compared to the RCTs and larger analyses identified for this question, this is a small, retrospective study undertaken in a younger group of patients with DCIS.

Smith, Haffty, Buchholz, Smith, Galusha, Bekelman & Gross . Effectiveness of radiation therapy in older women with ductal carcinoma in situ. J Natl Cancer Inst 98[18], 1302-1310. 2006.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: US, setting: Secondary care

Inclusion criteria

3409 patients with DCIS of age 66 years or more with details held on the US Surveillance, Epidemiology and End Results (SEER) database; treated with breast conserving surgery between January 1992 and December 1999.

Exclusion criteria

Non ductal histology (558);
Biopsy or mastectomy as primary treatment (3183);
History of prior malignancy (160);
Second primary within 9 months (147);
Inadequate Medicare records (1877);
Unknown laterality at diagnosis (8);
Patients who developed a contralateral breast cancer (159); leaving 3409 patients for analysis.

Population

number of patients = 3409, median age = 74 years.

Interventions

Aim: to examine whether RT performed in older patients (of age 66 years or more) after breast conserving surgery (BCS) is associated with a reduction in the risk of a second breast cancer event.

Two treatment groups were defined retrospectively:

BCS + RT (n=1676);

BCS alone (n=1733).

In addition patients were classified into subgroups according to pre-specified criteria assumed to predict risk of breast events:

High risk group (n=1570): defined by any of age 66-69 years, tumour size >2.5cm, comedo histology, high grade.

Low risk group (n=539): defined by the absence of all of these criteria.

Unclassified (n=1300); due to missing data.

Outcomes

Second breast cancer event, defined as either:

1. Subsequent ipsilateral in-situ or invasive breast tumour reported by SEER, and/or;
2. Subsequent mastectomy reported by Medicare claims data.

Analysis was by the Kaplan-Meier method and the relationship between RT and risk of subsequent event was examined using a Cox proportional hazards model, adjusting for the following co-variates:

Age, race, urban-rural status, median income, marital status, comorbidity, tumour size, histology and grade.

NB age and comorbidity were included due to clinical relevance; all other variables were chosen due to their statistical significance in univariate analysis.

Follow up

Median 5 years

Results

Unadjusted risk of breast events:

5-year risk of second breast cancer event:

BCS alone: 10.7%

BCS + RT: 3.6%

Difference: 7.1% [95% CI 5.2%-9.0%], $p < 0.001$

Adjusted effect of RT:

RT was associated with a reduced risk of the following breast cancer events:

Event	HR	95% CI	p value
Ipsilateral, in-situ	0.23	0.12-0.45	<0.001
Ipsilateral, invasive	0.27	0.16-0.45	<0.001
Mastectomy	0.42	0.29-0.60	<0.001
Any event	0.32	0.24-0.44	<0.001

Effect of other factors on any breast cancer event (statistically significant results):

Factor	HR	95% CI	p value
Advanced age	0.97	0.95-1.00	<0.05
Large tumour size	1.14	1.02-1.26	<0.05
Comedo histology	1.40	1.00-1.97	<0.05

High grade	2.38	1.24-4.56	<0.05

There was no significant interaction between RT and these factors i.e. the benefit of RT was similar for patients at low risk for an event to that for those at high risk for an event.

Effect of RT in reducing risk of any breast event, by risk group (ARR = absolute risk reduction, expressed in number of events per 100 persons):

Group	ARR	95% CI	p value (log-rank test)
Low risk	7.3 3	6-11	<0.001
High risk	9.8 6	5-13.2	<0.001
Unclassified	5	1 2.2-8.1	<0.001

General comments

'Mastectomy' as a surrogate outcome for breast cancer recurrence does not appear to have laterality defined, but since patients with subsequent contralateral breast cancers were excluded, it is reasonable to accept mastectomy as an ipsilateral procedure.

Margin status was not reported; neither was use of tamoxifen.

Receipt of RT correlated with the following baseline characteristics: younger age, absence of comorbidity, comedo histology and high grade.

Rakovitch, E., Pignol, J., Hanna, W., Narod, S., Spayne, J., Nofech-Mozes, S., Chariter, C., Paszat, L. (2007) Significance of Multifocality in Ductal Carcinoma In Situ: Outcomes of Women treated with Breast Conserving Therapy *Journal of Clinical Oncology* 25;35:5591-5596

Design: Retrospective case series **Evidence Level:** 3

Country: Canada

Aim: To evaluate the risk of local recurrence risk among women with multifocal DCIS who were treated with breast conserving surgery and to determine whether multifocality is an independent risk factor for local recurrence.

Inclusion criteria: All patients with DCIS diagnosis who were referred to a single regional centre between 1982 and 2000.

Exclusion criteria: Cases treated with mastectomy

Population N=615

Interventions: 310 treated with breast conserving surgery only
305 treated with breast conserving surgery and radiotherapy

Outcomes: Local Recurrence

Results:

Among women treated with breast conserving surgery only, 21% developed local recurrence as compared with 9% of women treated with breast conserving surgery and radiotherapy.

The 5 year actuarial local recurrence free survival rates were 85% for women treated with breast conserving surgery alone and 93% for those treated with BCS plus radiotherapy.

		5 year actuarial	10 year actuarial
Local recurrence free survival rates	BCS Alone	85%	72%
	BCS + RT	93%	82%
Invasive local recurrence free survival rates	BCS Alone	95%	85%
	BCS + RT	99%	92%

Median time to local recurrence was 4.2 years (Range; 0.3-16.7 years) following BCS Alone and 3.0 years (Range; 0.6-8.7) following BCS + RT.

On univariate analysis, administration of radiation (HR: 0.48 (95% CI; 0.30-0.75), P=0.002), presence of comedonecrosis (HR: 1.7 (95% CI; 1.02-2.85), P=0.04) and resection margins of 4mm or smaller (HR: 1.89 (1.20-2.98), P=0.006), were significantly associated with the development of local recurrence. Administration of radiation and positive or close resection margins (≤4mm) were associated with the development of an invasive recurrence.

On multivariate analysis multifocality (HR: 1.8 (95% CI; 1.2-2.8), P=0.01), radiotherapy (HR

0.46 (95% CI; 0.29-0.74), P=0.001), margin width 4mm or smaller (HR: 1.7 (95% CI; 1.0-2.9), P=0.04) and high nuclear grade (HR: 1.6 (95% CI; 1.0-2.7), P=0.04) were predictors of local recurrence.

For women treated with breast conserving surgery alone, the 5 year actuarial local recurrence free survival rates were 82% for women with multifocal disease and 87% for those with unifocal disease. At ten years the recurrence-free survival rate was significantly lower; 59% for women with multifocal disease compared to 80% for women with unifocal disease (p=0.02). There was no significant impact of multifocality among women that received radiation therapy.

General comments

There is currently no agreement on the precise definition of multifocality and in most RCT's and cohort studies of DCIS it is not routinely evaluated.

Authors Comment: The results of the study indicate that multifocality an independent risk factor for the development of local recurrence following breast conserving surgery for DCIS. However BCS is still an option for women with multifocal DCIS with low recurrence rates achieved through complete excision with negative resection margins followed by adjuvant radiotherapy.

Schouten van der Velden, A., van Vught, Roel, van Dijck, J., Leer, J., Wobbes, T. (2007) Local Recurrences After Different Treatment Strategies for Ductal Carcinoma In Situ of the Breast: A Population Based Study in the East Netherlands. *Int. J. Radiation Oncology Biol. Phys.* 69;3:703-710

Design: Retrospective Case Series **Evidence Level:** 3

Country: Netherlands

Aim: To assess the risk of local recurrences following different treatment strategies for DCIS and to determine whether RT decreased the risk of local recurrences.

Inclusion criteria: All patients recorded in the Cancer Registry with breast tumours classified as *in situ* between January 1989 and December 2003.

Exclusion criteria: Patients with a history of or a simultaneous invasive breast cancer and other malignancies (apart from nonmelanoma skin cancer and *in situ* cervical carcinoma).

Population: 888 of which 90 had inaccessible medical records thus leaving a study population of 798 patients.

Interventions:

237 patients treated with BCS only

153 patients treated with BCS followed by RT

408 patients treated with mastectomy

9 patients treated with either adjuvant chemotherapy or hormonal therapy

Outcomes: Local recurrence, defined as non-invasive and invasive carcinoma anywhere within the treated breast.

Results:

19 patients died of non-breast cancer related causes and 113 patients developed a breast cancer related failure in either the treated or contra-lateral breast during the follow-up period. 83 patients developed recurrent disease (39 invasive carcinomas) within the treated breast, which were considered as true recurrences.

The median time from surgery to recurrent disease was 38 months and the 5-year local recurrence survival was 90% for all patients.

The 5 year recurrence free survival by treatment type was as follows (p<0.01):

	5-Year Recurrence Free Survival
BCS	75% (61 recurrences in 237 patients)
BCS + RT	91% (11 recurrences in 153 patients)
Mastectomy	98.7% (11 recurrences in 408 patients)

Patients with close or involved margins had a lower recurrence free survival rate than patients with surgical margins free of tumour (p<0.01).

On multivariate analysis, presence of comedo necrosis and treatment strategy were significant predictors of recurrent disease (p<0.01).

Margin status was a non-significant predictor for recurrent disease, though excluding patients treated with mastectomy resulted in significance at multivariate analysis (HR, 2.0; 95% CI; 1.1-4.0).

General comments

Treatment by mastectomy is a viable option for DCIS resulting in excellent cure rates and should be considered in line with patient preferences and/or tumor characteristics.

The low numbers of patients receiving BCS + RT can be explained by the fact that this treatment procedure for DCIS was only recommended in the regional guideline after 1999 and the number of patients receiving BCS + RT has increased significantly since then (7% pre 1999 and 62% post 1999).

Authors Comment: Our data support the beneficial effect of radiotherapy in the prevention of local recurrences.

Prospective cross sectional study

Amichetti, Caffo, Arcicasa, Roncadin, Lora, Rigon, Zini, Armaroli, Coghetto, Zorat, Neri & Teodorani . Quality of life in patients with ductal carcinoma in situ of the breast treated with conservative surgery and postoperative irradiation. Breast Cancer Research & Treatment 54[2], 109-115. 1999.

Design

Design: Prospective cross sectional study (harm), evidence level: 3
Country: Italy, setting: Community

Inclusion criteria

106 women treated in six Italian institutions of DCIS with breast conserving surgery plus RT between 1980 and 1990, all of whom were free of disease at the time of the survey.
75% were married;
19% lived alone;
70% were either retired or were 'homemakers'
11% were on prescribed psychotherapeutic medication for non-severe conditions.

Exclusion criteria

None reported.

Population

number of patients = 83, age range 32 to 94 years, median age = 54 years.

Interventions

Aim: to measure quality of life (QOL) in patients treated with breast conserving surgery plus RT for DCIS.

A questionnaire was administered, consisting of 34 items grouped into five fields of post-treatment adjustment:

Physical well being;
Sexual adaptation;
Aesthetic outcome;
Emotional/psychological well being;
Relational behaviour.

General items

In addition further questions explored the adequacy of information given at the time of treatment and the effects of treatment on social and overall life.

Outcomes

The relationship between items and the following possibly relevant variables: Age, marital status, employment, follow-up, degree of information, use of psychotherapeutic drugs; assessed by ANOVA or Wilcoxon tests.

Follow up

Median 54.5 months

Results

Physical well being

Patients reported that they were in good physical condition:

71% felt energetic;

76% felt physically well;

10% felt ill;

19% felt tired.

Poor physical condition correlated with the use of psychotherapeutic drugs and a low level of information given at the time of treatment.

Sexual adaption

93% of respondents completed these items, 73% of whom were sexually active. Limitations in sexual activity items were reported by between 6% and 8% of respondents. No external factor statistically significantly predicted sexual adjustment but patients with a poor perception of their body image or thought they were less attractive after treatment had a lower rate of sexual resumption.

Aesthetic outcome

16% perceived a worsened body image;

14% experienced discomfort at the surgical scar;

18% felt less attractive than before their treatment;

41% viewed the treated breast as similar to the untreated breast;

50% reported a good/excellent cosmetic outcome.

There was a close correlation between aesthetic outcomes and sexual outcomes.

Emotional/psychological well being

46% felt tense;

48% nervous;

29% lonely;

59% anxious;

41% depressed.

There was no correlation between responses and any assessed variables.

Relational behaviour

14% reported a lower frequency of meeting relatives;

16% reported a lower frequency of meeting friends.

There were no differences in subgroups stratified by the assessed variables.

General items

8% of patients declared that treatment had a bad effect on their social life;

18% reported that their current life was affected by treatment.

75% reported that the information provided at the time of treatment was sufficient.

Authors conclude that this study reveals a good QOL in patients treated for DCIS with breast conserving surgery plus RT, with a preserved favourable body image and little negative

impact on sexual activity.

General comments

Of 106 patients sent a questionnaire, 83 (78%) responded. There were no statistically significant difference in demographic characteristics between those who responded and those who did not.

The questionnaire was assessed for reliability and content/construct validity, with satisfactory results.

6.3 Which groups of patients should receive chest wall radiotherapy after mastectomy?

Short Summary

A large volume of high quality evidence was available examining both post-mastectomy and breast conserving surgery (BCS) with adjuvant radiotherapy. Several meta-analyses of RCTs were available including a recent analysis from the EBCTCG (Clarke *et al.* 2005; two additional meta-analyses were reviewed that included some of the same studies as the EBCTCG, as well as additional RCTs (Gebski *et al.* 2006; Killander *et al.* 2007, Kyndi *et al.* 2008; Whelan *et al.* 2000). Some analyses were conducted in specified subgroups of the Danish Breast Cancer Cooperative Group (Nielsen *et al.* 2006; Overgaard *et al.* 2007), and another used all trials from the EBCTCG (Van de Steene *et al.* 2000). Evidence from other studies included Bartelink *et al.* 2000; Bellon *et al.* 2006; Fisher *et al.* 2002; Gustavsson *et al.* 1999; Hojris *et al.* 2000; Hojris *et al.* 1999; Recht *et al.* 2001; Smith *et al.* 2006; Truong *et al.* 2004.

There was general consistency that radiotherapy reduced locoregional recurrence. The effects of radiotherapy on overall survival were of benefit for women of all ages with positive lymph nodes, but of less benefit for women with negative lymph nodes.

Loco-regional recurrence

Clarke *et al.* (2005) reported that radiotherapy after mastectomy with axillary clearance significantly reduced locoregional recurrence. The absolute reduction in local recurrence was greater in lymph node-positive than lymph node-negative disease (17% versus 4%). Whelan *et al.* (2000b) included some of the trials from the EBCTCG and found a large reduction in locoregional recurrence and for any recurrence after post-mastectomy radiotherapy. A 25 year follow-up of an RCT (Fisher *et al.* 2002) reported no significant differences between the three groups of women with negative lymph nodes or between the two groups of women with positive nodes for disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival. A subgroup analysis of the DBCG 82 b and c trials was performed to evaluate the loco-regional recurrence rate in relation to number of positive lymph nodes (1-3 or 4 or more) (Overgaard *et al.* 2007). The risk of loco-regional recurrence was most pronounced in patients with 4+ positive nodes. Another subgroup analysis of the DBCG 82 b and c trials by Nielsen *et al.* (2006) found the frequency of locoregional recurrence was 30% among patients randomised to no radiotherapy and 5% for patients randomised to radiotherapy.

Mortality

The EBCTCG (Clarke *et al.* 2005) reported that in trials of radiotherapy after mastectomy with axillary clearance there was a reduction in 15 year all cause mortality of 4.2% with radiotherapy for node negative disease and in node-positive disease, the reduction in 15-year all-cause mortality in the radiotherapy group was 4.4%. In a meta-analysis by Gebski *et al.* (2006) studies were categorised according to how the radiotherapy dose was delivered. Category 1 studies were defined as delivering optimal radiation therapy doses in the range of 40-60 Gy in 2-Gy fractions or as a biologically equivalent dose to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes. At a follow-up of 5 years category 1 studies gave a statistically significant 13% relative survival advantage associated with radiation therapy, compared with no radiation therapy. This equates to an absolute 2.9% increase in survival. At a follow-up of 10 years; category 1

studies gave a statistically significant 22% increase in relative survival associated with radiation therapy, compared with no radiation therapy. This corresponds to an absolute 6.4% increase in survival. In trials of high-risk patients (patients with lymph node positive disease) a separate analysis found that an absolute 5.2% increase in survival (52 per 1000) at 10-year follow-up was associated with adjuvant radiation therapy compared with no radiation therapy. In the analysis by Whelan *et al.* (2000) radiation was shown to significantly reduce mortality. The Danish Breast Cancer Cooperative Group (DBCCG) (2006) reported that with 18 years follow-up the probability of loco-regional recurrences (with or without distant metastases) or loco-regional recurrences alone was significantly lower in the post-mastectomy radiotherapy group than the no radiotherapy group. It also showed that overall fewer patients have distant metastases. Killander *et al.* (2007) reported that post-mastectomy radiotherapy significantly reduced loco-regional recurrences, but overall survival was not improved. At 20 years, a lower mortality was recorded for non-irradiated patients treated with tamoxifen. A survival benefit was found for node 1-3 and node 4+ patients in the analysis of high risk patients by Overgaard *et al.* (2007) from the DBCCG trials only. A further analysis comparing locoregional recurrence and survival in patients with 1-3 positive lymph nodes and 4+ positive lymph nodes showed that the values were almost identical irrespective of the number of positive lymph nodes. Another analysis of the same trials by Nielsen *et al.* (2006) assessed the independent prognostic factors for survival after locoregional recurrence from multivariate analysis. Significant factors reducing survival were a large tumour size (larger than 21mm), number of involved lymph nodes, extra-capsular invasion, and site of local recurrence. The meta-analysis of the EBCTCG reported no significant reduction in 15 year breast cancer mortality with radiotherapy. Kyndi *et al.* (2008) reported that there were significantly smaller improvements in locoregional recurrence control after post-mastectomy radiotherapy were found for ER-negative and PgR-negative tumours compared with the ER-positive and PgR-positive tumours and for the triple-negative, and the ER-negative and PgR-negative/human epidermal growth factor receptor 2 (HER2) positive subtypes compared with the ER-positive PgR-positive /HER2-negative subtype.

PICO

Patients	Interventions	Comparisons	Outcomes
Patients treated for invasive breast cancer with mastectomy (excluding patients with DCIS)	RT to the chest wall following mastectomy	Mastectomy alone	Disease-free survival Overall survival Rates of local recurrence Morbidity Lymphoedema

Evidence Summary

A large volume of high quality evidence was available which included both postmastectomy and BCS with adjuvant radiotherapy. Several meta-analyses of RCTs were available including a recent analysis from the EBCTCG (Clarke *et al.* 2005). Two additional meta-analyses were reviewed that included some of the same studies as the EBCTCG, as well as additional RCTs (Gebski *et al.* 2006, Whelan *et al.* 2000). Some analyses were conducted in specified subgroups of the Danish Breast Cancer Cooperative Group (Nielsen *et al.* *et al.* 2006, Overgaard *et al.* 2007), and another used all trials from the EBCTCG (Van de Steene *et al.* 2000). Data on morbidity was only available from the DBC Cooperative Group trials and the

South Sweden breast cancer trial. One retrospective cohort from the SEER database was assessed since data were available for elderly breast cancer patients (Smith *et al.* 2006). A number of guidelines were found and two recent ones were included originating in Canada and the USA.

Local Recurrence

Level 1++

A large systematic review of individual patient data conducted by the EBCTCG (Clarke *et al.* 2005) reported that RT after postmastectomy with axillary clearance significantly reduced locoregional recurrence. The absolute reduction in local recurrence was greater in node positive than node negative disease (17% vs.4%). The 5 year local recurrence risks of women with 1-3 positive nodes were again greater in the no RT than the RT group. Larger rates were seen in women with N4+ disease but the magnitude of absolute 5 year reduction was similar to those with 1-3 positive nodes. At 15 years the reductions in local recurrence between RT and no RT arms were similar in magnitude to 5 year rates however the rates of recurrence were larger. Local recurrence rates increased with increasing node involvement, however recurrence risk was lower in the RT arm of node positive participants.

The absolute effects of post-mastectomy radiotherapy on the risk of local recurrence were approximately independent of age (local recurrence reductions of 17%, 18%, and 18% for women aged <50, 50–59, and 60–69 years respectively; there were few older women in these trials). For women with node-positive disease in trials of RT after mastectomy and axillary clearance, RT produced similar proportional reductions in local recurrence risk, irrespective of age, tumour grade, tumour size, ER status, or amount of node involvement. Within each subgroup the absolute benefit produced by RT was determined largely by the magnitude of local recurrence risk in un-irradiated women.

A second systematic review of RCTs by Whelan *et al.* (2000) which included some of the trials from the EBCTCG found a large reduction in locoregional recurrence (OR 0.25) and for any recurrence after postmastectomy RT.

A 25 year follow-up of an RCT (Fisher *et al.* 2002) included in the EBCTCG analysis reported no significant differences between the three groups of women with negative nodes or between the two groups of women with positive nodes for disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival. The comparisons made were between women who had radical mastectomy, total mastectomy and total mastectomy + RT.

Level 1+

A subgroup analysis of the DBCG 82 b and c trials was performed to evaluate the loco-regional recurrence rate in relation to number of positive nodes (1-3 or 4 or more) (Overgaard *et al.* 2007). The risk of loco-regional recurrence was most pronounced in patients with 4+ positive nodes.

Another subgroup analysis of the DBCG 82 b and c trials by Nielsen *et al.* (2006) found the frequency of locoregional recurrence was 30% among patients randomized to no RT and 5% for patients randomized to RT. For patients in the no RT group a multivariate analysis found that independent risk factors for locoregional recurrence in node positive patients were:

Primary tumour size larger than 50mm (RR=1.64, 95%CI 1.16–2.29)

Malignancy grade III (RR=1.96, 95%CI 1.45–2.65)

Invasion of the fascia (RR=1.38, 95%CI 1.05–1.81)
Less than 8 removed nodes (RR=1.64, 95%CI 1.33–2.04)
4+ positive nodes (RR=1.96, 95% CI 1.56–2.45).

Overall mortality

1++

The EBCTCG (Clarke *et al.* 2005) reported that in trials of RT after postmastectomy with axillary clearance there was a 15 year loss of 4.2% with RT for node negative disease in all cause mortality. In node-positive disease, the reduction in 15-year all-cause mortality in the RT group was 4.4%. At 20 years, the reduction in breast cancer mortality remained unchanged at 5.4% (66.4% vs. 61.0%), while that for all cause mortality, although still significant, was 3.5% (72.3% vs. 68.8%), indicating a continuing excess of non-breast-cancer mortality long after treatment with the older radiotherapy regimens.

In a meta-analysis by Gebiski *et al.* (2006) studies were categorized according to how the RT dose was delivered. Category 1 studies were defined as delivering optimal radiation therapy doses in the range of 40 – 60 Gy in 2-Gy fractions or as a BED to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes. At a follow-up of 5 years category 1 studies gave a statistically significant 13% relative survival advantage associated with radiation therapy (OR of death from any cause = 0.87, 95% CI 0.79 to 0.96; $p = 0.006$), compared with no radiation therapy, this equates to an absolute 2.9% increase in survival. At a follow-up of 10 years category 1 studies gave a statistically significant 22% increase in relative survival associated with radiation therapy (OR = 0.78, 95% CI = 0.70 to 0.85; $p < 0.001$), compared with no radiation therapy. This corresponds to an absolute 6.4% increase in survival. In trials of high-risk patients (i.e., patients with lymph node positive disease) a separate analysis found that an absolute 5.2% increase in survival (52 per 1000) at 10-year follow-up was associated with adjuvant radiation therapy (OR = 0.80, 95% CI = 0.64 to 1.0) compared with no radiation therapy.

In the analysis by Whelan *et al.* (2000) radiation was shown to reduce mortality with an odds ratio of 0.83 (95% CI, 0.74 to 0.94; $p = 0.004$). On multivariate analysis the timing of radiation therapy was statistically significant ($p=0.03$), with treatment given before 6 months after surgery being more effective (OR 0.78 (95%CI 0.69-0.89). Radiation technique was also found to be statistically significant ($p=0.05$) favouring megavoltage rather than orthovoltage (OR 0.78 (95%CI 0.69-0.89).

1+

A survival benefit was found for node 1-3 and node 4+ patients in the analysis of high risk patients by Overgaard *et al.* (2007) from the DBC Cooperative Group trials only. A further analysis comparing LRR and survival in patients with 1-3 positive nodes and 4+ positive nodes found that the values were almost identical irrespective of number of positive nodes. For every ten patients irradiated approximately two LRR and one death could be avoided suggesting that overall postmastectomy radiotherapy is beneficial in high-risk patients and unrelated to the number of positive lymph nodes.

Another analysis of the same trials by Nielsen *et al.* (2006) assessed the independent prognostic factors for survival after LRR from multivariate analysis. Significant factors reducing survival were a large tumour size (larger than 21mm), number of involved nodes, extra-capsular invasion, and site of local recurrence.

Breast cancer mortality

1++

The meta-analysis of the EBCTCG reported no significant reduction in 15 year breast cancer mortality with RT. (3.6% increase in comparison with no RT, $p=0.01$) in women with node negative disease.

In node positive disease the 15-year breast cancer mortality with and without post-mastectomy radiotherapy was 54.7% versus 60.1%, an absolute reduction of 5.4% (SE 1.3, $2p=0.0002$).

Outcome	Study	RT	No RT	
Local recurrence Node negative Node positive	EBCTCG	5 yr risk reduction 2.3% 5.8%	5 yr risk reduction 6.3% 22.8%	Absolute 5 yr gain 4% 17%
Local Recurrence Node positive N 1-3 N 4+	EBCTCG	5 yr local recurrence risk 4% 12%	5 yr local recurrence risk 16% 26%	Absolute 5 yr reduction 12% 14%
Local Recurrence Node positive N 1-3 N 4+	EBCTCG	15 yr local recurrence risk 5.8% 15.4%	15 yr local recurrence risk 19.5% 35.2%	Absolute 15 yr reduction 14% 20%
Locoregional recurrence Any recurrence	Whelan 2000	OR 0.25 (95% CI, 0.19 to 0.34) $p=0<0.000001$ OR 0.69 (95% CI, 0.58 to 0.83) $p = 0.00004$		
Locoregional recurrence N 1-3 N 4+	Overgaard 2007	15 year actuarial value for LRR 4% 10%	15 year actuarial value for LRR 27% 51%	Relative risk 0.10 (95% CI 0.05–0.22) 0.17 (95% CI 0.10–0.28)
All cause mortality Node negative N1-3 N 4+	EBCTCG	15 year loss 4.2% 15 year gain 1.6% 15 year gain 1.7%		$P=0.0002$ NS NS
Overall survival Node positive	GebSKI 2006	At 5 years for RT group (death by any cause) [Category 1 trials] OR = 0.87, 95% CI 0.79 to 0.96 At 10 years OR = 0.78, 95% CI = 0.70 to 0.85 OR = 0.80, 95% CI = 0.64 to 1.0		Absolute increase of 2.9% 6.4%

				5.2%
Mortality	Whelan 2000	OR = 0.83 95% CI, 0.74 to 0.94		
Survival (overall)	Overgaard 2007	39%	29%	RR = 0.63 (95% CI 0.49–0.81) RR of 0.69 (95% CI 0.50–0.97) RR of 0.49 (95% CI 0.31–0.76)
15 yr actuarial Node 1-3		57%	48%	
Node 4+		21%	12%	
Overall survival at 25 years Node negative	Fisher 2002	Hazard Ratios: RM vs. TM+RT: 1.08 (95% CI 0.91 to 1.28, $p=0.38$) TM vs. RM: 1.03 (95% CI 0.87 to 1.23, $p=0.72$) TM+RT vs. TM 0.96 (95% CI 0.81 to 1.13, $p=0.60$)		
Overall survival at 25 years Node positive	Fisher 2002	Hazard Ratio RM vs. TM+RT: 1.06 (95% CI 0.89 to 1.27, $p=0.49$)		
Breast cancer mortality (15 yr) Node negative Node positive	EBCTCG			Absolute difference +3.6% with RT (NS) -5.4% with RT (2 $p=0.0002$)

Another analysis of EBCTCG trials by Van de Steene (2000) found that on univariate analysis begin year of trial, number of patients in the trial, fraction dose, and crude survival in the trial to be statistically significant for overall survival.

The univariate analysis reported a significant survival benefit in the radiotherapy arm for:

- Recent trials (2P < 0.05), the more recent the trial the larger the survival benefit (21.1% gain for trials started after 1980);
- Large trials produce a larger survival benefit (2P < 0.03);
- Trials that used standard fractionation of 1.8-2.5 Gy/fraction (2P < 0.02);
- Trials with a favourable crude survival (2P < 0.03).

Surgical adjuvant radiotherapy significantly improves overall survival of breast cancer patients provided that current techniques are used and treatment is given with standard fractionation.

Postmastectomy radiation and survival in older women with breast cancer

2+

The analysis of data from women aged > 70 years from the SEER database (Smith *et al.* 2006) found that adjuvant PMRT was associated with a survival benefit for high risk (T3/4 and/or N2/3) breast cancer (Hazard Ratio, 0.85; 95% CI, 0.75 to 0.97; P = 0.02). Five-year adjusted survival was 50% for patients not treated with PMRT or chemotherapy, 56% for

patients treated with PMRT only, 57% for patients treated with chemotherapy only, and 59% for patients treated with both PMRT and chemotherapy. PMRT was not associated with survival in the elderly for low- and intermediate-risk patients.

Morbidity

Three RCTs examined the effects of RT on non-cancer morbidity. Two RCTs used data from the DBC Cooperative Group (Hojris *et al.* 1999, 2000), the other used data from the Swedish trials (Gustavssen 1999).

Lymphedema (1++)

Lymphedema was measured in 14% of the irradiated patients versus 3% of the non-irradiated patients (NS). Slightly decreased shoulder morbidity was measured in 52% of the irradiated women versus 15% of the non-irradiated patients, but moderate or more severe impairment was seen in only 5% of irradiated patients and in none of the non-irradiated patients ($p = 0.004$). Seventeen percent of irradiated patients and 2% of non-irradiated patients found that impairment of shoulder movement caused symptoms ($p = 0.001$) (Hojris *et al.* 2000).

Ischaemic Heart Disease (1++)

More women in the no-radiotherapy group than in the radiotherapy group died of breast cancer (799 [52.5%] vs 674 [44.2%]). Similar proportions of each group died from ischaemic heart disease (13 [0.9%] vs 12 [0.8%]). The relative hazard of morbidity from ischaemic heart disease for patients in the radiotherapy compared with the no-radiotherapy group was 0.86 (95% CI 0.6-1.3), and that for death from ischaemic heart disease was 0.84 (0.4-1.8). The hazard rate of morbidity from ischaemic heart disease in the radiotherapy group compared with the no-radiotherapy group did not increase with time from treatment. Postmastectomy radiotherapy with this regimen did not increase the actuarial risk of ischaemic heart disease after 12 years (Hojris *et al.* 1999).

Late Cardiac Effects (1++)

No cardiac deaths were found among the original 275 patients randomized to adjuvant radiotherapy. In the 90 patients examined, abnormal findings were recorded for ECG (14 patients), exercise test (5 patients), myocardial scintigraphy (6 patients), thickening of valve cusps (14 patients), and mild valvular regurgitation (20 patients). All patients had normal systolic function. Diastolic dysfunction was observed in 6 patients (abnormal relaxation in 4 patients and restrictive filling abnormality in 2 patients). Although no significant differences were found between the 3 study groups, there was a tendency to more abnormal findings after radiotherapy.

Guidelines

There was a general consensus for RT in women with large tumours and more than 4 positive nodes. The role of RT for women with 1-3 positive nodes was less clear. However the guidelines predate the recent EBCTGC and DBC analyses.

UPDATE EVIDENCE:

Danish Breast Cancer Cooperative Group Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J (2006). Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol May 20;24(15):2268-75.

Aim: The aim of this follow up analysis was to evaluate the overall failure pattern among high-risk breast cancer patients who were randomly assigned to RT or no RT in addition to systemic therapy (as part of the Danish Breast Cancer Cooperative Group (DBCG) 82 b and c trials).

Results

LRR:

- The probability of any first BC event (LRR, simLRR-DM, DM, or CBC) was significantly reduced among patients in the RT group: RR=0.68 95% CI 0.63-0.75, P< 0.001).
- The median time to any first BC event was 3.9 after no RT and 7.9 years after RT, (P<0.001).
- The 18-year probability of LRR (with or without DM) or LRR alone was significantly lower in the RT group than the no RT group.
- The frequency of all sites of LRR was lower with RT than without RT.
- Overall, 22% of the patients with LRR in the no-RT group appeared with simultaneous DM, whereas 48% of the patients with LRR in the RT group also had DM at the time of diagnosis of LRR.

DM:

- The 18-year probability of DM subsequent to LRR = 35% after no RT and 6% after RT (P<0.001). The 18-year probability of any DM = 64% after no RT and 53% after RT (P<0.001)
- The median time to DM = 6.5 years in the no-RT group and 12.3 years in the RT group (P=0.04).
- In the no-RT group: DM after LRR and DM as first site of failure were equally common
- In the RT group, DM occurred most often as the first site of failure.
- To assess if the risk of DM was time dependent in the two groups, the hazard rates for 2-year time interval were calculated:
- The DM hazard rates were at all times increased among patients in the no-RT group compared with patients in the RT group.
- In both groups, the DM hazard rate decreased with time after mastectomy (authors note that even 18 years after mastectomy, a small risk of DM was present in both groups).

Kyndi M, Sorensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J, et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol 2008 Mar 20;26(9):1419-26.

Aim: To examine the effect of oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2), and constructed subtypes patients who received or did not receive post-mastectomy radiotherapy (PMRT).

Results

- As reported in the DBCG82 series, overall mortality was significantly reduced (HR=0.84; 95% CI, 0.72 to 0.97), DM (HR=0.80; 95% CI, 0.68 to 0.94) and LRR (HR=0.17; 95% CI, 0.10 to 0.26) probabilities after PMRT were found within the subgroup of 1,000 patients.
- A significantly improved overall survival after PMRT was reported in patients with good prognostic markers such as hormonal receptor-positive and HER2- patients (including the two Rec+ subtypes).

- No significant overall survival improvement after PMRT was reported in patients with an a priori poor prognosis, that is the hormonal receptor–negative and HER2+ patients, and in particular the Rec–/HER-2+ subtype.
- When comparing hazard ratios and 95% CIs, there were significantly smaller improvements in locoregional recurrence control after PMRT were found for ER– and PgR– tumours compared with the ER+ and PgR+ tumors (P=0.003 and 0.04, respectively), and for the triple-negative (P=0.02), and the Rec–/HER-2+ subtypes (P=0.003) compared with the Rec+/HER2– subtype.

Killander F, Anderson H, Rydén S, Möller T, Aspegren K, Ceberg J, et al. Radiotherapy and tamoxifen after mastectomy in postmenopausal women -- 20 year follow-up of the South Sweden Breast Cancer Group randomised trial SSBCG II:I. European journal of cancer (Oxford, England : 1990) 2007;43(14):2100-8.

Aim: To evaluate long-term effects of radiotherapy and tamoxifen after mastectomy on recurrence and survival in stage II breast cancer.

LRR:

- The cumulative incidence of loco-regional recurrences as first event at 20 years of follow-up was significantly reduced, with 71%, with radiotherapy ($p < 0.001$), and 18.5% (95% CI 13.8–23.8%) in the tamoxifen group compared to 5.3% in the RT + tamoxifen group and 6.7% (95% CI 3.8–10.4%) in patients randomised to RT with and without tamoxifen.
- In N0 patients: 7% loco-regional recurrences were diagnosed after 20 years in the Tamoxifen group, versus 6% in the RT + Tam group.
- In the N1–3 subgroup: the incidence was 25.9% (95% CI 17.5– 35.1%) in the Tamoxifen group, and 2.6% (95% CI 0.5–8.3%) in the RT + Tamoxifen group.

Cumulative incidence of systemic disease

- At 20 years the cumulative incidence of systemic disease = 50% in the RT group, 40% in the RT + Tamoxifen group and 45% in the tamoxifen group ($p = 0.33$ comparing RT + Tam versus Tam, and $p = 0.047$ comparing RT vs RT + Tam)
- Considering only receptor positive patients the numbers were 54% (RT only) , 40% (tamoxifen) and 41% (RT plus tamoxifen), ($p = 0.047$ comparing RT versus RT + Tamoxifen).
- In patients with more than three lymph nodes, there was a significant difference between RT and RT + Tamoxifen (88% versus 67%, $p = 0.02$).
- There were no significant differences reported for node negative patients.

Survival:

- Overall mortality at 20 years = 71% with RT, 68% with RT + tamoxifen group and 62% in tamoxifen group.
- The difference between RT + Tamoxifen versus Tamoxifen was not significant ($p = 0.14$).
- The difference between was not significantly different between RT and RT + Tamoxifen ($p = 0.50$).
- WRT hormone receptor positive patients the mortality rates at 20 years were 74% in the RT arm, 67% in the combination arm, and 54% in the Tamoxifen group.

- No statistically significant difference was reported when comparing RT to RT + Tamoxifen ($p = 0.28$) but the comparison of RT + Tamoxifen versus Tamoxifen was significant in favour of patients not receiving radiotherapy ($p = 0.047$)
- In the N1–3 group, mortality at 20 years was 74%, 65% and 64% (but there was no significant difference).

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Evidence Tables

Systematic review of RCTs

Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y, Early Breast Cancer Trialists' Collaborative Group (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.[see comment]. [Review] [33 refs]. *Lancet* **366**, 2087-2106.

Design: Systematic review of individual patient data

Level 1++

Country: Multinational

Aim: To update previous meta-analyses of individual patient data from randomised trials of the effects of radiotherapy and extent of surgery on local disease control and cause-specific mortality in early breast cancer. To quantify the relationship between local control and long term mortality.

Inclusion criteria

Randomised trials of mastectomy alone or with axillary clearance (AC) or axillary sampling (AS), then radiotherapy (RT) versus no RT. (Other studies involving breast conserving surgery were also included in the overview).

Exclusion criteria

Trials considered to be confounded, e g., no difference in treatment groups in the use of systemic therapy.

Population

Comparison

Trials

Women

Mastectomy + AC then RT versus no RT

25

9933

Mastectomy + AS then RT versus no RT

4

647

Mastectomy alone, then RT versus no RT

7

5597

Interventions

Update of individual patient data from randomised trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) from results up to the year 2000. The randomised trials compare local treatments of various types of surgery or radiotherapy (RT) or both. The intervention categories relevant to this topic were mastectomy alone or with axillary clearance or sampling, then RT or no RT.

Outcomes

Breast cancer recurrence (ipsilateral locoregional, contralateral or distant). Includes residual breast tissue, scar area, chest wall, ipsilateral regional lymph nodes. 5 year risk.

Cause-specific mortality

Breast cancer mortality- 15 year risk

Overall mortality

Incidence of second primary cancers before breast cancer recurrence.

Follow up –

This is an ongoing systematic overview of randomised trials with an update every 5 years. The current publication (2005) used a pooled analysis of individual patient data from the included studies rather than the primary studies themselves.

Results

A number of analyses were conducted after stratification by trial, time since randomization and nodal status (positive or negative). The main outcomes of local recurrence, breast cancer mortality and overall mortality were also stratified by age at randomization (<40, 40-49, 50-59, 60-69, > 70 years).

Local recurrence

Results of a meta-analysis of 36 trials in 3 subgroups (by type of surgery) were provided as a Forest plot in the paper.

RT was compared with no RT by node status. Data are shown in the following table:

	Events by year 5		5 year risk (actuarial %)		Absolute reduction in 5 year risk (%) for addition of RT Reduction (SE)
	Mast +RT	Mast only	Mast +RT	Mast only	
Mastectomy + AC (25 trials)					
Node negative	13/662	41/691	2.3	6.3	4.0% (1.1)
Node Positive	214/4170	778/4170	5.8	22.8	17.1% (0.9)
Mastectomy + AS (4 trials)					
Node negative	13/225	52/224	6.1	24.5	18.5% (3.5)
Node Positive	11/95	43/103	13.8	50.1	36.3% (7.5)
Mastectomy only (7 trials)					
Node negative	70/1427	307/1477	5.6	23.3	17.6% (1.4)
Node Positive	88/837	243/836	11.6	33.5	21.9% (2.3)

AC = Axillary Clearance
AS = Axillary Sampling

There were reductions in the risk of local recurrence in the radiotherapy arms compared to no radiotherapy after all three types of surgery at 5 years. The absolute reductions were greatest amongst node positive women. The lowest absolute reduction occurred in the subgroup of women who were node negative after mastectomy with axillary clearance followed by RT.

Node negative disease

5 year risk of local recurrence after mastectomy with AC was 6.3% without RT and 2.3% with RT ($2p=0.0002$). This corresponds to an absolute 5 year gain of 4% (SE 1.1).

Node positive disease

5 year risk of local recurrence after mastectomy with AC was 22.8% without RT and 5.8% with RT corresponding to an absolute 5 year gain of 17% (SE 0.9).

Breast cancer mortality

Breast cancer mortality data for women after mastectomy with axillary clearance (AC) were reported by subgroup.

Node negative disease (n=1428)

There was no significant reduction in 15 year breast cancer mortality with RT. A small increase in mortality (3.6%, SE 2.6) with RT was reported, however the number of events was small.

Breast cancer mortality (%) at 15 years:

31.3% after mastectomy + AC + RT

25.7% after mastectomy + AC excluding data beyond 15 years logrank $2p=0.18$

Node positive disease (n=8505)

In node positive disease the 15-year breast cancer mortality rate with post-mastectomy radiotherapy was 54.7%, and 60.1% without RT. The absolute gain of 5.4% with post-mastectomy RT was significant (SE 1.3, logrank $2p=0.0002$).

The authors comment that although 8505 women had mastectomy with AC in node positive disease, inclusion of the 2500 women with AS would not have substantially altered breast cancer mortality or local recurrence rates.

In a further analysis the authors suggest that the avoidance of a local recurrence (during the first 5 years) may reduce mortality (after the first 5 years) from trials of post-mastectomy RT and post BCS RT.

Subgroup analyses

Treatment comparisons were analysed by subgroups of age and tumour characteristics (grade, size, ER status, node involvement). For women with node-positive disease in trials of RT after mastectomy with axillary clearance, RT produced similar absolute reduction rates in local recurrence risk, irrespective of age, tumour grade, tumour size, ER status, or amount of node involvement. Within each subgroup the absolute benefit produced by RT was determined largely by the magnitude of local recurrence risk in unirradiated women.

Effects of age and tumour characteristics on 5 year risks of local recurrence in trials of RT after mastectomy and AC in women with node-positive disease are shown in the table below which is taken from the paper.

5 year local recurrence risk (%) after mastectomy with AC in women with node positive disease

Subgroup	5 year risk of local recurrence (%) in RCTs of RT after mastectomy + AC (node positive)	
	RT vs. control	Absolute reduction (SE)
Age (years)		
<50	6 vs 23	17 (1)
50-59	6 vs 24	18 (2)
60-69	5 vs 23	18 (2)
≥ 70	-	-
Tumour grade		
Well differentiated	4 vs 22	18 (3)
Moderately differentiated	4 vs 30	26 (2)
Poorly differentiated	6 vs 40	34 (4)
Tumour size (T category)		
1-20mm (T1)	5 vs 22	17 (2)
21-50mm (T2)	6 vs 30	24 (2)
> 50mm (T3 or T4)	8 vs 36	28 (4)
ER status		
ER poor	8 vs 28	20 (2)
ER positive	6 vs 24	18 (2)
N of involved nodes		
1-3	4 vs 16	12 (2)
>4	12 vs 26	14 (2)
All women	6 vs 23	17 (1)

Age

There was no trend in 5 year risk of local recurrence (in the chest wall or lymph nodes) with age among women with mastectomy, axillary clearance and node-positive disease with or without RT. Consequently the absolute effects of post-mastectomy radiotherapy on the risk of local recurrence were also independent of age:

Age	5-year risk reduction
< 50 years	17%
50-59	18%
60-69	18%

Tumour characteristics

Women with large tumours or with direct extension to the skin or chest wall (T2/T3/T4 tumours), or poorly differentiated tumours had a higher 5 year risk of local recurrence when RT was omitted. ER status did not appear to affect this risk.

The number of involved nodes (1–3 or ≥4) was unavailable for more than half the women who were node positive and had mastectomy with axillary clearance. The data that was available is reported below:

5-year local recurrence risks	RT	no RT	Risk reduction
Node 1-3	4%	16%	12% (SE 2)
Node ≥ 4	12%	26%	14% (SE 2)

Local recurrence and node status

The 15-year isolated local recurrence rates for women with 1 to 3 or with 4 or more involved nodes were very different and are reported below (from webtables published in the original paper):

MAST+AC ± RT (15 year outcome) for women with 1-3 involved lymph nodes (pN1-3) (Life table curves 1890 women) and for women with 4 or more involved lymph nodes (pN4+) (Life table curves 1868 women):

15-year local recurrence risks	RT	no RT	5 year gain
Node 1-3	5.8%	19.5%	11.6% (SE 1.5)
Node ≥ 4	15.4%	35.2%	14.8% (SE 2.3)

Overall mortality, breast cancer mortality and node status

At 15 years the reduction in all-cause mortality (4.4%) in trials of radiotherapy after mastectomy with axillary clearance in node-positive disease was lower than the reduction in 15-year breast cancer mortality (5.4%). When the data is was extended to 20 years, the reduction in breast cancer mortality remained unchanged, and that for all cause mortality was lower than at 15 years. The authors suggest that this indicates an excess of non-breast-cancer mortality long after treatment with the older radiotherapy regimens. The data is reported below:

All node positive (n=8505)	RT	no RT	Gain
15 year all-cause mortality	59.8%	64.2%	4.4% (SE 1.2, 2p 0.0009)
15 year breast cancer mortality	54.7%	60.1%	5.4% (SE 1.3, 2p 0.0002)
20 year all-cause mortality	68.8%	72.3%	3.5%
20 year breast cancer mortality	61.0%	66.4%	5.4%

The 15 year outcomes of the subgroup of women with 1-3 involved nodes are reported below:

Node 1-3 positive (n=1890)	RT	no RT	Gain
15 year all-cause mortality	51.1%	52.7%	1.6% (SE 2.6, 2p >0.1; NS)
15 year breast cancer mortality	43.3%	47.7%	4.4% (SE 2.6, 2p >0.1; NS)

The 15 year outcomes of the subgroup of women with 4 or more involved nodes are reported below:

Node 4+ positive (n=1868)	RT	no RT	Gain
15 year all-cause mortality	70.8%	72.4%	1.7% (SE 2.5, 2p >0.1; NS)
15 year breast cancer mortality	68.0%	70.3%	2.3% (SE 2.3, 2p >0.1; NS)

Node negative disease

A further analysis of all women with node negative nodes (n=1428) was also conducted, and results are reported below:

All node negative (n=1428)	RT	no RT	Gain
15 year isolated local recurrence	3.1%	8.1%	4.0% (SE 1.1)
15 year all-cause mortality	42.4%	38.2%	4.2% (SE 2.7, 2p 0.0002)
When data beyond 15 year excluded			2p=0.12
15 year breast cancer mortality	31.3%	27.7%	3.6% (SE 2.6, 2p 0.01)
When data beyond 15 year excluded			2p=0.18

A 5 year gain of 4% (SE 1.1%) was achieved with RT in local recurrence rates in women with node negative disease. Conversely there was a 15 year loss with RT for node negative disease in breast cancer mortality (3.6% SE 2.6) and all cause mortality (4.2% SE 2.7). Both these findings were statistically significant, however, when data beyond 15 years was excluded the findings were not significant.

Author conclusions (from the paper)

In trials of radiotherapy after mastectomy and axillary clearance, the 5-year risk of local recurrence in controls depended on the number of involved nodes, (risks 6%, 16%, and 26% respectively for 0, 1–3, and ≥4 involved nodes). Among women with mastectomy, axillary clearance, and node-negative disease the absolute reduction in 5-year local recurrence risk after radiotherapy was 4% (2% vs. 6%) If one death from the original breast cancer is avoided for every four local recurrences avoided, then the expected reduction in 15-year breast cancer mortality after radiotherapy would be

1% (less the adverse effects of any increase in contralateral disease). However, sample size was small in this subgroup and the effect of radiotherapy on breast cancer mortality was unfavourable.

Among all women with mastectomy, axillary clearance, and node-positive disease, the absolute effects of radiotherapy on 5-year local recurrence risk were substantial (6% vs. 23%), particularly if the tumour was poorly differentiated or large, and breast cancer mortality was correspondingly reduced. In these post-mastectomy trials age had little influence on local recurrence (mainly in the nodes or chest wall).

In early breast cancer, local treatments that substantially improve local control have little effect on breast cancer mortality during the first few years, but have definite, although moderate, effects by 15 years, and avoidance of local recurrence in a conserved breast and elsewhere are of comparable relevance to 15-year breast cancer mortality. These trials of radiotherapy and of the extent of surgery show that, in the hypothetical absence of other causes of death, about one breast cancer death over the next 15 years would be avoided for every four local recurrences avoided. Although the management of early breast cancer continues to change, it is reasonable to assume that this approximate four-to-one relationship will continue to apply and will still be of relevance to future treatment choices.

General comments -

Updated 2018

Gebski, V., Lagleva, M., Keech, A., Simes, J., & Langlands, A. O. 2006, "Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective.[see comment][erratum appears in J Natl Cancer Inst. 2006 Jun 21;98(12):876]", *Journal of the National Cancer Institute*, vol. 98, no. 1, pp. 26-38

Design: Meta-analysis of RCTs that had been previously included in earlier published meta-analyses and systematic reviews. Trials were identified up to 2002.

Country: Australia

Level 1++

Aim: The association between post-mastectomy radiation therapy for early breast cancer and overall survival was assessed in a meta-analysis of 36 randomized trials containing 38 comparisons that were unconfounded (addition of radiation therapy was the sole discriminant between treatments being compared). The specific issues of radiation dosage and target volume coverage were of interest. Studies using optimal BED (Biological Equivalent Dose) and appropriate target volumes were assessed for any observed benefit of radiation therapy.

Inclusion criteria

- 1) Studies were of operable breast cancer that was initially treated by mastectomy. (Stage I and stage II disease and selected cases of stage III disease were considered operable).
- 2) Studies were randomized controlled clinical trials that compared adjuvant radiation therapy with no such therapy. This treatment was the sole discriminating factor between the two arms of the trial. Other treatments, including extent of surgery, endocrine therapy, and chemotherapy, if given, had to be common to each arm.

Three studies that reported the use of randomization but may have used date of birth as the allocation method were included in the primary analysis but were excluded from a sensitivity analysis.

Exclusion criteria

Population

Thirty-eight unconfounded randomized comparisons from 36 trials were identified, with data available from a total cohort of 13 199 patients. Thirty-three of these comparisons were included in the EBCTCG analysis. Because of access to individual patient data for some studies, the EBCTCG was able to provide comparisons in addition to or different from those in published reports, so a direct comparison between this meta-analysis and the EBCTCG was not always possible.

Interventions

Radiotherapy treatment for each trial was classified into three major categories:

Category 1

Optimal radiation therapy: studies that delivered optimal radiation therapy defined as doses in the range of 40 – 60 Gy in 2-Gy fractions (where 50 Gy = 5000 rads) or as a BED to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes.

Category 2

Inadequate or excessive radiation therapy: studies that delivered inadequate or excessive radiation therapy defined as either doses of less than 40 Gy in 2-Gy fractions (or, for other fractionation schedules, the calculated BED being less than 40 Gy) or if greater than 60 Gy in 2-Gy fractions (or for other fractionation schedules the calculated BED being more than 60 Gy). (The authors state that the BED was calculated by use of α/β , a ratio that reflects the weight of the dose per fraction in the schedule to the total dose delivered, equal to 10, standardized to 2-Gy fractions).

Category 3

Incomplete tissue coverage: studies in which radiation therapy provided incomplete tissue coverage by restricting the target volume to areas of less than the area of the chest wall and regional lymph nodes. Techniques for which the target volume was restricted were considered to be inappropriate because an area at risk of recurrence received no radiation therapy.

Category 2 studies provided treatment that delivered an inadequate or excess dose irrespective of

target volume. Those studies in category 3 provided treatment that delivered an inappropriate target volume irrespective of dose. Studies that met category 2 and 3 criteria were included in category 2.

Outcomes

The primary outcomes were 5-year and 10-year overall survival rates calculated by intention-to-treat analysis.

Follow up

Results

38/40 RCTs compared postoperative radiation therapy with no RT and were not confounded.

Category 1: 25 RCTs used optimal RT with appropriate target volume.

Category 2: 7 RCTs used inadequate or excessive doses of RT.

Category 3: 6 RCTs used inappropriate target volumes.

26 studies with follow-up data at 5 years included a total of 13 199 patients
19 studies with follow-up data at 10 years included a total of 8921 patients
Thirteen studies compared megavoltage, one compared orthovoltage, two compared both orthovoltage and megavoltage, and one compared radiation energy not stated.

For eight of the 38 comparisons, no systemic chemotherapy was given and for the comparisons in the primary analysis, no systemic chemotherapy was given in four of the early studies — the Stockholm study (1993) the Edinburgh study (1994), NSABP-04 (1980, 1985), and the Wessex study (1978); the rest of the studies included chemotherapy and/or hormone therapy.

Pooled weighted estimates were calculated for survival at 5 and 10 years.

5 year follow-up

A meta-analysis of the association between post-mastectomy RT and mortality at 5 years of follow-up was conducted and included 38 comparisons from 36 unconfounded trials.

At a follow-up of 5 years category 1 studies gave a statistically significant 13% relative survival advantage associated with radiation therapy (OR of death from any cause = 0.87, 95% CI = 0.79 to 0.96; $P = 0.006$), compared with no radiation therapy.

This translates into an absolute 2.9% increase in survival (or 29 lives per 1000 patients treated) and a number needed to treat of 34 (i.e., on average, for every 34 patients treated, one life would be saved over 5 years).

10 year follow-up

A meta-analysis of the association between post-mastectomy RT and mortality at 10 years of follow-up was conducted and included 19 comparisons from 18 unconfounded trials.

After follow-up of 10 years studies in category 1 gave a statistically significant 22% increase in relative survival associated with radiation therapy (OR = 0.78, 95% CI = 0.70 to 0.85; $P < 0.001$), compared with no radiation therapy. This corresponds to an absolute 6.4% increase in survival (64 per 1000) and number needed to treat of 16.

Node positive disease

In trials of high-risk patients (i.e., patients with lymph node positive disease) a separate analysis found that an absolute 5.2% increase in survival (52 per 1000) at 10-year follow-up was associated with adjuvant radiation therapy (OR = 0.80, 95% CI = 0.64 to 1.0; $P = 0.05$, with no evidence of heterogeneity), compared with no radiation therapy.

There was no statistically significant association between radiation therapy and survival after 5 or 10 years for category 2 (inadequate or excessive dose) or 3 (inappropriate target volume) studies.

(5 year category 2: OR 0.92 (95% CI 0.81-1.04); category 3: OR 1.03 (95% CI 0.73-1.44).

(10 year category 2: OR 0.91 (95% CI 0.75-1.11); category 3: OR 0.97 (95% CI 0.61-1.55).

Application of classification system to EBCTCG trials (from data in year 2000)

Overall survival

In the 23 studies from the EBCTCG report that were classified as category 1, overall survival improved significantly. An absolute survival benefit associated with radiation therapy was reported of 3.9% (39 per 1000), and a relative benefit of 13% (OR of death = 0.87, 95% CI = 0.80 to 0.94, $P < 0.001$). The association was stronger than for category 2 studies (OR = 0.97, 95% CI = 0.87 to 1.09) and category 3 studies (OR = 1.26, 95% CI = 1.03 to 1.53) showed substantial harm. Heterogeneity was statistically significant over the three classification groups (P heterogeneity = 0.006).

Data from nine category 1, four category 2 and one category 3 trials of the EBCTCG were used for a meta-analysis of the association between radiotherapy and isolated local recurrence, breast cancer mortality and non-breast cancer mortality.

Local recurrence rates varied by category, radiation therapy was associated with an 80% reduction in local recurrence in category 1 studies, a 70% reduction in category 2, and a 64% reduction in category 3 studies. Heterogeneity was statistically significant between these categories (P heterogeneity < 0.001). However, heterogeneity was not statistically significant between the studies of radiation therapy associated with non-breast cancer mortality, although some was detected for breast cancer mortality (P heterogeneity = 0.07).

An analysis of the 9 category 1 studies found a 20% reduction in breast cancer deaths associated with radiation therapy (OR = 0.8, 95% CI = 0.73 to 0.88), and a 15% increase in non-breast cancer deaths associated with radiation therapy (OR = 1.15, 95% CI = 0.97 to 1.36).

Author conclusions

By restricting meta-analyses to trials that used the optimal radiation therapy dose delivered to appropriate target volumes the authors found that radiation therapy was associated with improved overall survival. Over all such trials with available data and among those eligible trials included in the EBCTCG overview (23 of 26 have common comparisons), improved 5-year survival and 10-year survival was associated with optimal radiation therapy.

Evidence from randomized trials of other outcomes (isolated local recurrence and cause-specific deaths) appeared to consistently support the findings. Among EBCTCG trials with available data, trials that used optimal radiation therapy found a statistically significant association of radiation therapy with a lower risk of local recurrence than trials using another radiation therapy regimen. Furthermore, studies that used optimal radiation therapy might show a larger reduction of breast cancer mortality and a smaller reduction of non-breast cancer mortality (because of less radiation to inappropriate target volumes). Among EBCTCG trials that reported cause-specific mortality, the results were consistent with this expectation but not definitive, possibly because of the small number of trials with available data.

The results of both the primary analysis and reanalysis of the EBCTCG indicate that the balance between breast cancer and non-breast cancer deaths should favour radiation therapy for women with a high risk of death from breast cancer, particularly when the proportion of non-breast cancer deaths is low (i.e., there is a low risk of non-breast cancer deaths among all women at high risk of breast cancer death).

General comments –

Definitions:

EBCTCG: the statistics for breast cancer mortality are derived by logrank subtraction (i.e. subtraction of the logrank statistics for mortality from causes other than breast cancer from the logrank statistics for any death). The EBCTCG report breast cancer deaths and any death. It is not clear how the analysis by GebSKI et al has measured non-breast cancer mortality or breast cancer mortality.

Limitations:

The authors state that survival data at 5 and 10 years follow-up was missing in several trials which

may have contributed to a biased estimate of effect favouring postoperative RT. Also the analyses of survival at 5 and 10 years follow-up ignore the late effects after 10 years.

An Editorial by Prosnitz and Marks (2006) points out further limitations of this analysis which are reported below:

(Journal of the National Cancer Institute (2006); 98 (1): 3-4. Post-mastectomy Radiotherapy: Quality Counts!

Additional limitations of this analysis are as follows:

1) The inclusion of many studies in which adjuvant systemic therapy was not used. In a disease with a high frequency of systemic relapse, local-regional therapy is most likely to improve survival when effective systemic therapy is used.

2) The inclusion of patients with various risks of relapse (i.e., high, medium, and low). Potential absolute survival benefits of radiation therapy will be less in the low-risk group.

3) Ten-year analysis may not fully reflect the impact of radiation therapy-related mortality, which is primarily cardiac mortality and usually occurs more than 10 years after treatment. Radiation therapy-induced cardiac damage is largely a technical issue; the heart can, for the most part, be avoided with modern treatment planning. Recent studies have suggested no increase in cardiac deaths after post-mastectomy radiation therapy, but further follow-up is desirable. One can account for length of follow-up by performing meta-analyses subdivided by year of onset of the trial.

Comparison of results for EBCTG 2005 and Gebski 2006

Outcome	Clarke 2005	Follow-up	RT	No RT	Absolute difference for RT arm	Gebski 2006	Relative difference for RT arm
Local recurrence	Node negative	5 years	2.3%	6.3%	-4%	Optimal BED RT OR 0.20 (95%CI 0.17-0.23) From analysis of 9 EBCTG trials with optimal RT (All participants node +ve or -ve)	-80%
	Node positive	5 years	5.8%	22.8%	-17.1%		
	Overall	5 years	6.9%	25.8%	-15.0%		
Breast cancer mortality	Node negative	15 years	31.3%	27.7%	-3.6% 2p=0.01	Optimal BED RT OR 0.80 (95%CI 0.73-0.88) From analysis of 9 EBCTG trials with optimal RT (All participants node +ve or -ve)	-20%
	Node positive	15 years	53.7%	60.1%	+5.4% 2p=0.0002		
	Overall	15 years	51.1%	55.2%	+4.1% 2p=0.006		
Any death	Node negative	15 years	42.4%	38.2%	-4.2% 2p0.0002	5 years 17 trials Node +ve and -ve OR 0.87 (95%CI 0.79-0.96) P=0.03	+13% Absolute increase +2.9%
	Node positive	15 years	59.8%	64.2%	+4.4% 2p0.0009		
	Overall	15 years	57.1%	60.2%	+3.1% 2p>0.1		
						10 years 13 trials Node +ve and -ve OR 0.78 (95%CI 0.70-0.85) P<0.001	+22% Absolute increase +6.4%

Whelan, T. J., Julian, J., Wright, J., Jadad, A. R., & Levine, M. L. 2000, "Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis", *Journal of Clinical Oncology*, vol. 18, no. 6, pp. 1220-1229.

Design: Systematic review of RCTs (1966-1999) Level 1++

Country: Canada

Aim: To review all trials of locoregional radiation therapy in women treated with systemic therapy to determine if the mortality effects observed in recently published studies were consistent with those in other trials and to assess the generalizability of these findings to current practice. Specific objectives were to conduct a systematic review of randomized trials that examined the effectiveness and toxicity of locoregional radiation therapy in patients with breast cancer treated by definitive surgery and adjuvant systemic therapy, to perform a meta-analysis of the results of these trials, and to consider possible factors (patient- and treatment-related) that could influence the treatment effect.

Inclusion criteria

Published in a peer-reviewed journal in any language;

All patients were treated by definitive surgery, either radical/modified radical mastectomy or lumpectomy plus axillary dissection;

Patients in both treatment arms received the same systemic therapy;

Allocation of locoregional radiation treatment was randomized;

Radiation therapy was delivered to the regional lymph nodes and chest wall or breast;

Median follow-up of 5 years or more.

Exclusion criteria

None reported

Population

Patient characteristics

Trials were heterogeneous regarding patient characteristics.

Most trials included both pre- and postmenopausal women.

Two trials included only pre-menopausal patients, one trial included only postmenopausal patients.

Most trials limited eligibility to patients with positive nodes. One trial limited patients with more than four positive nodes, and two trials limited patients with stage III disease.

Several trials included patients with node-negative breast cancer and stage III disease.

One trial included patients with node-negative breast cancer with primary tumours 2 to 5 cm.

Interventions

In the majority of trials, patients were treated with modified radical mastectomies. No trials treated patients with lumpectomies and axillary dissections. The extent of axillary dissection was reported in 12 trials.

A majority of trials delivered radiation to the chest wall, supraclavicular, axilla, and internal mammary nodal areas.

Field arrangements or techniques varied between and within trials. The chest wall was irradiated with two tangential fields or with a single direct electron or photon field.

Radiation was delivered primarily with megavoltage linear accelerators. The radiation dose ranged from 35 to 60 Gy in 12 to 30 fractions and was delivered over 2.5 to 7 weeks. The most common fractionation schedule was 50 Gy in 25 fractions over a 5-week period.

Compliance with radiation therapy where reported ranged from 68% - 100% (median, 96%).

All trials included patients treated with systemic therapy. Chemotherapy was used in 19 trials; combined chemo-endocrine therapy in three trials; tamoxifen alone in two trials; and immunotherapy with chemotherapy in two trials.

Outcomes

Toxicity

Any recurrence, locoregional recurrence

Mortality

Follow up

Median follow-up ranged from 7.5 to 14.5 years.

Results

Eighteen randomized trials met the inclusion criteria with a total of 6367 patients

Toxicity

Eight trials provided data on toxicity.

Acute toxicity was reported infrequently and included: severe skin toxicity, 2.7% and 5% (2 trials); myelosuppression attributed to radiation therapy, 2% and 32% (2 trials); and radiation pneumonitis, 1%, 15%, and 23% (3 trials). Radiation oesophagitis occurred in 17% of patients in one trial. This study had particularly high rates of acute and long-term toxicity and was the only trial in which radiation was given concurrently with chemotherapy.

Late toxicity:

- No cases of brachial plexus neuropathy were reported.
- Arm oedema was reported in three trials. The incidence ranged from 0% to 25% (median, 3%) in non-irradiated patients and from 10% to 54% (median, 12%) in irradiated patients.
- Cardiac toxicity, primarily congestive heart failure, was reported in six trials. In trials using CMF, no cardiac complications were reported in patients treated with chemotherapy alone (2 trials). One case of pericarditis was reported in a patient treated with CMF and radiation therapy (1 trial). In patients treated with anthracycline-containing chemotherapy (4 trials), the incidence of congestive heart failure in non-irradiated patients ranged from 0% to 19.2% (median, 2.6%), whilst in irradiated patients cardiac failure ranged from 1.9% to 23.6% (median, 3.2%).
- In two studies, no increase in 12-year cumulative morbidity or mortality from ischemic heart disease was observed in irradiated patients.
- The incidence of secondary cancers was reported in two trials; no increase was noted in irradiated patients. One case of acute myelogenous leukaemia was reported in a patient treated with CMF and radiotherapy.

Recurrence

Data on recurrence were available from 13 trials.

Radiation therapy significantly reduced the risk of any recurrence [odds ratio 0.69 (95% CI 0.58-0.83; $p = 0.00004$)].

This was mainly due to a reduction in locoregional recurrence [odds ratio 0.25 (95% CI, 0.19-0.34; $p=0<0.000001$)].

Mortality

Mortality data were available for all trials.

Radiation therapy significantly reduced mortality [odds ratio 0.83 (95% CI 0.74-0.94; $p = 0.004$)]. Heterogeneity was not significant ($p = 0.26$).

A positive treatment effect was seen in 6/9 trials of more than 200 patients.

Two of three trials had negative treatment effects, compliance with radiation therapy was poor in these studies.

A further statistical analysis using univariate and multivariate tests found that timing of RT (≥ 6 months vs. < 6 months) was statistically significant, with RT given early reducing mortality:

< 6 months	12 studies OR 0.78 (95%CI 0.69-0.89)	
≥ 6 months	3 studies OR 1.14 (95%CI 0.80-1.62)	$p=0.05$

All other univariate comparisons were not statistically significant for effect on mortality:

Early vs advanced disease
Axillary dissection: less extensive vs. extensive
Anthracycline use
Radiation technique: megavoltage vs. orthovoltage
Extent of radiation: all sites vs. not all sites
Radiation dose: $\geq 45\text{Gy}$ vs. $< 45\text{Gy}$
Locoregional recurrence: $> 24\%$ vs. $\leq 24\%$
Methodological quality: ≥ 2 vs. < 2

When multivariate analysis was conducted timing of radiation remained statistically significant ($p=0.03$). Radiation technique megavoltage vs. orthovoltage was also found to be statistically significant:

Megavoltage	13 studies OR 0.78 (95%CI 0.69-0.89)	
Orthovoltage	5 studies OR 0.94 (95%CI 0.74-1.19)	$p=0.05$

Author Conclusions

Locoregional radiation after surgery in patients treated with systemic therapy reduced mortality. Several questions remain on how these results should be translated into current-day clinical practice.

General comments -

Updated 2018

Overgaard M, Nielsen HM, Overgaard J, Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiotherapy & Oncology* 2007 Mar;82(3):247-53.

Design: Subgroup analysis of DBCG 82 b and c RCTs (1982-1990) Level 1+
Country: Denmark

Aim: A subgroup analysis of the DBCG 82 b and c trials was performed to evaluate the loco-regional recurrence rate and survival in relation to number of positive nodes (1-3 or 4 or more), and whether this is a relevant descriptor of the indication for postmastectomy radiotherapy in high risk patients receiving systemic therapy.

Inclusion criteria

The DBCG 82 b and c trials enrolled 3083 pre- and postmenopausal high-risk women who were randomized to postoperative RT in addition to adjuvant systemic therapy. The present analysis was limited to 1152 node positive patients with 8 or more nodes removed. All patients were aged < 70 years.

Exclusion criteria

Patients with distant metastases occurring within one month of the LRR were not included in this analysis.

Population

3083 patients included;
1708 pre- and menopausal (DBCG 82b);
1375 patients postmenopausal and < 70 years of age (DBCG 82c);
Only high-risk patients were included, defined as patients with positive nodes and/or a T3 or T4 tumour and/or skin or deep fascia invasion.

Interventions

All patients were treated with total mastectomy and partial axillary dissection to remove level 1 and some level 2 axillary nodes, and all macroscopically enlarged lymph nodes.

After surgery, adjuvant systemic therapy was administered, and patients were randomized to postoperative radiotherapy or no radiotherapy.

Systemic therapy in premenopausal and menopausal patients as 8–9 cycles of CMF. Postmenopausal patients received Tamoxifen 30 mg daily for 48 weeks.

Radiotherapy was given as a dose of 48–50 Gy in 22–25 fractions over 5 weeks to the chest wall, and regional lymph nodes (internal mammary nodes, peri-clavicular nodes, axilla).

The applied radiotherapy avoided irradiation of the heart, and no excess cardiac morbidity and death was recorded.

Outcomes

Definitions:

A loco-regional recurrence (LRR) was defined as any reappearance of cancer in the ipsilateral chest wall and/or axillary and/or supra/infraclavicular nodes without any prior or simultaneous distant failure.

Outcomes:

Overall survival

Loco-regional recurrence after mastectomy without simultaneous distant metastases.

Follow up

The evaluation date for recurrences and survival was November 15, 2004, which resulted in a median follow-up time after mastectomy of 18 years (range 15–22).

Results

Patient and tumour characteristics of the 1152 patient cohort did not differ substantially from the original cohort of 3083 patients, although p values were not reported. The group of patients with 1-3 positive nodes did not appear to differ from the group with 4+ positive nodes (again p values were not reported).

At 15 years:

179 (16%) patients had a LRR

762 (66%) patients had died

Loco-regional recurrence

The distribution of LRR between treatment groups is shown below:

LRR	Patients	15 year actuarial value for LRR	
RT group	23/563 (4%)	6%	
No RT	156/589 (26%)	37%	p<0.001

Relative risk (RR) of 0.12 (95% CI 0.07–0.19)

Survival

A similar effect was seen when evaluating the outcome for survival:

	Patients	15 year actuarial survival values	
RT group	343/563 (61%) deaths	39%	
No RT group	419/589 (71%) deaths	29%	p=0.015

RR of 0.63 (95% CI 0.49–0.81)

The results were also analysed by node status for patients with 1-3 positive lymph nodes and 4+ positive lymph nodes.

Loco-regional recurrence

The distribution of LRR between treatment groups and node status is shown below:

Node 1-3

LRR	Patients (1-3 +ve nodes)	15 year actuarial values for LRR	
RT group	8/276 (3%)	4%	
No RT	63/276(23%)	27%	p<0.001

Relative risk (RR) of 0.10 (95% CI 0.05–0.22)

Node 4+

LRR	Patients (4+ +ve nodes)	15 year actuarial values for LRR	
RT group	15/287 (5%)	10%	
No RT	93/313(30%)	51%	p<0.001

Relative risk (RR) of 0.17 (95% CI 0.10–0.28)

Survival

Node 1-3

	Patients (1-3 +ve nodes)	15 year actuarial survival values	
RT group	118/276 (43%) deaths	57%	
No RT group	143/276 (52%) deaths	48%	p=0.03

RR of 0.69 (95% CI 0.50–0.97)

Node 4+

	Patients (4+ +ve nodes)	15 year actuarial survival values	
RT group	225/287 (78%) deaths	21%	
No RT group	276/313 (88%) deaths	12%	p=0.03

RR of 0.49 (95% CI 0.31–0.76)

Other analyses were conducted by tumour size:

15 year LRR failure	RT	No RT
Tumours ≤ 20mm	4%	29%
Large tumours	7%	43%

15 year survival:	RT	No RT
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Tumours ≤ 20mm	50%	36%
Large tumours	33%	25%

The 15-year survival benefit was most marked in patients with smaller tumours (≤20 mm), whilst the reduction in the 15-year loco-regional failure rate was most pronounced in patients with large tumours.

The absolute and relative risk reduction and number of patients needed to treat were similar in both subgroups (N1-3 and N4+). For every 10 patients irradiated approximately two LRR and one death could be avoided. The authors suggest that overall this indicates that postmastectomy radiotherapy is beneficial in the described cohort of high-risk patients and is unrelated to the number of positive lymph nodes

A summary of outcomes is shown below:

Outcome 15 year actuarial values	RT	No RT	p value
LRR	6%	37%	< 0.001
	RR = 0.12 (95% CI 0.07–0.19)		
Survival	39%	29%	0.015
	RR = 0.63 (95% CI 0.49–0.81)		
	1-3 positive nodes	4+ positive nodes	
LRR			
Relative risk reduction	87%	82%	
Absolute risk reduction	20%	24%	
NNT	5	4	
Deaths			
Relative risk reduction	17%	11%	
Absolute risk reduction	9%	10%	
NNT	11	10	

Author conclusions

The survival benefit after postmastectomy RT was substantial and similar in patients with 1-3 and 4+ positive lymph nodes. Furthermore, it was not strictly associated with the risk of loco-regional recurrence, which was most pronounced in patients with 4+ positive nodes. The indication for RT seems therefore to be at least equally beneficial in patients with 1-3 positive nodes, and future consensus should be modified accordingly.

General comments –

In the discussion the authors state that there is accumulating information from other subgroup analyses to support these results. The 20-year results of the British Columbia study have shown that the impact of radiation therapy for all survival outcomes in the subgroup with 1–3 nodes involved was similar to the subgroup with 4+ nodes involved and had a similar magnitude of risk reduction. The 2005 EBCTCG overview also showed a similar magnitude of benefit of radiotherapy to node 1-3 and 4+ patients, however, most of the patients in this EBCTG subgroup were from the DBCG 82 trials.

RT was also applied to the regional lymph nodes as well as the chest wall.

Nielsen, H. M., Overgaard, M., Grau, C., Jensen, A. R., & Overgaard, J. 2006, "Loco-regional recurrence after mastectomy in high-risk breast cancer--risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials", *Radiotherapy & Oncology*, vol. 79, no. 2, pp. 147-155

Design: 2 RCTs (1982-1990)

Level 1+

Country: Denmark

Aim: The aim of the study was to identify risk factors for loco-regional recurrence (LRR), to evaluate the treatment of LRR and to examine the prognosis after LRR

Inclusion criteria

The DBCG 82 b and c trials enrolled 3083 pre- and postmenopausal high-risk women (<70 years) who were randomized to postoperative RT in addition to adjuvant systemic therapy.

Exclusion criteria

If a distant metastasis occurred within 1 month of the locoregional recurrence (LRR) the patient was not included in this analysis.

Population

Of 3083 patients included, 1708 were pre- and menopausal (DBCG 82b), and 1375 patients were postmenopausal and below 70 years of age (DBCG 82c). Only high-risk patients were included, defined as patients who were node positive and/or a T3 or T4 tumour and/or skin or deep fascia invasion.

Interventions

Patients were randomized to ±RT in addition to systemic therapy after total mastectomy and partial axillary dissection. Adjuvant systemic therapy was CMF. Post-menopausal patients had tamoxifen 30 mg daily for 1 year. Of the 1538 patients randomized to RT, 1341 patients (87%) had megavoltage RT to the chest wall and regional lymph nodes including the axillary, supra/infraclavicular and ipsilateral internal mammary nodes with the prescribed dose of 48–50 Gy in 22–25 fractions, four or five fractions per week; 120 patients (8%) had orthovoltage RT (36 Gy/20 fx, 5 fx/week) and 77 patients (5%) never began or completed RT.

Outcomes

Locoregional recurrence (LRR)

Subsequent LRR (LRR2)

Overall survival at 10 years

Follow up

Recurrences and survival were assessed in November 15, 2004, resulting in a median follow-up time after mastectomy of 18 years (range 15–22). The median follow-up time after LRR was 3.2 years. The follow-up time for survivors was 12.7 years, and 2.6 years for patients who died.

Results

Definitions:

A LRR was defined as (1) any reappearance of cancer in the ipsilateral chest wall or skin or soft tissue overlaying the ipsilateral chest wall, axilla or supra/infraclavicular region; or 2) cancer spread to the ipsilateral axillary nodes or 3) ipsilateral supra/infraclavicular nodes.

The endpoints for evaluating prognosis after LRR, were overall survival, second LRR (LRR2) and distant metastases.

The median time from mastectomy to LRR was 23 months among patients randomized to no RT and 32 months among patients randomized to RT. None of the 456 patients initially randomized to no RT received post-mastectomy RT.

Risk factors for developing LRR were only evaluated for the 1545 patients randomized to no RT, since LRR among patients randomized to RT were infrequent.

Locoregional recurrence

A total of 535/3083 patients had a LRR as first site of failure (chest wall: N=259 (48%), axilla: N=153, supra/infraclavicular: N=44, multiple LRR: N=79).

Frequency of LRR was:

30% (456/1545) in the no RT arm
 5% (79/1538) in the RT arm.

Of the 535 patients with a LRR, 82% (441/535) had died at the time of analysis.

Of the 79 patients with LRR randomized to RT, 15% (12/79) never began or completed RT, 71% (56/79) had megavoltage RT and 14% (11/79) had orthovoltage RT.

Risk factors for locoregional recurrence (18 year probability)

1545 patients were randomized to no RT, the probabilities of LRR, chest wall alone and axillary failure alone were analysed for this group.

- In a univariate analysis risk factors for developing a LRR were: increasing tumour size, ductal carcinoma, increasing malignancy grade, invasion of the fascia, few removed nodes, many positive nodes and extracapsular invasion.
- Patients with 4+ positive axillary nodes had a high probability of LRR, with 59% having a LRR within 18-years of follow-up.
- A multivariate analysis stratified by ductal versus non-ductal carcinoma and excluding N0 disease found independent risk factors for LRR:
- Primary tumour size larger than 50mm (RR=1.64, 95%CI 1.16–2.29)
- Malignancy grade III (RR=1.96, 95%CI 1.45–2.65)
- Invasion of the fascia (RR=1.38, 95%CI 1.05–1.81)
- Less than 8 removed nodes (RR=1.64 95%CI 1.33–2.04)
- 4+ positive nodes (RR=1.96, 95% CI 1.56–2.45).

Risk factors for locoregional recurrence in the chest wall (18 year probability)

A univariate analysis of risk factors for chest wall failures within 18 years of follow-up were:

- Increasing tumour size (p<0.001)
- Ductal carcinoma (p=0.04)
- Invasion of the fascia (p=0.003)
- Many positive nodes and approximately 30% of patients with tumour size of 50 mm or larger (p<0.001)
- Invasion of the fascia (p=0.003) and
- Four or more positive nodes (p<0.001)

Risk factors for locoregional recurrence in the axilla (18 year probability)

On univariate analysis:

- Increasing malignancy grade (p=0.05)
- Few removed nodes (<8) (p=0.001)
- Many positive nodes (p<0.001)
- Extracapsular invasion (p=0.001)

Prognosis after LRR

A univariate analysis of prognostic factors that were statistically significant for survival, a second locoregional recurrence and distant metastases were: many positive nodes, extracapsular invasion and a short interval to LRR.

A univariate analysis of prognostic factors for survival and distant metastases were: site of the LRR at the supra/infraclavicular region and at multiple sites, and the following original primary tumour variables: large tumour size, high malignancy grade and invasion of the fascia.

The significant independent prognostic factors for overall survival after LRR from multivariate analysis are shown in the table from the paper below (n=482):

Variable	P value	RR (95% CI)
Tumour size:	0.006	
<21mm		1.00
21-50 mm		1.33 (1.03-2.14)
> 50 mm		1.66 (1.19-2.32)
Positive nodes	0.04	
1-3		1.00
4+		1.27 (1.01-1.61)

Extracapsular invasion	0.05	
No		1.00
Yes		1.25 (1.01-1.57)
Site of LRR	<0.001	
Chest wall		1.00
Axilla		0.92 (0.72-1.17)
Supra/infra		1.48 (1.02-2.14)
Multiple LRR		1.70 (1.25-2.27)
Interval to first LRR	<0.001	
> 2 years		1.00
≤2 years		1.97 (1.59-2.44)

A poor survival after LRR was seen among patients (N=482) with primary tumour characteristics of a large tumour size, many (4+) positive nodes and extracapsular invasion. Localization of the LRR at the supraclavicular region or at multiple loco-regional sites and a short interval, less than 2 years from mastectomy to LRR, were also independent poor prognostic factors.

Author conclusions

Twenty-seven percent of LRR patients had no distant metastases 5 years after failure. Initial randomization group did not alter the prognosis after LRR. Primary tumour characteristics, localization of the LRR and time interval from mastectomy to LRR were important for outcome after LRR, whilst postmastectomy RT did not alter this prognosis. There is a need for further examination of the optimal treatment modalities of patients with LRR. Combined treatment of the LRR with surgery and RT improved persistent loco-regional control compared with surgery or RT alone.

General comments –

RT was applied to the regional lymph nodes as well as the chest wall in some patients.

Updated 2019

Van de Steene, J., Soete, G., & Storme, G. 2000, "Adjuvant radiotherapy for breast cancer significantly improves overall survival: The missing link", *Radiotherapy & Oncology*, vol. 55, no. 3, pp. 263-272.

Design: Analysis of EBCTCG RCTs

Level 1+

Country: Belgium

Aim: To explore the trials analyzed by the EBCTCG to discover essential mutual differences between the trials, based on hypotheses (pointing to determinants for the effect of adjuvant radiotherapy) in the literature.

Inclusion criteria

Randomized clinical trials comparing radical mastectomy or breast conserving surgery with (in the study group) and without (in the control group) adjuvant radiotherapy.

Exclusion criteria

Population

The 36 trials of the EBCTCG (Early breast cancer trialists', collaborative group, 1995). Total number of patients treated 17 273.

Interventions

Each of the studies was characterized by a number of objective features which may influence a treatment effect. Most of these were biological or technical factors related to either the patient population, the trial or the radiotherapy. The influence of these factors on overall survival was investigated.

Outcomes

Overall survival

Crude survival (% of deaths in the trial) was a surrogate for global prognosis of patients in the trial. If the trial included low stage patients than the crude survival was high and vice versa.

Follow up

Results

In a univariate analysis, the start year of the trial, number of patients in each trial, fraction dose, and crude survival in the trial had a statistically significant effect on overall survival. Relevant data for these four factors are summarized below from the paper:

Variable	N of patients	Odds Ratio (95% CI)	Odds reduction (%)	P value
<i>Trial start date</i>				
> 1970	12567	0.935 (0.88-1.00)	6.5	0.048
> 1980	4936	0.882 (0.77-1.02)	11.8	0.080
<i>N of patients in trial</i>				
> 600	11354	0.932 (0.88-0.99)	6.8	0.028
< 150	933	1.304 (1.07-1.59)	-30.4	0.008
<i>Fractionation (Gy/fraction)</i>				
All known	12960	0.933 (0.88-0.99)	6.7	0.034
≥ 1.8 ≤ 2.0	7915	0.896 (0.82-0.98)	10.4	0.016
Other	5054	0.973 (0.89-1.07)	2.7	0.557
≥ 1.8 ≤ 2.5	9060	0.894 (0.83-0.97)	10.6	0.006
Other	3909	1.005 (0.90-1.12)	-0.5	0.931
<i>Crude survival</i>				
≥ 80%	3337	0.799 (0.66-0.97)	20.0	0.025
≤ 35%	398	1.272 (1.01-1.61)	-27.2	0.044

Factors that were not significant to overall survival were adjuvant systemic therapy (hormonal or chemotherapy or both), beam energy (ortho- or megavoltage), radiotherapy dose intensity (≥ 12.6 Gy/w) and extension of radiotherapy target volume.

On univariate analysis a significant survival benefit for the radiotherapy arm was found for:

- Recent trials (2P < 0.05), the more recent the trial the larger the survival benefit (21.1% gain for trials started after 1980);

- Large trials produced a larger survival benefit ($2P < 0.03$);
- Trials that used standard fractionation of 1.8-2.5 Gy/fraction ($2P < 0.02$);
- Trials with a favourable crude survival ($2P < 0.03$).

Significant parameter-effect relationships were found for these factors. In recent and large trials the odds reduction was 12.4% ($2P = 0.004$).

Author conclusions:

Surgical adjuvant radiotherapy significantly improves overall survival of breast cancer patients provided that current techniques are used and treatment is given with standard fractionation. For the best subgroups we observed an odds of death reduction of more than 20%. The results of this study stress the importance of reducing cardiovascular and other late toxicity in adjuvant radiotherapy for breast cancer.

General comments –

All EBCTG studies were used for the analysis and included patients who were treated with mastectomy or BCS.

Updated 2018

Randomized controlled trials

Fisher, B., Jeong, J. H., Anderson, S., Bryant, J., Fisher, E. R., & Wolmark, N. 2002, "Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation.[see comment]", *New England Journal of Medicine*, vol. 347, no. 8, pp. 567-575.

Design: RCT (1971-1974)

Level 1++

Country: USA, setting:

Aim: To determine whether patients with either clinically negative or clinically positive axillary nodes who received local or regional treatments other than radical mastectomy would have outcomes similar to those achieved with radical mastectomy.

Inclusion criteria

Women with primary operable breast cancer

Exclusion criteria

Population number of patients = 1765

1079 women with clinically negative axillary nodes underwent radical mastectomy (RM) (n=362), total mastectomy without axillary dissection but with postoperative irradiation (n=352), or total mastectomy (TM) plus axillary dissection (n=365) only if they developed positive nodes.

A total of 586 women with clinically positive axillary nodes either underwent radical mastectomy (n=292) or total mastectomy without axillary dissection but with postoperative regional irradiation (n=294).

70% of women in each group were 50 years or more at time of entry. On pathological examination, the mean (SD) diameter of the largest tumour was 3.3 +/- 2.0 cm in women with negative nodes and 3.7 +/- 2.0 cm in women with positive nodes.

Interventions

Radiotherapy was delivered with supervoltage equipment.

Node negative received 50 Gy in 25 fractions;

Node positive received an additional boost of 10 to 20 Gy. A dose of 45 Gy in 25 fractions was delivered to both the internal mammary nodes and the supraclavicular nodes.

The chest wall was treated with 50 Gy in 25 treatments using tangential fields.

No patients received adjuvant systemic therapy.

Outcomes

Disease free survival (DFS)

Relapse free survival

Distant disease free survival

Overall survival

Follow up

87% were followed for at least 25 years. Data collected up to March 2001.

Results

Definitions used:

Local recurrences: tumour recurrences in the chest wall, the surgical scar, or both.

Regional recurrences: recurrences in supraclavicular, subclavicular, or internal mammary nodes or in the ipsilateral axilla of patients treated with either radical mastectomy or total mastectomy and regional irradiation.

Women with negative nodes who had total mastectomy alone and who subsequently had ipsilateral positive nodes that required axillary dissection were not considered to have had a recurrence unless the nodes could not be removed, this occurred in one patient.

DFS: events considered were the first local, regional, or distant recurrence of tumour; contralateral breast cancer or a second primary tumour not in the breast; and death of a woman who had no evidence of cancer.

Relapse free survival: the first local, regional, or distant recurrence or an event in the contralateral breast that was judged to be a recurrence.

Distant-disease-free survival: distant recurrences that occurred either as the first recurrence or after a local or regional recurrence, contralateral breast cancers, and other second primary cancers.

Overall survival: all deaths.

Disease-free Survival and Relapse-free Survival

No significant difference in disease-free survival was observed between the three groups of women with negative nodes with or without radiotherapy ($P=0.65$) (Table below). Similarly for women with positive nodes, there was no significant difference in disease-free survival between mastectomy alone vs. mastectomy + RT.

No significant difference in relapse-free survival was observed between the three groups of women with negative nodes ($P=0.46$) (Table below). Similarly for women with positive nodes, there was no significant difference in relapse-free survival between mastectomy alone vs. mastectomy + RT.

Outcome	Radical mastectomy (RM)	Total mastectomy and irradiation (TM+RT)	Total mastectomy (TM)	P value
DFS (25 yrs) Negative nodes	19% (SE2%)	13% (SE2%)	19% (SE2%)	$p=0.65$
Hazard Ratios*	RM vs. TM+RT: 1.06 (95% CI 0.90 to 1.25, $p=0.49$) TM vs. RM: 1.07 (95% CI 0.91 to 1.27, $p=0.39$) TM+RT vs. TM: 1.02 (95% CI 0.87 to 1.21, $p=0.78$)			
DFS (25 yrs) Positive nodes	11% (SE2%)	10% (SE2%)		
Hazard Ratio	RM vs. TM+RT: 1.12 (95% CI 0.94 to 1.33, $p=0.20$)			
RFS (25 yrs) Negative nodes	53% (SE3%)	52% (SE4%)	50% (SE3%)	$p=0.46$
Hazard Ratios	RM vs. TM+RT: 0.96 (95% CI 0.76 to 1.21, $p=0.74$) TM vs. RM: 1.14 (95% CI 0.91 to 1.42, $p=0.27$) TM+RT vs. TM: 1.18 (95% CI 0.94 to 1.48, $p=0.15$)			
RFS (25 yrs) Positive nodes	36% (SE3%)	33% (SE3%)		
Hazard Ratio	RM vs. TM+RT: 1.09 (95% CI 0.89 to 1.35, $p=0.40$)			

* not clear from paper which is the reference set
SE standard error

Time to first event

20% of women with negative nodes and 13% of women with positive nodes were alive and event-free after 25 years of follow-up (See Table below). Most first events were distant recurrences of tumour and non-breast cancer deaths, irrespective of node status. The frequency of events between groups with negative or positive nodes were similar. (No statistical data were provided for these comparisons).

Event	Negative nodes			Positive nodes		All Women (N=1665)
	RM (n=362)	TM (n=365)	TM + RT (n=352)	RM (n=292)	TM + RT (n=294)	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Event	281 (78)	287 (79)	292 (83)	254 (87)	258 (88)	1372 (82)
Any recurrence*	135 (37)	156 (43)	131 (37)	165 (57)	168 (57)	755 (45)
Local	19 (5)	26 (7)	5 (1)	23 (8)	8 (3)	81 (5)
Regional	15 (4)	23 (6)	15 (4)	22 (8)	33 (11)	108 (6)
Distant	101 (28)	107 (29)	111 (32)	120 (41)	127 (43)	566 (34)
Contralateral breast cancer	19 (5)	27 (7)	32 (9)	13 (4)	15 (5)	105 (6)
Deaths (no evidence of disease)	104 (29)	86 (24)	101 (29)	64 (22)	58 (20)	413 (25)
Alive (event free)	81 (22)	78 (21)	60 (17)	38 (13)	36 (12)	293 (18)

* except contralateral breast

Node negative

There was a statistically significant difference between the 3 groups of women with negative nodes for the cumulative incidence of local or regional recurrence ($p=0.002$ for 3 way comparison). The rate was lowest in the total mastectomy with RT group, indicating a significant benefit of RT in reducing local recurrence. In contrast there were no statistically significant differences between the 3 groups in the cumulative incidence of distant recurrence as a first event ($p=0.61$).

Node positive

There were no significant differences in women with positive nodes between the RM and TM + irradiation groups for cumulative incidence of local or regional recurrence ($P=0.67$). Similarly there were no significant differences between the RM and TM + irradiation groups for the incidence of regional recurrence or the incidence of distant recurrence ($P=0.44$). However there was a significant reduction in the incidence of local recurrence after radiation therapy.

Distant-Disease-free Survival and Overall Survival

There were no significant differences in distant-disease-free survival between the 3 treatment groups with negative nodes at 25 years ($p = 0.63$ for three-way comparison). For women with positive nodes, there was no significant difference in distant-disease-free survival between the radical mastectomy and total mastectomy plus radiation therapy groups (See table below).

There was no significant difference in overall survival between the 3 treatment groups with negative nodes at 25 years ($p=0.68$ for three-way comparison). In women with positive nodes there was also no significant difference in overall survival between the radical mastectomy and total mastectomy plus radiation therapy groups (See table below).

Outcome	Radical mastectomy (RM)	Total mastectomy and irradiation (TM+RT)	Total mastectomy (TM)	P value
Distant-DFS (25 yrs) NO	46% (SE3%)	38% (SE3%)	43% (SE3%)	$p=0.63$
Hazard Ratios	RM vs. TM+RT: 1.08 (95% CI 0.88 to 1.34, $p=0.44$) TM vs. RM: 1.10 (95% CI 0.89 to 1.35, $p=0.39$) TM+RT vs. TM: 1.02 (95% CI 0.83 to 1.25, $p=0.85$)			
Distant-DFS (25 yrs) Positive nodes	32% (SE3%)	29% (SE3%)		
Hazard Ratio	RM vs. TM+RT: 1.07 (95% CI 0.87 to 1.32, $p=0.51$)			
Overall Survival (25 yrs) NO	25% (SE3%)	19% (SE2%)	26% (SE3%)	$p=0.68$
Hazard Ratios	RM vs. TM+RT: 1.08 (95% CI 0.91 to 1.28, $p=0.38$) TM vs. RM: 1.03 (95% CI 0.87 to 1.23, $p=0.72$) TM+RT vs. TM: 0.96 (95% CI 0.81 to 1.13, $p=0.60$)			
Overall Survival (25 yrs) Positive nodes	14% (SE2%)	14% (SE2%)		
Hazard Ratio	RM vs. TM+RT: 1.06 (95% CI 0.89 to 1.27, $p=0.49$)			

Positive Axillary Nodes after Total Mastectomy without Radiation Therapy

A total of 68/365 (18.6%) women with negative nodes who underwent total mastectomy with no radiation therapy subsequently developed positive ipsilateral nodes.

The time to recurrence of involved nodes was:

Within 2 years after surgery	51/68 (75%)
> 2 < 5 years after surgery	10/68 (15%)
>5 <10 years after surgery	6/68 (9%)
> 10 < 25 years after surgery	1/68 (1%)

The median time from mastectomy to the identification of positive axillary nodes was 14.8 months (range, 3.0-134.5).

Author conclusions

The findings validate earlier results showing no advantage from radical mastectomy. Although

differences of a few percentage points cannot be excluded, the findings fail to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy.

General comments –

This trial was included in the EBCTCG and GebSKI (2006) reviews.

In the discussion by the authors an important finding of the study reported was that about 40% of women with clinically negative nodes treated with radical mastectomy had pathological confirmation of tumour-positive axillary lymph nodes. Since the women were randomized to treatment groups, an estimate of about 40% of those undergoing total mastectomy alone having positive nodes that were not removed at the time of initial surgery is also assumed. About half of these women subsequently received a diagnosis of positive axillary nodes as a first event. Some investigators suggest that the frequency of delayed occurrence of positive axillary nodes is underestimated because patients with nodes that became positive after a distant recurrence should also have been included in the analysis. They suggest that axillary dissection in all women with clinically negative axillary nodes is justified. This may achieve local control of disease; however, the data from this trial indicate that leaving positive nodes unremoved did not significantly increase the rate of distant recurrence or breast-cancer-related mortality.

Another point was made about there being no survival advantage for the RT plus total mastectomy group with negative nodes at 25 years follow-up. These findings agree with two other studies at 10 year follow-up (Cancer Research Campaign. Br Med J 1976;1:1035-8; Cancer Research Campaign Working Party Lancet 1980;2:55-60), but differ from 3 studies reporting a 10% decrease in overall survival (Overgaard 1997, 1999; Ragaz 1997). They suggest that the use of systemic therapies in conjunction with postoperative RT may have relevance to these variations.

Updated 2018

Hojris, I., Andersen, J., Overgaard, M., & Overgaard, J. 2000, "Late treatment-related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone", *Acta Oncologica*, vol. 39, no. 3, pp. 355-372.

Design: RCT (subgroup analysis) (1982-1990) 1++

Country: Denmark, setting: Single institution.

Aim: The aim of the study was to evaluate late treatment-related morbidity in the DBCG 82b and c trials by assessing the morbidity in survivors living in the county of Aarhus.

Inclusion criteria

Mastectomy and axillary dissection, no evidence of metastatic disease, no previous history of cancer, no bilateral breast cancer, age less than 70 years, high risk (defined as node positive and/or tumour size > 5cm and/or invasion to skin or fascia).

Exclusion criteria

Patients without previously treated local recurrence

Population number of patients = 84 of 118 eligible patients.

Median age at mastectomy = 50 years (range 35–69 years)

Interventions

The primary surgical treatment included total mastectomy and axillary node dissection involving level I and partly level II (Waat-Boolsen et al 1988). The pectoral fascia was stripped and neither the major, nor the minor pectoral muscles were removed. All patients were treated on a linear accelerator in one institution. The target volume included the chest wall and regional lymph nodes, i.e. supraclavicular, infraclavicular, axillary and ipsilateral internal mammary nodes in the four upper intercostal spaces. The median dose was 50 Gy in 25 fractions, 5 fractions per week, with a dose variation of less than 10%. The lung and heart cauda to the first rib was protected by individually shaped blocks, and the chest wall covering this part was treated through two anterior shaped electron fields. Chest wall thickness- the distance from the skin surface to the pleural surface- was measured with ultrasound, and the electron energy was chosen to include the clinical target volume within the 85% isodose curve.

Adjuvant systemic therapy was also administered (CMF, tamoxifen or CMF + tamoxifen).

Systemic treatment plus radiotherapy (RT-group) n= 42

Systemic treatment alone (no RT-group) n=42

Significantly more patients in the no RT-group received adjuvant tamoxifen than in the RT-group, otherwise the two groups were comparable.

Outcomes

Patients were assessed by a structured interview and physical examination by a single observer (1995-1996).

LENT SOMA tables (Late Effects Normal Tissues; Subjective, Objective, Management, Analytic)

Grade 0 = no toxicity

Grade 5 = death or loss of organ

Other definitions:

Occasional = monthly; intermittent = weekly; persistent = daily; refractory = constant

Lymphoedema was assessed by measuring the differences in circumference of the ipsilateral arm and contralateral arm using standard anatomical criteria (15 cm above and 10 cm below the olecranon) as well as the difference in arm volume.

Follow up

81% of invited participants took part in the follow-up study (95/118 eligible patients). Patients were followed for a median of 9 years (range 6–13 years).

Results

Lymphoedema

Objective assessment: 14% of irradiated patients versus 3% of the non-irradiated patients had lymphoedema (not significant).

Subjective assessment: 17% of irradiated women noticed a periodic swelling of the ipsilateral arm, and 26% felt a constant swelling in the arms. This was significantly more than in the non-irradiated group

($p=0.02$).

Lymphoedema –pain/discomfort (subjective)

A few patients described more than minimal pain/discomfort related to lymphoedema (NS).

Lymphoedema – function (subjective)

17% of irradiated and 9% of non-irradiated patients felt that swelling in the arms had an impact on their lives in addition to interfering with athletic recreation (grade>1) (NS).

Mobility of shoulder

Subjective assessment: 38% of RT-group and 5% of the no RT-group noticed some degree of shoulder movement impairment ($p<0.01$).

Objective assessment: 52% of irradiated patients and 15% of non-irradiated patients had some degree of impaired shoulder movements, mainly slightly decreased ($p<0.01$).

Shoulder function (subjective)

16% of irradiated patients and 2% of the non-irradiated patients found that impairment of shoulder functions interfered with work and/or daily activities (grade >1) ($p=0.02$).

Shoulder pain (subjective)

Occasional or intermittent pain from the shoulder was frequent in both treatment groups, whilst daily pain (grade 3) was more pronounced in the irradiated patients (NS).

Univariate and multivariate analyses were performed of possible factors contributing to lymphedema and impaired shoulder movements. Factors included in the analyses were radiotherapy treatment, chemotherapy treatment, endocrine treatment, number of nodes removed (0-3, 4-6, 7-9, >9), number of positive nodes removed (0-10), tumour size (6-60), age (44-82), obesity (BMI >30) and smoking.

Factors that were significant in increasing the risk of lymphoedema on multivariate analysis were:

Number of axillary lymph nodes removed OR 4.5 (95% CI 1.2-16; $p=0.02$)

Age of patient OR 1.1 (95% CI 1.0-1.2; $p=0.01$)

Radiotherapy was the only factor shown to reduce shoulder movements OR 7.0 (95% CI 2.2-22; $p=0.0008$).

Paresthesia

Subjective assessment: paresthesia of the arm was more common in irradiated than non-irradiated patients, the frequency was more than occasional (>grade 1) in 7% of irradiated and was absent in the non-irradiated patients ($p<0.01$).

Objective examination: paresthesia/hypesthesia occurred 21% of irradiated patients and 7% of non-irradiated patients (NS).

Decreased arm strength (subjective)

28% of the RT-group and 19% of the no RT group noticed a weakness in the arm, usually mild (NS).

Decreased arm strength (objective)

14% of irradiated patients and 2% of the non-irradiated patients had slightly decreased strength in the ipsilateral arm (NS).

Other morbidities

Chest x-rays showed apical lung fibrosis in 60% of irradiated patients, but this was not reflected in pulmonary symptoms (dyspnea or coughing). There were no differences between irradiated and non-irradiated patients in cardiac morbidity by assessment of angina pectoris.

Hojris, I., Overgaard, M., Christensen, J. J., & Overgaard, J. 1999, "Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: Analysis of DBCG 82b and 82c randomised trials", *Lancet*, vol. 354, no. 9188, pp. 1425-1430.

Design: RCT (subgroup analysis) (1982-1990)

Level 1++

Country: Denmark, setting: Single institution.

Aim: To assess morbidity and mortality from ischaemic heart disease in patients treated with postmastectomy radiotherapy.

Inclusion criteria

Mastectomy and axillary dissection, no evidence of metastatic disease, no previous history of cancer, no bilateral breast cancer, age less than 70 years, high risk (defined as node positive and/or tumour size > 5cm and/or invasion to skin or fascia).

Exclusion criteria

Registered ischaemic heart disease.

Population number of patients = 3083 randomized from the DBCG trials.

1538 in RT group, 1545 no RT group.

Interventions

Radiotherapy was delivered to the chest wall, including the surgical scar and regional lymph nodes (ie, supraclavicular, infraclavicular, axillary, and ipsilateral internal mammary nodes). An anterior photon field was used to treat the periclavicular region and the axilla. The lung and heart caudal to the first rib were protected by

individually shaped blocks, and the chest wall covering this part was treated through two anterior shaped electron fields.

Chest-wall thickness (the distance from the skin surface to the visceral pleura) was measured by ultrasonography. The target depth for the ipsilateral internal mammary nodes in the four upper intercostal spaces was defined as chest-wall thickness plus 0.5 cm, and the target depth for the scar region was defined as chest-wall thickness minus 1 cm. The electron energy was chosen to include the clinical target volume in the 85% isodose. Most were treated using a linear accelerator.

Outcomes

Ischaemic heart disease, including acute myocardial infarction (ICD8 codes 410–14 or ICD10 codes I20–I25) and acute myocardial infarction alone (ICD8 code 410 or ICD10 codes I21 and I22).

Diagnostic, therapeutic, and follow-up data were obtained from the DBCG and National Patient Registers. Data were validated blind to intervention group.

Follow up

Follow-up was from the date of mastectomy until the first occurrence of ischaemic heart disease as well as the first occurrence of acute myocardial infarction.

The median follow-up for patients alive at time of assessment was 117 months (range 81–171), and median time to death was 45 months (1–170).

Results

1393/3046 women were alive at the time of analysis.

Cumulative survival at 12 years was significantly better for women in the radiotherapy group than the no-radiotherapy group (46 vs. 36%, $p < 0.0001$). At the end of follow-up, more women in the no-radiotherapy group than in the radiotherapy group died of breast cancer. Similar proportions of each group died of ischaemic heart disease (IHD) (see table below from the paper).

	RT (n=1525)	No RT (n=1521)
Alive	766 (50.2%)	627 (41.2%)
Cause of death		
Breast cancer	674 (44.2%)	799 (52.2%)
Other cancers	36 (2.4%)	37 (2.4%)
IHD	12 (0.8%)	13 (0.9%)
Unknown	5 (0.3%)	4 (0.3%)
Other causes	32 (2.1%)	41 (2.7%)

An analysis of the cumulative incidence of morbidity and mortality from IHD found that it increased over time with no significant differences between the RT and no RT arms. Morbidity and mortality of ischaemic heart disease and acute myocardial infarction also did not differ significantly between treatment groups. This also applied to tumour laterality (left or right breast) and menopausal status (pre / perimenopausal or postmenopausal).

A further analysis to assess the risk of IHD with time after treatment found no increase in hazard rate

of morbidity from ischaemic heart disease with increasing time by radiotherapy status.

Author conclusions

Morbidity and mortality from ischaemic heart disease were not significantly altered by use of adjuvant radiotherapy after mastectomy. The actuarial risk of ischaemic heart disease did not increase after 12 years.

General comments -

Updated 2018

Gustavsson A, Bendahl P-O, Cwikiel M, Eskilsson J, Lofvander Thapper K, Pahlm O. No serious late cardiac effects after adjuvant radiotherapy following mastectomy in premenopausal women with early breast cancer. *Int J Radiat Oncol Biol Phys* 1999 Mar;43(4):745-54.

Design: RCT (subgroup analysis) (1978-1983) Level 1++

Country: Sweden, setting: RT given at 2 centres

Aim: To assess, with sensitive, noninvasive techniques, the prevalence and degree of late cardiac effects, namely coronary artery disease, decreased left and/or right ventricular function, and morphological and/or functional abnormalities in the cardiac valves, in women younger than 65 years of age with Stage II breast cancer 10–17 years after standardized, adjuvant radiotherapy following mastectomy.

Inclusion criteria

Patients treated during the period 1978–83, 65 years or younger at examination, and with no relapse or new malignancy.

Exclusion criteria

One patient with bilateral breast cancer and RT

Population number of patients = 153/275 (56%) eligible, 91 enrolled.

The patients were evenly distributed between the three original therapy groups.

Number	Age (median yrs)	RT	No RT
34	59 (50-64yrs)	Left side	
33	57 (45-64yrs)	Right side	
23	57 (45-63yrs)		Cyclophosphamide

Interventions

Following modified radical mastectomy and axillary clearance, premenopausal women were randomized into three groups: (a) postoperative radiotherapy; (b) postoperative radiotherapy plus cyclophosphamide, 130 mg/m² orally, days 1–14, 28-day cycle length, 12 cycles; and (c) cyclophosphamide alone.

Radiotherapy technique:

The target volume was divided into four areas: lymph nodes of the supra- and infraclavicular fossae, the axilla, the ipsilateral internal mammary lymph nodes, and the chest wall.

Ventral photon beams were used for the supra- and infraclavicular fossae and the axilla. Ventral electron beams were used for the internal mammary nodes and an adjacent orthovoltage field covered the chest wall. A specified target dose of 38-48 Gy was administered in daily fractions of 1.9-2.4 Gy, 5 days/week.

At follow-up patients were interviewed about cardiovascular and hypothyroid symptoms, risk factors (smoking, hypertension, and diabetes mellitus), and the occurrence of heart disease in the family. All patients had a physical examination, TSH (thyroid stimulating hormone) and blood lipid levels (cholesterol and triglycerides) were analyzed.

Outcomes

Myocardial scintigraphy

Exercise test

ECG

Echocardiography

Follow up

10-17 years after radiotherapy

Results

95/275 women had died, however none died from cardiac disease.

Causes of death were:

Disseminated breast cancer in 88 patients

Another malignancy in 5 patients

Subarachnoid haemorrhage in one case

Cerebral haemorrhage in 1 case

10 patients died of metastatic disease and on autopsy 4 had cardiovascular abnormalities: 1 coronary artery sclerosis (right-sided radiotherapy); 1 (without irradiation) had slight aortic valve sclerosis and moderate sclerosis of the coronary arteries; one (left-sided radiotherapy) with slight hypertrophy of the left ventricle; and one (without irradiation) dilation of the right ventricle, possibly due to massive pulmonary metastases. None of the patients still alive with recurrent disease had any cardiac symptoms.

Myocardial scintigraphy

Reversible defects were not found in any patient.

Abnormal findings were present in 6 patients, with reduced uptake at rest indicating infarction or fibrosis, (four with left-sided and two with right-sided radiotherapy). The defects in four patients with left-sided radiotherapy had an apical, septal, anterior-septal or inferior-septal location, and in two patients with right-sided radiation the location of the defects was inferior or septal-inferior.

Exercise capacity

The average exercise capacity for all groups was slightly above 100% of the value expected (chemotherapy 106%; radiotherapy 104%; radiotherapy left 105%; and radiotherapy right 102%).

Resting ECG

Eighteen patients had abnormal or borderline abnormal resting ECGs. Patients given radiotherapy had significantly ($p = 0.03$) more resting ECG changes than those treated with chemotherapy only (26% vs. 4%). No significant differences were found between patients treated with right-sided or left-sided irradiation. The authors considered that the ECG signs of left ventricular hypertrophy (in three patients without hypertension) or a short P-R interval could not possibly be related to the radiotherapy given.

Echocardiography

Pericardial effusion was not found in any patients.

Systolic function was not reduced (<25%) in any patient.

Left ventricular diastolic function (E/A Ratio) was significantly lower in both irradiated groups: left-sided radiotherapy ($p = 0.024$), and right-sided radiotherapy ($p = 0.017$), when compared to patients without irradiation. No difference was found between the two radiotherapy groups ($p = 1.0$).

Author conclusions:

Women younger than 50 years of age at the time of adjuvant radiotherapy following mastectomy in early breast cancer, had no serious cardiac sequelae 13 years (median) later, despite partly old-fashioned radiation techniques.

General comments -

Observational Studies (eg. Prospective Cohort or Retrospective Cohort or Case Series):

Smith, B. D., Haffty, B. G., Hurria, A., Galusha, D. H., & Gross, C. P. 2006, "Postmastectomy radiation and survival in older women with breast cancer", *Journal of Clinical Oncology*, vol. 24, no. 30, pp. 4901-4907.

Design: Retrospective Cohort NRS (1992-1999)

Level 2+

Country: USA, setting: Multi-centre

Aim: To determine whether postmastectomy radiotherapy (PMRT) improves survival for older women with breast cancer.

Inclusion criteria

Women identified from the SEER database aged over 70 years

Exclusion criteria

No invasive component, not pathologically confirmed, histology not epithelial in origin, distant metastases, prior malignancy, bilateral disease, not treated with mastectomy, received neoadjuvant chemotherapy.

Population number of patients = 11 594 women identified

Median age 77 years (73-81)

Median tumour size 2cm (interquartile range 1.2-3.0cm)

8297 (72%) had ductal histology

9565 (82%) ER +ve

3909 (34%) pathologically involved lymph nodes

1529 (13%) had PMRT

1490 (13%) had chemotherapy

7416 (64%) low risk; 2125 (18%) indeterminate risk; 2053 (18%) high risk

Interventions

Surgery classified by ICD-9 coding. The most extensive surgical procedure during the first 9 months after diagnosis was considered definitive. Treatment with radiation according to ICD-9 coding.

Outcomes

Overall survival

Follow up

Median follow-up of 6.2 years (4.2-8.5)

Results

Factors associated with increased use of PMRT were:

Young age ($p < 0.0001$)

Black race ($p = 0.008$)

No co-morbid illness ($p < 0.0001$)

Large tumour size ($p < 0.0001$)

Clinical stage T4 ($p < 0.0001$)

High tumour grade ($p < 0.0001$)

Lobular histology ($p < 0.0001$)

Multiple involved lymph nodes ($p < 0.0001$)

High risk groups were more likely to receive both PMRT (38%, 785/2053) and chemotherapy (32%, 659/2053). Those with lobular histology had increased utilization of PMRT.

Multivariate analyses

Entire cohort:

PMRT at 6.2 years follow-up was not associated with improved survival overall (HR 1.03 95% CI 0.95-1.13; $p = 0.49$)

Chemotherapy was associated with a trend in improved survival (HR 0.92 95% CI 0.84-1.01; $p = 0.08$)

Lobular histology was associated with a decreased risk of death (HR 0.80 95% CI 0.72-0.88; $p < 0.0001$)

Overall survival (by risk status)

Neither PMRT nor chemotherapy were associated with survival in the low and intermediate risk groups, but were significant in the high risk group (only PMRT results are included in the table below).

ER/PR Positive tumours:

Improved overall survival was associated with PMRT for patients with ER or PR positive (n=9860) tumours in the high risk group, and with chemotherapy (HR 0.77 95% CI 0.64-0.91; $p = 0.003$). There was no association of survival benefit with PMRT for low or intermediate risk groups with ER or PR positive tumours.

ER/PR negative tumours:

There was no association of survival benefit with PMRT for the low or intermediate risk groups with ER or PR negative tumours. A trend towards improved overall survival was associated with PMRT for patients with ER or PR negative (n=1652) tumours in the high risk group (although not statistically significant), and with chemotherapy (HR 0.48 95% CI 0.31-0.75; $p = 0.001$).

Risk group	PMRT HR (95% CI)	P value
Low (T1/2 N0)	1.06 (0.90-1.24)	0.48
Intermediate (T1/2 N1)	1.23 (0.99-1.52)	0.06
High (T3/4 and/or N2/3)	0.85 (0.75-0.97)	0.02
All risk groups	1.03 (0.95-1.13)	0.49
ER/PR status		
High (ER/PR +ve)	0.86 (0.74-0.99)	0.04
Low (ER/PR -ve)	0.97 (0.63-1.48)	0.87
Intermediate (ER/PR -ve)	2.23 (1.19-4.18)	0.01
High (ER/PR -ve)	0.80 (0.55-1.18)	0.26

Author conclusions

Adjuvant PMRT was associated with a survival benefit for women aged 70 years or more with a high risk (T3/4 and/or N2/3) breast cancer. However only 38% of high risk women were treated with PMRT in this cohort (1992-1999). Further studies are indicated to determine utilization of PMRT and barriers to receipt of PMRT.

General comments –

Limitations:

Unreported confounders associated with the delivery of the intervention (PMRT) and outcomes of interest may have influenced the treatment assignment bias.

Guidelines

Recht, A., Edge, S. B., Solin, L. J., Robinson, D. S., Estabrook, A., Fine, R. E., Fleming, G. F., Formenti, S., Hudis, C., Kirshner, J. J., Krause, D. A., Kuske, R. R., Langer, A. S., Sledge, G. W., Jr., Whelan, T. J., & Pfister, D. G. 2001, "Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology", *Journal of Clinical Oncology*, vol. 19, no. 5, pp. 1539-1569

Design: Canadian guideline development process.

Country: USA

Inclusion criteria

Exclusion criteria

Population

Methods

The ASCO guideline was developed by an expert multi-disciplinary panel who reviewed relevant information from the published literature through to July 2000. Searches were conducted on MEDLINE and other databases. In evaluating the evidence of the role of PMRT the panel followed the process of guideline development established by the Canadian Medical Association. The guidelines were validated by seven external reviewers, the American Society of Clinical Oncology (ASCO) Health Services Research Committee members, and the ASCO Board of Directors.

Outcomes

Locoregional recurrence
Freedom from distant failure
Freedom from any relapse
Overall survival
Treatment toxicity

Follow up -

Results

Recommendations from the paper are reported below:

The panel found that the weight of the evidence from randomized trials was sufficient to recommend the routine use of PMRT for patients with four or more positive axillary lymph nodes. It is much less certain that the benefits of PMRT are sufficient to justify its use in most patients with T1/2 tumours with one to three positive nodes.

The panel did not find sufficient evidence regarding the impact of other tumour-related, patient-related, or treatment related factors to make recommendations or suggestions for modifying these guidelines.

Since the chest wall is the site at greatest risk of recurrence, we suggest that adequately treating the chest wall is mandatory. The situation is less clear regarding irradiation of the regional lymph nodes. However, because the risk of axillary recurrence after a complete or level I/II dissection is very low, and because the combination of axillary dissection and full axillary irradiation markedly increases the risk of lymphoedema, the panel suggests that axillary radiotherapy *not* be given routinely to patients undergoing complete or level I/II axillary dissection.

There is insufficient evidence to suggest or recommend whether internal mammary nodal irradiation should or should not be used routinely. The conclusions of the panel concerning the impact of radiotherapy on relapse-free and overall survival were therefore predominantly supported by level II evidence rather than level I evidence.

PMRT reduced the risk of LRF after mastectomy in patients receiving systemic therapy by a substantial amount in all trials. The majority of available trials, particularly the larger ones, also showed that PMRT improves relapse-free and overall survival rates to a lesser, but clinically relevant, degree.

General comments -

Truong, P. T., Olivotto, I. A., Whelan, T. J., & Levine, M. 2004, "Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy", *CMAJ: Canadian Medical Association Journal*, vol. 170, no. 8, pp. 1263-1273.

Design: Review of meta-analyses, consensus statements and treatment guidelines.

Country: Canada

Inclusion criteria Searches between 1966 – Nov 2002

Exclusion criteria

Population

Methods

The guideline was based on a review of all meta-analyses, consensus statements and other guidelines published between 1966 and November 2002. Searches of MEDLINE and CANCERLIT for English-language randomized controlled trials published between 1995 and November 2002 were also conducted to supplement the literature previously reviewed by the American Society of Clinical Oncology (ASCO) Health Services Research Committee panel in a published guideline. A nonsystematic review of the literature was continued through to June 2003.

Validation: The authors' original text was submitted for review, revision and approval by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Subsequently, feedback was provided by 11 oncologists from across Canada. The final document was approved by the steering committee.

Outcomes

Locoregional control

DFS

OS

Treatment related toxicity

Follow up -

Results

Recommendations (from the paper):

- Locoregional PMRT is recommended for women with an advanced primary tumour (tumour size 5 cm or greater, or tumour invasion of the skin, pectoral muscle or chest wall).
- Locoregional PMRT is recommended for women with 4 or more positive axillary lymph nodes.
- The role of PMRT in women with 1 to 3 positive axillary lymph nodes is unclear. These women should be offered the opportunity to participate in clinical trials of PMRT.
- Locoregional PMRT is generally not recommended for women who have tumours that are less than 5 cm in diameter and who have negative axillary nodes.
- Other patient, tumour and treatment characteristics, including age, histologic grade, lymphovascular invasion, hormone receptor status, number of axillary nodes removed, axillary extracapsular extension and surgical margin status, may affect locoregional control, but their use in specifying additional indications for PMRT is currently unclear.
- PMRT should encompass the chest wall and the supraclavicular, infraclavicular and axillary apical lymph node areas.
- To reduce the risk of lymphedema, radiation of the entire axilla should not be used routinely after complete axillary dissection of level I and II lymph nodes.
- A definite recommendation regarding the inclusion of the internal mammary lymph nodes in PMRT cannot be made because of limited and inconsistent data.
- The use of modern techniques in radiotherapy planning is recommended to minimize excessive normal tissue exposure, particularly to the cardiac and pulmonary structures.
- Common short-term side effects of PMRT, including fatigue and skin erythema, are generally tolerable and not dose-limiting. Severe long-term side effects, including lymphedema, cardiac and pulmonary toxicities, brachial plexopathy, rib fractures and secondary neoplasms, are relatively rare.
- The optimal sequencing of PMRT and systemic therapy is currently unclear. Regimens containing anthracyclines or taxanes should not be administered concurrently with radiotherapy because of the potential for increased toxicity.

Reviews

Bartelink (2000)

Bartelink, H. 2000, "Post-mastectomy radiotherapy: Recommended standards", *Annals of Oncology*, vol. 11, no. SUPPL. 3, pp. 7-11.

In the paper Bartelink suggests that there is a general consensus that a loco-regional recurrence rate of 20% at 10 years or more justifies postoperative radiotherapy. This proportion (or higher) is frequently seen in patients with a microscopically incomplete resection, a T3 N0 tumour with unfavourable histological signs or positive nodes, and for patients with four or more positive lymph node metastases (N4+). The indications for postoperative irradiation of the chest wall and axilla should be considered separately since the recurrence rate for the axilla is much lower than in the chest wall. The most difficult question concerns whether patients with T1–2 and N1 still need post-mastectomy radiotherapy, since the major benefit in survival is seen in this patient group from the Danish trials. The indications for post-mastectomy radiotherapy should be discussed in a multidisciplinary team including the pathologist, surgeon and radiation oncologist. They should consider the surgical technique, such as the adequacy of the axillary dissection, and pathological factors associated with a high local recurrence rate, such as vascular invasion and extra nodal spread, together with the proximity of the tumour to the resection margins. Of importance is that, for patients receiving neo-adjuvant chemotherapy, the indication for post-mastectomy should be based on the pre-treatment tumour extension.

Indications for postoperative chest wall irradiation (from the paper)

Incomplete resection (micro- or macroscopic)
4 or more positive lymph nodes
T3 tumours with grade 2 or 3 and/or vascular invasion
T3 N+ tumours
Diffusely growing tumours in more than one quadrant

Bellon (2006)

Bellon, J. R., Katz, A., & Taghian, A. "Radiation therapy for breast cancer", *Hematology/Oncology Clinics of North America*, vol. 2006 Apr; 20, no. 2, pp. 239-257.

Bellon et al describe the benefits of post-mastectomy RT following adjuvant systemic therapy on survival for premenopausal women (Overgaard 1997; Ragaz 1997), and post-menopausal women (Overgaard 1999). The findings from these studies are presented in the following table:

Author	Patients	Follow-up (Years)	DFS			OS		
			CT (%)	CT+RT(%)	p	CT (%)	CT+RT(%)	p
Ragaz 1997	Node +ve Premenopausal	20	38	53	0.008	47	37	0.03
Overgaard 1997	High risk Premenopausal	10	34	48	0.001	45	54	0.001
Overgaard 1999	High risk Postmenopausal	10	24	36	0.001	36	45	0.03

CT = chemotherapy
RT = Radiotherapy

Survival benefit was demonstrated in high risk patients, e.g., four or more positive lymph nodes, as well as for women at lower risk with 1-3 positive lymph nodes. Controversy still exists for this latter group.

Update Evidence

Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006 May 20;24(15):2268-75.

Design: RCT (extended follow-up) Level 1+

Country: Multinational

setting:

Aim: The aim of this follow up analysis was to evaluate the overall failure pattern among high-risk breast cancer patients who were randomly assigned to RT or no RT in addition to systemic therapy (as part of the Danish Breast Cancer Cooperative Group (DBCG) 82 b and c trials).

Inclusion criteria

- High-risk BC patients who had total mastectomy and partial axillary dissections were included.
- Patients had no evidence of distant metastases (DM), had no history of cancer, had unilateral BC, and were age younger than 70 years. All patients were at high risk of recurrence because of a tumour size larger than 5 cm, and/or positive axillary nodes, and/or invasion of the skin or pectoral fascia.
- The adjuvant systemic therapy to the pre-menopausal patients consisted of CMF

Exclusion criteria

Not described in this paper

Population

A long-term follow-up was performed among the 3,083 patients from the Danish Breast Cancer

Cooperative Group 82 b and c trials, except in those already recorded with distant metastases (DM) or contralateral breast cancer.

Interventions

- Patients were randomly assigned to RT or no RT in addition to systemic therapy
- The RT in the DBCG82 b and c trials was intended to cover the chest wall and regional lymph nodes including the axillary, supra/intra-clavicular, and ipsilateral internal mammary nodes.

Outcomes

- Locoregional recurrences (LRR)
- Distant metastases (DM)

LRR alone was defined as an LRR with no sign of subsequent DM within 1 month, whereas patients with LRR followed by DM within the same month were recorded as simultaneous failures (simLRR-DM)

- Contralateral breast cancer (CBC)
- Disease-free survival (DFS)

- Overall survival (OS)

Follow up –

- According to DBCG protocol, follow-up information was recorded routinely at regular intervals for up to 10 years or until first recurrence, death, or the occurrence of a new primary cancer, whichever came first.
- Follow-up was continued until DM, CBC, emigration, or death. Nine patients were lost to follow-up because of emigration; otherwise, the follow-up was complete.

Median follow-up = 18 years

Results

LRR:

- The probability of any first BC event (LRR, simLRR-DM, DM, or CBC) was significantly reduced among patients in the RT group: RR=0.68 95% CI 0.63-0.75, P< 0.001).
- The median time to any first BC event was 3.9 after no RT and 7.9 years after RT, (P<0.001).
- The 18-year probability of LRR (with or without DM) or LRR alone was significantly lower in the RT group than the no RT group.

The table below lists the site of first LRR alone and first simLRR-DM.

The frequency of all sites of LRR was lower with RT than without RT.

- Chest wall failures were the most common type of LRR, with involvement of this site in 55% in the no-RT group and 70% in the RT group.
- Axillary failures were especially pronounced among patients in the no-RT group, with involvement of this site in 43%.
- In the RT group, the axilla was involved in 24% of the LRRs.
- In the no-RT group, chest wall and axillary failures most commonly occurred without simultaneous DM, whereas supra/infraclavicular failures were associated as often with DM.

Overall, 22% of the patients with LRR in the no-RT group appeared with simultaneous DM, whereas 48% of the patients with LRR in the RT group also had DM at the time of diagnosis of LRR.

DM:

- The 18-year probability of DM subsequent to LRR = 35% after no RT and 6% after RT (P<0.001). The 18-year probability of any DM = 64% after no RT and 53% after RT (P<0.001)
- The median time to DM = 6.5 years in the no-RT group and 12.3 years in the RT group (P=0.04).

In the no-RT group: DM after LRR and DM as first site of failure were equally common
In the RT group, DM occurred most often as the first site of failure. See table 2 in paper.

- To assess if the risk of DM was time dependent in the two groups, the hazard rates for 2-

year time interval were calculated:

- The DM hazard rates were at all times increased among patients in the no-RT group compared with patients in the RT group.
- In both groups, the DM hazard rate decreased with time after mastectomy (authors note that even 18 years after mastectomy, a small risk of DM was present in both groups).
- The six most common sites of first DM were bone; lung; pleura; liver; CNS and skin.
- Bone: 18-year probability of bone metastases = 40% after no RT and 32% after RT (P=0.003)
- The 18-year probabilities of lung metastases, CNS metastases and skin metastases outside the ipsilateral chest wall were significantly lower in the RT group.

Overall Comments:

In high-risk breast cancer patients who had had total mastectomy and partial axillary dissection, this study showed that post-mastectomy RT reduced loco-regional recurrences as the first site of failure, and overall fewer patients have distant metastases.

Updated 2018

Kyndi M, Sorensen FB, Knudsen H, Overgaard M, Nielsen HM, Overgaard J, et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. *J Clin Oncol* 2008 Mar 20;26(9):1419-26.

Design: RCT – subgroup analysis, evidence level 1+

Country: Denmark

Aim: To examine the effect of oestrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER-2), and constructed subtypes patients who received or did not receive post-mastectomy radiotherapy (PMRT).

Inclusion criteria

High-risk breast cancer patients:

High-risk was defined as either positive lymph nodes and/or tumour size larger than 5 cm and/or invasion of tumour to surrounding skin or pectoral fascia. All women had a total mastectomy and a partial axillary dissection.

Exclusion criteria

Population

3,083 high-risk breast cancer patients randomly assigned to PMRT in the Danish Breast Cancer Cooperative Group (DBCG) protocol 82 trials b and c.

The premenopausal women were enrolled in the DBCG82 b protocol and were assigned to either radiotherapy plus CMF or to CMF chemotherapy alone.

The postmenopausal women were enrolled in the DBCG82 c protocol and were assigned either to radiotherapy plus tamoxifen or to tamoxifen alone.

1,000 patients had invasive tissue available for tumour marker identification and analysis but successful identification could be done for all three markers in 996 patients.

For statistical analyses four subgroups were constructed from hormonal receptors (Rec).

- Rec+ was defined as ER+ and/or PgR+
- Rec– as both ER– and PgR–
- The four subgroups were Rec+/HER2–, Rec+/HER2+, Rec–/HER2– (triple negative), and Rec–/HER2+

Interventions

- Patients were randomly assigned to RT or no RT in addition to systemic therapy

Outcomes

- LRR, distant metastasis(DM) (including patients presenting with LRR and DM at the same time), and overall survival.
- End points have been described in detail previously – see Nielson 2006
- Hazard ratios (HRs) presented on Kaplan-Meier OS probability plots were for overall

mortality.

Follow up –

Within the subgroup of 1,000 patients, median follow-up time was 17 years for the patients alive and still at risk.

Results

- As reported in the DBCG82 series, overall mortality was significantly reduced (HR=0.84; 95% CI, 0.72 to 0.97), DM (HR=0.80; 95% CI, 0.68 to 0.94) and LRR (HR=0.17; 95% CI, 0.10 to 0.26) probabilities after PMRT were found within the subgroup of 1,000 patients.
- A significantly improved overall survival after PMRT was reported in patients with good prognostic markers such as hormonal receptor–positive and HER2- patients (including the two Rec+ subtypes).
- No significant overall survival improvement after PMRT was reported in patients with an a priori poor prognosis, that is the hormonal receptor–negative and HER2+ patients, and in particular the Rec–/HER-2+ subtype.
- When comparing hazard ratios and 95% CIs, there were significantly smaller improvements in locoregional recurrence control after PMRT were found for ER– and PgR– tumours compared with the ER+ and PgR+ tumors (P=0.003 and 0.04, respectively), and for the triple-negative (P=0.02), and the Rec–/HER-2+ subtypes (P=0.003) compared with the Rec+/HER2– subtype.

Updated 2018

Killander F, Anderson H, Rydén S, Möller T, Aspegren K, Ceberg J, et al. Radiotherapy and tamoxifen after mastectomy in postmenopausal women -- 20 year follow-up of the South Sweden Breast Cancer Group randomised trial SSBCG II:I. *European journal of cancer* (Oxford, England : 1990) 2007;43(14):2100-8.

Design: RCT, evidence level 1-

Country:

setting:

Aim: To evaluate long-term effects of radiotherapy and tamoxifen after mastectomy on recurrence and survival in stage II breast cancer.

Inclusion criteria

Postmenopausal women who had modified radical mastectomy (MRM) and the presence of stage II invasive mammary adenocarcinoma and age below 71 years

Exclusion criteria

Population

724 postmenopausal women; 713 patients could be followed up for survival, and 668 were fully evaluable

Interventions

A RCT with three treatment alternatives:

1. Radiotherapy 50 Gy/25 fractions to chest wall and regional lymph nodes (RT).
2. Radiotherapy and tamoxifen 30 mg/day for one year (RT + tam)
3. Tamoxifen (tam).

Outcomes

time to recurrence, type of recurrence and overall survival.

In the present long-term analysis, we have added time to systemic disease, incidence of other events and side effects.

Follow up

Follow-up for survival was 23 years

Results

LRR:

- The cumulative incidence of loco-regional recurrences as first event at 20 years of follow-up was significantly reduced, with 71%, by radiotherapy ($p < 0.001$), 18.5% (95% CI 13.8–23.8%) in the tamoxifen group compared to 5.3% in the RT + tamoxifen group and 6.7% (95% CI 3.8–10.4%) in patients randomised to RT with and without tamoxifen.
- In N0 patients: 7% loco-regional recurrences were diagnosed after 20 years in the Tamoxifen group, versus 6% in the RT + Tam group.
- In the N1–3 subgroup: the incidence was 25.9% (95% CI 17.5– 35.1%) in the Tamoxifen group, and 2.6% (95% CI 0.5–8.3%) in the RT + Tamoxifen group.
- Authors note that in patients who developed loco-regional recurrences, the majority later developed distant metastases in spite of salvage therapy. Salvage treatment after recurrence was thus successful in 31% of patients non-irradiated after mastectomy but

only in 4% of irradiated patients.

Cumulative incidence of systemic disease

- At 20 years the cumulative incidence of systemic disease = 50% in the RT group, 40% in the RT + Tamoxifen group and 45% in the tamoxifen group ($p = 0.33$ comparing RT + Tam versus Tam, and $p = 0.047$ comparing RT vs RT + Tam)
- Considering only receptor positive patients the numbers were 54% (RT only) , 40% (tamoxifen) and 41% (RT plus tamoxifen), ($p = 0.047$ comparing RT versus RT + Tamoxifen).
- In patients with more than three lymph nodes, there was a significant difference between RT and RT + Tamoxifen (88% versus 67%, $p = 0.02$).
- There were no significant differences reported for node negative patients.

Survival:

- Overall mortality at 20 years = 71% with RT, 68% with RT + tamoxifen group and 62% in tamoxifen group.
- The difference between RT + Tamoxifen versus Tamoxifen was not significant ($p = 0.14$).
- The difference between was not significantly different between RT and RT + Tamoxifen ($p = 0.50$).
- WRT hormone receptor positive patients the mortality rates at 20 years were 74% in the RT arm, 67% in the combination arm, and 54% in the Tamoxifen group.
- No statistically significant difference was reported when comparing RT to RT + Tamoxifen ($p = 0.28$) but the comparison of RT + Tamoxifen versus Tamoxifen was significant in favour of patients not receiving radiotherapy ($p = 0.047$)
- In the N1–3 group, mortality at 20 years was 74%, 65% and 64% (but there was no significant difference).

Overall Comments:

This study reported a very clear relative reduction in loco-regional recurrences, 71%, was obtained with radiotherapy which is in common with the majority of adjuvant radiotherapy trials.

Patient numbers in the comparative groups were not balanced and due to long follow up (20 years) there were some losses of data. The authors claim that this should not have affected the findings.

6.4 What is the most effective radiotherapy dose fractionation regimen for patients receiving external beam radiotherapy after surgical excision of the breast?

Short Summary

Two systematic reviews of high quality were identified that compared hypofractionated radiotherapy with no radiotherapy (RT) (EBCTCG 2002, and GebSKI *et al* 2006). The strongest evidence was from randomised controlled trials (RCT) (Owen *et al* 2006; START A and B 2008; Whelan *et al* 2002; Yarnold *et al* 2005). An earlier trial by Bates *et al.* (1998) did not use the conventional 50 Gy in 25 fractions radiotherapy dose as comparator. The remaining two trials were small and of lower quality (Goel *et al* 2000, Taher *et al* 2004).

Side effects or cosmesis were assessed in five RCTs (Bates 1988, Goel *et al* 2000, Taher *et al* 2005, Whelan *et al* 2002, Yarnold *et al* 2005) two cohort studies (Olivotto *et al* 1996, Marhin *et al* 2007) and four non-randomised (NRS) studies (Marcenaro *et al* 2004, Mladenovic 2001, Wallace *et al* 1993 and Yamada *et al* 1999). One NRS focussed on women aged 65 years or over (Mladenovic *et al.* 2001). Two guidelines originating in Canada were included (Cancer Care Ontario Practice Guidelines Initiative 2002, Whelan *et al* 2003).

Rates of local recurrence were not significantly different between conventional 50Gy fractions and hypofractionated schedules (Owen *et al* 2006, Whelan *et al* 2002, Dewar *et al* 2007, Bates 1988, Goel *et al* 2000, Mladenovic 2001, START A 2008, Yamada *et al* 1999). Distant relapse was lower in the hypofractionated arm of the START B (2008) trial and this improved the rates of disease free survival and overall survival. Assessments of cosmetic outcomes were less consistent, and depended on the comparisons made. One strong RCT (Whelan *et al* 2002) reported no significant difference between the 50 Gy and 42.5 Gy arms, whilst another (Yarnold *et al* 2005) reported a significantly poorer cosmetic outcome in the 42.9 Gy arm when compared to the 39 Gy arm. The hazard ratio for no change in breast appearance was significantly improved in the 39 Gy arm of the START A trial compared to 50 Gy; whilst there was no difference between the 50 Gy and 41.6 Gy arms in START A or between 50 Gy and 40 Gy in START B.

Global cosmetic outcomes were also less consistent since effects were reported at different times and between different fractionation doses. Breast oedema, fibrosis, lymphedema and telangiectasia were reported in few studies. Only one study reported on quality of life in terms of daily living (Wallace *et al* 1993).

The START trials reported late normal tissue effects on cardiac and lung morbidity, however the follow-up period was too short to allow the assessment of all potential late effects.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with early invasive breast cancer <ul style="list-style-type: none"> • following 	RT: <ul style="list-style-type: none"> Using fraction sizes greater than 2Gy i.e. • at total lower doses 	50 Gy in 25 fractions	<ul style="list-style-type: none"> • Quality of life • Overall Survival (OS) • Patient acceptability (including cosmesis)

<p>BCS</p> <ul style="list-style-type: none"> • following mastectomy 	<p>than 50Gy</p> <ul style="list-style-type: none"> • fewer number of fractionations than 25 for a) whole breast RT b) chest wall RT 		<ul style="list-style-type: none"> • Local Recurrence • Late effects • Normal tissue effects • Adverse effects • Cosmesis
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The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence Summary

The literature search identified papers published between 1973 and 2008. The strongest evidence was from RCTs (Owen *et al* 2006, START A and B 2008, Whelan *et al* 2002, Yarnold *et al* 2005) which were all quality graded as 1++. The articles by Owen and Yarnold refer to the same trial. An earlier trial by Bates (1988) did not use the conventional 50 Gy in 25 fractions radiotherapy dose as comparator. The remaining two trials were small and of lower quality (Goel *et al* 2000, Taher *et al* 2005, 1-).

Two cohort studies one from an RCT analysis (Olivotto *et al* 1996, 2+) and another from a large population database (Marhin *et al* 2001, 2+) assessed side effects or cosmesis. Four non-randomized (NRS) studies were also included (Marcenaro *et al* 2004, Mladenovic 2001, Wallace *et al* 1993 and Yamada *et al* 1999). One NRS focussed on women aged 65 years or over (Mladenovic 2001). Two guidelines originating in Canada were included (Cancer Care Ontario Practice Guidelines Initiative 2002, Whelan *et al* 2003).

The majority of RCTs compared the conventional schedule of 50 Gy in 25 fractions with a hypofractionated schedule. Exceptions were the studies by Bates (1988) and Goel *et al* (2000) that compared hypofractionated schedules only. The cohort study by Olivotto *et al* (1996) was of a hypofractionated schedule only, whilst that by Marhin *et al* (2001) classified the radiation dose into greater or less than 2 Gy fractions. Two of the non-randomized studies compared 50 Gy in 25 fractions with a hypofractionated schedule, and the third compared 51 Gy in 16 fractions with a hypofractionated schedule. Both systematic reviews compared no radiotherapy with radiotherapy and are not directly relevant to the question, but were included for the subgroup analyses of comparisons between fractionation schedules. The patient population included women after BCS or mastectomy for invasive early breast cancer. One study was conducted amongst older women (Mladenovic *et al.* 2001). Where a number of papers were published on the same trial, only the most recent follow-up was included, unless more data were available from the other publications. A Cochrane review (James *et al.* 2008) was published subsequently to this report being prepared; it does not cover any new evidence from what is reported here and it does not include the START trials most recent publications.

The study characteristics for RT schedules and outcomes assessed are shown in the following table:

Table 5.6.1 Study characteristics and outcomes assessed

Author Year	Quality score	Comparisons	Outcomes
SR			
Gebski 2006	1++	50 Gy in 25 fr vs no RT Hypofractionated RT doses vs no RT	5 year overall survival
EBCTCG 2000	1++	Subgroup analysis of different doses RT vs no RT	Local recurrence
RCTs			
START A	1++	50 Gy in 25 fr (5 weeks) 41.6 Gy in 13 fr (5 weeks) 39 Gy in 13 fr (5 weeks)	Locoregional relapse Disease free survival Overall survival Normal tissue effects Cosmesis
START B	1++	50 Gy in 25 fr (5 weeks) 40 Gy in 15 fr (3 weeks)	Locoregional relapse Disease free survival Overall survival Normal tissue effects Cosmesis
Owen 2006 (same RCT as Yarnold)	1++	50 Gy in 25 fr (5 weeks) 39 Gy in 13 fr (5 weeks) 42.9 Gy in 13 fr (5 weeks)	Recurrence free survival Local relapse (in ipsilateral breast) Distant relapse (bone, liver, lung, CNS)

Whelan 2002	1++	50 Gy in 25 fr (35 days) 42.5 Gy in 16 fr (22 days)	Local recurrence (in ipsilateral breast) Distant recurrence (regional lymph nodes, bone, liver, lung, CNS) Overall survival Global cosmetic outcome Radiation toxicity
Yarnold 2005	1++	50 Gy in 25 fr (5 weeks) 39 Gy in 13 fr (5 weeks) 42.9 Gy in 13 fr (5 weeks)	Cosmesis Fibrosis Ipsilateral recurrence
Bates 1988	1+	45-51 Gy in 12 fr over 28 days 31-35 Gy in 6 fr over 18 days	Local recurrence in irradiated breast Normal tissue effects
Goel 2000	1-	40 Gy in 17 fractions over 3.2 weeks 45 Gy in 20 fractions over 4 weeks	Locoregional recurrence Distant recurrence Skin reactions
Taher 2005	1-	50 Gy in 25 fr (5 weeks) 42.5 Gy in 16 fr (5 weeks)	Cosmesis Acute skin reactions
Ongoing or abstract			
Dewar 2007		Group A: 50 Gy in 25 Fr (5 wks) vs. 41.6 Gy in 13 Fr vs 39Gy in 13 Fr (5 wks) Group B: 50 Gy in 25Fr (5 wks) vs. 40 Gy in 15 Fr (3 wks)	Local recurrence Late normal tissue effects Cosmesis Quality of life
NSABP B-39, RTOG 0413		50 Gy in 2Gy fr or 50.4Gy in	Local recurrence

		1.8Gy fractions vs 38.5Gy in 3.85Gy fr with 3D conformal external beam RT	Overall survival
Nielsen 2004		50Gy/25fr 5 fr/week 48Gy/22fr 4fr/week 36Gy/20fr	15 year looregional recurrence
Cohorts			
Olivotto 1996	2+	44 Gy in 16 fr (22 days)	Cosmesis Normal tissue effects
Marhin 2001	2+	± 2 Gy fractions	Cardiac mortality

Non- randomised studies			
Marcenaro 2004	3	50 Gy in 25 Fr (5 weeks) 45 Gy in 15 Fr (5 weeks)	Late toxic effects Cosmesis
Mladenovic 2001	3	24-26Gy in 4 fr every 2 nd day 51Gy in 16 fr every 2 nd day	Acute and late reactions Local relapse Distant relapse
Wallace 1993	3	50 Gy in 25 Fr (6 weeks) 40 Gy in 15 fr (4 weeks)	QoL Hospital anxiety and depression scale (HADS)
Yamada 1999	3	50 Gy in 25 Fr (5 weeks) 40 Gy in 16 fr (3 weeks)	Local recurrence in irradiated breast at 5 yr 5 year overall survival
Guidelines			
Cancer Care Ontario 2002	4	Optmal fractionation schedule not established	
Update of Whelan 2003	4	42.5Gy in 16 fr comparable to 50Gy in 25 fr.	

Evidence from systematic reviews (1++)

Gebiski *et al* 2006

This systematic review aimed to assess the benefits of a biological equivalent dose for different RT schedules and target volumes. All RT schedules were compared with no RT. When the studies delivering an optimal dose were compared against each other the hypofractionated trials achieved comparable 5 year overall survival rates to the conventional schedule of 50 Gy in 25 fractions.

Early Breast Cancer Trialists' Collaborative Group (2002)

A subgroup analysis (non-randomized) of the effects of different types of radiotherapy schedules showed that the proportional reduction in isolated local recurrences was slightly greater in trials delivering 2.0 Gy/fraction to the breast or chest wall than those delivering 2.5 or 3.0 Gy/fraction. The comparisons within trials were against no radiotherapy to the breast or chest wall.

Data on outcomes are shown in the following two tables. The first table reports recurrence and survival outcomes. The second table reports cosmesis, late normal tissue effects and quality of life outcomes.

Evidence from RCTs (1++, 1+, 1-) and NRS (3)

Local Recurrence

Evidence was identified from five RCTs and two NRS. At 10 years the rate of local recurrence in the ipsilateral breast in one strong RCT was lowest in the hypofractionated arm delivering 42.9Gy in 13 fractions, although not significantly different from the other two arms (50Gy and 39Gy), (Owen *et al* 2006). Similarly Whelan *et al* (2002) in another strong RCT reported a small non-significant absolute difference between the 50Gy and 42.5Gy arms for local recurrence in the ipsilateral breast. The START A and B trials support these findings with no significant differences observed between arms for locoregional relapse when compared with the standard fractionation scheme of 50Gy in 25 fractions in both trials (A and B). The remaining lower quality RCTs did not compare hypofractionated schedules with the conventional fraction of 50Gy but reported similar rates of locoregional recurrence (Bates 1988, Goel *et al* 2000). The NRS also reported similar rates of local relapse (Mladenovic 2001, Yamada *et al* 1999).

One abstract (Nielsen *et al* 2004) reported comparable locoregional recurrence rates between 50Gy and hypofractionated schedules.

Distant recurrence

Two strong studies reported distant recurrences (START A and B, Whelan *et al* 2002). The disease free survival rates were not significantly different between arms in the Canadian trial (Whelan *et al* 2002). The Hazard Ratios for distant recurrence were not significantly different in comparison to the 50 Gy arm in the START A trial, however in START B there was a

significant reduction in distant recurrences in the shorter hypofractionated 40 Gy arm delivered over 3 weeks in comparison to 50 Gy over 5 weeks.

Overall survival

Two strong studies reported overall survival (START A and B, Whelan *et al* 2002). The survival rates were not significantly different between arms in the Canadian trial (Whelan *et al* 2002). The Hazard Ratios for all cause mortality were not significantly different in comparison to the 50 Gy arm in the START A trial, however in START B there was a significant reduction in all cause mortality in the shorter hypofractionated 40 Gy arm in comparison to 50 Gy as a possible consequence of the lower rate of distant recurrences.

Table 5.6.2 Local and distant recurrence, and overall survival

Author	Dose fractionation	Local recurrence	Distant recurrence	Overall survival
Owen (2006) RCT 1++	50 Gy in 25 fr (5 weeks) 42.9 Gy in 13 fr (5 weeks) 39 Gy in 13 fr (5 weeks)	In ipsilateral breast 10 yr Kaplan-Meier 12.1% (8.8-15.5) 9.6% (6.7-12.6) 14.8% (11.2-18.3)		
Whelan 2002 RCT 1++	50 Gy in 25 fr (35 days) 42.5 Gy in 16 fr (22 days)	5 yr LR free survival 96.8% 97.2% Absolute difference: 0.4% (-1.5 to 2.4)	N=26 N=48 DFS Log rank test p=0.37	Deaths N=24 N=14 Log rank test p=0.78
START A RCT 1++	50 Gy in 25 Fr (5 wks) 41.6 Gy in 13 Fr (5wks) 39Gy in 13 Fr (5 wks)	HR for locoregional relapse at 5 years (ref 50Gy) 1.05 (0.63-1.75) 1.26 (0.77-2.08)	HR at 5 yrs 0.92 (0.66-1.28) 1.29 (0.95-1.76)	HR All cause mortality at 5 yrs 1.04 (0.77-1.40) 1.00 (0.74-1.36)
START B RCT 1++	50 Gy in 25Fr (5 wks)	HR for locoregional relapse at 5 years (ref 50Gy) 0.79 (0.48-1.29)	HR at 5 yrs 0.69 (0.53-	HR All cause mortality at 5 yrs 0.76 (0.59-

	40 Gy in 15 Fr (3 wks)		0.91)	0.98)
Dewar 2007 RCT	Group A: 50 Gy in 25 Fr (5 wks) vs. 41.6 Gy in 13 Fr vs 39Gy in 13 Fr (5 wks) Group B: 50 Gy in 25Fr (5 wks) vs. 40 Gy in 15 Fr (3 wks)	HR for locoregional relapse at 5 years START A 50Gy vs 41.6Gy: 1.05 (95% CI 0.63 to 1.75) 50Gy vs 39Gy 1.26 (95% CI 0.77 to 2.08) START B 50Gy vs 40Gy 0.79 (95% CI 0.48 to 1.29)		
Bates 1988 RCT 1+	45-51 Gy in 12 fr over 28 days 31-35 Gy in 6 fr over 18 days	Locoregional recurrences at 10 years 12.8% 12.5%		
Goel 2000 RCT 1-	40 Gy in 17 fr 3.2 weeks 45 Gy in 20 fr 4 weeks	Locoregional recurrences: 16% 13%	32% 28%	
Mladenovic 2001 NRS 3	51Gy in 16 fr every 2 nd dy	Local relapse at median 30 mths: 15% 15%	20% 10%	Deaths from primary disease 18% 13%

	24-26Gy in 4 fr every 2 nd day			
Yamada 1999		Local control at 5 y		Overall survival at 5 years
NRS 3	50 Gy in 25 Fr (5 weeks)	93%		84%
	40 Gy in 16 fr (3 weeks)	88%		84%
		NS		NS

Cosmetic and radiation effects

Global cosmetic scores

These were graded as 0 to 3 (excellent to poor) using EORTC criteria. One of the strongest RCTs found no difference at 5 years between arms [50Gy vs. 42.5Gy] (Whelan *et al* 2002); whilst Yarnold *et al* (2005) reported a significantly poorer cosmetic outcome at 10 years in patients treated with 42.9Gy compared with 39Gy. The weaker RCT (Taher *et al* 2005) reported fewer grade 2-3 (fair-poor) cosmetic outcomes in the 42.5Gy hypofractionated arm than the conventional 50Gy arm, however the sample size was very small. A cohort study (Olivotto *et al* 1996) reported more excellent or good (0-1) cosmetic outcomes than fair or poor outcomes from a hypofractionated schedule of 44Gy in 16 fractions at 5 years. A NRS (Marcenaro *et al* 2004) reported similar proportions of grade 0-1 and grade 2-3 cosmetic outcomes between 50Gy and 45Gy schedules.

Changes in breast appearance (photographic)

These were assessed at baseline, 2 and 5 years by self-assessment and physician assessment. In START A the 39 Gy arm had a significantly improved hazard ratio for no change in breast appearance compared with the 50 Gy arm. However in START B the difference between 50 Gy and 40 Gy arms was not significant, but favoured the 40 Gy arm.

Skin toxicity

The strongest RCT (Whelan *et al* 2002) reported high rates (> 80%) of patients with no toxic skin effects in both arms (50Gy vs 42.5Gy). grade 2 and 3 toxicity were reported in two weaker RCTs (Goel *et al* 2000, Taher *et al* 2005). There was a lower frequency of grade 2 events in the latter study in the hypofractionated arm (42.5Gy).

Very little skin erythema was reported in one cohort study at 5 years with a hypofractionated schedule (Olivotto *et al* 1996). One NRS of older women reported a larger occurrence of erythema in the hypofractionated arm (24-26Gy) at 30 months (Mladenovic 2001).

Subcutaneous toxicity

Subcutaneous toxicity was mainly low grade 0-1 in one strong RCT in both arms (Whelan *et al* 2002).

Moderate to marked breast oedema was significantly lower in the 39Gy arm compared to the 42.9Gy arm in one strong RCT at 10 years (Yarnold *et al* 2005). Rates were low in both arms of one NRS (Marcenaro *et al* 2004) and in one cohort of a hypofractionated schedule at 5 years (Olivotto *et al* 1996).

Moderate to marked fibrosis was significantly lower in the 39Gy arm compared to the 42.9Gy arm in one strong RCT at 10 years (Yarnold *et al* 2005). Mild to moderate fibrosis was reported more frequently in the 45-51Gy arm than the 31-35Gy arm of a weaker RCT (Bates 1988). There was some mild fibrosis (17%) at 5 years in one cohort of a hypofractionated schedule (Olivotto *et al* 1996). Rates of fibrosis were similar between arms of one NRS at 15 months (Marcenaro *et al* 2004); another NRS of older women reported larger rates of fibrosis in the breast and axilla in the hypofractionated arm (Mladenovic 2001).

Rates of telangiectasia at 10 years were not statistically different between the 3 arms of the RCT by (Yarnold *et al* 2005). Mild telangiectasia was reported in 13% of women in the cohort study receiving 44Gy by Olivotto *et al* (1996). Low rates of grade 2-3 were reported in the NRS by Marcenaro *et al* (2004) in both arms.

Quality of life

Quality of life measured as “not up to par” was similar in 50 Gy and 40 Gy arms of the NRS by Wallace *et al* (1993). A lower proportion reported “positive outlook” in the 50 Gy than the 40 Gy arm (63% vs. 76%) of the same study at 6 months. Anxiety and depression scores were not statistically significantly different between arms.

Outcomes are reported in the following Table:

Table 5.6.3 Cosmetic and radiation effects, and quality of life

Author	Dose fractionation	Global cosmetic outcome (EORTC)	Skin toxicity	Subcutaneous toxicity	Telangiectasia
Whelan 2002		5 yr absolute difference			
RCT 1++	50 Gy in 25 fr (35 days)	-0.6% 95%CI (-6.5 to 5.5)	Majority grade 0	Majority grade 0-1	
	42.5 Gy in 16 fr (22 days)		82%	60%	
			87%	66%	
			No grade 4 toxicity	No grade 4 toxicity	

RCT 1-	fr(3.2 weeks) 45 Gy in 20 fr (4 weeks) 40 Gy in 17 fr (3.2 weeks) 45 Gy in 20 fr (4 weeks)		50% 45% Grade 3 20% 5% No grade 4 toxicity	6% 2%	
Taher 2005 RCT 1-	50 Gy in 25 fr (5 weeks) 42.5 Gy in 16 fr (5 weeks) 50 Gy in 25 fr (5 weeks) 42.5 Gy in 16 fr (5 weeks)	Grade 2-3 65% 35%	Grade 2 60% 33% Grade 3 0% 7%		

Author	Dose fractionation	Global cosmetic outcome (EORTC)	Skin toxicity	Subcutaneous toxicity	Telangiectasia
Olivotto 1996 Cohort 2+	44 Gy in 16 fr 22 days	Cosmesis at 5 yrs Excellent or good 87% Fair or poor 11%	Erythema at 5 yrs None 94% Mild 6%	Fibrosis 5 years None 82% Mild 17% Mod/severe 2% Oedema 5 years None	At 5 years None 86% Mild 13% Mod/severe 1%

				97%	
				Mild 3%	
				Mod/severe 0%	
Marcenaro 2004		At median 15 mths:		Fibrosis 15 months	15 months
NRS 3	50 Gy in 25 Fr (5 weeks)	Excellent or good:		Grade 2 28%	Grade 2-3 10%
	45 Gy in 15 Fr (5 weeks)	45%		Grade 2-3 21%	Grade 2 7%
	50 Gy in 25 Fr (5 weeks)	Acceptable or poor:		Breast oedema	
	45 Gy in 15 Fr (5 weeks)	56%		Grade 2 10%	
		50%		Grade 2 7%	
Mladenovic 2001			At median 30 months	At median 30 months	
NRS 3	51Gy in 16 fr every 2 nd dy		Erythema	Fibrosis of breast and axilla	
	24-26Gy in 4 fr every 2 nd day		25%		
	51Gy in 16 fr every 2 nd dy		92%		
	24-26Gy in 4 fr every 2 nd day		Dry desquamation	10%	
			55%	38%	
			8%		
Wallace 1993		Quality of life	HADS 6 months		

NRS 3		6 months			
	50 Gy in 25 Fr (6 weeks)	Not up to par 21%	Anxiety score 5.3		
	40 Gy in 15 fr (4 weeks)	Not up to par 23%	Anxiety score 3.0		
			NS		
	50 Gy in 25 Fr (6 weeks)	Positive outlook 63%	Depression 3.2		
	40 Gy in 15 fr (4 weeks)	Positive outlook 76%	Depression 2.8		
			NS		

Cardiac mortality

One population cohort (Marhin *et al* 2001, 2+) reported no statistical difference in the rates of cardiac mortality in women treated with hypofractionated RT (>2Gy) compared to women treated with conventional fraction sizes of ≤2 Gy irrespective of laterality. In women with right-sided breast cancer neither age, nor fraction size influenced cardiac mortality.

Other late normal tissue effects

The START A and B trials reported very low rates (<1%) of adverse events at 5 years for ischaemic heart disease, rib fracture, lung fibrosis, pneumonitis, brachial plexopathy and acute skin reactions.

Guidelines

No recent guidelines were available. The Canadian clinical practice guidelines (2003) suggest a hypofractionated schedule of 42.5Gy in 16 fractions over 22 days is comparable to the usual schedule of 50 Gy in 25 fractions over 35 days. However this recommendation was limited to women with node negative breast cancer.

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Evidence Tables

Gebski, V., Lagleva, M., Keech, A., Simes, J., & Langlands, A. O. 2006, "Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective.[see comment][erratum appears in J Natl Cancer Inst. 2006 Jun 21;98(12):876]", *Journal of the National Cancer Institute*, vol. 98, no. 1, pp. 26-38.

Design: Meta-analysis of RCTs that had been previously included in earlier published meta-analyses and systematic reviews. Trials were identified up to 2002.

Country: Australia

Level 1++

Aim: The association between post-mastectomy radiation therapy for early breast cancer and overall survival was assessed in a meta-analysis of 36 randomized trials containing 38 comparisons that were unconfounded (addition of radiation therapy was the sole discriminant between treatments being compared). The specific issues of radiation dosage and target volume coverage were of interest. Studies using optimal BED (Biological Equivalent Dose) and appropriate target volumes were assessed for any observed benefit of radiation therapy.

Inclusion criteria

- 1) Studies were of operable breast cancer that was initially treated by mastectomy. (Stage I and stage II disease and selected cases of stage III disease were considered operable).
- 2) Studies were randomized controlled clinical trials that compared adjuvant radiation therapy with no radiation therapy. This treatment was the only discriminating factor between the two arms of the trial. Other treatments such as extent of surgery, endocrine therapy, and chemotherapy, if given, had to be common to each arm.

Three studies that reported the use of randomization but may have used date of birth as the allocation method were included in the primary analysis but were excluded from a sensitivity analysis.

Exclusion criteria

Population

Thirty-eight unconfounded randomized comparisons from 36 trials were identified, with data available from a total cohort of 13 199 patients. Thirty-three of these comparisons were included in the EBCTCG analysis. Because of access to individual patient data for some studies, the EBCTCG was able to provide comparisons in addition to or different from those in published reports, so a direct comparison between this meta-analysis and the EBCTCG was not always possible.

Interventions

Radiotherapy treatment for each trial was classified into three major categories:

Category 1

Optimal radiation therapy: studies that delivered optimal radiation therapy defined as doses in the range of 40 – 60 Gy in 2-Gy fractions (where 50 Gy = 5000 rads) or as a BED to the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes.

Category 2

Inadequate or excessive radiation therapy: studies that delivered inadequate or excessive radiation therapy defined as either doses of less than 40 Gy in 2-Gy fractions (or, for other fractionation schedules, the calculated BED being less than 40 Gy) or of greater than 60 Gy in 2-Gy fractions (or for other fractionation schedules the calculated BED being more than 60 Gy). (The authors state that the BED was calculated by use of α/β , a ratio that reflects the weight of the dose per fraction in the schedule to the total dose delivered, equal to 10, standardized to 2-Gy fractions).

Category 3

Incomplete tissue coverage: studies in which radiation therapy provided incomplete tissue coverage by restricting the target volume to areas of less than the area of the chest wall and regional lymph nodes. Techniques for which the target volume was restricted were considered to be inappropriate because an area at risk of recurrence received no radiation therapy.

Category 2 studies provided treatment that delivered an inadequate or excess dose irrespective of target volume. Those studies in category 3 provided treatment that delivered an inappropriate target volume irrespective of dose. Studies that met category 2 and 3 criteria were included in category 2.

Outcomes

The primary outcomes were 5-year and 10-year overall survival rates calculated by intention-to-treat analysis.

Follow up -

Results

38/40 RCTs compared postoperative radiation therapy with no RT and were not confounded.

Category 1: 25 RCTs used optimal RT with appropriate target volume.

Category 2: 7 RCTs used inadequate or excessive doses of RT.

Category 3: 6 RCTs used inappropriate target volumes.

Only the findings from the optimal dose category 1 trials are reported in the table.

The trials delivering the optimal dose vs. no RT (category 1) that used hypofractionated schedules are shown in the table below:

Trial	Year	Comparison	Dose* (Gy)	N of fractions	BED (Gy)	5 year Overall
-------	------	------------	------------	----------------	----------	----------------

						Survival OR (95% CI)
Edinburgh 1	1974	SM vs SM+XRT	43	10	51.2	1.60 (0.90- 2.82)
ECOG EST3181	1982	RM+T+C vs RM+T+C +XRT	46	23	46	0.88 (0.55- 1.39)
BCCA Vancouver	1978	RM +C vs RM+C+XRT	40	16	42	0.73 (0.45- 1.21)
Helsinki	1981	RM +C vs RM+C+XRT	45	15	49	2.46 (0.89- 6.82)
Klefstrom	1976	RM +C vs RM+C+XRT	45-50	15-25	49- 50	0.19 (0.05- 0.76)
Wessex	1973	SM vs SM+XRT	46	20	47.2	0.42 (0.21- 0.86)
Nottingham	1985	SM +C vs SM+C+XRT	45	15	49	0.74 (0.30- 1.83)
Manchester Q	1949	RM vs RM+XRT	35-40	15	35.4- 43	1.13 (0.84- 1.52)
N1-3 DFCI Boston	1974	RM +C vs RM+C+XRT	45	20	46	1.04 (0.37- 2.91)
N4+ DFCI Boston	1974	RM +C vs RM+C+XRT	45	20	46	1.18 (0.58- 2.41)

C= Chemotherapy

RM= Radical Mastectomy

SM= Simple Mastectomy

T= Tamoxifen

XRT= Radiotherapy

* Dose applied to breast, chest wall, axilla and supraclavicular fossa.

These trials compared the hypofractionated dose vs. no RT rather than the conventional 50Gy in 25 fractions dose that is relevant to this question.

Trials delivering the optimal dose vs. no RT (category 1) that used a 50Gy dose in 25 fractions:

Trial	Year	Comparison	Dose* (Gy)	N of fractions	BED (Gy)	5 year Overall Survival OR (95% CI)
BMFT 03 Germany	1984	RM +C vs RM+C+XRT	50	25	50	0.83 (0.46- 1.51)
SECSG 1 (N4+)	1976	RM +C vs RM+C+XRT	50	25	50	0.82 (0.50- 1.32)

DBCG82b pre	1982	SM +C vs SM+C+XRT	50	25	50	0.73 (0.60- 0.90)
DBCG82c post	1982	SM +T vs SM+T+XRT	50	25	50	0.96 (0.77- 1.19)
NSABC Israel	1980	RM +C vs RM+C+XRT	46-50	24	45.4- 51	1.25 (0.44- 3.52)

Author conclusions

Improved overall 5 and 10 year survival was associated with optimal radiation therapy. When compared with no RT hypofractionated trials achieve comparable 5 year overall survival rates to the conventional schedule of 50 Gy in 25 fractions. All confidence intervals overlap with at least one other study.

Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group.[see comment]. Lancet 2000 May 20;355(9217):1757-70.

Design: Meta analysis

Level 1++

Country: UK

Aim: To determine the longer term effects of radiotherapy on breast cancer mortality.

Inclusion criteria

RCTs from the EBCTCG database that began before 1990 and were not confounded.

Exclusion criteria

Population 45 trials identified, 40 available.
Total of 19582 participants.

Interventions

Trials comparing radiotherapy plus other treatments (including breast surgery) versus the same other treatments without radiotherapy.

Outcomes

First local recurrence (as defined by each trial)

Follow up -

Results

Overall trials:
2756 isolated local recurrences
9838 deaths

A subgroup analysis (non-randomized) of the effects of different types of radiotherapy schedules showed that the proportional reduction in isolated local recurrences was slightly greater in trials delivering 2.0Gy/fraction to the breast or chest wall than those delivering 2.5 or 3.0Gy/fraction. The comparisons within trials were against no radiotherapy to the breast or chest wall.

Breast dose per fraction (intervention) vs no radiotherapy (control)

Breast dose/fraction	Events/women Allocated radiotherapy	Events/women Adjusted control (no RT)
1.8Gy – 2.2Gy	313/5351 (5.85%)	1142/5394 (21.2%)
2.3Gy – 2.7Gy	125/1168 (10.7%)	339/1164 (29.1%)
2.8Gy – 3.2Gy	43/359 (12.0%)	96/368 (26.1%)
Various/other	205/2539 (8.07%)	575/2572 (22.4%)
Chi2 = 7.6; 2p= 0.006		

The proportional reduction in local recurrence did not appear to be influenced by the total dose of radiation to the breast axilla or internal mammary chain (p=NS).

The protective effects of RT against local recurrence were sufficiently strong to make the subgroup analyses statistically reliable.

Randomized controlled trials

Dewar JA, Haviland JS, Agrawal RK, Bliss JM, Hopwood P, Magee B, et al. Hypofractionation for early breast cancer: First results of the UK standardization of breast radiotherapy (START) trials. J Clin Oncol (Meeting Abstracts) 2007 Jun 20; 25(18_suppl):LBA518.

Design: RCT (1999-2002)

Meeting abstract

Country: UK, setting: Multicentre (N=35)

Aim: To test the hypothesis that breast cancer is as sensitive to fraction (Fr) size as late reacting normal tissues, with an α/β value of about 4Gy.

Inclusion criteria

Women with completely excised invasive breast cancer (T1-3, N0-1, M0).

Exclusion criteria

Population

Number of patients = START A 2236

Number of patients = START B 2215

Interventions

Hypofractionated post-operative RT

START A: 50Gy in 25Fr (5 wks) vs 41.6Gy vs 39Gy, both in 13Fr on alternate days (5 wks).

START B: 50Gy in 25Fr (5 wks) vs 40Gy in 15Fr (3 wks).

Centres chose either the START A or START B fractionation schedules.

Stratification was by centre, surgery and boost.

Outcomes

Local-regional (LR) relapse

Late normal tissue effects (NTE) were assessed by breast photographs, clinical examination and quality of life (QoL) questionnaires

Estimates of absolute differences in relapse rates were obtained from the rates in the 50Gy control arms and the Hazard Ratio (HR)

Follow up START A median 5.1 years

START B median 6 years

Results

Locoregional recurrence

Results for local regional relapses are shown in the following table.

Outcome	START A	START B
LR relapse at 5 years	N=93 4.1% (95% CI 3.2 to 5.0%)	N= 65 2.8% (95% CI 2.1 to 3.5%)
Hazard Ratio for locoregional relapse at 5 years	41.6 vs 50Gy 1.05 (95% CI 0.63 to 1.75)	40 vs 50Gy 0.79 (95% CI 0.48 to 1.29)

	39 vs 50 Gy 1.26 (95% CI 0.77 to 2.08)	
Absolute difference LR rates at 5 years compared with 50Gy	For 41.6Gy: +0.2% (95% CI -1.3 to 2.6%) For 39Gy: +0.9% (95% CI -0.8 to 3.7%)	For 40 Gy: -0.6% (95% CI -1.7 to 0.9%)
α/β estimate for tumour control	5.0Gy (95% CI -2.7 to 12.7%)	

No significant differences were observed between arms for LR relapse when compared with the standard fractionation scheme of 50Gy in 25 fractions in both trials (A and B).

Late normal tissue effects

Late normal tissue effects are shown in the table below.

Outcome	START A n (%)	START B n (%)
Severe acute reactions	3 (0.1)	16 (0.7)
Brachial plexopathy	1	-
Symptomatic rib fracture	29 (1.3)	34 (1.5)
Symptomatic lung fibrosis	18 (0.8)	31 (1.4)
Ischaemic heart disease	45 (2.0)	46 (2.1)

Side effects appeared to be low in both trials. Statistical differences were not reported.

Cosmesis

Outcome	START A	START B
Mild/marked change in photographic breast appearance	Lower in 39Gy vs 50Gy HR 0.69 (95% CI 0.52-0.91)	Lower in 40Gy vs 50Gy HR 0.83 (95% CI 0.66-1.04)
α/β estimate for change in breast appearance	3.1Gy (1.6 to 4.6)	
Rates of induration, telangiectasia and breast oedema	Lower in 39Gy vs 50Gy	Lower in 40Gy vs 50Gy

QoL results were reported as consistent with the clinical findings.

Author conclusions: The fractionation sensitivity of breast cancer is comparable to that of late reacting normal tissues, confirming the results of a recent pilot trial. These results support the use of hypofractionated RT schedules for early breast cancer.

The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.

Design: RCT (1998-2002)

Level 1++

Country: UK, setting: Multi-centre (17)

Aim: To test two dose levels of a 13-fraction radiotherapy schedule against the standard regimen to measure the sensitivity of normal and malignant tissues to fraction size.

Inclusion criteria Women with operable invasive breast cancer (pT1-3a pN0-1 M0), requiring radiotherapy after surgery (breast conserving surgery or mastectomy with clear tumour margins \geq 1mm) aged over 18 years.

Exclusion criteria Surgical reconstruction

Population number of patients = 2236

Mean age 57.2 (SD 10.6) years

BCS 85% (same proportion in all 3 groups)

Mastectomy 15% (same proportion in all 3 groups)

Pathological node positive 28.8% (similar proportions in all 3 groups)

Pathological node negative 69.2% (similar proportions in all 3 groups)

Not known 2%

Tumour size (cm):

< 1 3.3%

1- 47.6%

2- 27%

3- 21.6%

Tumour grade:

1 20.4%

2 49.9%

3 28.1%

Adjuvant therapies were evenly distributed between treatment groups.

14% had regional RT which was planned before randomisation.

60.6% of BCS patients had tumour bed boost.

Interventions

Randomised to either:

50 Gy in 25 fractions over 5 weeks (control) 5 fractions / week

41.6 Gy in 13 fractions over 5 weeks (intervention) 5 fractions / fortnight

(M,W,F Tu,Thu)

39 Gy in 13 fractions over 5 weeks (intervention) 5 fractions / fortnight (M,W,F

Tu,Thu)

The target volume was the whole breast with a 1cm margin. Where regional RT was indicated the target volume was supraclavicular nodes with or without axillary chain. Treatment was with 6MV x-rays in most patients, otherwise higher energies or cobalt γ -rays were used.

Outcomes

Local relapse – ipsilateral local tumour relapse in breast or chest wall
Loco-regional relapse - regional relapse in ipsilateral axilla or supraclavicular fossa within the irradiated target volume

Normal tissue effects in the breast, arm, and shoulder

Disease free survival (DFS) time to any breast cancer related event (loco-regional or distant relapse, contralateral breast cancer, death from breast cancer)

Overall survival (OS)

Change in breast appearance – photographic (none, mild, moderate). Self assessment and physician assessment at baseline, 2 and 5 years.

Quality of life assessments of normal tissue effects.

Follow up Patients reviewed every year for tumour relapse and radiation induced normal tissue effects. Median follow-up 5.1 years (IQR 4.4-6.0), maximum follow-up 8 years.

Results

Quality of life study n=1129

Photographic assessment study n=1306

1881 (84.1%) alive without relapse

36 (1.6%) alive with locoregional relapse (without distant relapse)

52 (2.4%) alive with distant relapse (includes 14 with locoregional relapse)

256 (11.4%) had died

The survival analyses for relapse and mortality are reported in the following table:

	Events/total (%)	Estimated % with event at 5 years (95% CI)	Crude hazard ratio (95% CI)	Wald test p value
Local relapse				
50 Gy	25/749 (3.3)	3.2 (1.9-4.6)	1	
41.6 Gy	28/750 (3.7)	3.2 (1.9-4.5)	1.09 (0.64-1.88)	0.74
39 Gy	31/737 (4.2)	4.6 (3.0-6.2)	1.25 (0.74-2.12)	0.40
Locoregional relapse				
50 Gy	28/749 (3.7)	3.6 (2.2-5.1)	1	
41.6 Gy	30/750 (4.0)	3.5 (2.1-4.3)	1.05 (0.63-1.75)	0.86
39 Gy	35/737 (4.7)	5.2 (3.5-6.9)	1.26 (0.77-2.08)	0.35
Distant relapse				
50 Gy	73/749 (9.7)	9.8 (7.5-12.0)	1	
	69/750 (9.2)		0.92 (0.66-	0.64

41.6 Gy 39 Gy	93/737 (12.6)	9.5 (7.3- 11.7) 11.9 (9.5- 14.4)	1.28 1.29 (0.95- 1.76)	0.10
Any breast cancer related event				
50 Gy	102/749 (13.6)	13.6 (11.0- 16.2)	1 0.87 (0.65- 1.15)	0.33
41.6 Gy 39 Gy	91/750 (12.1) 115/737 (15.6)	12.0 (9.6- 14.5) 15.2 (12.5- 17.9)	1.14 (0.87- 1.49)	0.33
All cause mortality				
50 Gy	84/749 (11.2)	11.1 (8.7- 13.4)	1 1.04 (0.77- 1.40)	0.81
41.6 Gy 39 Gy	89/750 (11.9) 83/737 (11.3)	11.3 (8.9- 13.7) 10.7 (8.3- 13.1)	1.00 (0.74- 1.36)	0.99

The rates for distant relapse, any breast cancer event and all cause mortality were similar between fractionation schedules.

Locoregional relapse (LRR)

93 (4.2%) patients had locoregional relapse at 5 years.

Absolute differences in LRR compared with 50Gy dose were not significantly different:

41.6Gy absolute difference = 0.2% (95% CI -1.3 to 2.6)

39Gy absolute difference = 0.9% (95% CI -0.8 to 3.7)

Estimates of excess risk in comparison to the 50Gy dose were:

41.6Gy excess risk 2.1% maximum

39Gy excess risk 3.2% maximum

The α/β ratio for LRR was 4.8Gy (95% CI 0-16.3)

Other sites of relapse are reported in the following table:

	Total	50 Gy	41.6 Gy	39 Gy
Contralateral breast cancer	26 (1.2%)	13 (1.7%)	5 (0.7%)	8 (1.1%)
2 nd primary cancer	44 (2%)	15 (0.7%)	10 (0.4%)	19 (0.8%)

Change in breast appearance (photographic)

Data were available for 1055 patients for at least a baseline and one follow-up image. These are summarized in the following table:

Changes in breast appearance (photographic)	
Mild changes at 5 years [n (%)]	302 (28.6%)

Marked changes at 5 years [n (%)]	32 (3%)
Hazard ratio for any change in appearance (mild or marked) Reference 50Gy	41.6 Gy 1.09 (95% CI 0.85-1.40, p=0.62) 39 Gy 0.69 (95% CI 0.52-0.91, p=0.001)
α/β ratio	3.1Gy
α/β ratio when data from earlier RMH/GOC trial (n=1202) and START A combined	Any change in breast appearance adjusted for age, chemotherapy, tamoxifen, breast size, surgical deficit 3.4 Gy (95% CI 2.3-4.5)

The 39 Gy arm had a significantly improved hazard ratio for no change in breast appearance compared with the 50 Gy arm.

Quality of life

Patient self assessments for late normal tissue effects were available for 1080 (95.7%) of patients in this study. The most common effects were changes in breast appearance and breast hardness (BCS patients). The rates of marked or moderate effects by 5 years were similar after 50 Gy and 41.6 Gy. The rates of marked or moderate effects were lower after 39 Gy than 50 Gy. There was a significantly lower rate of change in skin appearance after 39 Gy than 50 Gy (p=0.004). The survival analyses of the photographic and patient QoL self-assessments of late normal tissue effects for START A were displayed as a Forest plot. The rates of effects were similar for the comparison of 41.6 Gy with 50 Gy. Effects favoured the 39 Gy group in comparison with 50 Gy.

The incidence of adverse events was low at this stage in the trial and the findings are reported in the following table:

Event	Fractionation schedule			T=2236
	50 Gy n=749	41.6 Gy n=750	39 Gy n=737	
Ischaemic heart disease (confirmed)[left sided]	3 (0.4%) [1]	2 (0.3%) [0]	3 (0.7%) [4]	10 (0.4%) [5]
Symptomatic rib fracture (confirmed)	1 (0.1%)	2 (0.3%)	1 (0.1%)	4 (0.2%)
Symptomatic lung fibrosis (confirmed)	0 (0%)	2 (0.3%)	1 (0.1%)	3 (0.1%)
Pneumonitis	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Brachial plexopathy	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Acute skin	2 (0.3%)	0 (0%)	0 (0%)	2 (0.3%)

reaction (moist desquamation)				
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Author conclusions

The data are consistent with the hypothesis that breast cancer and the dose-limiting normal tissues respond similarly to change in radiotherapy fraction size. 41.6 Gy in 13 fractions was similar to the control regimen of 50 Gy in 25 fractions in terms of local-regional tumour control and late normal tissue effects, a result consistent with the result of START B trial. A lower total dose in a smaller number of fractions could offer similar rates of tumour control and normal tissue damage as the international standard fractionation schedule of 50 Gy in 25 fractions.

General comments –

Short term follow-up of 5 years.

No subgroup analyses of the effects of ER status, node status, boost dose, or adjuvant systemic treatments on outcomes, although these were evenly distributed between groups.

The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial.

Design: RCT (1999-2001)

Level 1++

Country: UK, setting: Multi-centre (23)

Aim: To test the benefits of radiotherapy schedules using fraction sizes larger than 2.0 Gy in terms of local-regional tumour control, normal tissue responses, quality of life, and economic consequences in women prescribed post-operative radiotherapy.

Inclusion criteria Women with operable invasive breast cancer (pT1-3a pN0-1 M0), requiring radiotherapy after surgery (breast conserving surgery or mastectomy with clear tumour margins \geq 1mm) aged over 18 years.

Exclusion criteria Surgical reconstruction

Population number of patients = 2215

Mean age 57.4 (SD 10.0) years

BCS 92% (similar proportions in each group)

Mastectomy 8% (similar proportions in each group)

Pathological node positive 22.8% (similar proportions in each group)

Pathological node negative 73.8% (similar proportions in each group)

Not known 3.8%

Tumour size (cm):

< 1 14.4%

1- 49.4%

2- 26%

3- 9.9%

Tumour grade:

1 27.9%

2 47.4%

3 23.0%

Adjuvant therapies were evenly distributed between treatment groups.

Interventions

Randomised to either:

50 Gy in 25 fractions over 5 weeks (control) 5 fractions / week

40 Gy in 15 fractions over 3 weeks (intervention) 5 fractions / week

Stratification was by hospital, type of surgery, and intention to give a tumour bed boost or not.

The target volume was the whole breast with a 1cm margin. Where regional RT was indicated the target volume was supraclavicular nodes with or without axillary chain. Treatment was with 6MV x-rays in most patients, otherwise higher energies or cobalt γ -rays were used.

Outcomes

Local relapse – ipsilateral local tumour relapse in breast or chest wall

Loco-regional relapse - regional relapse in ipsilateral axilla or supraclavicular fossa within the irradiated target volume

Normal tissue effects in the breast, arm, and shoulder
 Disease free survival (DFS) time to any breast cancer related event (loco-regional or distant relapse, contralateral breast cancer, death from breast cancer)

Overall survival (OS)

Change in breast appearance – photographic (none, mild, moderate). Self assessment and physician assessment at baseline, 2 and 5 years.

Quality of life assessments of normal tissue effects

Follow up Median follow-up 6.0 years (IQR 5.0-6.2), maximum follow-up 8 years

Results

Quality of life study n=1079

Photographic assessment study n=1094

1872 (84.5%) alive without relapse

34 (1.5%) alive with locoregional relapse (without distant relapse)

45 (2.0%) alive with distant relapse (includes 4 with locoregional relapse)

245 (11.1%) had died

Relapse and mortality

The survival analyses for relapse and mortality are reported in the following table:

	Events/total (%)	Estimated % with event at 5 years (95% CI)	Crude hazard ratio (95% CI)	Log-rank test p value
Local relapse				
50 Gy	34/1105 (3.1)	3.3 (2.2-4.4)	1	0.21
40 Gy	25/1110 (2.2)	2.0 (1.1-2.8)	0.72 (0.43-1.21)	
Locoregional relapse				
50 Gy	36/1105 (3.2)	3.3 (2.2-4.5)	1	0.35
40 Gy	29/1110 (2.6)	2.2 (1.3-3.1)	0.79 (0.48-1.29)	
Distant relapse				
50 Gy	122/1105 (11.0)	10.2 (8.4-12.1)	1	0.01
40 Gy	87/1110 (7.8)	7.6 (6.0-9.2)	0.69 (0.53-0.91)	
Any breast cancer related event				
	164/1105	14.1 (12.0-	1	

50 Gy 40 Gy	(14.8) 127/1110 (11.4)	16.2 10.6 (8.7- 12.4)	0.75 (0.60- 0.95)	0.02
All cause mortality			1	
50 Gy 40 Gy	138/1105 (12.5) 107/1110 (9.6)	11.0 (9.1- 12.9) 8.0 (6.4- 9.7)	0.76 (0.59- 0.98)	0.03

Locoregional relapse (LRR)

65 (2.9%) patients had locoregional relapse at the time of analysis. There were no significant differences between the 50 Gy and 40 Gy schedules in the rates of local or locoregional relapses.

The absolute difference in LRR between 40 Gy fraction compared with the 50Gy dose was not significantly different at 5 years:

Absolute difference = -0.7% (95% CI -1.7 to 0.9)

Estimated maximum excess risk in comparison to the 50Gy dose was 0.6% for the 15 fraction schedule.

The 5 year rate of distant relapse was significantly lower in the 40 Gy group, this contributed to the higher rates of DFS and OS in this group compared with the 50 Gy group.

Other sites of relapse are reported in the following table:

	Total	50 Gy	40 Gy
Contralateral breast cancer	36 (1.6%)	19 (1.7%)	17 (1.5%)
2 nd primary cancer	58 (2.6%)	32 (2.9%)	26 (2.3%)

Change in breast appearance (photographic)

Data were available for 923 patients for at least a baseline and one follow-up image. These are summarized in the following table:

Changes in breast appearance (photographic)	
Mild changes at 5 years [n (%)]	284 (30.8%)
Marked changes at 5 years [n (%)]	28 (3%)
Hazard ratio for any change in appearance (mild or marked) Reference 50Gy	40 Gy 0.83 (95% CI 0.66-1.04, p=0.06)

The treatment differences were seen at 2 years and persisted to 5 years but were not significant.

Quality of life

Patient self assessments for late normal tissue effects were available for 1037 (96.1%) of patients in this study. The most common effects were changes in breast appearance and breast hardness (BCS patients). The rates of marked or moderate effects by 5 years were lower after 40 Gy than 50 Gy. There was a significantly lower rate of change in skin appearance after 40 Gy than 50 Gy ($p=0.02$). The survival analyses of the photographic and patient QoL self-assessments of late normal tissue effects for START B were displayed as a Forest plot. Effects favoured the 40 Gy group in comparison with 50 Gy.

The incidence of adverse events was low at this stage in the trial and the findings are reported in the following table:

Event	Fractionation schedule		T=2215
	50 Gy n=1105	40 Gy n=1110	
Ischaemic heart disease (confirmed)[left sided]	12 (1.1%) [4]	7 (0.6%) [3]	19 (0.9%) [7]
Symptomatic rib fracture (confirmed)	2 (0.2%)	2 (0.2%)	4 (0.2%)
Symptomatic lung fibrosis (confirmed)	1 (0.1%)	3 (0.3%)	4 (0.2%)
Brachial plexopathy (n=161)	0 (0%)	0 (0%)	0 (0%)
Acute skin reaction (moist desquamation)	13 (1.2%)	3 (0.3%)	16 (0.7%)

Author conclusions A radiation schedule delivering 40 Gy in 15 fractions seems to offer rates of local-regional tumour relapse and late adverse effects at least as favourable as the standard schedule of 50 Gy in 25 fractions.

General comments –

In START B more patients had tumours < 1cm (14.4%) than START A (3.3%); fewer patients had tumours of 3cm or more in START B (9.9%) than START A (21.6%).

More patients had grade 1 tumours in START B (27.9%) than START A (20.4%); and fewer had grade 3 tumours in START B (23%) than START A (28.1%).

Nielsen HM, Overgaard J, Grau C, Overgaard M. Loco-regional control rate in relation to radiotherapy technique and fractionation in the Danish DBCG 82b & c studies with 1538 high-risk breast cancer patients randomized to postmastectomy radiotherapy. *Radiother Oncol* 2004;73:S1 p193 (Abstract only).

Design: Analysis of RCTs

Abstract

Country: Denmark

Aim: To describe any differences in the locoregional control rate related to treatment (dose/fractionation) characteristics from a subset of patients.

Inclusion criteria

Women with stage II and III breast cancer (high risk)

Exclusion criteria

Population number of patients = 3083 from DBCG. Subset of 1538 patients.

Interventions

Randomized to postmastectomy RT vs no RT.

Three groups:

- 1) megavoltage photon/electron 3 field technique with two different fractionation schedules (n=1221). Fractionation was 50Gy/25 fractions, 5 fractions/week (n=903, group 1a); or 48Gy in 22 fractions, 4 fractions/week (n=318, group 1b).
- 2) megavoltage 3-field tangential photon beam technique (n=97) with fractionation of 50Gy in 25 fractions, 5 fractions/week.
- 3) Orthovoltage treatment using McWhirter technique (n=128), 36 Gy in 20 fractions

44 patients (3%) had an unknown type of RT or were treated with unconventional techniques, dose or fractionation.

48 patients (3%) assigned for RT had no RT.

Outcomes

Locoregional recurrence (LRR)

Follow up Median 17 years

Results

150/1538 (9.7%) patients experienced a LRR

Locations of recurrences were:

Chest wall n=85 (57%)

Axilla n=21 (14%)

Supra/infraclavicular region n=21 (14%)

Multiple sites n=21 (14%)

Unknown n=3 (2%)

Findings by group are reported in the following table:

	Group 1a	Group 1b	Group 2	Group 3
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	n=903	n=318	n=97	n=128
Type of RT	Megavoltage photon/electron 3 field technique	Megavoltage photon/electron 3 field technique	Megavoltage 3 field tangential photon beam	Orthovoltage McWhirter technique
Dose	50Gy/25fr 5 fr/week	48Gy/22fr 4fr/week	50Gy/25fr 5 fr/week	36Gy/20fr
15 year actuarial LRR	0.11 (0.09-0.14)	0.14 (0.10-0.19)	0.12 (0.06-0.22)	0.21 (0.14-0.31)

It should be noted that the three megavoltage groups had different patient numbers and consequently the two groups with low patient numbers have wider confidence intervals than the largest group (n=903). There is also overlap between the confidence intervals of these three LRR findings. The LRR rates appear similar for the megavoltage groups, no p values were reported.

Megavoltage techniques produced better control than orthovoltage techniques (p=0.02).

A multivariate analysis was also conducted for risk of LRR. Factors analyzed are shown in the following table:

Factor	Odds Ratio (OR)
Tumour size: 21-50mm	1.57 (1.39-4.05)
> 50mm	2.37 (1.39-4.05) ? misprint in abstract
More than 3 positive lymph nodes	3.40 (1.66-7.00)
Invasion of fascia	1.59 (1.05-2.42)
Invasion of skin	1.71 (1.07-2.75)
Group 1a vs other groups	0.66 (0.47-0.93)

Author conclusions were that megavoltage gave better local control than orthovoltage, and that patients treated with the megavoltage combined photon/electron 3 field technique using 50Gy/25fr also had better local control from the multivariate analysis.

Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *The lancet oncology* 2006;7(6):467-71

Design: RCT (1986-1998)

Level 1++

Country: UK, setting: Two cancer centres

Aim: To determine whether fewer, larger radiotherapy fractions are at least as safe and effective as standard regimens

Inclusion criteria

Operable invasive breast cancer (T 1-3, N 0-1, M 0)

Age < 75 years at presentation

Breast conserving surgery.

Exclusion criteria Not reported

Population number of patients = 1410

Interventions

50 Gy radiotherapy given in 25 fractions or

39 Gy given in 13 fractions or

42.9 Gy given in 13 fractions.

All schedules given over 5 weeks

Outcomes

Recurrence free survival

Local relapse defined as any malignant disease in the ipsilateral breast.

Distant relapse defined as malignant disease outside the ipsilateral breast and regional lymph nodes.

Follow up Median follow-up 9.7 years (IQR 7.8-11.8). Maximum follow-up of 18.4 years.

Results

18 patients (1%) lost to follow-up.

Outcomes are reported in the following table.

Outcome	Number of patients
Alive without local relapse	838 (59%)
Alive with local recurrence (no distant relapse or contralateral breast cancer)	46 (3%)
Alive with distant relapse (10 with local relapse and 5 with contralateral breast cancer)	46 (3%)
Alive with second primary cancer in contralateral breast (incl 3 with local relapse)	35 (2%)
Deaths (99 had a local relapse)	445 (32%)

Alive with local relapse	158 (11%)
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106 (67%) of local recurrence events occurred within 5 years of follow-up.

Survival analysis of local relapse data by fractionation schedule is shown in the following table (50Gy fractionation used as reference):

Fraction (Gy)	N local relapse /person years	Crude Hazard Ratio (95% CI)	Kaplan-Meier estimate local recurrence (95% CI)		Smoothed estimate of absolute difference in local recurrence (95% CI)	
			5 yr	10 yr	5 yr	10 yr
50	50/3965	1	7.9% (5.4-10.4)	12.1%(8.8-15.5)	-	-
42.9	42/3840	0.86 (0.57-1.30)	7.1% (4.6-9.5)	9.6%(6.7-12.6)	-1.1%(-3.3-2.3)	-1.6%(-5.0-3.3)
39	66/3890	1.33 (0.92-1.92)	9.1% (6.4-11.7)	14.8%(11.2-18.3)	2.5%(-0.6-6.7)	3.7%(-0.9-9.8)

A further analysis of fractionation data showed a significant absolute difference between 42.9 and 39 Gy groups for the probability of local recurrence.

Outcome	Number of patients
Probability of local recurrence between 42.9 and 39Gy groups	Absolute difference 3.7% (95% CI 0.3 to 8.3) p=0.027 (favours 42.9Gy)
Hazard ratios over first 5 years	0.90 (95%CI 0.55 – 1.46) for 42.9Gy compared with 50Gy at 5 years 1.14 (95%CI 0.72 – 1.79) for 39Gy compared with 50Gy at 5 years
Hazard ratios from 5 years onwards	0.77 (95%CI 0.36 – 1.69) for 42.9Gy compared with 50Gy 1.81 (95%CI 0.96 – 3.41) for 39Gy compared with 50Gy P=0.1 (no significant difference from 5 year values)

The recurrence free survival curves show that the three fractionation schedules diverge only after 5 years of follow-up.

The sensitivity of breast cancer to dose per fraction was estimated to be 4.0 Gy (95% CI 1.0-7.8), which is similar to that estimated for the late adverse effects in healthy tissue from breast radiotherapy.

Author conclusions: Breast cancer tissue is probably just as sensitive to fraction size as dose-limiting healthy tissues. If this finding is confirmed,

radiotherapy schedules can be greatly simplified by the delivery of fewer, larger fractions without compromising effectiveness or safety, and possibly improving both.

Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *Journal of the National Cancer Institute* 2002;94(15):1143-50.

Design: RCT (1993-1996)

Level 1++

Country: Canada, setting: Multi-centre

Aim: To determine whether a 22-day fractionation schedule is as effective as the more traditional 35-day schedule in reducing recurrence.

Inclusion criteria Women with invasive breast cancer treated by lumpectomy who had pathologically clear resection margins and negative axillary lymph nodes.

Exclusion criteria

Level I and II axillary dissection not performed

Tumours > 5cm or stage T4

Previous breast cancer

Bilateral malignancy of breast, previous or concomitant malignancies

Patients geographically inaccessible for follow-up

Patients unable to commence RT within specified time for last surgical procedure or last chemotherapy dose

Population number of patients = 1234

42.5 Gy in 16 fractions n=622

50 Gy in 25 fractions n=612

Interventions

Randomization to receive whole breast irradiation of 42.5 Gy in 16 fractions (2.7Gy/fraction) over 22 days (short arm – 3 weeks) or whole breast irradiation of 50 Gy in 25 fractions (2Gy/fraction) over 35 days (long arm- 5 weeks). Stratification was by age (< 50 or > 50 years); tumour size <2cm or > 2cm); adjuvant systemic therapy (tamoxifen, any chemotherapy, no therapy); and centre.

The breast at risk and chest wall were irradiated.

Radiation was delivered by 4-6 mV LINAC or cobalt-60.

Outcomes

Local recurrence of invasive breast cancer in the treated breast

Distant recurrence (in regional lymph nodes –ipsilateral, axilla, supraclavicular, imc- bone, liver, lung, CNS).

Local recurrence free survival - interval from randomization to local recurrence as first event

Disease Free Survival – interval from randomization to any recurrence or death

Overall survival

Histological confirmation required for any local recurrence and first recurrence at other sites if possible.

Global cosmetic outcomes (EORTC)

Graded as:

0 no difference or excellent
 1 = small difference or good
 2 = moderate difference or fair
 3 = large difference or poor

Radiation toxicity (RTOG/EORTC late morbidity scale) on skin and subcutaneous tissue:

0 = No toxicity
 1 = slight
 2 = moderate
 3 = marked
 4 = severe

Follow up Median follow-up was 69 months.

Results

ITT analysis of all randomized patients

Drop outs:

Did not receive RT – 1 in short arm 3 in long arm

Did not complete RT – 2 in short arm 2 in long arm

Local recurrence free survival

Outcome	Short arm	Long arm	Absolute difference % (95% CI)
Breast cancer recurrence as first event	N=21	N=23	
Local recurrence free survival at 5 years	97.2%	96.8%	0.4% (-1.5 to 2.4)
DCIS local recurrences	4	3	

A stratification of 5 year local recurrence rates by age of patient, tumour size, and adjuvant systemic therapy showed no significant differences between arms (from confidence intervals).

Disease free and overall survival

There were no statistically significant differences in DFS or OS between arms.

The number of deaths and distribution of breast cancer recurrences are shown in the following table.

Outcome	Short arm	Long arm
Any recurrence or death as first event	N=91	N=79
Local recurrences	21	23
Regional recurrences	8	6
Distant recurrences	48	26
Deaths	14	24
DFS (2 sided log-rank test)	P=0.37	

OS (2 sided log-rank test)

P=0.78

Cosmetic outcomes

Assessed at baseline, 3 and 5 years.

Cosmetic outcomes assessed in 1220 patients at baseline, 1013 at 3 years and 735 at 5 years.

Global cosmetic outcomes (EORTC)	Short arm	Long arm
Baseline N=1220 Excellent or good	83.8%	82.6%
3 years N= 1013 Excellent or good	76.8%	77.0%
5 years N= 735 Excellent or good	76.8%	77.4%
5 year absolute difference	-0.6% 95%CI (-6.5 to 5.5)	

Radiation toxicity

No grade 4 toxicity was observed and the incidence of grade 2 or 3 toxicity was very low in both treatment arms. Toxicity effects for the skin and subcutaneous tissue are shown in the following table.

Site	Grade	% at 3 years		% at 5 years	
		Short arm (n=515)	Long arm (n=492)	Short arm (n=394)	Long arm (n=358)
Skin	0	90	87	87	82
	1	8	11	10	15
	2/3	2	2	3	3
No skin toxicity				87%	82%
5 year absolute difference				Abs difference 5% (95% CI -0.3 to 10.0)	
Subcutaneous tissue	0	69	63	66	60
	1	27	32	29	33
	2/3	4	5	5	7
No subcutaneous tissue toxicity				66%	60%
5 year absolute difference				Abs difference 6% (95% CI -1.2 to 13.0)	

Radiation pneumonitis: 4 cases (2 in each intervention arm)

Rib fracture: 1 case (long arm)

Author conclusions: The more convenient 22-day fractionation schedule appears to be an acceptable alternative to the 35-day schedule.

Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2005;75(1):9-17.

Design: RCT (1986-1998)

Level 1++

Country: UK, setting: Two Oncology Centres

Aim: To test the effects of radiotherapy fractions >2.0 Gy on late normal tissue responses in the breast after tumour excision and radiotherapy for early breast cancer.

Inclusion criteria

Patients with operable invasive breast cancer (T1-3, N0-1, M0)

Age under 75 years at presentation, had BCS and complete macroscopic resection of invasive carcinoma.

Exclusion criteria

Population number of patients = 1410 enrolled

Mean age 54.5 years (range 25-78)

67.3% underwent axillary staging and were node negative.

Randomisation was to 3 alternative schedules and stratified by centre and the presence of microscopic foci close to the nearest margin (<3mm).

Interventions

All patients had level II/III axillary dissection – exceptions were women over 50 years with impalpable axillary lymph nodes at one centre, and some at the other centre had axillary sampling.

Patients with positive axillary pathology were offered RT to the supraclavicular fossa at one centre, whilst at the other centre this was reserved for patients with heavy node level I/II involvement and any level III involvement.

Axillary RT was recommended after axillary sampling if the axillary nodes were positive, and at one centre if no axillary surgery was undertaken.

A sub-randomization to boost versus no boost was performed, and this closed in May 1994, when all patients were offered an elective boost.

Control arm 50Gy in 25 fractions of 2Gy over 5 weeks

(n=470)

39Gy in 13 fractions of 3Gy over 5 weeks (5 x per fortnight)

(n=474)

42.9 Gy in 13 fractions of 3.3Gy over 5 weeks (5 x per fortnight)

(n=466)

α/β ratio of 1.8 Gy for 3.0 Gy; 6.0Gy for 3.3Gy.

6 MV X-rays were used in the majority of patients.

Lung corrections were applied at one centre but not the other.

Outcomes

Late change in breast appearance compared to post-surgical appearance (by 3 observers blinded to treatment allocation) from annual photographs:

None/minimal 0

Mild 1

Marked 2

Fibrosis

Ipsilateral tumour recurrence.

Follow up Maximum total 15 years, median 8.1 years.

Results

Pairs of photos available at each time point:

1128 at 1 year

1004 at 2 years

525 at 3 years

472 at 4 years

765 at 5 years

141 at 10 years

420 patients (34.9%) experienced some change in breast appearance.

The risk of developing any radiation effect was lower in the 39Gy /13 fraction compared with the 42.9Gy /13 fraction group. There was also a significant difference between the 50 and 39 Gy arms over this time period ($p=0.01$ Log rank test), but weaker evidence for a difference between 50 and 42.9Gy ($P=0.05$ Log rank test).

Changes in breast appearance were relatively small, 76/1202 (6.3%) of patients scored a grade 2 (marked). However a lower risk of marked change was observed in patients treated with 39 Gy compared with 42.9 Gy (see Table). There was also a difference between the 50 and 42.9 Gy arms of the trial for marked change in appearance ($P=0.01$ Log rank test), but not between 50 and 39 Gy ($P=0.18$ Log rank test).

The value of the α/β ratio estimated from the Cox proportional hazards regression model for any change in breast appearance is 3.6 Gy (95% CI 1.8–5.4 Gy), and is 2.9 Gy (95% CI 1.0–4.8 Gy) for marked change in breast appearance. The α/β value for palpable breast induration was 3.1 Gy (95% CI 1.8-4.4). The α/β values were unchanged if photographic data were restricted to events emerging at 3 or more years when earlier, non-permanent, changes in breast appearance due to, e.g. surgical oedema are censored in the analysis.

Survival analyses of changes in breast appearance and clinical assessments of late radiation effects at 10 years by fractionation schedule are shown in the following table.

Endpoint	Fractionation schedule	Events/total (%)	Estimated % with no event at	Log rank test comparing
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			10 years (95%CI)	all 3 schedules (p)
Photographic assessment				
Any change in breast appearance	50Gy 42.9Gy 39Gy	140/396 (35.4) 168/397 (42.3) 112/409 (27.4)	46.6 (37.2- 55.9) 42.0 (33.0- 51.0) 43.9 (30.8- 57.0)	<0.001
Marked change in breast appearance	50Gy 42.9Gy 39Gy	22/396 (5.6) 40/397 (10.1) 14/409 (3.4)	90.2 (85.0- 95.5) 84.4 (77.7- 91.1) 93.4 (87.8- 99.0)	<0.001
Clinical assessment				
Cosmesis (fair/poor)	50Gy 42.9Gy 39Gy	165/271 (60.9) 175/266 (65.8) 136/269 (50.6)	28.8 (22.3- 35.4) 25.6 (19.3- 31.8) 42.0 (34.9- 49.1)	<0.001
Breast shrinkage (moderate/marked)	50Gy 42.9Gy 39Gy	147/271 (54.6) 148/266 (55.8) 124/269 (46.1)	36.2 (29.3- 43.1) 34.2 (27.0- 41.5) 44.4 (37.0- 51.7)	0.026
Breast distortion (moderate/marked)	50Gy 42.9Gy 39Gy	132/271 (48.9) 148/266 (55.8) 115/269 (42.8)	41.5 (34.4- 48.6) 38.0 (31.4- 44.6) 51.4 (44.4- 58.4)	0.005
Breast oedema (moderate/marked)	50Gy 42.9Gy 39Gy	34/271 (12.6) 54/266 (20.3) 29/269 (10.8)	86.2 (81.8- 90.7) 78.5 (73.1- 83.9) 88.5 (84.4- 92.7)	0.004
Induration (moderate/marked)	50Gy 42.9Gy 39Gy	77/271 (28.6) 108/266 (40.8) 55/269 (20.4)	63.7 (56.6- 70.7) 48.9 (41.5- 56.4) 72.3 (65.5- 79.2)	<0.001
Telangiectasia	50Gy	37/271	81.9 (76.5-	0.065

(moderate/marked)	42.9Gy 39Gy	(13.8) 38/266 (14.3) 23/269 (8.6)	87.3) 82.0 (76.5- 87.5) 88.0 (83.0- 92.9)	
Arm oedema (moderate/marked)	50Gy 42.9Gy 39Gy	17/271 (6.3) 22/266 (8.3) 16/269 (5.9)	92.3 (88.6- 96.1) 89.5 (85.1- 93.8) 93.0 (89.2- 96.8)	0.494
Shoulder stiffness (moderate/marked)	50Gy 42.9Gy 39Gy	21/271 (7.8) 48/266 (18.1) 19/269 (7.1)	90.0 (85.6- 94.3) 78.2 (72.3- 84.0) 89.9 (85.3- 94.6)	<0.001

The estimates of late radiation effects for the 50 Gy arm were generally between those for 39 and 42.9 Gy. The only clinical parameter that failed to demonstrate a dose response between the 39 and 42.9 Gy treatment arms was arm oedema. This may reflect the small proportion of patients who underwent any form of lymphatic RT.

Author conclusions: An alpha/beta value of around 3 Gy for late normal tissue changes in the breast is derived from the estimated equivalence of 41.6 Gy in 13 fractions and 50 Gy in 25 fractions over 5 weeks, in line with trial predictions.

General comments –This is the same trial as the Owen paper.

Bates TD. The 10-year results of a prospective trial of post-operative radiotherapy delivered in 3 fractions per week versus 2 fractions per week in breast carcinoma. The British journal of radiology 1988; 61(727):625-30.

Design: RCT (1968-1974)
Level 1+
Country: UK, setting: Single Hospital
Aim: Ten year follow-up of dose fractionation trial.

Inclusion criteria

Breast carcinoma treated by mastectomy (majority simple mastectomy)

Exclusion criteria

Presence of distant metastases.

Population number of patients = 411

Interventions

Many had additional removal of lower axillary lymph nodes.
N0 and N1 groups were randomized to treatment with:
N= 203 received 12 fractions in 28 days
N= 208 received 6 fractions in 18 days

Cervico-axillary chain treated with Cobalt 60 teletherapy:
Tissue dose 45-51Gy in 12 fractions over 28 days (3.75-4.25 Gy / fraction)
Or
Tissue dose 31-35Gy in 6 fractions over 18 days (5.17 – 5.83 Gy / fraction)

IMC treated with Cobalt 60 and Caesium 137 teletherapy:
Tissue dose 52Gy in 12 fractions over 28 days
Or
Tissue dose 35Gy in 6 fractions over 18 days

The chest wall was treated with X rays:
37Gy in 12 fractions over 28 days
Or
31.5Gy in 6 fractions over 18 days

Outcomes

Local recurrence – tumour recurrence within the irradiated volume, before and after metastases
Effects of radiation on normal tissues

Follow up 10 years

Results

8 patients were lost to follow-up

Sites of local recurrence at 10 years are shown in the following table:

Site	6 fractions (n=208)	12 fractions (n=203)
Chest wall	15	14

Regional nodes	8	10
Both	3	2
Total	26 (12.5%)	26 (12.8%)

There were more distant metastases and more deaths from all causes in the 6 fraction group, but the differences were not statistically significant. The actuarial survival rates were similar for each fractionation schedule. The actuarial local recurrence rates were similar for each fractionation schedule (10% for N0 and 17% for N1 at 10 years).

Normal tissue reactions are shown in the following table:

Outcome	6 fractions (n=208)	12 fractions (n=203)
<i>Early radiation reactions</i>		
Vomiting	4%	4%
Lassitude	58%	45%
Dysphagia	~50%	~50%
Skin reaction on chest wall at 2 weeks	Score 1.46 (mild erythema)	Score 1.62 (mild erythema)
<i>Late radiation reactions (at 6 months, 5 and 10 years)</i>		
Chest wall scores 1=minimal skin changes 2=moderate skin changes 3=severe skin changes	6 mths to 5 years 1.7; 1.4 10 years 1.5	6 mths to 5 years 1.7; 1.4 10 years 1.3
Subcutaneous fibrosis (sc, ic and axilla) 0=none 1=mild 2=moderate 3=severe	5 years 0.7 10 years 0.8	5 years 1.3 10 years 1.2
Shoulder movement (lower score =more movement)	10 years 0.13	10 years 0.82
Lymphoedema of arm 1=slight 2= moderate 3=severe	6 months 1 (14.5%) 1 year 1.07 (22%) 5 years 1.47 (18%) 10 years 1.57 (12%)	6 months 1 (13.5%) 1 year 1.05 (20%) 5 years 1.83 (27.5%) 10 years 1.89 (29.5%)
Apical pulmonary fibrosis	6 months 1.03	6 months 1.09

	1 year	1 year
	1.03	1.12
	5 years	5 years
	1.40	1.48
	10 years	10 years
	1.67	1.62

The early radiation effects on the normal tissues were similar. The late skin changes in the chest wall (treated with 70 kV X rays) were progressive and at 10 years were more marked with 6 fractions. Late subcutaneous fibrosis in the axilla (treated with cobalt-60 teletherapy), was lower in the 6-fraction group. Twelve fractions resulted in greater restriction of shoulder movement and an increased incidence of lymphoedema of the arm. The incidence of lymphoedema was higher in the N1 group than N0.

Author conclusions: In this trial, the 6-fraction technique showed an advantage over the 12-fraction technique. It was equally effective in controlling local recurrence and had fewer late sequelae. It was also convenient for patients and economic in the use of radiotherapy resources.

Taher AN, El-Baradie MM, Essa H, Zaki O, Ezzat S. Hypofractionation versus conventional fractionation radiotherapy after conservative treatment of breast cancer: early skin reactions and cosmetic results. Journal of Egyptian National Cancer Institute 2004 Sep;16(3):178-87.

Design: RCT (Aug 2002-May 2003)

Level 1-

Country: Egypt, setting: Single university hospital

Aim: To compare in a prospective trial the acute skin reaction and late cosmetic effects of normal fractionation versus hypofractionation radiotherapy after breast conserving surgery.

Inclusion criteria

Patients < 65 years with T1-2, N0, M0 tumours and ≥ 1cm negative surgical margin.

At least 10 dissected nodes.

Distance from midline to mid-axillary line < 25cm.

Exclusion criteria

Contralateral breast cancer

Multicentric disease

Serious non-malignant disease

Severe mental or physical disorders

Delay of RT treatment > 4 months after surgery

Population number of patients = 30

Mean age 47.5 ± 10 years (range 25-65)

T stage

T 1 Group A Conventional n=1 (6.7%); hypofractionated n=7 (46.7%)

T 2 Group B Conventional n=14 (93.3%); hypofractionated n=8 (53.5%)

P=0.04

Interventions

Randomization (by sealed envelope) was to:

Group A: Whole breast irradiation of 50Gy in 25 fractions of 2 Gy over 5 weeks (5 fractions/ week)

Or

Group B: Whole breast irradiation hypofractionated into 42.5Gy in 16 fractions of 2.66 Gy over 5 weeks (5 fractions/ week).

Only the breast and chest wall were included in the target volume using a 6 MV linear accelerator. In Group A the tumour bed received a boost of electrons.

Patients also received systemic chemotherapy (n=20 (67%) before RT, and tamoxifen.

Outcomes

RTOG (LENT) scoring system

Cosmesis scored at 6, 12 and 24 months (appearance of scar, breast size, shape, nipple position, shape of areola in comparison to the untreated breast).

4 point scale : excellent (0); good (1); fair (2); poor (3)

Acute (early) skin reactions: Mild (G0-G1); severe (G2-G4)

Follow up Mean of 23 ± 3 months (range 18-27 months)

Results

T stage was the only baseline characteristic that differed significantly between groups – the data is reported in the population section.

Acute skin reactions

Acute skin reactions are reported in the following table:

Grade	Conventional (n=15) n (%)	Hypofractionation (n=15) n (%)	P value
0	0 (0)	2 (13.3)	
1	6 (40)	7 (46.7)	
2	9 (60)	5 (33.3)	0.47
3	0 (0)	1 (6.7)	
4	0 (0)	0 (0)	

Severe skin reactions (G2) occurred in 9 patients in the conventional group and 6 patients (5 G2 and 1 G3) in the hypofractionated group. The difference was not statistically significant. The peak incidence of severe skin reactions occurred in the 5th week of RT in the conventional group and lasted for 3 weeks. In the hypofractionated group the peak reaction occurred in the 3rd week of RT and lasted for 5 weeks.

A further comparison between groups of factors that may contribute to acute skin reactions found that none were significant. Age, menopausal status, stage (T1 or T2), pathology (ductal or lobular), breast volume, tumour volume and the interval between surgery and RT were not significantly different between groups. However the overall incidence of grade II and III acute skin reactions was found to be significantly more frequent in women with breast volumes > 1100cc when the groups were combined. There was no significant difference between groups A and B when analysed by breast volume. These group sizes were very small and may be underpowered to detect any differences. This also applied to the duration of acute skin reactions where the overall difference was significantly shorter among women with breast volumes < 1100 cc, but there were no differences in duration of reaction by breast volume when comparing groups A and B.

Factor	Conventional (group A) n=15			Hypofractionation (group B) n=15		
	Mild	Severe	P	Mild	Severe	p
Breast volume (cc)	904 ± 282	1131 ± 297	0.16	807 ± 547	1238 ± 399	0.09
Incidence of severe skin reactions						

Breast volume	Total	P value	Group A	Group B	P value
≤ 1100cc	7/18 (38.8%)	0.016	5/9 (55.6%)	2/9 (22.2%)	0.14
> 1100cc	10/12 (83.3%)		5/6 (83.3%)	5/6 (83.3%)	1.00
Duration (weeks)					
	Total	P value	Group A	Group B	P value
≤ 1100cc	2 ± 2.9	0.013	2 ± 1.4	4.5 ± 2	0.11
> 1100cc	4.8 ± 2.6		4 ± 2.4	4.5 ± 3	0.76

Cosmetic outcomes

These were classified as satisfactory – excellent or good
Unsatisfactory – fair or poor

Cosmetic outcome	Conventional (group A) n=15	Hypofractionation (group B) n=14	Total (%)	P value
Satisfactory	4 (33.3%)	8 (66.7%)	12 (41%)	0.14
Unsatisfactory	11(65%)	6 (35%)	17 (59%)	Not reported

Prognostic factors affecting cosmesis

	Satisfactory (n=12)	Unsatisfactory (n=17)	P value	
Lumpectomy volume	329.6 ± 184.3	548.2 ± 341.1	0.05	
Lumpectomy /breast volume ratio	0.3 ± 0.2	0.5 ± 0.2	0.02	

There was a higher incidence (73%) of unsatisfactory cosmesis in patients who developed early severe skin reactions (11/15) but this was not significant (p=0.13).

Other factors found to influence breast cosmesis were lumpectomy volume and lumpectomy/breast volume. Other factors tested including fractionation group, acute skin reaction (mild or severe), age, menopausal status, stage (T1 or T2), pathology (ductal or lobular), breast volume, tumour volume, chemotherapy and the interval between surgery and RT, were not significantly different between groups.

Author conclusions: Preliminary results support the use of a shorter fractionation schedule of 42.5Gy/16f/22 days in patients with breast conserving surgery. The study is still going on to study the late effects on a larger number of patients for final evaluation of this regimen.

Goel A, Kaushal V, Hooda HS, Das BP. Comparison of two radiation dose schedules in post mastectomy carcinoma of the breast. Indian journal of medical sciences 2000;54(7):278-83.

Design: RCT (1989-1992) Level 1-

Country: India, setting: Single Centre

Aim: To compare two radiation dose schedules in post mastectomy carcinoma of the breast.

Inclusion criteria Patients surgically treated with modified radical mastectomy, Karnofsky performance status (KPS) >70

Exclusion criteria Patients with distant metastases, inoperable cases, fixed inoperable nodes, any surgery other than MRM, KPS < 70

Population number of patients = 108

Median age 46 years (31-70)

N=54 40 Gy in 17 fractions over 3.2 weeks (Group A)

N=54 45 Gy in 20 fractions over 4 weeks (Group B)

	Group A	Group B
Postmenopausal	56%	60%
Axillary mass	44%	50%
Stage III	58%	54%

Interventions

Method of randomisation not reported.

Modified radical mastectomy

Postoperative RT to chest flap and drainage areas.

Group A: 40 Gy in 17 fractions over 3.2 weeks

Group B: 45 Gy in 20 fractions over 4 weeks

Cobalt 60 teletherapy machine

Outcomes

Chest wall failure

Axillary node failure

Distant metastases

Skin reactions

Follow up

Results

4/54 patients in group A did not complete the treatment and were excluded from the study.

Results are reported in the following table.

Outcome	Group A (n=50)	Group B (n=54)
No evidence of disease at last follow-up	26 (52%)	32 (59%)
Chest wall failure	5 (10%)	3 (5.6%)
Axillary lymph node	3 (6%)	4 (7%)

failure		
Distant metastases	16 (32%)	15 (28%)
Radiation reactions		
Skin reactions		
Grade 0	5 (10%)	11 (20%)
Grade I	10 (20%)	16 (30%)
Grade II	25 (50%)	24 (45%)
Grade III	10 (20%)	3 (5%)
Grade IV	0	0
Difficulty in swallowing	38 (76%)	40 (74%)
Nausea/vomiting	6 (12%)	7 (13%)
Infection	2	3
Lymphedema	3	1
Shoulder restriction	1	1
Brachial plexus involved	0	0

Author conclusions

No statistically significant difference in local control and efficacy of these two radiation dose schedules was observed in postmastectomy carcinoma of the breast. (No statistical tests were reported).

General comments –

Very small sample size, may be underpowered to detect any differences between groups. No time period reported.

Ongoing RCTs

A randomized phase III study of conventional whole breast irradiation versus partial breast irradiation for women with stage 0, I, or II breast cancer. Clinical Advances in Hematology and Oncology 2006;4(10):719-21

Design: RCT (NSABP B-39, RTOG 0413)

Country:, setting:

Aim: To compare conventional WBI with PBI following lumpectomy on local tumour control.

Inclusion criteria Patients undergoing BCS for stages 0, I and II breast cancer

Exclusion criteria

Population Target number of patients = 3000

Interventions

Random assignment to either Whole Breast Irradiation (WBI) or partial breast irradiation (PBI) after lumpectomy.

WBI:

50Gy (2Gy/fraction) or 50.4Gy (1.8Gy/fraction) to the whole breast, followed by an optional boost to 60-66.6Gy.

PBI:

34Gy in 3.4Gy fractions using multi-catheter brachytherapy OR

34Gy in 3.4Gy fractions using Mammosite catheter OR

38.5Gy in 3.85Gy fractions using 3D conformal external beam radiation

For all PBI interventions RT given to tissue surrounding lumpectomy cavity only.

Outcomes

Local control

Overall survival

Cosmesis

Acute and late toxic effects

Follow up

Results

Not available

General comments -

Non-randomized studies

Marhin W, Wai E, Tyldesley S. Impact of fraction size on cardiac mortality in women treated with tangential radiotherapy for localized breast cancer. *International Journal of Radiation Oncology Biology Physics* 2007;69(2):483-9.

Design: Population retrospective cohort (1984-2000)

Level 2+

Country: Canada, setting: Single province

Aim: To determine whether fraction size affects the risk of cardiac mortality in women treated with adjuvant radiotherapy (RT) for left-sided breast cancer.

Inclusion criteria

Women aged 20-80 years

Stage pTis – 2, pN0-1, M0

Exclusion criteria

Women receiving irradiation to other sites for a second malignancy, contralateral breast primary, prior history of cancer.

Patients receiving any RT fields in addition to breast tangents and breast boosts, including regional lymph nodes (axilla, internal mammary, or supraclavicular fossa).

Population number of patients = 7447 records from the Oncology Reporting System database in British Columbia

Mean age 57.2 years (25-80 years)

Patient characteristics were similar between women with right and left-sided breast cancers.

Left-sided breast cancer n=3781

Right-sided breast cancer n=3666

Interventions

BCS or mastectomy with adjuvant RT to breast or chest wall with megavoltage tangential irradiation with or without a breast boost.

21% received adjuvant chemotherapy

35% received adjuvant hormonal therapy

(not all systemic therapy was systematically recorded)

Outcomes

Cardiac related deaths (from death records)

Follow up Median follow-up 7.9 years (0.3-20.5)

Results

Deaths n=1067

9% of deaths attributed to cardiac disease

Left-sided cancer deaths n=52

Right-sided cancer deaths n=47

Patient and treatment related factors were evenly distributed between right and left sided groups.

Median RT dose was 44Gy

Median number of fractions was 16

Median fraction size 2.75Gy

Treatment characteristics by laterality are shown in the following table and were evenly distributed by site of cancer:

Characteristics	Laterality of breast cancer			
	Left (n=3781)		Right (n=3666)	
Age (yr)	≤ 60	> 60	≤ 60	> 60
Radiotherapy: Dose (Gy)				
Mean	44.19	44.03	44.15	43.85
Median	44	44	44	44
Number of fractions				
Mean	17	17	17	17
Median	16	16	16	16
Fraction size (Gy)				
Mean	2.6	2.62	2.6	2.63
Median	2.75	2.75	2.75	2.75
Fraction size (n of patients)				
≤2	342	239	361	198
>2	1846	1354	1804	1303

Treatment characteristics of women who died from cardiac causes by laterality of breast cancer:

	Laterality of breast cancer	
	Left (n=52)	Right (n=47)
Mean age (years)	71.5 ± 7	69.2 ± 8
Breast RT		
Mean dose (Gy)	42.8 ± 6	42.6 ± 6
Mean n of fractions	16.2 ± 3	15.9 ± 3
Mean fraction size (Gy)	2.7 ± 0.2	2.7 ± 0.3
Fraction size (Gy)		
≤2	4 (0.6%)	4 (0.7%)
>2	48 (1.5%)	43 (1.4%)

Treatment and patient characteristics were evenly distributed between left and right – sided cancers of women who died from a cardiac event. There were no significant differences in the number of deaths from all causes ($p=0.3$) or cardiac specific deaths ($p=0.69$) in women treated for left-sided vs. right-sided early stage breast cancer.

There was no significant difference in the number of cardiac deaths in women < 60 years treated for left vs. right-sided breast cancer ($p=0.17$). In women > 60 years the authors suggest there was an increase in cardiac deaths in women with left-sided breast cancer, however, this was not statistically significant compared to women with right-sided breast cancers ($p=0.39$).

There was no statistical difference in the rates of cardiac mortality in women treated with hypofractionated RT (>2Gy) compared to women treated with conventional fraction sizes of ≤ 2 Gy irrespective of laterality. In women > 60 years with left-sided breast cancer the authors suggested that adjuvant RT with fraction sizes > 2Gy may increase cardiac mortality 5-10 years after treatment, however, this was not statistically significant ($p=0.22$). When comparing left with right – sided RT of > 2Gy fractions in women aged > 60 years the relative risk of cardiac death was 1.22 (95%CI 0.75-2.01) [reference right sided RT]. However, this is not significant – confidence interval encompasses 1.00. In women with right-sided breast cancer neither age, nor fraction size influenced cardiac mortality.

Relative risks of cardiovascular deaths stratified by age and fraction size are shown in the following table:

Age (years)	Fraction size (Gy)	Laterality	Cumulative incidence of cardiac death at 10 year follow-up (%)	Relative risk (95% CI) at 10 year follow-up
All ages	≤ 2	Right	1.01	1.00
		Left	0.96	0.95 (0.24 – 3.78)
	>2	Right	1.73	1.00
		Left	1.86	1.07 (0.68 – 1.69)
≤ 60	≤ 2	Right	0.00	1.00
		Left	0.00	Not available
	>2	Right	0.70	1.00
		Left	0.34	0.49 (0.15 – 1.62)
> 60	≤ 2	Right	2.68	1.00
		Left	2.37	0.90 (0.23 – 3.53)

	>2	Right	3.05	1.00
		Left	3.74	1.22 (0.75 – 2.01)

Relative risk of cardiac death for women with left-sided compared with right-sided breast cancer adjusted for age and fraction size

Since there were fewer patients in the ≤ 2 Gy fraction group and a short median follow-up time, the authors also suggested that the small differences found in this study may become significant over time or with larger patient numbers.

Author conclusions: There was no evidence for increased risk of cardiac mortality in women treated with adjuvant RT after a median follow-up of 7.9 years in our cohort. Hypofractionated adjuvant RT regimens did not significantly increase the risk of cardiac mortality.

General comments –

Non-fatal cardiac events may be under-represented since mortality data were collected from death certificates.

Systemic therapy may be a confounding factor for cardiac mortality. The distribution of those receiving systemic therapy was similar between groups in this study, however the database did not capture all systemic therapy in the province. The authors suggested that this would not influence their conclusions.

Wallace LM, Priestman SG, Dunn JA, Priestman TJ. The quality of life of early breast cancer patients treated by two different radiotherapy regimens. Clinical oncology (Royal College of Radiologists (Great Britain)) 1993;5(4):228-33.

Design: Cohort from RCT
3

Level

Country:, UK setting: Single Hospital

Aim: To determine differences between radiotherapy schedules in terms of their impact on the patient's quality of life and whether measures of coping style and trait anxiety could be used to predict the subjective response to treatment.

Inclusion criteria

Women in the West Midlands Oncology Association (WMOA) trial who received postoperative RT after lumpectomy. Women chose whether or not to participate.

Exclusion criteria

Population number of patients = 63

N = 31 short RT course

N = 32 long RT course

Mean age short course 55.0 years.

Mean age long course 53.6 years.

Interventions

Lumpectomy followed by either:

40Gy in 15 daily fractions over 4 weeks (short course)

50Gy in 25 daily fractions over 6 weeks (long course)

Both groups also received a boost of 15Gy in 5 fractions over the short or long course.

Treatment was delivered by Cobalt-60 megavoltage using a 4 field technique.

The breast and ipsilateral axilla, supraclavicular and first station internal mammary lymph nodes were irradiated. All patients received tamoxifen.

Outcomes

Global Quality of life : five parameters- activity, daily aid from others, wellness, family support, outlook.

Hospital Anxiety and Depression Scale (HADS)

HADS anxiety score clinically significant >10.

HADS depression score clinically significant >10.

Interviews took place 7 days after completion of RT.

Follow up Pre and post treatment questionnaires, 6 month follow-up.

Results

27/63 6 were lost to follow-up at 6 months.

Pre-radiotherapy measures:

Outcome	Group short n=31	Group long n=32	P value
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	Mean (95% CI)	Mean (95% CI)	
HADS anxiety	6.2 (4.5-7.9)	6.7 (5.2-8.2)	0.39
HADS depression	3.7 (2.2-5.2)	3.8 (5.1-2.5)	0.69

No differences were found between scores for the short and long course pre-RT treatment.

Post RT treatment scores for anxiety and depression:

HADS scale	1 week post RT			6 months post RT		
	Short (SE) N=31	Long (SE) N=32	P value	Short (SE) N=17	Long (SE) N=19	P value
Anxiety	3.8 (0.59)	5.2 (0.63)	0.13	3.0 (0.56)	5.3 (1.04)	0.2
Depression	3.9 (0.64)	3.4 (0.52)	0.77	2.8 (0.65)	3.2 (1.0)	0.96

On completion of treatment there was a reduction in anxiety scores overall (p=0.001).

There was no significant difference between the 2 groups (p=0.28).

Depression scores did not change significantly pre and post treatment.

Global Quality of Life scores pre and post treatment:

Global QoL	Short			Long		
	Pre (n=31)	Post (n=31)	6 months (n=17)	Pre (n=32)	Post (n=32)	6 months (n=19)
Wellness: Not up to par	11	13	4 (23%)	15	15	4 (21%)
Outlook: Positive	23	23	13 (76%)	19	16	12 (63%)

There was no statistically significant difference between the short and long groups at 6 months for positive outlook.

The treatment disruption scale showed a minimal impact of RT on patients' daily lives (family and sexual relationships, finances, work and general activities).

The symptom distress scale showed a significant increase in scores for four parameters on completion of RT (not clear whether this applied to both groups combined):

Nausea p=0.012

Tiredness p<0.001

Sleep disturbance $p=0.02$

Skin irritation $p<0.0001$

There was also a larger incidence of weight gain in the long course group ($p=0.01$)

Author conclusions: Overall, radiotherapy had little effect on quality of life and the differences between the two regimens were minor with significantly more of those women on the longer treatment schedule experiencing a transient weight change, disruption of private life and loss of positivity compared with those on the shorter schedule. The HADS test may be used to detect patients who may benefit from extra reassurance and/or referral for psychiatric support.

General comments –

Clear definitions of the measured parameters were not provided. Some of the findings have not been reported because it was not clear which groups they applied to.

Olivotto IA, Weir LM, Kim-Sing C, Bajdik CD, Trevisan CH, Doll CM, et al. Late cosmetic results of short fractionation for breast conservation. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 1996;41(1):7-13.

Design: Cohort from RCT (1986-1991)

Level 2+

Country: Canada, setting: Single Cancer Centre

Aim: Analysis of results of data on short fractionation schedules after BCS up to 5 years after completion of RT.

Inclusion criteria

Women with invasive T1 and T2 pathologically node negative breast cancer.

Lumpectomy with negative margins.

Negative axillary dissection with at least 4 nodes recovered.

Exclusion criteria

Contraindications to RT or unsuitable for RT.

Allergy to acetylsalicylic acid (ASA).

Lupus erythematosus

Scleroderma

Rheumatoid arthritis

Diabetes

Population number of patients = 184

Median age 54.5 years (range 28-81)

Interventions

Following BCS and axillary dissection patients were randomized to receive 325mg of enteric coated acetylsalicylic acid (ASA) or placebo daily for 1 year.

All patients had a breast dose of 44 Gy in 16 daily fractions (2.75Gy) over 22 days, paired, opposed tangential fields were used.

Cobalt -60 or 4MV photons were used.

13 patients with pathological close margins also received a boost to the tumour bed (5Gy in 2 fractions).

Median time between surgery and first day of RT was 5.6 weeks.

87% started \leq 8 weeks

Outcomes

Cosmesis (patient and physician assessments)- excellent, good, fair, poor.

Breast discomfort – none, mild, moderate, severe

Erythema

Oedema

Induration

Telangiectasia

Follow up Median 6.7 years

Results

Actuarial overall survival at 5 years = 92% (SE \pm 3%)

Actuarial breast recurrence rate at 5 years = 6%

Cosmetic and normal tissue scores before RT and at 3 and 5 years are reported below:

	Prior to RT (N=184)	3 yrs post RT (N=145)	5 yrs post RT (N=135)
Eligible cases	n (% known)	n (% known)	n (% known)
Patient assessment of cosmesis			
Excellent	83 (47.7)	80 (56.3)	67 (56.3)
Good	67 (38.5)	50 (35.2)	47 (39.5)
Fair	22 (12.6)	11 (7.7)	4 (3.4)
Poor	2 (1.1)	1 (0.7)	1 (0.8)
Not stated	10 -	3 -	16 -
Physician assessment of cosmesis			
Excellent	85 (46.2)	76 (52.4)	65 (48.9)
Good	75 (40.8)	54 (37.2)	53 (39.8)
Fair	22 (12.0)	15 (10.3)	12 (9.0)
Poor	2 (1.1)	0 (0.0)	3 (2.3)
Not stated	0 -	0 -	2 -
Discomfort			
None	116 (65.2)	100 (77.9)	99 (79.8)
Mild	54 (30.3)	25 (17.9)	22 (17.7)
Moderate or severe	8 (4.5)	6 (4.3)	3 (2.4)
Not stated	6 -	5 -	11 -
Erythema			
None	152 (83.1)	130 (93.5)	117 (93.6)
Mild	26 (14.2)	6 (4.3)	8 (6.4)
Moderate or severe	5 (2.7)	0 (0.0)	0 (0.0)
Not stated	1 -	6 -	10 -
Oedema			
None	133 (73.4)	133 (95.7)	113 (97.4)
Mild	45 (24.9)	6 (4.3)	3 (2.6)
Moderate or severe	3 (1.7)	0 (0.0)	0 (0.0)

Not stated	3 -	6 -	19 -
Induration			
None	74 (40.7)	118 (85.5)	102 (81.6)
Mild	81 (44.5)	19 (13.8)	21 (16.8)
Moderate or severe	27 (14.8)	1 (0.7)	2 (1.6)
Not stated	2 -	7 -	10 -
Telangiectasia			
None	184 (100.0)	127 (90.7)	107 (86.3)
Mild	0	12 (8.6)	16 (12.9)
Moderate or severe	0	1 (0.7)	1 (0.8)
Not stated	0	5 -	11 -

Cosmesis

At 5 years after RT 96% (114/119) of patients and 89% (118/133) of physicians rated the cosmetic outcome as good to excellent. The illustrations in the paper showed an initial transient period of worsening cosmesis which then improved and was stable between 2 and 5 years.

Other outcomes

Breast discomfort, erythema, oedema and induration were related to both surgery and RT. 35%, 17%, 27% and 59% of patients had mild discomfort, erythema, oedema or induration respectively before commencement of RT. The RT aggravated these conditions which all showed an improvement over 1 to 3 years. At 5 years 20% had breast discomfort, 18% had induration, 6% had erythema and 3% had some degree of breast oedema. Fewer patients had these effects at 5 years than immediately after primary surgery.

The likelihood of telangiectasia was 14% (SE \pm 9.7%) at 5 years. This was mild and occurred in the inframammary fold of women with large breasts.

Induration was present in 15% and 18% of patients evaluated at 3 and 5 years after RT. This was more frequent after 3 years if induration was present before initiation of RT. The difference between patients with or without induration prior to RT then assessed at 3 to 5 years was statistically significant (38% vs. 21% respectively before RT, $p=0.022$).

Author conclusions: Results are comparable to those reported from centres employing more conventional fractionation. Short fractionation produces acceptable cosmetic results for the majority of women if there are no contraindications to RT and in the absence of significant post-operative breast induration.

General comments

Although this study randomized patients to ASA or not, this was not evaluated in the analysis since the authors report that "no ASA effect was seen for any parameter evaluated" and the group is treated as a single group. For this reason this study is quality scored as a cohort.

Mladenovic J. Hypofractionated radiotherapy in elderly women with breast cancer. Journal of the Balkan Union of Oncology 2001;6(1):49-54.

Design: NRS (1 year period)

Level

3

Country: Serbia, setting: Single centre

Aim: To evaluate two different regimes of fractionation (conventional and hypofractionated) in the radiotherapy of elderly (over 65 years) women with breast cancer, and to estimate benefits and risks of the hypofractionation approach.

Inclusion criteria

Histologically confirmed breast carcinoma, age 65 or over.

Exclusion criteria

Population number of patients = 88

Group A median age 72.4 years (range 65-80)

Group B median age 67.9 years (range 65-73)

Stage I to IV

Five patients in Group A had Stage IV disease, two were unstaged.

Two patients in Group B had Stage IV disease, one was unstaged.

Thirty patients in Group A had concomitant disease.

Twelve patients in Group B had concomitant disease.

Interventions

Group A: 26 had BCS and 22 biopsy only

Group B: 10 had BCS and 30 biopsy only.

Group A: N=48 treated with hypofractionated RT every 2nd day, dose 24-26Gy in 4 fractions to the breast.

Regional lymph nodes treated with 19Gy in 4 fractions every 2nd day (3 anterior fields: axillary, parasternal, supraclavicular). RT was applied using Cobalt-60 over 8 working days alternately to the breast and lymph nodes. The same treatment was repeated after 28 days.

Group B: N=40 treated conventionally with 51Gy in 16 fractions (every 2nd day) to the breast.

Regional lymph nodes treated with 45Gy in 15 fractions. Breast and lymph nodes were irradiated on alternate days over 31 working days. The breast was given a boost of 20Gy and the axilla 12Gy.

RT was completed in 41 working days.

Outcomes

Acute and late complications

Relapse rate

Overall survival

Follow up The median follow-up in group A was 30 months (5-48) and in group B 26 months (1-45).

Results

Acute and delayed radiation related side effects are listed in the following table:

Outcome	Group A (n=48)	Group B (n=40)
<i>Acute reactions</i>		
Erythema	91.7%	25%
Dry desquamation with hyperpigmentation	8.3%	55%
Moist desquamation	0%	20%
<i>Delayed reactions</i>		
Fibrosis of breast and axilla	37.5%	10%

No other types of delayed radiation effects occurred, e.g., brachial plexopathy, lymphoedema, fractures. There were significant statistical differences between the 2 groups for the acute reactions ($p < 0.01$), and for fibrosis ($p = 0.003$).

Local recurrences and metastases are shown in the following table:

Outcome	Group A (n=48)	Group B (n=40)
Local relapse	7 (14.6%)	6 (15%)
Local relapse and distant metastases	5 (10.4%)	6 (15%)
Distant metastases	5 (10.4%) ⁰	8 (20%)
Total	17 (35.4%)	20 (50%)
Disease free	28 (58.4%)	15 (37.5%)
Lost to follow-up	3 (6.2%)	5 (12.5%)

There was no significant difference between groups for the total events (35.4% vs. 50%; $p = 0.47$)

Median relapse free interval was 11.3 months (range 4-30) in Group A and 16.2 months (range 3-32) in Group B ($p = 0.065$).

Patient status at the end of follow-up is shown in the following table:

Outcome	Group A (n=48)	Group B (n=40)	P value
Alive No Evidence of Disease (NED)	27 (56.3%)	11 (27.5%)	0.009
Alive with disease	6 (12.5%)	10 (25.0%)	
Death from primary disease	6 (12.5%)	7 (17.5%)	
Death from concurrent	6 (12.5%)	7 (17.5%)	

disease			
Lost to follow-up	3 (6.2%)	5 (12.5%)	

Kaplan Meier survival curves at 3 years showed no difference between groups for overall survival ($p=0.1$). However, disease free survival was better in group A than group B at 3 years ($p=0.025$)

Author conclusion: Hypofractionated radiotherapy is a suitable, effective, and comfortable therapeutic approach in the management of breast cancer in elderly women.

Marcenaro M, Sacco S, Pentimalli S, Berretta L, Andretta V, Grasso R, et al. Measures of late effects in conservative treatment of breast cancer with standard or hypofractionated radiotherapy. Tumori 2004;90(6):586-91.

Design: Non-randomised retrospective study (1999-2002)

Level 3

Country: Italy, setting: single centre

Aim: To compare the conventional schedule and a hypofractionated schedule in terms of late effects and cosmetic results in patients treated with adjuvant radiotherapy after BCS.

Inclusion criteria

Women with breast cancer treated with BCS.

Exclusion criteria

Population number of patients = 58

Stage pT1-T2

pN0-2

Median age 65 years (mean 61 years)

Interventions

Surgical interventions available for 21 and 22 patients in group A and B respectively.

Lumpectomy: 2 in group A and 6 in Group B

Segmentectomy/quadrantectomy 19 in group A and 16 in Group B

Conventional fractionation of 50 Gy in 25 daily fractions over 5 weeks (Gp A)
n=29

Or

Hypofractionated schedule of 45 Gy in 15 daily fractions over 5 weeks (3 fractions /week)
(Gp B) n=29

Fractionation schedules were chosen on the basis of the patients' logistical situation, e g, distance between home and RT department. No boost to the tumour bed was applied.

Outcomes

Late toxicity effects evaluated with SOMA-LENT scoring system (Grade 1 to 4, the higher the grade the poorer the outcome)

Cosmesis – 5 point scale (very good, good, acceptable, poor, very poor)
evaluated by 2 observers

Patient satisfaction with cosmetic result – same 5 point scale

Skin toxicity in comparison to untreated breast

Skin elasticity measured using a dedicated device

Follow up Median 15 months (range 7-46 months) Group A and median 10 months in Group B.

Results

SOMA-LENT scores are reported in the following table:

Outcome	Group A n=29	Group B n=29
Pain	Grade 2-3 5 (17%)	Grade 2-3 5 (17%)
Breast oedema	Grade 2 2 (7%)	Grade 2 3 (10%)
Fibrosis	Grade 2-3 6 (21%)	Grade 2 8 (28%)
Telangiectasia	Grade 2 2 (7%)	Grade 2-3 3 (10%)
Arm oedema	Grade 2 1 Grade 4 1	Grade 2 1
Atrophy and ulcerations	No ulceration Atrophy grade 1 2	No ulceration
Breast and arm oedema	Grade 3 breast and Grade 2 arm oedema 2	Grade 3 breast and Grade 2 arm oedema 1
Ulceration or atrophy	0	0

Cosmetic evaluation results are shown below:

Outcome	Group A	Group B
Very good	7 (25%)	2 (7%)
Good	7 (25%)	11 (38%)
Acceptable	8 (29%)	8 (29%)
Poor	6 (21%)	8 (27%)

Median skin elasticity loss due to treatment was -4.19% in group A and -6.29% in group B. These results are not statistically different.

Author conclusions: LENT-SOMA toxicities were minimal and no differences were observed between groups. Few patients in the hypofractionated group had very good cosmetic results, but it is debatable if radiotherapy was the only cause. Skin elasticity was not different between groups. Our results seem to suggest that it is possible to treat patients with both schedules, with similar late toxicity

Yamada Y, Ackerman I, Franssen E, MacKenzie RG, Thomas G. Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? International Journal of Radiation Oncology Biology Physics 1999;44(1):99-104.

Design: Non-randomised study (retrospective)

Level 3

Country: Canada, setting: Single centre

Aim: To explore the correlation between dose fractionation and local control for adjuvant radiotherapy of early stage breast cancer.

Inclusion criteria

Patients with invasive breast cancer, BCS with a 1cm clear margin. All had axillary dissection.

Exclusion criteria

Population number of patients =118 matched pairs

Group A = 512 treated 1987-1988

Group B - 118 patients were matched with group A.

Patients were matched on clinical prognostic factors: age, tumour size, receptor status, tumour grade and histology, presence or absence of DCIS, presence of capillary space involvement, axillary nodal status, surgical margin status, use of systemic therapy.

Interventions

Two fractionation schedules were compared:

50 Gy in 25 fractions over 5 weeks (Group A)

40 Gy in 16 fractions over 3 weeks (Group B)

Tangential parallel opposed external beams of cobalt 60 or 6 MV photons were applied to the whole breast and underlying chest wall. No boost was applied.

Patients with more than 3 involved nodes were given regional RT to the ipsilateral axilla and supraclavicular lymph nodes.

Outcomes

Local control in the irradiated breast (regional recurrences in lymph nodes were not considered local recurrences).

Overall breast recurrence rate (all relapses)

Survival

Follow up Group A median of 102 months; Group B median of 65 months

Results

	Group A	Group B
5 year local control	92.6%	87.6%
p=0.09		
5 year overall survival	84%	84%

Author conclusion: Although not statistically significant, there was a trend in the matched pair analysis which suggests that 40Gy in 16 fractions (BED = 65

cGy(4)) provides inferior local control compared to 50Gy in 25 fractions (BED = 75 cGy(4)). Moreover, the literature review demonstrates that a dose control relationship may exist for local control in the adjuvant setting. A dose fractionation schedule equivalent to 50Gy in 25 fractions to the whole breast may represent the optimal dose fractionation schedule for local control.

General comments –

Author conclusions were not supported by the statistical findings.

GUIDELINES

Cancer Care Ontario Practice Guidelines Initiative
Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast
Conserving Surgery. Practice Guideline Report #1-2 .

Design: Guideline (2002)

Level 4

Country: Canada

Inclusion criteria Update of 1997 searches in MEDLINE, PDQ and the Cochrane Library to January 2002. Internet sites and ASCO and ESMO Proceedings also searched.

Exclusion criteria

Population

Early invasive breast cancer (Stage I –II) after BCS.

Interventions

Outcomes

Follow up

Results

Evidence.

Fractionation schedules: Four randomized trials and two retrospective studies were identified. The optimal fractionation schedule could not be established from the available data.

Recommendations.

The optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. Outside of a clinical trial, two commonly used fractionation schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions. Shorter schedules (e.g., 40 or 44 Gy in 16 fractions) have also been used routinely in some centres. The enrolment of patients in ongoing clinical trials is encouraged.

General comments –

Full guideline available from Cancer Care Ontario.
(http://www.cancercare.on.ca/pdf/full1_2.pdf)

Clinical practice guidelines for the care and treatment of breast cancer

6. Breast radiotherapy after breast-conserving surgery

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer:

Design: Guideline (2003)

Level 4

Country: Canada

Aim: To help physicians and their patients arrive at optimal strategies for breast radiotherapy after breast-conserving surgery (BCS) for early breast cancer.

Inclusion criteria

Update of the 1997 guideline.

English language literature search using MEDLINE from 1966 and CANCERLIT from 1983 to 2002. Reference lists from recent published reviews were also scanned.

Exclusion criteria

Population

Early breast cancer

Interventions

Outcomes

Follow up

Results

(Only the recommendation for dose fractionation is included).

Recommendation

A number of different fractionation schedules for breast irradiation are used, the most common in Canada being 50 Gy in 25 fractions, however, recent data from a Canadian trial demonstrates that 42.5Gy in 16 fractions is comparable to the usual schedule.

Evidence

The commonest fractionation schedule used in Canada is 50 Gy in 25 fractions to the whole breast without a boost when excision margins are clear of disease. A Canadian trial compared 50 Gy in 25 fractions over 35 days with a shorter course of 42.5Gy in 16 fractions over 22 days in women with node negative breast cancer after lumpectomy (Whelan 2002). At a median follow-up of 5.8 years no difference in the rates of local recurrence or cosmetic outcome were reported. This trial was limited to patients with breasts less than 25 cm in width at the midpoint of the radiation field, and the results may not apply to women with larger breasts. It is likely that the results are generalizable to patients with node-positive disease.

General comments –

The original guideline was updated in 2003 in CMAJ. This was not available to the NCCC for copyright reasons.

6.5 What are the indications for an external beam radiotherapy boost to the site of local excision after breast conserving surgery?

Short Summary

Data from randomised controlled trials (RCTs) and non-randomized studies (NRS) were included for this topic. The most frequent study reported was the boost versus no boost EORTC 22881-10882 randomised trial. RCT data were consistent in the finding that a boost dose to the tumour bed reduced local recurrence but had little effect on overall survival. However most of the data were from the EORTC trial. One RCT compared the effects of the boost technique on local recurrence (Poortmans *et al* 2004) and found no difference between the three techniques. Most RCTs reported an association of local failure with age. The absolute failure rates and difference in failure rates between treatment groups decreased as age increased. Other factors associated with local failure were: no boost dose, high histological grade of tumour, size of the tumour, excision volume, and adjuvant systemic therapy.

Non-randomised studies reported that young age (≤ 45 years), lower T status, and close final margin status (≤ 2 mm) were the strongest predictors of local recurrence.

A range of cosmetic outcomes were reported and these were assessed by clinicians, patients, panels and digitizer measurements. Global cosmetic results following surgery were excellent or good (Vrieling *et al* 1999), however fibrosis and telangiectasia tended to be worse in the boost group (Bartelink *et al* 2007, Romestaing *et al* 1997).

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with invasive breast cancer (not DCIS) who have received breast conserving surgery	RT to the breast plus RT boost to the site of excision including: <ul style="list-style-type: none"> • Electrons • Implant 	Breast conserving surgery alone (no RT at all) RT breast with no boost	<ul style="list-style-type: none"> • Recurrence • Disease Free Survival (DFS) • Overall Survival (OS) • Cosmesis • Quality of life • Patient acceptability

The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence Summary

A moderate volume of literature was available with search dates ranging between 1984 and 2008. The most frequent study reported was the boost versus no boost EORTC 22881-10882 randomized trial. Another RCT of a smaller French study by Romestaing *et al* (1997) was also identified. The four lower quality cohort studies considered margin status and cosmesis in relation to a boost dose of radiotherapy to the tumour bed. There were a large number of cohort studies following groups of patients given the same treatment over a period of time

(Breast Conserving Surgery [BCS], external beam irradiation and a boost to the scar) that had no comparison arm of no boost to the scar which were excluded.

Inclusion criteria for the EORTC Trial were limited to women aged less than 70 years with stage T1-2, N0-1 and M0 invasive breast cancer. Surgical excision of primary tumour was made with a 1cm margin. All patients had external wide beam irradiation of the whole breast of 50 Gy with photon beams, and a boost to the scar of 16 Gy with electrons or an iridium-192 implant.

RCT data was consistent in the finding that a boost dose to the tumour bed reduced local recurrence but had little effect on overall survival. However most of the data were from a single study, the EORTC trial. One RCT compared the effects of the boost technique on local recurrence (Poortmans *et al* 2004) and found no difference between the three techniques. Most RCTs reported an association of local failure with age. The absolute failure rates and difference in failure rates between treatment groups decreased as age increased. Other factors associated with local failure were: no boost dose, high grade of tumour, size of tumour, excision volume, and adjuvant systemic therapy.

Non-randomized studies reported that young age (≤ 45 years), lower T status, and close final margin status (≤ 2 mm) were the strongest predictors of local recurrence.

A range of cosmetic outcomes were reported and these were assessed by clinicians, patients, panels and digitizer measurements. Global cosmetic results following surgery were excellent or good (Vrieling *et al* 1999), however fibrosis and telangiectasia tended to be worse in the boost group (Bartelink *et al* 2007, Romestaing *et al* 1997).

Randomized controlled trials

The outcomes assessed in randomized studies were mainly local recurrence, survival and cosmesis. A table is included of the collated data from RCTs for local recurrence and survival.

Local recurrence

Local recurrence was reported in 6 RCTs (Antonini *et al* 2007, Bartelink *et al* 2001 and 2007, Poortmans *et al* 2004, Romestaing *et al* 1997, Vrieling *et al* 2003). Five RCTs reported on the EORTC trial, whilst Romestaing reported on a French study.

Bartelink reported trial findings after 5 years (2001) and 10 years (2007). Disease recurrence in the ipsilateral breast occurred more frequently in the “no boost” than the “boost” arm of the trial at 5 and 10 years, with a hazard ratio of 0.59 (99% CI, 0.46 to 0.76) for the boost arm in both time periods. Antonini *et al* (2007) also reported a higher incidence of local recurrence in the no boost arm with a hazard ratio of 0.55 (95% CI 0.42 to 0.73) for the boost arm at 5 years for the same EORTC trial. Similar findings were reported by Romestaing *et al* (1997) in the Lyon trial with increased incidence of local recurrence in the no boost arm, and a relative risk of recurrence of 0.34 (95% CI, 0.12-0.95) at 5 years. Confidence intervals were wider in the Lyon RCT which is more likely with smaller numbers of participants.

Age related local recurrence

All the EORTC analyses found that the addition of the boost dose produced the greatest absolute benefit to the younger age groups. Both the absolute failure rates and difference in failure rates between groups decreased as age increased. Multivariate analyses of factors

associated with local failure (Antonini *et al* 2007) found younger age, no boost dose, high grade of tumour, the size of the tumour, excision volume, and adjuvant systemic therapy to be significantly associated with local failure. The multivariate model indicated that local recurrence risk decreased with increasing age for both boost and no boost groups.

At 10 years Bartelink *et al* (2007 and 2001) also reported that the observed absolute risk reduction between boost and no boost groups was larger in younger patients. The hazard ratios for local recurrence reduction favoured the boost arm for all age groups. Statistically significant reductions in the boost arm were also reported for pre- and post menopause status, tumour stages T1 and T2, and node N0 at 5 years. No difference was reported for node N1-2, however the number of events was small.

Another analysis of the EORTC trial by Vrieling *et al* (2003) of young patients and the association with patient characteristics, treatment and pathology found on multivariate analysis that age and the boost dose were the only significant factors that independently influenced local control at a median of 5 years.

Type of boost technique

Poortmans *et al* (2004) conducted an analysis of patients receiving the three different types of boost dose (electrons, photons, interstitial) delivered in the EORTC trial at 5 years. An overall local recurrence rate of 4.3% (95%CI 3.8-4.7%) was found and there did not appear to be a statistically significant difference between the three techniques although P values were not reported. The age of participants on the effect of local control was not associated with type of boost technique.

Non-randomized studies

Local recurrence

Polgar *et al* (2004) in a small prospective study comparing three different postoperative irradiation techniques reported the 5- and 7-year actuarial rates of ipsilateral breast recurrence for patients treated with Accelerated Partial Breast Irradiation (APBI) as 4.4% and 9.0% respectively, for Whole Breast Radiation Therapy (WBRT) as 4.7% and 14.8% respectively, and WBRT + Tumour Bed Boost (TBB) as 5.7% and 9.5% respectively. There were no statistically significant differences between the three techniques.

In a large prospective cohort Palazzi *et al* (2006) reported 5-year local, regional, and distant control rates as 98%, 99%, and 92%, respectively for a wide range of RT techniques (60% had a boost dose). On multivariate analysis older age and medical adjuvant treatment were the strongest predictors for local control. A lower N-stage, medical adjuvant treatment, lower T-stage, and lower histological grading were predictors for disease free survival. The use of a boost dose was not significant in improving local recurrence rates after quadrantectomy and 50 Gy to the whole breast.

Age related local recurrence

When stratified by age the prospective cohort by Nueschatz *et al* (2003) reported poorer Kaplan–Meier survival estimates for patients 45 years or younger with a 12-year local failure rate of 14.5%, compared with 6.4% for patients older than 45 years of age at diagnosis (Log-Rank P = 0.01). A comparison of 12-year Kaplan–Meier local failure rates by age and Final Margin Status (FMS) showed lower failure rates for the older age group; and on univariate

analysis age, FMS, and the presence of Extensive Intraductal Component (EIC) were all significant predictors of local failure. Total excision volume, re-excision, lymph node status, and tumour size were not predictive of local failure. On multivariate analysis closer FMS, defined as either positive or ≤ 2 mm, were associated significantly with late (>5 years) but not early (≤ 5 years) local failure. Regardless of whether the model divided FMS into positive/negative or ≤ 2 mm/greater than 2 mm, young age remained a highly significant predictor of local failure and EIC was of borderline significance ($P=0.02$ and $P=0.03$ respectively). The use of a boost dose was not significant in preventing local recurrence after quadrantectomy and 50 Gy to the whole breast in this study.

Similar findings were reported in the retrospective cohort by Perez *et al.* (2003) where the overall incidence of ipsilateral breast recurrence (IBR) in patients aged ≤ 40 years with T1 tumours was 9.6% (10/104); and for women aged > 40 years the overall incidence of IBR was 4.4% (41/935) ($p=0.03$). Corresponding IBR for women with T2 tumours were 15.5% (9/58) in patients aged ≤ 40 years and 7.1% (18/252) in women > 40 years ($p=0.04$). Actuarial breast relapse rates were 7% for T1 tumours and 11% for T2 tumours over 10 years. There was no significant difference in breast relapse rates between patients treated with a boost of either electrons or interstitial brachytherapy.

Local recurrence and margin status

A small increase in breast relapse for patients aged < 40 years with close or positive margins for stage T1 tumour types, was found (9% negative; 12-14% positive or close margins) in the study by Perez *et al.* (2003) at a median of 7 years follow-up. The overall differences for all margin status in stage T1 tumours between the age groups compared was statistically significant ($p=0.03$) favouring those over 40 years. The increase in breast relapse was larger for stage T2 tumour groups with close margins in women <40 years (13% negative; 50% close margins), with a small increase in older women. The overall difference for stage T2 tumours between age groups was also statistically significant ($p=0.04$) again favouring those over 40 years. Again young age remained the strongest predictor of local failure on multivariate analysis.

Randomized controlled trials

Survival

At 10 years Bartelink *et al* (2007) reported no difference in survival between the boost and no boost groups (81.7% (99% CI, 79.5% to 83.7% overall participants). There was also no difference in outcomes between the groups for breast cancer mortality, disease free survival or breast cancer related events.

Romestaing *et al* (1997) reported that the Disease Free Survival (DFS) rates at 5 years were similar between the boost and no boost groups with a relative risk for DFS of 0.63 (95% CI 0.39 to 1.01). This was also the case for overall survival, with a relative risk of 0.49 (95% CI 0.23 to 1.05) at 5 years.

Non-randomized studies

Survival

Polgar *et al* (2004, Level 3) reported no statistically significant differences in either the 7-year probability of relapse-free survival (79.8%, 73.5%, and 77.7% for APBI, WBRT, and WBRT + TBB, respectively) or cancer-specific survival (93.3%, 92.9%, and 93.9% for APBI, WBRT, and WBRT + TBB, respectively).

Randomized controlled trials

Cosmesis

Cosmesis included a range of different measures with assessment by patients, physicians, panels and digitizers. The outcomes assessed included: fibrosis, telangiectasia, global cosmetic scores, Breast Retraction Assessment (BRA). RCTs included the EORTC studies by Bartelink *et al* (2007); Poortmans *et al* (2004) and Vrieling *et al* (1999).

Global cosmetic score

From a panel assessment 82% of patients had an excellent or good global cosmetic result following surgery (Vrieling *et al* 1999). There was a trend favouring the no boost group for better global scores and breast shape scores after 3 years. Global score changes over time for breast size, breast shape, nipple position, and shape of areola were significant in the boost arm ($p < 0.001$) only. From digitizer measurements at 3 years there was an increase in mean pBRA of 0.6 in the boost group indicating an increase in nipple position asymmetry (pBRA 7.7 post-op and 8.3 at 3 years, $p=0.05$), of borderline statistical significance. In the no-boost group the change in pBRA over time was not significant (mean pBRA of 7.5 postoperatively and 7.6 at 3-year follow-up, $p = 0.94$).

Romestaing *et al* (1997) reported that 85% of patients were considered to have good or excellent cosmesis results with no difference between arms, and no poor results, from physician assessments.

Fibrosis

At 10 years Bartelink *et al* (2007) reported that severe and moderate fibrosis was significantly increased in both the whole breast and boost area of the boost group.

At 5 years Poortmans *et al* (2004) found that there was no significant difference in fibrosis in the boost area at 5 years between boost techniques ($p=0.67$); however, there was a significant difference in fibrosis to the whole breast at 5 years between boost techniques ($p=0.013$). The occurrence and grades of fibrosis in the whole breast and in the boost area were similar between the 3 boost techniques. Minor fibrosis was more common in both areas (whole breast and boost). A larger proportion of patients developed moderate to severe fibrosis at the site of primary tumour (25%) than in the whole breast (12%).

Telangiectasia

Grades 1 and 2 telangiectasia were reported as 5.9% of the no boost group and 12.4% of the boost group in the Romestaing *et al* (1997) study at 2 years. The difference was significant $p=0.003$.

Factors influencing cosmesis

A further multivariate analysis of the EORTC RCT data at 3 years by Vrieling *et al* (2000) found that the factors significantly associated with poorer cosmesis from panel evaluation were inferior tumour location, increased excision volume, breast complications and boost treatment. According to digitizer measurements a multivariate analysis showed that tumour location (central/superior), a large excision volume, increasing pathological tumour size and high maximum dose in the central plane were associated with an increased pBRA at 3 years, and poorer cosmetic outcome.

The prognostic factor analyses of both methods (by panel or digitizer) showed that a large excision volume, a boost dose, increased dose inhomogeneity, and the presence of postoperative breast complications had a large negative effect on cosmesis.

Non-randomized studies

Cosmetic outcomes

A comparison of tumour bed boost dose delivered by interstitial brachytherapy (APBI) vs electrons or photons reported that most cosmetic results were rated as excellent/good for all techniques, however, APBI had the highest proportion (84.4%) of excellent/good results, and the differences were statistically significant ($p=0.04$) favouring APBI (Polgar *et al* 2004, Level 3).

Palazzi *et al* (2006, 2++) reported overall cosmetic outcomes during a 7 year follow-up. 33% of patients scored "excellent," 47% as "good," 17% as "fair," and 3% as "poor." These scores were similar to pre-radiotherapy scores. Cosmetic failure rate increased from 18% before radiation to 20% during follow-up, suggesting that radiation did not worsen the cosmetic outcome after surgery.

Telangiectasia

When comparing APBI vs Whole Breast RT (WBRT) vs WBRT + tumour bed boost (electrons or photons) Polgar *et al* (2004) reported significantly poorer grade 2-3 telangiectasia in the WBRT+ Tumour bed boost group in comparison with the other two groups.

Fibrosis

In a comparison of APBI vs Whole Breast RT (WBRT) vs WBRT + tumour bed boost (electrons or photons) Polgar *et al* (2004) reported poorer outcomes of grade 2-3 fibrosis in both boost groups in comparison to the no boost group(WBRT), although the findings were not significant in this small study.

Fat necrosis

There were no significant differences in fat necrosis between the 3 arms of the Polgar *et al* (2004) study (APBI vs Whole Breast RT (WBRT) vs WBRT + tumour bed boost of electrons or photons).

Adverse effects

One non-randomized retrospective population cohort (Paszat 2007) reported that RT treatment to the left breast and the area of the boost dose were associated with an increased Hazard ratio for time to an event of acute myocardial infarction (AMI) and time to death by AMI.

Guidelines

Two guidelines were directly relevant to this topic and this was also included in section 6.1 (Jalili *et al* 2007; Whelan *et al* 2003).

Table 5.3.1 Summary of local recurrence and survival data from RCTs

Author	Outcome	EORTC		LYON	
		Boost N= 2661	No boost N=2657	Boost N=521	No boost N=503
Bartelink 2007	Total 5318				
	10 year local control				
	Cumulative incidence	6.2% (95% CI, 4.9% to 7.5%)	10.2% (95% CI, 8.7% to 11.8%)		
	Hazard Ratio (overall)	0.59 (99% CI, 0.46 to 0.76)			
	Age relatedHR	≤40 years 0.51 41 to 50 0.65 51 to 60 0.64 > 60 years 0.51			
Bartelink 2001	Survival at 10 years				
	Deaths (n)	521	522		
	Survival	81.7% (99% CI, 79.5% to 83.7%)			
	Breast cancer mortality (n)	346	344		
	5 year local control			Romestain 1997	5 year local control
Recurrences	N= 109/2661	N= 182/2657	N=10/521	N=20/503	
5 year actuarial rate of recurrence (cumulative incidence)	4.3% (95% CI, 3.8 to 4.7%)	7.3% (95% CI, 6.8 to 7.6%)	3.6% (95% CI 1.8% to 7.1%)	4.5% (95% CI 2.7% to 7.4%)	
Hazard Ratio (overall)	0.59 (99% CI, 0.43 to 0.81)		RR 0.34 (95% CI 0.12 to 0.95)		
Age related Actuarial 5 yr local control (recurrence rates)	≤40 years 10.2 (95%CI 7.9-12.5) 41 to 50 5.8 (95% CI 4.8-6.8) 51 to 60 3.4 (95% CI 2.7-4.1) > 60 years 2.5 (95% CI 1.9-3.2)	19.5 (95%CI 16.5-22.5) 9.5 (95% CI 8.2-10.7) 4.2 (95% CI 3.5-4.9) 4.0 (95% CI 3.2-4.7)		DFS at 5 years 86% (95% CI 81.0-89.8) RR for DFS 0.63 (95% CI 0.39 to 1.01)	82.2% (95% CI 77.3 - 86.3)

Menopausal status	Premenopausal	6.8 (95%CI 5.8-7.6)	10.3 (95% CI 9.2-11.4)	Overall survival at 5 years
	Postmenopausal	2.8 (95% CI 2.3-3.2)	4.6 (95% CI 4.1-5.2)	
Tumour stage	T1	4.0 (95% CI 3.3-4.6)	5.9 (95% CI 5.2-6.6)	RR for overall survival at 5 years 0.49 (95% CI 0.23 to 1.05)
	T2	4.5 (95% CI 3.9-5.2)	7.8 (95% CI 7.0-8.7)	
Nodal status	N0	4.2 (95% CI 3.4-4.6)	6.9 (95% CI 6.4-7.5)	
	N1-2	5.7 (95% CI 3.7-7.6)	5.6 (95% CI 3.7-7.4)	

Author	Outcome	EORTC	No	boost
Antonini 2007	5 year local control	Boost (n=2661)	(n=2657)	
	Cumulative incidence of recurrence within 5 years	n= 130	n=232	
	≤40 years	9.5%		19.3%
	Hazard Ratio (overall)	0.55, 95% CI 0.42 to 0.73		
	Multivariate analyses of factors associated with local failure	Age		
		Boost		
		Excision of biopsy (size)	HR 0.84 (0.74-0.94)	
		Tumour size	HR 1.27 (1.11-1.45)	
		High grade invasive tumour	HR 1.73 (1.04-2.86)	
		Adjuvant systemic therapy	HR 0.62 (0.42-0.92)	
Poortmans 2004	N=2661 (Boost only)	Electrons N=1635	Interstitial implant N=225	
	Photons N=753			
	5 yr local control	4.0% (95%CI 2.4-5.5)	4.7% (95%CI 3.6-5.9)	2.5% (95%CI 0.3-4.6)
	5 yr local recurrence rate	4.3% (95% CI: 3.8–4.7)		
		N=175 breast cancer deaths, N=234 all cause deaths		

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Evidence table
Randomized Controlled Trials

Bartelink E, Horiot J-C, Poortmans PMP, Struikmans H, Van den Bogaert W, Fourquet A, et al. Impact of a higher radiation dose on local control and survival in Breast-Conserving Therapy of Early Breast Cancer: 10 year results of the randomized Boost Versus No Boost EORTC 22881-10882 Trial. J Clin Oncol 2007 Aug 1;25(22):3259-66

Design: RCT (1989-1996) EORTC Trial
 Level 1++

Country:9 countries, setting: 31 centres

Aim: To report on the impact of a 16-Gy boost radiation dose after (Breast Conserving Therapy) BCT on local control, fibrosis, and survival for patients with stage I and II breast cancer at 10 years follow-up.

Inclusion criteria

Patients with T1-2, N0-1, and M0 breast cancer (International Union against Cancer: TNM Classification).

Exclusion criteria

Patients aged more than 70 years, pure carcinoma in situ, multiple tumour foci in more than one quadrant, a history of other malignant disease, Eastern Cooperative Oncology Group performance score greater than 2, residual micro-calcifications on mammography, or gross residual disease in the breast after lumpectomy (unless re-excision had been performed).

Population number of patients = 5318

2,657 were allocated to receive no boost

2,661 were allocated to receive a boost of 16 Gy to tumour bed

Median age at treatment 55 years.

pN0 = 78%

Post menopausal 62%

T1 = 52%

T2 = 48%

Protocol deviations:

26 patients in the intervention group did not receive a boost

53 patients in the no boost group received a boost

107 patients were older than 70 years.

343 patients were delayed between surgery and the start of radiotherapy for longer than allowed by the protocol.

Interventions

Patients received surgical excision of the primary tumour, with a 1-cm margin of macroscopically normal tissue and an axillary dissection.

Adjuvant systemic therapy was given to patients with axillary lymph node involvement:

pre-menopausal patients received chemotherapy and post-menopausal patients received tamoxifen.

Patients not given adjuvant chemotherapy began radiotherapy within 9 weeks

after lumpectomy.

Chemotherapy was prescribed more frequently in the boost arm for premenopausal N+ patients (88% vs. 79%).

Irradiation of the whole breast delivered by two tangential megavoltage photon beams (high-energy x-ray or tele-cobalt).

Total dose of 50Gy to the original tumour bed delivered over 5 weeks, with a dose of 2Gy / fraction.

The boost dose of 16 Gy in 8 fractions delivered with electrons or tangential fields; alternatively an iridium-192 implant at a dose rate of 0.5 Gy per hour was used.

251 patients with microscopically incomplete excision in the intervention arm were also randomized to a boost dose of either 10 or 26 Gy in a separate stratum.

No extra irradiation or boost dose was delivered to the comparison arm.

Outcomes

Local recurrence

Fibrosis:

Fibrosis scoring by treating physician - 4-point scale:

1 = none, 2 = minor, 3 = moderate, and 4 = severe

Breast cancer mortality

Survival

Follow up Median follow-up 10.8 years.

Results

Local recurrence and cumulative incidence

Outcomes are shown in the following table:

Outcome	Boost	No boost	P value
Recurrence in ipsilateral breast	165	278	
Regional recurrence in axilla and/or supraclavicular region	56	59	
Cumulative incidence of local recurrence at 10 years	6.2% (95% CI 4.9 to 7.5)	10.2% (95% CI 8.7 to 11.8)	< 0.0001
Hazard Ratio for local recurrence as first event	0.59 (99% CI 0.46 to 0.76)		< 0.0001

Overall, 47% of the local recurrences occurred in the primary tumour bed, 10% occurred in the scar, 29% occurred outside the original tumour area, and 13% were diffuse.

A chart of cumulative incidence of recurrence in the ipsilateral breast over time by age group was reported in the paper. The cumulative incidence of local recurrences correlated significantly with the age of the patient ($p < 0.0001$). The cumulative incidence was highest in the ≤ 35 age group, and decreased progressively with increasing age. The incidence was lowest in women aged > 60 years.

The absolute risk reduction by age group at 10 years in the boost and no boost groups is reported in the following table:

Age group	Absolute risk reduction (local recurrence) and Hazard Ratios		P value
	Boost	No boost	
≤ 40 years	13.5%	23.9%	0.0014
41 – 50	8.7%	12.5%	
51 – 60	4.9%	7.8%	
> 60	3.8%	7.3%	
≤ 40 years	Hazard ratio 0.51 favouring boost		$p=0.0014$
41 to 50 years	Hazard ratio 0.65 favouring boost		$p=0.01$
51 to 60 years	Hazard ratio 0.64 favouring boost		$p=0.012$
> 60 years	Hazard ratio 0.51 favouring boost		$p=0.0008$

The largest reductions in cumulative incidence between boost and no boost arms were seen in the younger age groups. The differences between boost and no boost arms were statistically significant for all age groups.

Distant metastases, breast cancer mortality and survival.

The cumulative risk of distant metastases was not statistically significant different between the two groups. There were 16.1% of distant relapse events in both groups at 10 years. The cumulative incidence of second primary tumour in the contralateral breast or other sites was similar between groups ($P>0.1$).

Mortality and disease-free survival were similar between groups

Deaths:

N=522 in no boost group

N= 521 in boost group

Survival at 10 years = 81.7% (99% CI, 79.5 - 83.7) for both arms.

Breast cancer mortality:

N= 344 events in no boost group

N= 346 events in boost group

Disease-free survival $P > 0.1$ between groups
 Overall incidence of breast cancer-related events also similar between groups.

Fibrosis

Severe and moderate fibrosis was significantly increased in both the whole breast and boost area.

Outcome	Boost Cumulative incidence (99% CI)	No Boost Cumulative incidence (95% CI)	P value
Cumulative incidence of severe fibrosis at 10 years	4.4% (99% CI, 3.5 to 5.7)	1.6% (99%CI, 1 to 2.3)	$P < 0.0001$
Cumulative incidence of moderate to severe fibrosis at 10 years	28.1% (99% CI, 27.6 to 28.6)	13.2% (99% CI, 11.5 to 15.0)	$P < 0.0001$

Author conclusions

After a median follow-up period of 10.8 years, a boost dose of 16 Gy led to improved local control in all age groups, but no difference in survival.

General comments -

Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den BW, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. The New England journal of medicine 2001;345(19):1378-87.

Design: RCT (1989-1996) EORTC Trial
Level 1++

Country:9 countries, setting: 31 centres

Aim: To report the effect of a supplementary dose of radiation to the tumour bed on rates of local recurrence among patients receiving radiotherapy after BCS for EBC.

Inclusion criteria

Patients with T1-2, N0-1, and M0 breast cancer

Exclusion criteria Same as Bartelink 2007

Population number of patients = 5318

Median age at treatment 55 years.

pN0 = 78%

Post menopausal 62%

T1 = 52%

T2 = 48%

Interventions

2,657 were randomized to receive no boost

2,661 were randomized to receive a boost of 16 Gy to tumour bed

Patients received surgical excision of the primary tumour, with a 1-cm margin of macroscopically normal tissue and an axillary dissection.

Adjuvant systemic therapy was given to patients with axillary lymph node involvement:

pre-menopausal patients received chemotherapy and post-menopausal patients received tamoxifen.

Patients not given adjuvant chemotherapy began radiotherapy within 9 weeks after lumpectomy.

Chemotherapy was prescribed more frequently in the boost arm for pre-menopausal N+ patients (88% vs. 79%).

Irradiation of the whole breast delivered by two tangential megavoltage photon beams (high-energy x-ray or tele-cobalt).

Total dose of 50Gy to the original tumour bed delivered over 5 weeks, with a dose of 2Gy / fraction.

The boost dose of 16 Gy in 8 fractions delivered with electrons or tangential fields; alternatively an iridium-192 implant at a dose rate of 0.5 Gy per hour was used.

251 patients with microscopically incomplete excision in the intervention arm were also randomized to a boost dose of either 10 or 26 Gy in a separate stratum.

No extra irradiation or boost dose was delivered to the comparison arm.

Outcomes

Local recurrence defined as all recurrences in the treated breast, before or after the detection of distant metastases.

Follow up Median follow-up period 5.1 years, maximum 10.2 years.

Results

24 percent of patients required a re-excision.

Axillary dissection was performed in 99 percent of patients.

Local recurrences

Data for local recurrences is shown in the following table:

Outcome	Boost (n=2661)	No boost (n=2657)	P value
Local Recurrence in ipsilateral breast	N=109	N=182	
Regional recurrence in axilla and/or supraclavicular region	N=56	N=59	
Actuarial rate of local recurrence at 5 years in ipsilateral breast	4.3% (95% CI 3.8 to 4.7)	7.3% (95% CI 6.8 to 7.6)	< 0.001
Local Recurrence as first event	3.3%	5.9%	
Hazard Ratio for local recurrence as first event	0.59 (99% CI 0.43 to 0.81) favours boost		

Eighteen local recurrences occurred after another recurrence (a distant metastasis, a regional metastasis, or contralateral breast cancer) in the no boost group; and 9 local recurrences occurred in the boost group. Overall 47% of local recurrences occurred in the primary tumour bed, 9% in the scar, 29% outside the area of original tumour, and 27% diffuse throughout the breast.

From a subgroup analysis patients aged 40 years or less benefited most at five years with a local recurrence rate of 19.5% with standard treatment and 10.2% with boost radiation (hazard ratio, 0.46 [99% CI 0.23 to 0.89]; P=0.002). The boost dose was significantly more effective in all factors in the subgroup analyses. An exception was patients with N1-2 status where no significant difference in local recurrences was reported, however the sample size was small in this subgroup and may not be statistically valid (n=20 recurrences in 391 patients).

The subgroup analyses of other prognostic factors are listed in the table below:

Outcome	Actuarial 5 yr Local recurrence rate (99% CI)		Hazard Ratio (99% CI)	Reduction in annual Odds of Local Recurrence (99% CI)	P value
	Boost	No boost			
AGE					
≤ 40 years	10.2	19.5	0.46	54 (25-71)	0.002
41-50 years	(7.9-12.5)	(16.5-22.5)	(0.23-0.89)	38 (8-58)	0.02
51-60 years	5.8	9.5 (8.2-10.7)	Not reported	36 (0-60)	0.07
> 60 years	3.4 (2.7-4.1)	4.2 (3.5-4.9)	Not reported	32 (0-60)	0.14
	2.5 (1.9-3.2)	4.0 (3.2-4.7)	Not reported		
Menopausal status					
Pre-menopausal	6.8	10.3		40 (19-56)	0.001
Postmenopausal	(5.8-7.6)	(9.2-11.4)		41 (15-59)	0.004
	2.8 (2.3-3.2)	4.6 (4.1-5.2)			
Tumour stage					
T1	4.0	5.9 (5.2-6.6)		42 (19-59)	0.001
T2	(3.3-4.6)	6.6		39 (16-56)	0.002
	4.5 (3.9-5.2)	7.8 (7.0-8.7)			
Nodal status					
N0	4.2	6.9 (6.4-7.5)		43 (27-55)	0.001
N1-2 (small number of events)	(3.4-4.6)	7.5		0 (0-56)	0.89
	5.7 (3.7-7.6)	5.6 (3.7-7.4)			

At five years in the 41 to 50 years age group no differences were found in rates of metastasis or overall survival (87% and 91%, respectively). The benefit of the additional dose in local control was independent of whether the patients received adjuvant systemic treatment.

Author conclusions

In patients with early breast cancer who undergo breast-conserving surgery and receive 50 Gy of radiation to the whole breast, an additional dose of 16 Gy of radiation to the tumour bed reduces the risk of local recurrence, especially in patients younger than 50 years of age.

General comments –

This is an earlier report of the EORTC trial providing follow-up data at 5 years. Confidence intervals were reported as 95% in tables but as 99% in the text and figures.

Antonini N, Jones H, Horiot JC, Poortmans P, Struikmans H, den Bogaert WV, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiotherapy & Oncology* 2007;82(3):265-71.

Design: Analysis of RCT data EORTC Trial (1989-1996)
Level 1++

Country: Europe, USA setting: Multi-centre

Aim: To determine whether the effect of an additional "boost" radiation after breast conservative therapy (BCT) on local control depends on age and evaluate the impact of a treatment policy with an age threshold.

Inclusion criteria

Patients with microscopically complete excision.

Exclusion criteria

251 patients with incomplete resection were not included.

Population number of patients = 5318

2657 to no boost arm

2661 to boost arm

Patients were stratified according to age, menopausal status, presence or absence of intra-ductal component in or adjacent to the invasive tumour, clinical tumour size, clinical nodal status, and treatment centre.

Interventions

Whole breast irradiation of 50 Gy after breast conserving therapy. Intervention arm received a boost dose of 16Gy to the tumour bed.

Patients with positive lymph nodes also received systemic therapy of adjuvant CMF chemotherapy if pre-menopausal or tamoxifen (20 mg) if postmenopausal.

Outcomes

Local Recurrence in the ipsilateral breast.

Univariate analyses were stratified for age, menopausal status, performance status, grade and margin of invasive tumour and DCIS according to central review or local pathologists, adjuvant chemotherapy or hormonal treatment, tumour size, clinical N stage, axillary dissection, second operation, multi-focal tumour in one quadrant, histological type, first excision microscopically complete, oestrogen and progesterone receptor status, total volume of the excision biopsy specimen, number of axillary nodes examined, and number of positive nodes (Level of significance with Bonferroni.correction applied was $P < 0.002$).

Multivariate analyses were performed with treatment (boost) and age as explanatory covariates. Additional relevant clinical factors were also assessed. The interaction of the variability of the boost effect on local recurrence and patient age were of particular interest. Separate multivariate analyses were performed for margin status.

Analysis

Age was used as an independent factor to investigate the effectiveness of the boost treatment on local recurrence using the Cox proportional hazard model. A “missing value category” was used when data was missing from relevant factors, e.g. receptor status (30% missing), and margin of invasive tumour and DCIS (70% missing for central review; 55% for local pathology).

Follow up

Median follow-up 77.4 months (range: 0–147.6 months), 16 months longer than the first report on the primary endpoint (Bartelink 2001, Vrieling 2003).

Results

Local recurrence

A total of 362 local recurrences occurred.
 5 year local recurrence rate = 94.6%
 232 local recurrences occurred in the no boost group.
 130 local recurrences occurred in the boost group.

The boost dose significantly changed the time to local failure ($P < 0.0001$) overall patients. The number of local failures decreased by an approximate factor of 2 (HR 0.55, 95% CI 0.42 to 0.73). The cumulative incidence of local failure for boost and no boost arms differed between age groups.

Both the absolute failure rate and difference in failure rate between groups decreased as age increased as shown in the following Table.

Outcome	Patients < 40 Years	Patients > 60 YEARS
Cumulative incidence of recurrence within 5 years	No boost 19.3% Boost 9.5% Difference 9.8% (SE = 3.4%)	Difference 1.9% (SE = 0.86%)

Univariate analyses (Table below):

Factors that were significant by univariate Cox proportional hazard regression analysis are shown in the following Table:

Variable	Local failure at 5 yrs (95% CI)	Hazard Ratio (95% CI)	P value
Age (yrs):			
≤40	14.5 (11.1-	1.00	
41-50	18.0)	0.52 (0.36-	<0.0001
51-60	7.24 (5.80-	0.76)	<0.0001
>60	8.72)	0.28 (0.19-	<0.0001
	3.75 (2.84-	0.42)	
	4.66)	0.26 (0.17-	
	3.22 (2.35-	0.40)	
	4.09)		
Menopausal status:	8.08 (6.84-	1.00	

Pre-menopausal	9.33)		0.51	(0.39-	<0.0001
Menopausal	3.69 (3.02-4.37)		0.67)		
Hormone receptor oestrogen					
Negative	7.31 (5.68-9.03)		1.00		
Positive	4.53 (3.73-5.34)		0.70 (0.50-0.99)		0.0073
Unknown	5.54 (4.33-6.76)		0.76 (0.53-1.11)		0.064
Hormone receptor progesterone					
Negative	6.62 (5.18-8.07)		1.00		
Positive	4.61 (3.73-5.50)		0.75 (0.59-0.98)		0.031
Unknown	5.46 (4.36-6.57)		0.77 (0.59-1.10)		0.058
Histology grade					
Low	3.1 (1.9-4.4)		1.00		
Intermediate	5.3 (3.1-7.7)		1.04 (0.71-1.52)		0.84
High	10.0 (7.0-14.0)		2.50 (1.61-3.89)		<0.0001
No pathology review	5.4 (4.6-6.1)		1.55 (1.11-2.18)		0.011
Adjuvant hormone therapy					
No	6.12 (5.38-6.87)		1.00		
Yes	2.14 (1.23-3.05)		0.48 (0.30-0.75)		<0.0001

The strongest associations of increased risk of local failure were young age (≤ 40 years) a high grade of invasive tumour, pre-menopausal status and no adjuvant hormonal therapy (all had $p < 0.0001$). There was a weaker association between local failure and larger tumour size ($p = 0.002$), negative oestrogen receptor status ($p = 0.0073$), and negative progesterone receptor status ($p = 0.031$). Patients with a 10 mm or more margin from the local pathology reports had a significant reduction in risk of local failure ($P = 0.03$). After adjustment with the Bonferroni correction for overall statistical significance of multi-comparisons the variables that remained statistically significant were age, high grade of invasive tumour, no adjuvant hormonal treatment and pre-menopausal status.

Multivariate analyses

Multivariate Cox proportional hazard regression analysis found that age, boost dose, size of excisional biopsy specimen, tumour size, high grade of invasive tumour and adjuvant systemic therapy were independent predictors of local failure. The relevant data are shown in the following Table (only data from local pathology are shown here, the paper includes data from the central review, however the differences were minor):

Multivariate analysis on time to local recurrence

Variable	Hazard Ratio (95% CI)	P value
Age		<0.0001
Boost		<0.0003
Total size of excisional biopsy	0.86 (0.76-0.96)	0.011
Tumour size	1.27 (1.12-1.45)	0.0003
High grade	1.76 (1.06-2.92)	0.029
Adjuvant hormone therapy	0.63 (0.43-0.93)	0.021
Adjuvant chemotherapy	0.66 (0.46-0.95)	0.026

Using a natural spline regression model the data were plotted as a function of age vs. log of hazard ratio (local failure risk). The curves for the boost and no boost groups were parallel with the no boost group showing the highest risk of local failure for all ages. The relative local recurrence risk decreased with age equally for both treatment groups. A flattening of both curves occurred between the ages of 50 and 60 during menopause. A similar model with age categories of 5 year intervals also showed the same form.

Age selection for boost dose administration

To assess the effectiveness of a treatment strategy by age of patient. Between the ages of 35 to 70 years a boost dose reduced the 5 year local recurrence rate from 6.9% to 3.8% for all age groups. The greatest reduction was found between the ages of 40 to 60 years. If the boost dose was limited to patients aged 50 years or less then the overall 5 year recurrence rate would be predicted as 5.1%; similarly limiting the boost to patients aged 60 years or less would reduce the predicted overall 5 year recurrence rate to 4.4%. Recurrence rates would be higher at 5 years when limiting the boost to those aged 35 years or lower (6.4%), or to those aged 40 years or lower (6.1%).

Author conclusions

The relative local recurrence rate after a boost dose of 16Gy was reduced by a factor of 2 (HR = 0.55), independent of age. In younger patients a boost dose resulted in a greater absolute reduction of local failure. The relative risk reduction was however similar for all ages. Applying a treatment policy with a threshold-age of 60 would result in 0.6% increase in local failure in the total study population, while sparing the boost to 1/3 of the patients.

General comments –

The authors report that one of the limitations of this study was the missing data for some of the variables including margin of invasive tumour, hormone receptor status and grade of invasive tumour. The authors added that the missing data did not influence the analysis.

Poortmans P, Bartelink H, Horiot JC, Struikmans H, Van den BW, Fourquet A, et al. The influence of the boost technique on local control in breast conserving treatment in the EORTC 'boost versus no boost' randomised trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2004;72(1):25-33.

Design: RCT (1989-1996 EORTC Trial)

Level 1++

Country: Europe, setting: Multi-centre

Aim: To describe the influence of boost technique on local control and fibrosis after breast conserving therapy in the group of patients receiving a boost dose in a large prospective randomized multi-centre trial.

Inclusion criteria

Patients with T1-2, N0-1, and M0 breast cancer were eligible for the EORTC trial.

Exclusion criteria

Patients aged more than 70 years, pure carcinoma in situ, multiple tumour foci in more than one quadrant, a history of other malignant disease, Eastern Cooperative Oncology Group performance score greater than 2, residual micro-calcifications on mammography, or gross residual disease in the breast after lumpectomy (unless re-excision had been performed).

Population number of patients = 2661 in boost arm of trial

Patients had a complete excision of the primary tumour and were randomized to receive a boost dose of 16 Gy to the primary tumour bed.

Interventions

Whole-breast irradiation (WBI) was administered by two tangential megavoltage photon (high-energy X-ray or tele-cobalt) beams. A dose of 50 Gy, in 2 Gy fractions, was delivered over 5 weeks.

The target area for the boost dose was the original site of primary tumour, with a 1.5 cm safety margin around the primary tumour after microscopic complete excision, and 3 cm for invasive cancer with an extensive DCIS component.

Types of boost technique:

High energy photons - the boost dose of 16 Gy (eight fractions of 2Gy) were delivered at the centre of the tumour excision area, either as tangential or wedged oblique fields (753/2661, 29%).

Fast electrons - the 16Gy boost (eight external beam fractions of 2Gy) were delivered to a depth of Dmax with the 85% isodose encompassing the target volume (1635/2661, 63%).

Interstitial boost- 15 Gy of iridium-192 implant was delivered at a rate of 10 Gy per 24 hours (225/2661, 9%).

The choice of boost technique was not prescribed and could be individualized based on experience and on patient and tumour specific parameters.

Outcomes

Fibrosis was scored by the oncologist on a 4-point scale (none–minor–moderate–severe). The worst score reported over the follow-up period was used for this report.

Local recurrence by type of tumour boost.

(Data on the boost technique were missing for 22 patients and 26 patients did not receive a boost).

Follow up

At the time of this report, the median follow-up was 5.11 years (maximum 10.2 years).

Results

In the 2661 patients with a microscopically complete resection randomized to receive a boost, 234 deaths had occurred, of which 175 (74.8%) were due to breast cancer. Local failure rates were estimated using the Kaplan–Meier technique.

Local recurrence was observed in 109/2661 of patients randomized to receive an additional 16 Gy boost after 50 Gy WBI, corresponding to a 5-year actuarial local recurrence rate of 4.3% (95% CI: 3.8–4.7%).

Sites of local recurrence:

48% in the primary tumour bed

9% in the scar

28% outside the original tumour area

14% were diffuse.

The 5 year local failure rates for the 3 boost techniques are shown in the table below. Although fewer events occurred in the interstitial boost group the differences between the 3 techniques were not statistically significant in the boost area.

Outcome	Electrons (n=1635)	Photons (n=753)	Interstitial (n=225)	Overall (N=2661)
5 year local failure rate	n=74 4.7% (95%CI 3.6-5.9)	n=28 4.0% (95%CI 2.4-5.5)	n=6 2.5% (95%CI 0.3-4.6)	n=109 4.3% (95%CI 3.8-4.7)

Since age is the strongest prognostic factor for local control, the effects of different boost techniques were analyzed in four different age groups. No differences were found, and this excluded age as a confounding factor for treatment effects across the boost techniques.

Fibrosis

The findings of the grade of fibrosis by type of boost technique in the whole

breast and boost area are shown in the following table:

Type of boost	Unknown (N=48) N (%)	Electrons (N=1635) N (%)	Photons (N=753) N (%)	Interstitial (N=225) N (%)	Total (N=2661) N (%)
Palpable fibrosis in whole breast					
None	14 (29.2)	824 (50.4)	383 (50.9)	118 (52.4)	1339 (50.3)
Minor	12 (25.0)	575 (35.2)	243 (32.3)	78 (34.7)	908 (34.1)
Moderate	2 (4.2)	148 (9.1)	97 (12.9)	14 (6.2)	261 (9.8)
Severe	0 (0)	14 (0.9)	16 (2.1)	2 (0.9)	32 (1.2)
Unknown	20 (41.7)	74 (4.5)	14 (1.9)	13 (5.8)	121 (4.5)
% with fibrosis at 5 years (95% CI)		47.2 (44.5-49.9)	48.2 (44.4-52.1)	39.6 (33.8-46.3)	P=0.013
Palpable fibrosis in boost area					
None	15 (31.3)	533 (32.6)	285 (37.8)	59 (26.2)	892 (33.5)
Minor	5 (10.4)	661 (40.4)	256 (34.0)	91 (40.4)	1013 (38.1)
Moderate	4 (8.3)	320 (19.6)	165 (21.09)	51 (22.7)	540 (20.3)
Severe	0 (0)	46 (2.8)	33 (4.4)	10 (4.4)	89 (3.3)
Unknown	24 (50.0)	75 (4.6)	14 (1.9)	14 (6.2)	127 (4.8)
% with fibrosis at 5 years (95% CI)		65.6 (63.0-68.2)	61.4 (57.6-65.1)	67.2 (60.6-73.9)	P=0.67

There was no significant difference in fibrosis in the boost area at 5 years between boost techniques (p=0.67); there was a significant difference in fibrosis to the whole breast at 5 years between boost techniques (p=0.013).

The occurrence and grades of fibrosis in the whole breast and in the boost area were similar between the 3 boost techniques. Minor fibrosis was more common in both areas (whole breast and boost). A larger proportion of patients developed moderate to severe fibrosis at the site of primary tumour (25%) than in the whole breast (12%).

Author conclusions

Although the three groups were unequal in size, the results of the interstitial boost seem similar in terms of fibrosis and at least as good in terms of local control, despite a lower treatment volume and a longer overall treatment time.

General comments -

Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? European journal of cancer 2003;39(7):932-44).

Design: RCT (1989-1996 EORTC Trial)

Level 1++

Country: Europe, setting: Multi-centre

Aim: To identify patient, tumour and treatment related factors to explain high local recurrence rates in younger patients.

Inclusion criteria

Patients with T1-2, N0-1, and M0 breast cancer were eligible for the EORTC trial.

Exclusion criteria

Patients aged more than 70 years, pure carcinoma in situ, multiple tumour foci in more than one quadrant, a history of other malignant disease, Eastern Cooperative Oncology Group performance score greater than 2, residual micro-calcifications on mammography, or gross residual disease in the breast after lumpectomy (unless re-excision had been performed).

Population number of patients = 5569

Age ≤ 35 years n=156

Age 36-40 years n=314

Age 41-50 years n=1407

Age 51-60 years n=1885

Age > 60 years n=1807

Median age at treatment 55 years.

Younger women had larger clinical and pathological tumour sizes.

When age groups were classified as ≤ 40 years vs. > 40 years the difference in T1 and T2 tumour sizes was not significant (p=0.08).

Other characteristics classified as ≤ 40 years vs. > 40 years:

Number of positive nodes (N0, N1-3, N>3) p=0.06

ER positive p=0.0001

40% ≤ 40 years were ER+

54% > 40 years were ER+

PR positive p=0.0006

36% ≤ 40 years were PR+

45% > 40 years were ER+

2,657 were allocated to receive no boost

2,661 were allocated to receive a boost of 16 Gy to tumour bed

pN0 = 78%

Post menopausal 62%

T1 = 52%

T2 = 48%

Interventions

Treatment involved tumourectomy (with a macroscopic tumour-free margin of 1 cm) and axillary dissection, followed by tangential irradiation of the whole breast of 50 Gy, with a dose per fraction of 2 Gy over 5 weeks.

Additional interventions were:

Patients with a microscopically complete excision were randomized to either no further treatment or a boost of 15 or 16 Gy (15 Gy for interstitial and 16 Gy for external beam therapy).

Patients with a microscopically incomplete excision were randomized to either a 10 Gy boost or a 25 or 26 Gy boost (25 Gy for interstitial and 26 Gy for external beam therapy).

The boost dose was delivered by 1 of 3 methods:

- i) Two external photon beams of either cobalt-60 or X-ray, 4-8 MV in the centre of tumour
- ii) One electron beam
- iii) Interstitial therapy with iridium-192 or caesium-137 wires at a dose rate of 50 cGy per hour.

Outcomes

Local recurrence

Multivariate Cox proportional hazard regression to assess influence of prognostic factors on local control

Follow up Median of 5.1 years (maximum 10.2 years)

Results

Local control

The probability of ipsilateral breast recurrence at 5 years by age group is shown in the following table:

Age group	Actuarial 5 year local control rate (95% CI)
≤ 35 years	82% (75-88%)
36-40 years	85% (80-89%)
41-50 years	92% (91-94%)
51-60 years	96% (95-97%)
> 60 years	97% (96-98%)

Local control increased with age despite the addition of a boost dose ($p < 0.0001$).

Tumour characteristics

Younger patients had more palpable tumours which were clinically and pathologically larger ($p = 0.001$). The authors suggest this may be due to the detection of tumours in women over 50 years by screening.

ER negative status was more common in younger patients ($p = 0.001$).

Multivariate analysis of patient and tumour characteristics found that palpable

tumour size, re-excision, and excision volume were significantly associated with age. Odds ratios are reported in the following table:

Characteristic	Odds Ratio (99% CI)	P value
Palpable tumour size	1.41 (1.18-1.69)	0.0001
Re-excision	1.80 (1.12-2.90)	0.0001
Excision volume	0.70 (0.56-0.87)	0.0001

As well as more palpable tumours younger patients had more frequent re-excisions and smaller total excision volumes.

Prognostic factor analysis for local control

Multivariate Cox proportional hazard regression analysis found that age, palpable tumours and progesterone receptor status were significant for local control:

Characteristic	Hazard Ratio (95% CI)	P value
Age	0.59 (0.48-0.71)	0.0001
Tumour palpation	2.14 (1.23-3.72)	0.007
Progesterone receptor	0.66 (0.49-0.87)	0.004

Higher local recurrence rates occurred in younger patients, those with palpable tumours or progesterone negative receptor status.

At higher significance levels only age remained significant: Hazard Ratio = 0.45 (99% CI 0.35-0.59) p= 0.0001.

When a multivariate analysis was conducted on patients with a complete excision to assess the effect of the boost dose on local control, both age and the boost dose were significant. Data are reported in the following table:

Characteristic	Hazard Ratio (99% CI)	P value
Age	0.60 (0.51-0.70)	< 0.0001
Boost dose	0.51 (0.37-0.70)	0.001

Author conclusions

This large European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated an increased local recurrence rate in young patients. Although several associations between patient, tumour and treatment factors and age were found, that might explain the high local recurrence rate in the younger patients, it appears that age itself and the boost dose were the only factors that were independently related to local control.

General comments -

Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1997;15(3):963-8.

Design: RCT (1986-1992)

Level 1+

Country: France, setting: Not clear

Aim: To define the role of a 10-Gy boost to the primary tumour in the conservative treatment of early infiltrating breast carcinoma treated by limited surgery and radiotherapy.

Inclusion criteria

Women with infiltrating ductal carcinoma of the breast (< or = 3 cm in diameter) and free pathological margins. Absence of distant metastases, age < 70 years and no history of cancer (exceptions were basal skin cancer or in situ cervical carcinoma).

Exclusion criteria None reported.

Population number of patients = 1024

Intervention (boost) n= 521

No boost n= 503

10 patients in the intervention group and 12 in the comparison group did not have free margins.

Patients were randomized and stratified according to tumour stage (T1 or T2) and node status (N0 = 73%; and N1-2 = 27%)

Interventions

Patients were treated by local excision (tumourectomy or quadrantectomy with a margin of 1cm), axillary dissection. Conventional 50-Gy irradiation was given in 20 fractions over 5 weeks with cobalt-60.

Patients were then randomly assigned to receive either no further treatment or a boost of 10 Gy by electrons to the tumour bed.

Outcomes

Local recurrence

Overall survival

DFS

Telangiectasia:

Scored as 0 absent; 1 a few visible areas in tumour bed; 2 covering one quadrant; 3 more than one quadrant.

Cosmesis score from physician and patient reports: 1 excellent; 2 good; 3 fair; 4 poor.

Follow up Median follow-up time was 3.3 years by September 1994.

Results

Local recurrence

At 5 years:

Probability of local recurrence in boost arm (10/521 patients): 3.6% (95% CI

1.8% to 7.1%)

Probability of local recurrence in no boost arm (20/503 patients): 4.5% (95% CI 2.7% to 7.4%)

Kaplan-Meier estimates for local recurrence favoured the boost arm with a statistically significant reduction in ipsilateral breast recurrence (Log rank test P=0.044). DFS at 5 years was also significantly improved in the boost arm (p=0.011), however there was no significant difference in overall survival at 5 years between the two groups.

Findings are reported in the following table:

Outcome	Boost N=521	No boost N=503	P value
Time to local recurrence	10 events 5.7 events/ 1000 person years	20 events 12.3 events/ 1000 person years	0.044
Relative Risk for time to local recurrence (Cox model)	0.34 (95% CI 0.12 to 0.95) favours boost		
Time to distant failure	16 events 9.7 events/ 1000 person years	21 events 12.8 events/ 1000 person years	
Disease Free Survival	46 events 25.8 events/ 1000 person years	67 events 41.3 events/ 1000 person years	
Disease Free Survival at 5 years	86% (95% CI 81.0% to 89.8%)	82.2% (95% CI 77.3% to 86.3%)	0.011
Relative Risk for Disease Free Survival	0.63 (95% CI 0.39 to 1.01) Favours boost		
Overall survival	23 events 12.6 events/ 1000 person years	29 events 17. events/ 1000 person years	
Overall Survival at 5 years	92.9% (95% CI 89.0 to 95.5%)	90.4% (95% CI 86.1 to 93.4%)	0.24
Relative Risk for Overall survival	0.49 (95% CI 0.23 to 1.05)		

Telangiectasia

At 2 years telangiectasia was recorded in 702 patients. None had grade 3 telangiectasia.

5.9% of the no boost group (n=339) and 12.4% of the boost group (n=363) reported grades 1 and 2 telangiectasia which was significant p=0.003.

Cosmesis

Physician reports: 85% of patients were considered to have good or excellent

results with no difference between arms, and no poor results. Self assessments of patients at 2 years reported no poor results (n=600), and 90% of patients scored good or excellent results with no significant difference between groups.

Author conclusions: Delivery of a boost of 10 Gy to the tumour bed after 50 Gy to the whole breast following limited surgery significantly reduces the risk of early local recurrence, with no serious deterioration in the cosmetic result. Additional follow-up evaluation will be required to assess the long-term results.

General comments -

Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot J-C, Jager JJ, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the eortc 'boost versus no boost' trial. *Int J Radiat Oncol Biol Phys* 1999;45(3):677-85.

Design: RCT
Level 1+ EORTC Trial (1989-1996)

Country: Europe, USA, setting: Multi-centre (31)

Aim: To evaluate the influence of a radiotherapy boost on the cosmetic outcome after 3 years of follow-up in patients treated with breast-conserving therapy (BCT).

Inclusion criteria

Stage I and II (T1-2, N0-1, M0) invasive breast cancer.

Exclusion criteria

Age over 70 years; carcinoma *in situ* (CIS) without invasive tumour; residual micro-calcifications on mammogram or gross residual disease in the breast after tumourectomy (unless re-excision had been performed); tumour foci in more than one quadrant; a prior history of malignant disease; or an Eastern Cooperative Oncology Group (ECOG) performance score of greater than 2.

Population number of patients = 5569

Panel patients:

No boost N=367

Boost N=364

Others N=4567

Digitizer patients:

No boost N=1580

Boost N=1621

Others N=2099

Interventions

Treatment involved tumourectomy (with a macroscopic tumour-free margin of 1 cm) and axillary dissection, followed by tangential irradiation of the whole breast of 50 Gy, with a dose per fraction of 2 Gy over 5 weeks.

Additional interventions were:

Patients with a microscopically complete excision were randomized to either no further treatment or a boost of 15 or 16 Gy (15 Gy for interstitial and 16 Gy for external beam therapy).

Patients with a microscopically incomplete excision were randomized to either a 10 Gy boost or a 25 or 26 Gy boost (25 Gy for interstitial and 26 Gy for external beam therapy).

The boost dose was delivered by 1 of 3 methods:

i) Two external photon beams of either cobalt-60 or X-ray, 4-8 MV in the centre of tumour

ii) One electron beam

iii) Interstitial therapy with iridium-192 or caesium-137 wires at a dose rate of 50 cGy per hour.

The volume of the boost was defined as site of primary tumour with a safety margin of 1.5cm after microscopically complete excision, or 3cm after incomplete excision or extensive intraductal component.

Late radiation telangiectasia was avoided by placement of the most superficial needles for interstitial therapy at least 5 mm below the overlying skin surface.

Outcomes

Cosmetic outcome was evaluated only for patients randomized to receive either no boost or a boost of 15 or 16 Gy since the surgical excision was microscopically complete in 95% of patients.

731 patients were assessed both postoperatively and after 3 years of follow-up. These patients were the first evaluable at both time points and not randomly selected.

The cosmetic outcome was evaluated by a panel (of 5 people), scoring 731 photographs of patients taken soon after surgery and after 3 years follow-up, and by digitizer measurements, measuring the displacement of the nipple of 3000 patients postoperatively and of 1141 patients 3 years later.

The treated breast was compared with the untreated breast for 6 items: global cosmetic result; appearance of the surgical scar; breast size; breast shape; nipple position; and shape of areola. A 4-point scale was used to score the results by averaging each score of the 5 reviewers into one of the following categories:

“0” an excellent result;

“1” a good result;

“2” a fair result;

“3” a poor result

The boost and no boost arms of the selected patients of panel and digitizer assessments were compared with the remainder of the patient population.

Follow up Postoperatively and at 3 years

Results

Panel results (n=731 from later paper 2000):

Postoperative:

Overall patients 82% of had an excellent or good global cosmetic result. Sixteen percent scored as fair, and a small proportion had a poor result. Global cosmetic results between the two treatment arms were similar.

Of the 6 cosmetic items evaluated only the appearance of the scar differed significantly between the two arms. Patients in the boost group had a slightly higher score (median 1.0) than the no-boost group (median 0.8; $p = 0.04$).

At 3 year follow-up:

86% of patients in the no-boost group had an excellent or good global result,

compared to 71% in the boost group.

13% of patients in the no-boost group had a fair global result, compared to 26% of the boost group ($p = 0.0001$). These results are shown in the following table:

Global cosmetic outcomes at 3 years

Score	Global cosmetic result	No boost (%)	Boost (%)
0	Excellent	41.7	32.7
1	Good	43.0	38.2
2	Fair	13.1	25.8
3	Poor	1.3	3.3

All the cosmetic items scored significantly worse in the boost group than the no-boost group ($p < 0.001$). More patients in the boost group had a fair outcome than in the no boost group. The latter group also had a higher proportion of excellent outcomes. Few patients had a poor result in either arm (0-1.6% in the no boost group; 0.6- 3.3% in the boost group).

There was a trend over time favouring the no boost group for better global scores and breast shape scores after 3 years:

Global cosmetic scores

No boost arm
21% worsened (score 0 after surgery);
11% worsened after 3 years (score 1 after surgery)

50% improved (score 2 after surgery)

Boost arm
35% worsened (score 0 after surgery)
25% worsened after 3 years (score 1 after surgery)

29% improved (score 1 after surgery)

Global score changes over time for breast size, breast shape, nipple position, and shape of areola were significant in the boost arm ($p < 0.001$) only.

Scar score was the only item that changed significantly over time in both treatment arms ($p < 0.0001$) with an overall improvement. However the trend favoured the no-boost arm where 45% of patients had an improved scar score after 3 years, compared to 34% in the boost arm.

Digitizer results (n=1141):

The mean pBRA (Breast Retraction Assessment) at 3 years in the no-boost group was 7.55 pBRA (95% CI, 7.11-8.02), compared with 8.26 pBRA (95% CI, 7.79-8.75) in the boost group. The difference in mean pBRA after 3 years between treatment arms was small (less than 1 pBRA); and of borderline statistical significance.

The median change in pBRA over 3 years was 0.3 (range -12.8 to +31.0); a large

proportion of patients (80%) had a change in score ranging from 26.2 to 17.0 pBRA. The change in pBRA over time in the no-boost group was not significant (mean pBRA of 7.5 postoperatively and 7.6 at 3-years, $p = 0.94$). There was an increase in mean pBRA of 0.6 in the boost group which suggested an increase in nipple position asymmetry (pBRA 7.7 postoperatively and 8.3 at 3 years) of borderline statistical significance ($p=0.05$).

Author conclusions

These results showed that a boost dose of 16 Gy had a negative, but limited, impact on the cosmetic outcome after 3 years.

General comments –

Some of the numbers (N and n values) reported in this paper were not very clear or fully explained. Patient characteristics were similar across arms at commencement of the interventions. More patients had digitizer measurements than a panel assessment, possibly because of the time involved in panel assessments. At the 3 year assessment only approximately one third of patients' data were reported for digitizer assessments (pBRA). The panel assessments were displayed as graphs with % values, no numerators or denominators were provided for % values cited in the text. The number of patients included in the table of cosmetic results at 3 years by panel assessment was also not provided.

A further analysis of this data was conducted by the authors and published in 2000. Analyses included ANOVA and reporting of Odds Ratios for cosmesis factors:

Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot J-C, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. *Radiotherapy & Oncology* 2000;55(3):219-32.

Aim: To analyze the influence of different patient, tumour, and treatment parameters on the cosmetic outcome after breast-conserving therapy at 3-year follow-up.

The patient population and interventions were the same as the 1999 paper. Univariate and multivariate analyses were used to evaluate the correlation between various patient, tumour, and treatment factors and cosmesis.

Results

Panel analysis

At 3 years the cosmetic outcomes were reported as:

Cosmetic result	No boost	Boost
Excellent	42%	33%
Good	44%	38%
Fair	13%	26%
Poor	1%	3%

On univariate analysis factors which had a significant negative impact on four or more of the six cosmetic items (global score, surgical scar, breast size, breast shape, nipple position, shape of areola) were inferior tumour location, increased pathological tumour size, increased excision volume, breast complications and boost treatment. On multivariate analysis inferior tumour location, increased excision volume, breast complications and boost treatment were significant.

The final multivariate model for the appearance of the surgical scar, breast size, breast shape and shape of areola were very similar. The final model for nipple position differed, since this was not influenced by tumour location and boost treatment.

Digitizer analysis

A univariate analysis found that tumour size, tumour location, volume of excision, maximum dose to central/superior tumour, maximum dose of boost fraction, boost treatment, and tamoxifen treatment were significant factors associated with an increased pBRA at 3 years, and poorer cosmetic outcome.

A multivariate analysis showed that tumour location (central/superior), a large excision volume, increasing pathological tumour size and high maximum dose in the central plane were associated with an increased pBRA at 3 years, and poorer cosmetic outcome.

The prognostic factor analyses by both methods showed that a large excision volume, a boost dose, increased dose inhomogeneity, and the presence of postoperative breast complications had a large negative effect on cosmesis.

Author conclusions: To achieve a good cosmesis, it is necessary to excise the tumour with a limited margin, to avoid postoperative complications, to assess the need for a boost in the individual patient, and to give the radiation dose as homogeneously as possible. As far as the method of evaluation is concerned, the panel evaluation is the most appropriate method for giving an overall impression of the cosmetic result after breast-conserving therapy (BCT). The use of the digitizer is recommended for comparing the cosmetic outcome of two different approaches to BCT or for analyzing cosmetic changes over time.

Non-randomized studies

Polgar C, Major T, Fodor J, Nemeth G, Orosz Z, Sulyok Z, et al. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. *Int J Radiat Oncol Biol Phys* 2004 Nov 15;60(4):1173-81.

Design: Prospective non-randomized study (1996-1998)
Level 3

Country: Hungary Setting: Single Oncology Institute.

Aim: To report 7-year results of a prospective study of accelerated partial breast irradiation (APBI) using interstitial high-dose-rate brachytherapy and compare the treatment results with standard, whole breast radiotherapy (WBRT), with or without a tumour bed boost (TBB).

Inclusion criteria

Patients with T1N0-N1mi (single nodal micro-metastasis), tumour size \leq 20mm, histological grade 2 or less; non-lobular breast cancer without the presence of an extensive intraductal component and with microscopically negative surgical margins.

Exclusion criteria

Pure ductal or lobular carcinoma in situ; invasive lobular carcinoma; extensive intraductal component (EIC).

Population number of patients = 125

N=45 selected patients receiving APBI

(n=35 (78%) had axillary dissection)

N=80 were treated with 50 Gy WBRT with (n = 36) or without (n = 44) a 10-16-Gy TBB. These patients were selected from a group of 621, only those meeting the APBI criteria were included.

Interventions

1) APBI used interstitial high-dose-rate (HDR) implants (Iridium-192) to the tumour bed after wide excision of primary tumour. A total dose of 30.3 Gy (n = 8) and 36.4 Gy (n = 37) in 7 fractions within 4 days was delivered to the tumour bed plus a 1-2-cm margin.

16% (7/45) also had adjuvant chemotherapy or hormonal therapy.

2) Conventional WBRT of tangential cobalt or 6-9MV photon fields, median dose 50 Gy (46-52Gy) after wide excision of primary tumour (n=44).

36/80 also received a tumour bed boost (TBB) of 10-16Gy of electrons (n=31) or 3 x 4.75Gy HDR-BT (n=5).

16% (13/80) also had adjuvant chemotherapy or hormonal therapy.

Outcomes

Cosmesis (Harvard criteria)

Local recurrence- any detection of cancer in the treated breast, proven histologically.

Relapse-free survival.

Cancer-specific survival.

Elsewhere breast failure (EBF) - defined as ipsilateral LR detected at least 2 cm from the surgical clips. All other LR was classified as true recurrence/marginal miss (TR/MM).

Late side effects

Follow up 81 months (range 66-96) for APBI, 83 months (range 52-96) for WBRT and Boost group.

Results

Breast cancer events

The crude incidence of breast cancer related events using data from the paper are shown in the following Table:

Event	APBI n(%) (n=45)	WBRT n(%) (n=44)	WBRT + TBB n(%) (n=36)
Local recurrence	3 (6.7)	5 (11.4)	3 (8.3)
TR/MM	0 (0)	1 (2.3)	2 (5.6)
EBF	3 (6.7)	4 (9.1)	1 (2.8)
Any first relapse	8 (17.8)	11 (25.0)	7 (19.4)
Breast cancer death	3 (6.7)	4 (9.1)	2 (5.6)
Contralateral breast cancer	0 (0)	2 (4.5)	1 (2.8)

A larger proportion of patients in both WBRT groups experienced an ipsilateral local recurrence than in the APBI group. Kaplan-Meier 5 and 7 year estimates for local recurrence were not statistically significantly different between the three groups.

No statistically significant differences were found in either the 7-year probability of relapse-free survival or cancer-specific survival. The 7-year actuarial elsewhere breast failure rate was 9.0% in the APBI group and 8.3% in the WBRT +/- TBB group (p = 0.80).

Kaplan Meier estimate	APBI	WBRT	WBRT + TBB
Local recurrence 5 year actuarial rate	4.4%	4.7%	5.7%
Local recurrence 7 year actuarial rate	9.0%	14.8%	9.5%
P values for local recurrence between groups	APBI/WBRT P=0.57	WBRT/ WBRT+TBB P=0.72	APBI/WBRT +TBB P=0.78

7 year relapse-free survival	79.8%	73.5%	77.7%
Cancer-specific survival	93.3%	92.9%	93.9%

Cosmetic outcomes (Refer to table below)

Most cosmetic results were rated as excellent/good for all 3 radiation techniques, however, APBI had the highest proportion (84.4%) of excellent/good results. The differences were statistically significant ($p=0.04$) between APBI and (WBRT/WBRT+TBB). Telangiectasia was significantly increased in the WBRT+TBB group compared to the other two groups. Findings for fibrosis and fat necrosis are reported in the following table, the differences between groups were not significant.

Outcome	APBI (n=45) n (%)	WBRT (n=35) n (%)	WBRT + TBB (n=28) n (%)
Cosmetic results	38 (84.4)	25 (71.4)	18 (64.3)
Excellent/good	7 (15.6)	10 (28.6)	10 (35.7)
Fair/poor			
Grade 2-3 telangiectasia	4.4% (2) APBI vs. WBRT $p=0.38$ APBI vs. WBRT + TBB $p=0.01$	8.6% (3)	25.0% (7)
Grade 2-3 fibrosis	20.0% (9) APBI vs. WBRT $p=0.06$ APBI vs. WBRT + TBB $p=0.68$	5.7% (2)	21.4% (6)
Fat necrosis	22.2% (10) APBI vs. WBRT +/- TBB $p=0.57$	17.1% (6)	25.0% (7)

Author conclusions

Accelerated partial breast irradiation using interstitial high-dose-rate implants, with proper patient selection and quality assurance, yields similar 7-year results to those achieved with standard breast-conserving therapy. APBI does not increase the risk of elsewhere breast failures.

Neuschatz AC, DiPetrillo T, Safaii H, Price LL, Schmidt-Ullrich RK, Wazer DE. Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy. *Cancer* 2003 Jan 1;97(1):30-9.

Design: Prospective cohort (1982-1994)

Level 2-

Country: USA, setting:

Aim: Long-term follow-up of a breast conserving therapy (BCT) treatment policy using margin assessment as the exclusive guide to the intensity of radiation therapy directed at the tumour bed.

Inclusion criteria

Tumours of histopathological subtypes: invasive ductal (IDC), invasive ductal with associated extensive intraductal component (EIC – includes EIC and DCIS with microinvasion), invasive lobular (ILC).

All tumour excisions performed for complete tumour removal with a normal tissue margin of greater than 5 mm. Final margin status (FMS) categories were defined as greater than 5 mm, greater than 2-5 mm, greater than 0-2 mm, and positive. For margins less than or equal to 2 mm or indeterminate, re-excisions were performed if feasible.

Exclusion criteria None reported

Population number of patients = 498 women with 509 Stage I/II breast cancer

Median age 56 years (range 25-86).

Interventions

All patients received whole breast irradiation to 50.0-50.4 Gy through parallel opposed tangential portals to the whole ipsilateral breast. Until 1983 whole breast treatment was delivered with a Cobalt-60 unit, and a 6-MV linear accelerator post 1983.

Final tumour bed boosts as a function of FMS were as follows:

No residual on re-excision, no boost performed;

FMS greater than 5 mm, electron boost of 10 Gy;

FMS greater than 2-5 mm, electron boost of 14 Gy;

FMS greater than 0-2 mm or positive, boost of 20 Gy with appositional electrons or Iridium-192 implant.

Cases were analyzed for local failure related to histology, age, tumour size, excision volume, re-excision, and total dose.

Additional interventions were systemic adjuvant chemotherapy for patients at risk of systemic micro-metastases. Postmenopausal women with tumours ≥ 20 mm and/or lymph node positivity who also had hormonally responsive tumours were prescribed tamoxifen.

Outcomes

Local failure:

Classified as central -recurrence within the excision bed; peripheral-recurrence within 3 cm of the excision bed; and remote- recurrence greater

than 3 cm from the tumour bed in the ipsilateral breast. All ipsilateral breast tumour recurrences were considered local failures. Patients were censored at last follow-up or at time of death.

Survival:

Kaplan-Meier analyses of local failure stratified by FMS and age.

Follow up Median follow-up 121 months.

All patients examined for tumour control at 3-6 month intervals after completion of therapy.

Results

The extent of surgical excisions performed varied, with a mean total excisional volume of 117 cm³ (range, 1–863 cm³) and a median of 79 cm³. Re-excision was performed in 55.6%; chemotherapy, tamoxifen, and implant boost were administered in a quarter of cases (24.4%, 26.3%, and 25.5%, respectively). Mean dose was 62.4 Gy.

Final Margin Status

FMS was strictly observed with 98.4% full compliance.

The main histological subtype was IDC (53.6%), 38.9% were EIC (including 11.6% DCIS with microinvasion), 7.3% were ILC, and less than 1% were unclassified. Stratification by margin status is shown in the table below.

Local Failure

Of the 509 cases 36 were ipsilateral breast carcinoma recurrences with an overall unadjusted local failure rate of 7.1%.

Stratification by FMS is shown in the table below with 12 year Kaplan-Meier failure rates (log-rank p = 0.009) (NRT no boost arm):

	FMS positive	>0-2mm	> 2-5mm	> 5mm	No Residual Tumour on re-excision (NRT)
FMS status	21%	20%	17%	14%	28%
K-M local failure (12yr)	17%	9%	5%	0%	6%

When all cases with FMS >2mm or NRT were combined a 12 year Kaplan-Meier local failure rate of 4.6% (Log-Rank P=0.003) was obtained when compared with FMS +ve and greater than 0-2mm (see table below):

FMS	FMS	FMS	Log Rank P value
Positive	> 0 ≤ 2mm	> 2mm or NRT	0.003
Positive	> 0 mm		0.002
≤ 2mm	> 2 mm		0.003

Stratification by age

When stratified by age Kaplan–Meier survival estimates for patients 45 years or younger showed a 12-year local failure rate of 14.5%, compared with 6.4% for patients older than 45 years of age at diagnosis (Log-Rank P = 0.01).

A comparison of 12-year Kaplan–Meier local failure rates by age and FMS showed lower failure rates among the older age group irrespective of margin status (see table below):

Age	FMS +ve	> 0-2mm	> 2.5mm	> 5mm	NRT
< 45 years	25%	19%	7%	0%	5%
> 45 years	14%	5%	5%	0%	3%

A Cox proportional hazards regression model for local failure found that age, FMS and late presence of EIC were significant predictors of local failure by univariate analysis.

On multivariate analysis increased local failure was predicted by young age (p=0.03) and FMS ≤ 2mm or positive predicted late recurrence (> 5 years), but not early (≤ 5 years) recurrence (p=0.003).

Author conclusions: Graded tumour bed dose escalation in response to FMS results in very low rates of local failure over the first 5 years for all FMS categories. However, tumours with close/positive margins have significantly increased local failure rates after 5 years of follow-up even with increased radiation boost dose. In addition, graded tumour bed dose escalation does not fully overcome the adverse influence of young age.

General comments -

Palazzi M, Tomatis S, Valli MC, Guzzetti R, Tonoli S, Bertoni F, et al. Impact of radiotherapy technique on the outcome of early breast cancer treated with conservative surgery: A multicenter observational study on 1,176 patients. *Int J Radiat Oncol Biol Phys* 2006 Aug 1;65(5):1361-7.

Design: Prospective cohort (1997)
Level 2+

Country: Italy, setting: Multi-centre

Aim: To quantify the impact of radiotherapy technique on cosmetic outcome and on 5-year local control rate of early breast cancer treated with conservative surgery and adjuvant radiation.

Inclusion criteria

Patients with no previous treatment for breast cancer; disease limited to one breast (with or without ipsilateral axillary involvement); surgery either tumourectomy/lumpectomy or quadrantectomy, with or without axillary dissection; invasive carcinoma by pathological examination; pT-stage either T1 or T2.

(Selection biases were avoided by including patients in the database that were automatically selected on a sequential basis from the general waiting list (i.e., an average of 1 in 4 cases were assigned by secretarial staff to the single radiation oncologist participating to the study).

Exclusion criteria

No patient exclusions were allowed after verification of eligibility criteria.

Population number of patients = 1176

Age 25-50 years, 32%; 51-65 years, 44%, 66-80 years, 24%

Menopausal status: Pre 31%; Post 69%

Histological type: Invasive ductal 76%; invasive lobular 11%; other invasive 13%.

pT stage: T1a, 3%; T1b, 21%; T1c, 54%; T2, 19%

pN stage: N0, 71%; N+ (1-3 positive nodes), 21%; N+ (>3), 8%

Interventions

A wide range of radiotherapy techniques were used by participating centres and this was acknowledged in the report.

Treatment characteristics of study population for radiotherapy are described below:

Radiation treatment:

Use of immobilization device Yes, 17%;
no, 83%

Treatment planning Fluoroscopic simulation, 8%; external profile-based, 20%;

CT-based, 72%

Treatment unit Telecobalt, 37%; 4-6 MV linear
accelerator, 63%

Treatment technique	Isocentric, 71%;	nonisocentric, 29%	
Irradiation of any nodal region	Yes, 10%;	no, 90%	
Use of wedge filters	Yes, 64%;	no, 36%	
Use of portal verification	Yes, 55%;	no, 45%	
Dose to the whole breast	<50 Gy, 7%;	50 Gy, 85%;	>50 Gy, 8%
Boost dose	0 Gy (no boost), 40%;	5–18 Gy, 60%	
Total dose to tumour bed	<50 Gy, 3%;	50 Gy, 31%;	>50 Gy, 66%

Surgical procedure was quadrantectomy in 97% of patients, with axillary dissection performed in 96%.

A boost dose to the tumour bed was delivered in 60% of cases.

Outcomes

Cosmesis – evaluated by the radiation oncologist using a 4 point scale (no, mild, intermediate or severe damage) for each of seven items.

Patients assigned a subjective 4 grade score (excellent, good, fair, poor) to the overall cosmetic outcome.

In the analysis of cosmetic outcome the last score recorded for each patient was used.

Disease-free, overall, and disease-specific survival curves were calculated using the Kaplan-Meier method, starting from the first day of radiotherapy.

Definitions:

Disease-free survival curves, all relapses and death from any cause were considered as events.

Local failure was defined as the pathologically confirmed evidence of a carcinoma of the same histological type of the original in the treated breast.

Regional failure was defined as a recurrence in the axillary, supraclavicular, or internal mammary regions.

All other recurrences were considered as distant relapses.

Follow up

Median follow-up of surviving patients was 6.8 years (range 0.2– 8.2 years) for this analysis (September 2005). Median follow-up time for cosmetic evaluation was 4.55 years.

Results

Univariate (log-rank test) and multivariate (backward stepwise Cox proportional hazards regression model) analyses were performed.

Survival (5 year rates)

5-year disease-free survival rate	89%
Overall survival rate	95%
Disease-specific survival rate	96%

Failure rates (at 5 years)

Local control rate	98%
Regional control rate	99%

Distant control rate 92%

On univariate analysis of the 8 radiation treatment characteristics assessed, only use of portal verification was significantly associated with improved local control (p=0.04). The use of a boost dose was not significant after quadrantectomy and 50 Gy to the whole breast in this cohort.

On multivariate analysis older age and medical adjuvant treatment were the strongest predictors of local control. Portal verification also remained significant. A lower N-stage, medical adjuvant treatment, lower T-stage, and lower histological grading were predictors of disease free survival.

Data are shown in the following table:

Variable	Hazard ratio (95% CI)	P value
Local control		
Age	0.95 (0.92-0.98)	0.001
Adjuvant therapy	0.50 (0.33-0.77)	0.002
Portal verification	0.33 (0.11-0.96)	0.05
Disease-free survival		
pN-stage	2.09 (1.58-2.75)	<0.001
pT-stage	1.48 (1.13-1.94)	0.005
Grade	1.44 (1.08-1.93)	0.013
Adjuvant therapy	0.69 (0.55-0.85)	0.001

Cosmetic outcomes

.Overall patients subjective cosmetic outcomes were scored during follow-up as:

Excellent	33%
Good	47%
Fair	17%
Poor	3%

These scores were similar to pre-radiotherapy scores. Cosmetic failure rate increased from 18% before radiation to 20% during follow-up, suggesting that radiation did not worsen the cosmetic outcome after surgery.

Further data were reported in the following table:

Outcome	Excellent (%)	Good (%)	Fair (%)	Poor (%)
Patients' subjective score				
Baseline (n=1079)	29	53	17	1
Follow-up (n=944)	33	47	17	3

Fibrosis				
Baseline (n=1079)	62	32	6	0.2
Follow-up (n=924)	72	24	4	0.3
Telangectasia				
Baseline (n=1079)	97	2	0.3	0
Follow-up (n=926)	93	5	2	0.3
Breast oedema				
Baseline (n=1079)	61	30	8	0.4
Follow-up (n=927)	93	5	1.4	0
Skin pigmentation				
Baseline (n=1079)	93	6	1	0.2
Follow-up (n=926)	86	13	1	0.1

The incidence of cosmetic failure (fair to poor) was small at a median of 4.5 years follow-up.

Author conclusions: Radiation technical factors impacted negatively on cosmetic outcome, but had relatively small effects on local control compared with other clinical factors

General comments -

Perez CA. Conservation therapy in T1-T2 breast cancer: past, current issues, and future challenges and opportunities. *Cancer Journal* 2003 Nov;9(6):442-53.

Design: Large cohort long-term (1970-1997) Retrospective review Level 2-
Country: USA, setting:

Aim: To assess the significance of patient age, race, tumour-related prognostic parameters, status of surgical excision margins, and irradiation boost on incidence of ipsilateral breast relapse, and to review current issues in the management of T1-T2 breast cancer patients with conservation therapy.

Inclusion criteria Records of 1037 patients with histologically confirmed stage T1 and 308 patients with T2 carcinoma of the breast treated with breast conservation therapy.

Exclusion criteria None specified.

Population number of patients = 1347

Histologically confirmed:

T1 n=1037

T2 n=308

Pathologically positive axillary lymph nodes:

T1 n=117 (11.2%)

T2 n=113 (37%)

Classification of tumours:

	Ductal	Lobular	Other histology
T1	866	64	109
T2	250	28	30

Interventions

Wide local excision of tumour with a minimum 1 cm margin of normal tissue and irradiation to the breast.

Wide excision was performed in 412 of T1 and 123 of T2 tumours.

Quadrantectomy was performed in 77 of T1 and 31 of T2 tumours.

Axillary dissection was performed in 902 (87%) of T1 and 260 (84%) of T2 tumours.

100 patients also had irradiation to lymphatics.

Re-excision was performed in 550 (53%) of T1 patients and 154 (50%) of T2 tumours.

RT was performed using tangential fields with either Cobalt-60 or 4 or 6 MV photons with a dose of 48-50 Gy over 5 weeks.

RT Boost:

RT boost was performed in 856 (83%) of T1 and 241 (78%) of T2 patients and delivered using 9 to 16 MeV electrons. An interstitial implant of Iridium-192 was delivered to 93 (9%) of T1 and 41 (13%) of T2 patients.

Boost doses (2Gy fractions with electrons or 10Gy/day with interstitial brachytherapy) were:

10Gy in patients with negative margins

14-16 Gy for final close margins (<3mm)

18-20 Gy for positive margins

90 (T1) and 28 (T2) patients did not receive any boost dose, usually because surgical margins were negative, and also radiation oncologist preference.

Outcomes

Local relapse

Follow up

The median follow-up for surviving patients was 6.6 years (range 4-30 years), with a minimum follow up of 4 years for all patients. Follow-up was complete in 99.6% of patients.

Results

Local relapse

There were 78 ipsilateral breast relapses (IBRs), the actuarial 10-year incidence of IBR was 7% for T1 and 11% for T2 tumours.

The overall incidence of IBR in patients with T1 tumours aged ≤ 40 years was 9.6% (10/104).

For women aged > 40 years the overall incidence of IBR was 4.4% (41/935) ($p=0.03$).

The incidence of IBR in patients with T2 tumours was 15.5% (9/58) in those aged ≤ 40 years, and 7.1% (18/252) aged > 40 years.

Actuarial breast relapse rates were 7% for T1 tumours and 11% for T2 tumours over 10 years.

IBR and surgical margin status

Incidence of IBR by age and margin status is shown in the following table:

Incidence of IBR by age and surgical margin status		
	Stage T1	
Margin status	Age ≤ 40 years	Age > 40 years
Negative	6/65 (9%)	19/562 (3%)
Close (≤ 3 mm)	2/14 (14%)	3/130 (2%)
Positive	1/8 (12%)	2/139 (2%)
Unspecified	1/17 (6%)	17/174 (10%)
Total ($P=0.03$)	10/104 (9.6%)	41/935 (4.4%)
	Stage T2	
Negative	4/31 (13%)	9/129 (7%)
Close (≤ 3 mm)	3/6 (50%)	3/25 (9%)
Positive	0/8	4/40 (10%)
Unspecified	2/16 (12%)	2/48 (4%)
Total ($P=0.04$)	9/58 (15.5%)	18/252 (7.1%)

A small increase in breast relapse for patients aged ≤ 40 years with close or positive margins for stage T1 tumour types, was found (9% negative; 12-14% positive or close margins). The overall difference for stage T1 tumours between age groups was statistically significant ($p=0.03$).

The increase in breast relapse was larger for stage T2 tumour groups with close margins in women ≤ 40 years (13% negative; 50% close margins), with a small increase in older women. The overall difference for stage T2 tumours between age groups was statistically significant ($p=0.04$).

It should be noted that some of the subgroups for T1 and T2 tumours were very small in the

younger age group, and that no confidence intervals were reported.

IBR and extensive intraductal component (EIC)

There was a large increase of breast relapse for women ≤ 40 years with stage T1 and T2 tumours and EIC. The differences in breast relapse for T1 tumours were statistically significant between age groups, but not for stage T2 tumours.(Table below):

Breast relapse and EIC				
	Stage T1		Stage T2	
EIC	Age ≤ 40 years	Age > years	Age ≤ 40 years	Age > years
Yes	4/24 (17%)	8/159 (5%)	2/8 (25%)	5/48 (10%)
No	6/80 (8%)	33/776 (4%)	7/50 (14%)	13/202 (6%)
	P=0.03		P=0.07	

Boost irradiation

There was no significant difference in breast relapse rates between patients treated with a boost of either electrons or interstitial brachytherapy.

T1 tumours

For patients with T1 lesions and negative margins the boost dose did not affect the relapse rate over a 10 year period (Boost n=66, no boost n=599; P=0.95).

In contrast for patients with either close or positive margins the breast relapse rate was 10% with no boost and 2% with a boost dose of 16Gy over the same period (Boost n= 215, no boost n=6; P=0.04).

(Please note data presented graphically, and the raw data cannot be derived from these).

T2 tumours

For T2 tumours a subgroup of 16 patients with negative margins did not receive a boost, the relapse rate was 12% appearing earlier than those with a boost dose. The difference over 10 years was not significant (No boost n=16, boost n=143; P=0.48).

For T2 tumours and close or positive margins, 5 patients had no boost, two of these relapsed (40%). This compares with a 15% relapse rate in patients receiving a boost dose (No boost n=5; boost n= 81). The difference was significant (p=0.01) although the sample sizes compared were small.

Author conclusions

Surgical excision margins status following adequate doses of radiation therapy was not a predictor of ipsilateral breast relapse. In patients younger than 40 years of age with extensive intraductal component, a somewhat higher breast relapse rate was noted but not enough to preclude breast conservation therapy. A boost of irradiation did not have a significant impact in the incidence of ipsilateral breast relapse in patients with negative margins, but it was of benefit to those with close or positive margins. Close attention to surgical margin status and delivery of higher doses of irradiation to the tumour excision site in patients with close or positive surgical margins will decrease the probability of breast relapses.

General comments –

Although this study appears to be large, following a cohort of more than 1000 patients, some of the subgroups used in the analysis were very small, and this should be considered when interpreting the findings. Univariate analyses were conducted, when multivariate may have been more appropriate, also no confidence intervals were provided for any of the data.

Guidelines

This guideline was also included in the related topic 23a.

Whelan T, Olivotto I, Levine M, Health Canada 's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. (2003) Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update). *CMAJ Canadian Medical Association Journal* **168**, 437-439.

Design: Guideline

(1966-2001)

Level 4

Country: Canada, setting:

Inclusion criteria A literature search was conducted using MEDLINE from 1966 to October 2001 and CANCERLIT from 1983 to September 2001 for a systematic review of English Language articles. A nonsystematic review of the literature was continued to April 2002.

Exclusion criteria Non-English language articles

Population

Interventions Breast radiotherapy after BCS

Outcomes

Local control, survival, quality of life, adverse effects of irradiation and cosmetic results.

Recommendations:

These are listed fully in the Evidence table for topic 23a. The most relevant recommendations for this topic are listed below:

- Additional irradiation to the lumpectomy site (boost irradiation) reduces local recurrence but can be associated with worse cosmesis compared with no boost. A boost following breast irradiation may be considered in women at high risk of local recurrence.
- Physicians should adhere to standard treatment regimens to minimize the adverse effects of breast irradiation.
- When choices are being made between different treatment options, patients must be made aware of the acute and late complications that can result from radiation therapy.

An update search identified a cohort study of the risk of myocardial infarction after radiotherapy (Paszat *et al* 2007) which is relevant to this topic and to the topic of radiotherapy after breast conserving surgery.

Paszat LF, Vallis KA, Benk VM, Groome PA, Mackillop WJ, Wielgosz A. A population-based case-cohort study of the risk of myocardial infarction following radiation therapy for breast cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2007;82(3):294-300.

Design: NRS Restrospective cohort (1982-1988) Level 2+
 Country: Canada, setting: Provincial Cancer Registry
 Aim: To describe the risk of Acute Myocardial Infarction (AMI) after radiation therapy (RT) in a population of women with breast cancer.

Inclusion criteria

Women receiving post-operative RT within 12 months of diagnosis
 Records containing a diagnosis code for ischaemic heart disease (including AMI) from this group of women
 Only AMI cases meeting MONICA criteria were classified as validated AMI (vAMI)
 AMI cases with cause of death as AMI who did not die in hospital, or any episode of hospital care associated with ischaemic heart disease after RT and date of death were classified as dAMI

Exclusion criteria

Right sided data from women with bilateral disease
 Data from subsequent episodes of ipsilateral or contralateral breast cancer

Population n=6680 records

Identification of all exposed AMI cases classified as:
 vAMI n= 121
 dAMI n= 92
 A random sample from the exposed population as a sub-cohort n=619
 vAMI n= 9/619
 dAMI n= 8/619

Interventions

Post-operative RT within 12 months of diagnosis
 There was a large variation in radiation exposure:
 Photon energy cobalt-60 to 6MV
 Dose to breast or chest wall 40-50 Gy
 Daily fractions 2.0 -2.67 Gy
 50% received anterior boost after WBRT – exceptions were those receiving post-mastectomy chest wall irradiation.
 Variations were found in the magnitude of boost dose and volume of target area:
 Boost dose 5 – 20 Gy
 Daily fractions 2.0 – 3.0 Gy
 Anterior boost field volume 25 – 144 cm²

Outcomes

Risk factors for AMI following radiotherapy (only results of multivariate analysis included)
 vAMI and dAMI were mutually exclusive categories.

Follow up Minimum of 13.5 years from date of last RT treatment

Results

Multivariate case-cohort Cox modelling was performed and the results are shown in the following table:

Adjusted case-cohort model of time to dAMI

Variable	Adj vAMI <60 yr HR (95% CI)	Adj vAMI ≥60 yr HR (95% CI)	Adj vAMI HR (95% CI)	Adj dAMI HR (95% CI)
Age at RT	NA	NA	2.32 (1.51-3.58)	7.11 (3.51-14.42)
Smoking history before RT	2.38 (1.21-4.70)	1.54 (0.85-2.78)	1.71 (1.11-2.64)	0.77 (0.41-1.44)
MI history before RT	4.01 (1.26-12.77)	1.67 (0.74-3.78)	2.01 (1.03-3.90)	1.68 (0.82-3.43)

Left breast	0.86 (0.44-1.68)	1.96 (1.09-3.54)	1.42 (0.92-2.17)	1.07 (0.65-1.72)
Daily dose >2.5Gy	0.48 (0.10-2.35)	1.18 (0.55-2.51)	0.97 (0.50-1.90)	1.37 (0.73-2.56)

Effect of age

Only univariate data were available for the effect of age on death by AMI because few events occurred in women < 60 years.

Smoking history and MI history increased the risk of vAMI in both age groups. There was a higher risk of vAMI in women ≥ 60 years with left breast irradiation and a daily dose ≥ 2.5 Gy.

Risk of dAMI or vAMI - all factors

Smoking history, MI history and left breast irradiation increased the risk of dAMI and vAMI in all age groups. The risk of dAMI was greater with a daily dose ≥ 2.5 Gy than that for vAMI (not significant from confidence intervals).

Effect of age and anterior boost field on dAMI and vAMI

The variation in area of the anterior boost field was associated with an increase in vAMI and dAMI in women receiving left-sided RT compared with right-sided RT.

Adjusted HR of time to vAMI from multivariate analysis were:

Age ≥ 60 years HR = 2.65 (95% CI 1.21 – 5.83)

Boost area HR = 1.02 (95% CI 1.00 – 1.03)

Adjusted HR of time to dAMI from multivariate analysis were:

Age ≥ 60 years HR = 1.01 (95% CI 1.01 – 1.03)

Boost area HR = 1.02 (95% CI 1.02 – 1.03)

Risk factors for AMI (increasing age, smoking history, previous MI history) were strongly associated with time to vAMI and time to dAMI. However, anatomic factors such as RT to the left breast and the volume of the boost area are associated with an added risk of AMI.

Author conclusions

The risks of vAMI and dAMI following RT for BrCa are related to anatomic sites of RT (left breast, area of anterior left breast boost field, and anterior IMC field).

General comments –

The rationale and methodology for statistical tests were not reported. P values for HRs were not provided. It was not always clear whether the authors were referring to results from univariate or multivariate analysis.

An update search identified another guideline (Jalali *et al* 2007) which has been included in the following table.

Jalali R, Singh S Budrukkar AN. Techniques of tumour bed boost irradiation in breast conserving therapy: Current evidence and suggested guidelines. <i>Acta Oncol</i> 2007;46(7):879-92.	
Design: Guideline and review Country: India	Level 4
Inclusion criteria Not reported	
Exclusion criteria Not reported	
Population Women with breast cancer	
Interventions Tumour bed boost	
Suggested guidelines <ul style="list-style-type: none">• Radiotherapy boost and whole breast radiotherapy after breast conserving surgery have been shown to improve local control rates in randomized studies• The patient population who would derive most benefit has not been defined, however, younger patients with close or positive margins, EIC, lymphovascular invasion, positive axillary lymph nodes, and negative hormone receptors have been shown to benefit• Ultrasound may be the best option to delineate intraoperative and post-operative brachytherapy boost• CT guided surgical clip placement is the best option for electron boost field delineation• A 2-2.5 Gy boost fractionation schedule to a total of 15-20 Gy is acceptable for local control and late effects on cosmesis• The role of concomitant boost is investigational• Boost dose delivery by photons, electrons or brachytherapy provide equal benefit of local control rates• Electrons and brachytherapy have similar effects on cosmesis. Photons may have adverse effects on underlying structures• The role of Intensity Modulated Radiation Therapy with conformal boost is investigational• Boost volumes should be delineated with caution for optimal cosmetic effects• Telangiectasia is more common in patients receiving brachytherapy	

Ongoing studies

Poortmans P, Collette L, Horiot JC, Van den Bogaert W, Fourquet A, Kuten A, et al. Impact of the boost dose on local control and survival in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10 years results of the randomized EORTC boost trial 22881/10882. *Radiother Oncol* 2006;81:S19.

No details of the abstract provided.

Romestaing P, Lehingue Y, Delaunay D, Carrie C. Role of a 10-Gy boost in the conservation treatment of early breast cancer: results of a randomized clinical trial in Lyon, France [abstract]. *International Journal of Radiation Oncology Biology Physics* 2001;51(3 Suppl 1):3-4.

Results: At 5 years the Kaplan-Meier estimate of local relapse rate was 3.6% in the boost group and 4.5% in the no boost group ($P=0.044$). After adjustment for the main prognostic variables such as the presence of an extensive in situ component in the tumour periphery, maximum diameter of the tumour, degree of histological differentiation, age at inclusion, no free margins, the relative risk was still significantly lower for the boost group (P value not reported). The occurrence of local relapse for 768 patients at 10 years was 26 in the boost group vs. 36 in the control group. However, only 4 patients died of cancer in the control group vs. 10 in the boost group.

Health Economics Summary

The only included study assessing the cost-effectiveness of an additional RT boost after BCS was conducted in USA. Hayman et al (2000) conducted a cost-utility analysis comparing treatment with an electron-beam boost versus treatment without the boost in EBC patients with stage I or II tumours and negative margins, who had undergone BCS in combination with RT. They adapted a previously published Markov model, considering a 10-year time horizon with 1-year cycles. A probabilistic sensitivity analysis using Monte-Carlo simulation was conducted by assigning distributions to the utility scores; deterministic sensitivity analyses were performed as well. Baseline rates were derived from the NSABP B-06 trial, while effectiveness of RT boost was obtained from the only RCT available at the time the study was conducted (which had been conducted in Lyon, France). Utility scores used for the estimation of QALYs were obtained through the standard gamble technique from 97 BC patients; expert judgment was used to estimate utilities of metastatic states (whose rate was the same across groups and therefore did not affect cost-effectiveness). The cost analysis seemed to have been conducted appropriately, although resources used were not reported separately from the unit costs. Overall, the study appeared to have been appropriately conducted, although it presented some minor limitations. The authors concluded that the addition of a RT boost after BCS and RT on EBC patients with stage I and II tumours and negative margins do not seem to be cost-effective, unless the patients place an unexpectedly large utility on small reductions in the likelihood of local recurrence or unless the cost of the RT boost decreases considerably (less than one half its actual USA cost), conditions that do not seem likely to be found in clinical practice. As the authors reported, omitting RT boost among EBC women with negative margins after BCS would lead to very important savings. They recommended to reconsider whether a RT boost should be used on EBC patients (with stage I and II tumours) and negative margins since, as they estimated, dropping the RT boost in USA would lead to an annual savings of approximately \$135 million (i.e. from $\frac{3}{4}$ of 150,000 women diagnosed with BC each year in the USA who would have negative margins).

Although the applicability of the study to the UK context is very limited given potential differences in clinical practice and unit costs, it is important to take into account that this study conducted extensive sensitivity analyses and a probabilistic sensitivity analysis (using Monte Carlo simulation) on the utility scores used to estimate QALYs (which were the parameters influencing more the results obtained). The results of the Monte Carlo simulations showed that the RT boost would be cost-effective in 0.085% of the simulations only. Additionally, deterministic sensitivity analyses showed that the costs of the RT boost should decrease to less than half the current cost, or the decrease in local recurrence should increase from 20% to 63% in order to make the RT boost cost-effective (i.e. less than \$50,000 per QALY) within the USA setting considering women aged 60.

References

Hayman JA, Hillner BE, Harris JR and Weeks JC. Cost-effectiveness of adding an electron-beam boost to tangential radiation therapy in patients with negative margins after conservative surgery for early-stage breast cancer. *Journal of Clinical Oncology* 2000. 18(2): p. 287-295.

Health Economics Evidence Tables

Non-UK Economic Evaluations: full studies

Hayman JA, Hillner BE, Harris JR, Pierce LJ and Weeks JC. Cost-effectiveness of adding an electron-beam boost to tangential radiation therapy in patients with negative margins after conservative surgery for early-stage breast cancer. *Journal of Clinical Oncology*, 2000. 18(2): p. 287-295.

Design:

Type of economic evaluation:

Cost-utility analysis that assessed whether or not the use of an electron-beam boost was cost-effective in EBC patients with negative margins. A previously published Markov model was adapted for the study, considering a 10-year time horizon with 1-year cycles. A probabilistic sensitivity analysis using Monte-Carlo simulation was conducted by assigning distributions to the utility scores. Additionally, deterministic sensitivity analyses were performed. Some assumptions considered were: adjuvant treatment did not depend on whether patients received boost; if local recurrence occurred, patients were treated with mastectomy followed by reconstructive surgery; the addition of the boost had not impact on distant metastasis. The perspective adopted was societal. Future costs and benefits were discounted at a 3% discount rate.

Clinical effectiveness:

Baseline rates were derived from the NSABP B-06 trial, while effectiveness of RT boost was obtained from the only available RCT (conducted in Lyon, France).

Utility scores used for the estimation of QALYs were obtained through the standard gamble technique from 97 BC patients; expert judgment was used to estimate utilities of metastatic states (whose rate was the same across groups and therefore had not impact on cost-effectiveness).

Cost estimation:

The cost categories included were: direct medical costs (i.e. facility and professional costs), time and transportation. The sources of the cost data were reported and seemed to be appropriate for the study question (i.e. USA sources). The cost analysis seemed to have been conducted appropriately, although resources used were not reported separately from the unit costs.

Country: USA, **setting:** Societal

Inclusion criteria

Patients diagnosed with EBC (stage I or II) who had undergone BCS and axillary dissection and had completed 5 weeks of daily treatment with tangential radiation therapy to the entire breast.

Exclusion criteria

None stated

Population

A hypothetical cohort

Interventions

Treatment with an electron-beam boost versus treatment without it after BCS.

Results –

OUTCOME OF INTEREST	With electron-beam boost	Without electron-beam boost
Costs (\$)	32,192	21,184
QALYs	7.1640	7.1575
ICER (\$ per QALY)	308,923	-

The results of threshold analyses showed that the relative reduction in local recurrences with the beam boost would need to increase from 20% to 63% to make the boost cost-effective at a threshold of \$50,000 per additional QALY gained (as usually considered in USA), which is unlikely to happen in clinical practice. Additionally, the cost of the boost should be reduced from \$2,400 to \$754 (i.e. the equivalent of 2 boost treatments) to make the boost cost-effective.

The results of the base-case analysis were very sensible to variations in the utility scores: if the utility of local recurrence increased from 0.92 to 0.925, the ICER would drop under \$50,000 per QALY. The Monte Carlo simulations resulted in a mean ICER of \$70,859 per QALY (95% CI: \$53,141 to \$105,182); the ICER was under \$50,000 just in 0.85% of the simulations.

Authors' conclusions –

The authors concluded that the use of a RT boost on EBC patients (with stage I and II tumours) and negative margins should be reconsidered since this intervention would not be cost-effective unless the patients place an unexpectedly large utility value on small reductions on the local recurrence rate or the cost of the boost diminishes considerably, both conditions unlikely to be met in clinical practice. The authors estimated that dropping the RT boost in USA would lead to an annual savings of approximately \$135 million (i.e. from ³/₄ of 150,000 women diagnosed with BC each year in the USA who would have negative margins).

General comments –

The study appeared to have been appropriately conducted, overall. The choice of clinical studies to provide data to populate the model seemed to be non-systematic and arbitrary, although the authors reported some justification for the studies chosen: the RCT used in the model for baseline recurrence rates had used RT according to USA clinical practice, while the French study was the only available assessing the effectiveness of a RT boost, according to the authors.

6.6 What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla?

Short Summary

Since there were few studies that directly addressed this question the available literature was grouped into those studies comparing surgery and regional node irradiation with mastectomy and axillary dissection or mastectomy only (Fisher *et al* 2002, Overgaard *et al* 1999, Ragaz *et al* 2005, Wallgren *et al* 1986); studies comparing Breast Conserving Surgery (BCS) with or without axillary dissection or axillary radiotherapy (Louis-Sylvestre *et al* 2004, Pejavar *et al* 2006, Veronesi *et al* 2005); studies applying radiation to the internal mammary lymph nodes (Arriagada *et al* 1988, Grabenbauer 2004, Kaija & Maunu 1995, Obedian and Haffty 1999, Vinod and Pendlebury 1999); one retrospective cohort of patients receiving breast conserving surgery with axillary dissection and no regional node irradiation (Livi *et al* 2006); a retrospective study of predictors of regional nodal failure where only a small proportion of patients received regional radiotherapy (Grills *et al* 2003); and two retrospective studies of node ratios as prognostic factors (Fortin *et al* 2006, Tai *et al* 2007).

The evidence from four strong RCTs delivering regional nodal irradiation (axilla, supraclavicular and internal mammary lymph nodes) after mastectomy found a reduction in local and regional recurrence rates in the RT group in both lymph node-positive and negative women. An exception occurred in one trial of lymph node-positive women where no difference in recurrence rates was found in the RT group (Fisher *et al* 2002). Overall survival was improved in the RT arm from two of these trials (Overgaard *et al* 1999, Ragaz *et al* 2005), however no difference in overall survival was reported in the remaining two trials (Fisher *et al* 2002, Wallgren *et al* 1986).

The evidence from two well conducted RCTs including women with clinically negative lymph nodes in which the interventions were BCS and breast radiotherapy with or without radiotherapy to the axilla (Veronesi *et al* 2005), or BCS and breast radiotherapy followed by axillary dissection or axillary radiotherapy (Louis-Sylvestre *et al* 2004) reported no difference between arms for disease free survival. The incidence of axillary metastases was not significantly different in the study by Veronesi *et al* (2005), but was significantly increased in the axillary radiotherapy arm compared to axillary dissection in the trial by Louis-Sylvestre *et al* (2004). Evidence comparing axillary dissection and axillary radiotherapy after BCS and radiotherapy to the breast in node positive and negative women found no difference between groups in lymph node recurrence (Pejavar *et al* 2006).

Radiation to the internal mammary chain (IMC) lymph nodes was assessed in one RCT (Kaija and Maunu 1995) after BCS with axillary dissection and breast radiotherapy. No significant differences in local and distant relapse rates were reported, however, the follow-up time was short (2.7 years). A systematic review also suggested that the short observation time was not sufficient to allow any conclusions as to the value of IMC irradiation (Vinod and Pendlebury 1999).

Evidence from observational studies reported conflicting findings for distant metastases and survival with or without IMC node irradiation. Arriagada *et al* (1988) found a benefit of IMC irradiation in these outcomes to patients with medial tumours, whilst Obedian & Haffty (1999) found no difference regardless of tumour location. In another cohort of patients (Grabenbauer

2004) overall survival and systemic disease free survival were comparable when patients were treated with radiotherapy to the IMN for medial tumours, but radiotherapy was omitted for lateral tumours.

A large cohort study that did not treat the regional lymph nodes of patients with radiotherapy (Livi *et al* 2006) assessed locoregional and node relapses (axilla, IMC or supraclavicular fossa) over a median of 8 years. Most patients were lymph node-negative at diagnosis. Multivariate analyses showed that node relapse were more likely in women with more than three positive lymph nodes, pathological T2 tumours and angiolymphatic invasion. Locoregional recurrences were also associated with these characteristics as well as younger age groups.

A further observational study determined the incidence and risk factors for regional nodal failure in a cohort of patients receiving BCS, axillary dissection and radiotherapy to the breast alone, a proportion of these (13%) also received radiotherapy to the regional lymph nodes (Grills *et al* 2003). A subgroup analysis found that axillary failure was significantly higher in patients with 4 or more positive lymph nodes who did not receive regional node irradiation (RNI); however supraclavicular failure was significantly higher in patients with 1-3 positive nodes who did receive RNI. However, rates of failure for lymph node-negative and all lymph node-positive patients were not significantly different between those receiving RNI and no RNI. Overall survival and distant metastases free survival were lowest in patients with positive nodes who received RNI compared with those not receiving RNI. Node-negative patients receiving RNI also had lower overall survival and distant metastases free survival rates. A multivariate analysis of all patients found that the only significant independent predictor of RNF was the maximal size of the nodal metastasis.

Two observational studies assessed the percentage (Fortin *et al* 2006) or ratio (Tai *et al* 2007) of involved nodes. Fortin *et al* (2006) assessed the effects on regional node failure, and Tai *et al* (2007) assessed the effects on survival. Regional radiotherapy was found to be more effective in patients with medium to high node ratios than low node ratios in both studies.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
Patients with operable invasive breast cancer who have received surgery (mastectomy or breast conserving surgery) – need	RT to any of the following sites: <ul style="list-style-type: none"> • supraclavicular fossa • internal mammary chain • Axilla – but they need to be considered separately, also dependent on what axillary surgery has been done i.e. 	Surgery alone (mastectomy or breast conserving surgery)	<ul style="list-style-type: none"> • Disease Free Survival (DFS) each site • Overall Survival (OS) • Recurrence • Quality of life • Patient acceptability • Cosmesis

to avoid palliative surgery	clearance or less than a clearance. For im nodes need to know whether sentinel node positive as some techniques for snb do show up im nodes		
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The search strategy developed from this PICO table and used to search the literature for this question can be found in Appendix A

Evidence Summary

The literature search identified papers published between 1978 and 2007. One systematic review included RCTs and non-randomized studies (Vinod & Pendlebury 1999). Three high quality RCTs (1++) compared regional node irradiation with no irradiation to the regional nodes (Fisher *et al* 2002, Ragaz *et al* 2005, Overgaard *et al* 1999). Two lower quality (1+) smaller RCTs (Louis-Sylvestre *et al* 2004, Wallgren *et al* 1986) compared surgery with radiotherapy (RT) to the breast and regional lymph nodes. Another two lower quality (1+) RCTs compared axillary RT with surgery alone (Veronesi *et al* 2005), or surgery with axillary dissection with or without RT to the Internal Mammary Node Chain [IMN or IMC] (Kaija & Maunu 1995). Seven non-randomized studies, four guidelines and three expert reviews were also included.

There were variations in treatment options and heterogeneity of the patient population which limited the applicability of the findings from these studies. The non-randomised studies were considerably heterogeneous and mainly retrospective cohort designs.

RCT evidence was consistent in reporting that regional irradiation reduced the local recurrence rate. One RCT found that isolated axillary recurrences were lower after AXD than axillary RT (Louis-Sylvestre *et al* 2004). Overall survival was less consistent between studies with some trials reporting improved survival after regional RT, and others reporting no difference between the RT and no RT groups.

Regional node irradiation (axilla, supraclavicular and IMC nodes)

Level 1++

Two strong RCTs compared radical or modified radical mastectomy and axillary dissection with or without RT to the regional nodes (Overgaard *et al* 1999, Ragaz *et al* 2005). Both groups were given chemotherapy in the Canadian trial (Ragaz *et al*), and both groups were given tamoxifen in the Swedish trial (Overgaard *et al*). Both these trials enrolled high risk node positive patients.

Local Recurrence

Locoregional recurrences were lower in the RT group for both RCTs

Ragaz *et al* 2005 28% vs. 10% (CT vs. CT+RT) for any recurrence before systemic relapse

Overgaard *et al* 1999 29% vs. 4% p <0.001 (Tam vs. Tam + RT) RR 0.64 (0.54-0.77)

favouring RT for any recurrence at 2 years.

When recurrences by node status were compared in the study by Overgaard *et al*, any recurrence was twice as likely in N>3 patients than N0-3 patients at 2 years:
N0-3 vs N>3: RR 2.18 (95% CI 1.80-2.64) $p<0.001$

Survival free of isolated locoregional recurrence in the study by Ragaz *et al* (2005) was significantly longer in the RT group (90% with RT and chemotherapy vs. 74% with chemotherapy alone) RR 0.36 (0.18-0.71) $p=0.002$.

Overall survival

All survival outcomes were improved for the RT group compared to chemotherapy alone at 20 years in the Canadian trial (Ragaz *et al* 2005). (Only overall survival is reported here, the other outcomes are reported in the table at the end of this summary).

Ragaz *et al* (2005) Overall survival 37% vs 47% (CT vs CT+RT) RR 0.73 (95% CI 0.55 - 0.98) $P = 0.03$.

There were no significant differences in survival outcomes when comparing node status (N1-3 or N≥4) although survival was improved in the RT group.

Overall Survival in the Swedish trial was 36% (Tam vs. tam+RT) [95% CI 33-40] vs. 45% [95% CI 41-49] providing a 9% absolute benefit for RT. RR 0.68 (0.55-0.83) favouring RT for survival to 4 years. Death after 4 years was almost twice as likely in patients with N>3 positive nodes than N0-3 nodes: RR 1.97 (95% CI 1.58-2.45) $p<0.001$.

A third strong three arm RCT by Fisher *et al* (2002) reported findings for node negative and node positive patients. Comparisons were made between all 3 arms (RM vs.TM no AXD vs.TM+RT) for node negative women, and between 2 arms (RM vs.TM+RT) for node positive women.

Local recurrence

Node negative

There was a statistically significant difference between the 3 groups of women with negative nodes for the cumulative incidence of local or regional recurrence ($p=0.002$ for 3 way comparison). The rate was lowest in the total mastectomy with RT group, indicating a significant benefit of RT in reducing local recurrence. In contrast there were no statistically significant differences between the 3 groups in the cumulative incidence of distant recurrence as a first event ($p=0.61$).

Node positive

Among women with positive nodes, there were no significant differences between the RM and TM + RT groups for cumulative incidence of local or regional recurrences ($p=0.67$). Similarly there were no significant differences between the RM and TM + RT groups for the incidence of regional recurrence or the incidence of distant recurrence ($p=0.44$). However there was a significant reduction in the incidence of local recurrence after radiation therapy.

Distant-Disease-free Survival and Overall Survival

There were no significant differences in distant-disease-free survival among the groups of women with negative nodes at 25 years ($p = 0.63$ for the three-way comparison). Among women with positive nodes, there was no significant difference in distant-disease-free survival between the radical mastectomy and total mastectomy plus radiation therapy groups

There were no significant differences in overall survival among the groups of women with negative nodes at 25 years ($p=0.68$ for the three-way comparison). In women with positive nodes there was also no significant difference in overall survival between the radical mastectomy and total mastectomy plus radiation therapy groups ($p=0.49$).

The findings validate earlier results showing no advantage from radical mastectomy and fail to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy.

Level 1+

An earlier RCT by Wallgren *et al* (1986) compared MRM alone with MRM and pre- or postoperative RT to the breast and regional nodes.

Local recurrence

There was a significant reduction in the cumulative incidence of locoregional disease in node negative patients at 11 years after MRM with postoperative RT compared to surgery alone (2.5% vs. 20%; $p<0.001$). The corresponding cumulative incidences in patients with lymph node metastases were 13% after MRM+ RT and 45% for surgery alone ($p<0.001$).

Distant metastases (cumulative incidence)

Distant metastases were reduced in node positive patients treated with surgery and postoperative RT compared to no RT at 11 years (47% vs. 60% $p=0.01$). There was no difference in cumulative incidence of distant metastases in node negative patients (approx 20% at 11 years, $p=0.82$).

Breast cancer deaths

The cumulative incidence of breast cancer deaths for node negative patients was not statistically significantly different between postoperative RT and surgery alone (approx 7% from survival curve, $p=0.78$). The survival gain for node positive patients in the postoperative RT group (54%) at 8 years vs. 47% in the surgery only group was also not statistically significant ($p=0.09$).

A subgroup analysis of the ratio of death rates was generally lower for the irradiated patients than the surgery only group but none of the factors compared reached statistical significance. Included in this comparison were bilateral and ipsilateral irradiation to the IMC nodes, and site of tumour (lateral, medial or central).

BCS with or without axillary dissection or axillary RT

Level 1+

Two RCTs assessed the effects of axillary dissection or axillary RT in women with N0 nodes. Veronesi *et al* (2005) compared BCS and RT to the breast + boost with or without axillary only RT. These women had tumours <1.2cm in diameter.

Axillary metastases

There were 4 clinically overt axillary metastases, one in the RT group and 3 in the no RT group:

Overall incidence 0.7% (95% CI 0.1-2.0%).

Disease free survival at 5 years (includes any event)

No difference between arms 96% (95%CI 94.1-97.9)
A hazard ratio of 1.59 (0.65-3.89) was reported (no direction of effect reported).

The authors concluded that the rate of axillary metastases in women treated by breast conservation without any axillary treatment was much lower than expected, leading to the hypothesis that occult axillary metastases might not progress to overt clinical metastases, and secondly, that occult metastases can be kept under control by axillary RT. (It should be noted that these participants were N0 with tumours <1.2cm).

Louis-Sylvestre *et al* (2004) compared BCS and breast RT with either axillary dissection or axillary RT.

Isolated axillary recurrences

These were lower in the group with axillary dissection (1%) than in the group with axillary RT (3%) at 15 years (RR 0.33 (95% CI, 0.11 to 0.98) $P = 0.04$).

Rates of overall survival, DFS, ipsilateral local recurrences and distant metastases or supraclavicular node involvement were not statistically different between groups. The authors concluded that at 15-year follow-up axillary dissection and axillary radiotherapy provided identical survival, although local control was better with axillary dissection.

Level 3

A NRS by Pejavar *et al* (2006) followed women treated with BCS followed by RT to the breast and a tumour bed boost. The 69% of patients receiving axillary dissection (AXD) were also irradiated in the supraclavicular nodes if node positive (26%). IMC irradiation was individualized in these patients. The 31% who received axillary RT were also irradiated in the supraclavicular nodes, again IMC irradiation was individualized.

There were no significant differences in the regional nodal control rates when analyzed as a function of regional treatment (AXD vs. regional nodal radiation) at 5 and 10 years:

Node recurrence free rates:

	5 years	10 years
RT with AXD	98.3%	97.4%
RT with no AXD	98.5%	97.9%

Possible prognostic factors for nodal recurrence were evaluated including age, race, stage, AXD status, pathologic lymph node status, chemotherapy, hormonal therapy, and oestrogen /progesterone receptor status. In a multivariate analysis age, race, and pathological nodal status remained independent significant predictors of nodal failure.

Age <35 yrs $p < 0.0001$

N+ve $p < 0.0001$

Non-Caucasian $p = 0.003$

The authors concluded that in patients undergoing BCS+RT, both regional nodal irradiation and AXD (including SNB) resulted in equally high rates of regional nodal control.

Radiation to the Internal Mammary Chain Nodes (IMC or IMN)

Level 1+

One RCT (Kaija & Maunu 1995) investigated patients with Stage I-II invasive breast cancer who were treated with BCS (segmental resection and axillary dissection) followed by radiotherapy. Randomisation was to a target volume of the ipsilateral parasternal area including the internal mammary chain (IMC-RT) or omitting the IMC (no IMC-RT). There was no significant difference in local and distant relapse rates between treatment groups after a median follow-up time of 2.7 years. The authors concluded that the short observation time in the present study did not allow any conclusions as to the comparative value of internal mammary chain irradiation in preventing breast cancer recurrences.

One systematic review of 6 RCTs published before 1998 (Vinod & Pendlebury 1999) examined the effects of IMC irradiation in breast cancer. The conclusion was that the only RCT evidence from one small trial (Kaija & Maunu 1995) found no difference between groups randomized to receive (Internal Mammary Node Chain) IMC irradiation or no IMC irradiation in relapse rates at 2 years. It was too early to assess the effects on local recurrences or survival. They also reported that the survival advantage in medial or central and axillary node-positive tumours from IMC irradiation, is not supported by this early data (2.7 years) from a single small RCT.

The remaining 5 trials in this review administered regional irradiation to the axilla, supraclavicular fossa and IMC. The chest wall was also irradiated in some trials. One randomized trial of patients with high risk operable breast cancer showed a survival advantage to post-mastectomy irradiation, but the contribution of IMC irradiation could not be separated out. The authors suggest there is no advantage to elective IMC irradiation. The only indication would be for palliative management of positive IMC nodes.

Level 3

Arriagada *et al* (1988)

In a large retrospective cohort of N+ patients the long term effects of treatment of the IMC by IMC dissection (IMCD) or RT were assessed for the risk of death or metastasis. For a total of 1195 patients there was a beneficial effect of treatment of the internal mammary chain (IMC) [vs. no treatment to the IMC] on the risks of death (RR 1.6 P=0.01) and distant metastasis (RR 1.5 P=0.05) in a subgroup of patients with medial tumours. No statistically significant differences were found for mortality and metastases for all patients, or for a subgroup of patients with lateral tumours. It should be noted that there were many changes in treatment protocols over the course of this study.

Obedian & Haffty (1999)

In a cohort of 984 patients treated with BCS and RT to the breast with and without RT to the IMC nodes found no significant differences between the IMC+RT and IMC-noRT groups for overall survival (72% IMC+RT vs. 84% IMC-noRT, p = NS) or distant metastasis-free survival (77% IMC+RT vs. 87% IMC-noRT, p = NS). A further subset analysis of node positive patients showed no benefit in the IMC+RT group regardless of age, number of nodes, location (medial vs. lateral or right vs. left), or type of irradiation (deep tangent vs. separate field). The findings for medial tumours contradict the earlier findings of the NRS by Arriagada *et al* (1988).

Level 4

Grabenbauer 2004

An overview of four selected non-randomised studies also found that overall survival, breast cancer specific survival and disease-free survival were significantly improved in patients with lateral than medial tumours. The data from a cohort of patients at the centre where this paper originated found that overall survival and systemic disease free survival were comparable when patients were treated with RT to the IMN for medial tumours (using a mixed beam to the breast and IMN), but RT was omitted for lateral tumours (RT to breast only):

Kaplan-Meier curves for overall survival were 79.1% and 64% at 5 and 10 years for medial tumours (n=330) with RT to the IMN, and 76.2% and 60.3% for lateral tumours (n=492) (p=0.2) with no IMN irradiation.

Systemic Disease-Free Survival from Kaplan-Meier curves were 72.6% and 70.1% at 5 and 10 years for medial tumours (n=330) with RT to the IMN, and 72.9% and 65.5% for lateral tumours (n=492) (p=0.3) with no IMN irradiation.

No node irradiation Level 3

In a large cohort study by Livi *et al* (2006) all patients received BCS with axillary dissection and breast RT. Locoregional recurrences occurred in 224/4185 patients (5.3%). Sites of recurrence were the breast (3.9%), axilla (0.3%), supraclavicular area (0.8%), and IMC (0.3%).

A multivariate analysis for locoregional recurrence in the breast, supraclavicular, axillary and internal mammary nodes found that Grade 3 tumour (p=0.01), age at presentation (p=0.001), more than three positive lymph nodes (p=0.004), pT2 (p=0.001) and angiolymphatic invasion (p=0.02) were statistically significant parameters.

A multivariate analysis for Node Relapse (NR) found pT2 (p=0.02), angiolymphatic invasion (p=0.002) and more than three positive lymph nodes (p=0.001) were statistically significant.

Limited node irradiation Level 3

A NRS (Grills *et al* 2003) of mainly N0 patients given BCS and axillary dissection, then RT to the breast alone (87%) or RT to the breast and regional nodes (13%) assessed predictors of Regional Nodal Failure (RNF) and conducted a series of complex analyses.

Regional nodal failure with and without Regional Nodal Irradiation (RNI)

10 year actuarial failure rates in the axilla were significant in patients with ≥ 4 positive nodes only (0% with RNI, 5% without RNI; p=0.027). For supraclavicular fossa failure a significant difference was reported in patients with 1-3 positive nodes only (8% with RNI, <1% without RNI; p=0.004). No statistically significant differences were reported between patients receiving RNI and no RNI in patients with no positive nodes (N0), unknown node status (Nx) or all N+ patients. A multivariate analysis of all patients found that the only significant independent predictor of RNF was the maximal size of the nodal metastasis (p = 0.013).

Survival with and without Regional Nodal Irradiation

An analysis by node status found that node-negative and patients with 1–3 positive nodes receiving RNI had statistically significant lower survival rates. NX patients and those with ≥ 4 positive nodes receiving RNI had similar survival rates to patients not treated with RNI. The number of lymph nodes excised also had an impact on overall survival, with 10-year survival rates of 33%, 65%, and 69% in patients with < 6 , 6-10, and > 10 nodes excised, respectively ($P = 0.05$).

Node ratios

Level 3

Two NRS looked at the percentage or ratio of involved nodes on regional node failure and survival.

Fortin *et al* (2006) assessed whether the percentage of positive nodes could be used to select patients for regional RT. Amongst patients not receiving regional radiotherapy, the percentage of involved nodes was significantly associated with axillary failure. Ten-year axillary control rates were 97% and 91% when the percentage of involved nodes was $< 50\%$ and $\geq 50\%$, respectively ($p = 0.007$).

Regional radiotherapy was significantly associated with a decrease in overall regional failure (axillary and/or supraclavicular), regardless of the percentage of involved nodes when compared with no regional radiotherapy. However, regional radiotherapy reduced the axillary failure rate (2% vs. 9%, $p = 0.007$) only when more than a specific percentage of nodes was involved ($\geq 40\%$ if N1-3 and $\geq 50\%$ if $N > 3$ nodes).

The authors concluded that the percentage of involved nodes should be taken into consideration in selecting patients for regional radiotherapy. Irradiation of the axilla should be reserved for patients with a specific ratio of: more than 40% involved nodes if N1-3 positive, and 50% or more involved nodes if N3+ positive nodes.

The second NRS by Tai *et al* (2007) examined the node ratio in relation to supraclavicular and axillary RT (SART). The NR correlated significantly with the primary tumour size, clinical stage group, pathological stage group and the risk of any first recurrence. For a low NR, the 10-year overall survival rate with and without SART was 57% and 58% ($p = 0.18$), and the cause-specific survival rate was 68% and 71% ($p = 0.32$), respectively. For a medium NR, the 10-year overall survival rate with and without SART was 48% and 34% ($p = 0.007$), and the cause-specific survival rate was 57% and 43% ($p = 0.002$), respectively. For a high NR, the 10-year overall survival rate with and without SART was 19% and 10% ($p = 0.005$), and the cause-specific survival rate was 26% and 14% ($p = 0.005$), respectively. The authors concluded that Node Ratio is a useful prognostic factor, and the study demonstrates that for patients with 10 or more nodes resected, regional RT significantly improves survival for the MNR and HNR groups, but not for the LNR group.

The node ratios calculated in these two studies were essentially measuring the same parameter. Fortin *et al* (2006) focussed on the selection of patients and node failure, whilst Tai *et al* (2007) examined the effects on survival. Regional radiotherapy was found to be more effective in patients with medium to high node ratios than low node ratios in both studies.

Study	Design	Tumour / patient characteristics	Intervention comparators	Outcome
Veronesi <i>et al</i>	RCT	N0 (not clinically)	BCS +/- axillary RT	Axillary metastases:

2005 1+	N=435 Median 5 yr	palpable) Tumours <1.2cm		No difference between arms N=4 (0.7%) 95% CI 0.1-2.0% 5 year DFS: No difference between arms 96% (95%CI 94.1-97.9) Hazard ratio: 1.59 (0.65-3.89)
Kaija & Maunu 1995 1+	RCT N=266 2.7 yr	Stage I-II N0 87% N positive 13%	BCS and axillary dissection, breast RT +/- IMC RT	No significant difference in local and distant relapse rates between treatment groups at 2.7 years
Wallgren <i>et al</i> 1986 1+	RCT N=960 11 yr	Stage I-III N0-N1	Modified Radical Mastectomy Three groups: Preoperative RT Postoperative RT Surgery alone RT to breast, chest wall, supraclavicular, axilla and IMC	Recurrence rate RT vs surgery: 0.65 (p<0.001) Sites of recurrence: Chest wall + nodes RT 46(7%) vs. no RT 84 (26%) p<0.001 All recurrences RT 199 (31.1%) vs. no RT 135 (42.1%) Survival No difference between groups for breast cancer deaths or all cause mortality at 8 years.
Louis-Sylvestre 2004 1+	RCT N=658 15 yr	N0 (No clinically involved lymph nodes) M0 Tumour size: 19% ≤1cm. 48% 1-2cm. 33% > 2cm.	BCS and breast RT + axillary dissection or axillary RT All had boost After axillary dissection included RT to IMC and supraclavicular nodes in patients with nodal metastases. In the axillary RT group the IMC were also irradiated.	Isolated axillary recurrences were lower in the group with axillary dissection (1%) than in the group with axillary RT (3%) at 15 years. RR 0.33 (95% CI, 0.11 to 0.98) <i>P</i> = 0.04 Rates of overall survival, DFS, ipsilateral local recurrences and distant metastases or supraclavicular node involvement were not statistically different between groups.
Fisher <i>et al</i> 2002 1++	RCT N=1765 25 yr	N0 (n=1079) N +ve (n=586) Tumour size 3.7cm +/- 2.0cm	3 groups: Radical Mastectomy (RM) Total Mastectomy without axillary dissection (TM) TM+RT RT delivered to breast, supraclavicular nodes, IMC. Women with positive nodes also received a boost dose to chest wall.	Cumulative incidence of local or regional recurrence (<i>p</i> =0.002 for 3 way comparison) in N0. Rate lowest in TM + RT group. Node positive- no significant difference between TM+RT and RM groups. Distant-Disease free Survival No significant differences between treatment groups for women with negative nodes or positive nodes. Overall survival No significant differences between treatment groups for women with negative nodes or positive nodes.
Ragaz <i>et al</i> 2005 1++	RCT N=318	Premenopausal N positive (pathological)	Modified radical mastectomy + Level I and II axillary dissection +/- RT to chest wall, regional lymph nodes including bilateral IMC. Both groups had chemotherapy (CT)	Isolated locoregional disease was lower in the RT group at 20 years 18% vs. 7% (CT vs. CT+RT) Any locoregional disease 28% vs. 10% (CT vs. CT+RT) Survival free of isolated regional disease 74% vs 90% (CT vs CT+RT) RR, 0.36; 95% CI, 0.18 to 0.71; <i>P</i> = 0.002 Survival free of regional disease at any time 61% vs 87% (CT vs. CT+RT) RR= 0.32 (95% CI, 0.18 to 0.57; <i>P</i> < 0.001) Event free survival higher in RT group 25% vs 35% (CT vs CT+RT) RR, 0.70; 95% CI, 0.54 to 0.92; <i>P</i> = 0.009 Breast cancer free survival higher in RT group 30% vs 48% (CT vs CT+RT) RR, 0.63; 95% CI, 0.47 to 0.83; <i>P</i> = 0.001 Systemic breast cancer free survival higher in RT group 31% vs 48% (CT vs

				<p>CT+RT) RR, 0.66; 95% CI, 0.49 to 0.88; $P = 0.004$ Breast cancer specific survival higher in RT group 38% vs 53% (CT vs CT+RT) RR, 0.67; 95% CI, 0.49 to 0.90; $P = 0.008$ Overall survival higher in RT group 37% vs 47% (CT vs CT+RT) RR, 0.73; 95% CI, 0.55 to 0.98; $P = 0.03$ There was no significant difference between N1-3 and N4+ patients for any of these outcomes.</p>
Overgaard <i>et al</i> 1999 1++	RCT N=1375	Postmenopausal Stage I 24% Stage II 44% Stage III 16% N0 10% N1-3 58% N>3 33% Tumour size <2.1cm 38% 2.1-5.0cm 49% >5.0cm 12%	Total mastectomy with axillary-node dissection (Level I-II). RT to chest wall, mid axilla (supraclavicular, infraclavicular and axilla) and bilateral IMC Comparison group was tamoxifen alone with no RT.	<p>Any recurrence after 2 yrs (n=879) N0-3 vs N>3 RR 2.18 (95% CI 1.80-2.64) $p<0.001$</p> <p>Tam alone vs RT+ Tam RR 0.64 (95% CI 0.54-0.77) $p<0.001$</p> <p>Death after 4 years (n=877) N0-3 vs N>3 RR 1.97 (95% CI 1.58-2.45) $p<0.001$</p> <p>Tam alone vs RT+ Tam RR 0.68 (95% CI 0.55-0.83) $p<0.001$</p>
NRS				
Livi <i>et al</i> 2006	NRS N=4185	T1-T2 N0 69% N1-3 20% N>3 9%	Wide excision or Quadrantectomy and Axillary dissection. RT to whole breast with tangential fields, then tumour bed boost. No RT to nodes.	Multivariate analysis for any node relapse Reference N0 N1-3 HR 1.7 (95% CI 0.8-3.2) $p=0.11$ N >3 HR 4.8 (95% CI 2.5-9.1) $p<0.001$ Ref pT1 pT2 HR 1.8 (95% CI 1.07-3.1) $p=0.002$
Fortin <i>et al</i> 2006	NRS N=1372	T1 50% T2 49% N1-3 67% N>3 33%	BCS with RT to the breast. 34% of patients received regional RT to the axilla and supraclavicular nodes.	For all N+ patients % of +ve nodes (HR 3.6 $p=0.02$) and local failure (HR 3.1 $p=0.04$) were associated with axillary failure .
Pejavar <i>et al</i> 2006	NRS N=1920	T1 80% T2 20% N0 74% N +ve 26% (for node status n=1330)	BCS with breast irradiation and boost. Axillary dissection in 1330 patients. For patients with AXD and node +ve supraclavicular fossa also irradiated and some had IMC irradiation. If no AXD then supraclavicular and axillary nodes irradiated and IMC in some.	<p>Node recurrence free rates: RT + AXD 10yr 97.4% RT no AXD 10 yr 97.9%</p> <p>Multivariate analysis significant predictors of node recurrence: Age <35 yrs $p<0.0001$ N+ve $p<0.0001$ Non-Caucasian $p=0.003$</p>
Tai <i>et al</i> 2007	NRS N=1255	T1 40% T2 43% T3 8% T4 7% N1 96% N2 3% N3 <1%	BCS or Mastectomy. Different combinations of RT to breast or chest wall, supraclavicular fossa, axilla, and/or internal mammary chain.	<p>Prognostic factors for OS: Supraclavicular and axillary RT $p<0.0001$ Age $p<0.0001$ Pathological stage $p=0.0004$ Clinical stage $p=0.01$ Node Ratio $p=0.02$</p> <p>Prognostic factors for Cause Specific Survival: Supraclavicular and axillary RT $p<0.0001$ Pathological stage $p=0.0009$ Clinical stage $p=0.01$ Node Ratio $p=0.02$ Performance status $p=0.03$</p>
Grills <i>et al</i> 2003	NRS N=1500	Tumour size only reported for node positive patients N0 72% N1-3 22% N4+ 5%	BCS and axillary dissection in 94% RT to breast alone 87% RT to breast and regional nodes 13%	Regional node failure A multiple regression analysis Regional Node Irradiation was the only significant independent factor predicting a reduced rate of RNF ($p = 0.03$, hazard ratio 0.046). The only significant predictor of RNF was the maximal size of the nodal metastasis.

Obedian & Haffty 1999	NRS N=984	T1 73% T2 26% T3 1% N0 42% N1-3 12% N>4 6%	BCS +/- AXD RT to breast (40% had no AXD) Node +ve had additional supraclavicular RT +/- IMC nodes	No significant differences between the IMC+RT and IMC-noRT group at 10 years: OS 72% vs. 84% NS DMFS 77% vs. 87% NS Significantly higher BRFS rates at 10 years in IMC-noRT than IMC+RT- group (84% IMC-noRT vs. 94% IMC+RT $p<0.001$) No significant differences between the IMC+RT and IMC-noRT groups at 10 years for OS, BRFS, DMFS
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Veronesi, U., Orecchia, R., Zurrada, S., Galimberti, V., Luini, A., Veronesi, P., Gatti, G., D'Aiuto, G., Cataliotti, L., Paolucci, R., Piccolo, P., Massaioli, N., Sismondi, P., Rulli, A., Lo, S. F., Recalcati, A., Terribile, D., Acerbi, A., Rotmensz, N., & Maisonneuve, P. 2005, "Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy", *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.*, vol. 16, no. 3, pp. 383-388.

Vicini, F. A., Horwitz, E. M., Lacerna, M. D., Brown, D. M., White, J., Dmuchowski, C. F., Kini, V. R., & Martinez, A. 1997, "The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy", *International Journal of Radiation Oncology Biology Physics*, vol. 39, no. 5, pp. 1069-1076. (Abstract only).

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Evidence table

Systematic review of RCTs

Vinod, S. K. & Pendlebury, S. C. 1999, "Review of internal mammary chain irradiation in breast cancer", <i>Breast</i> , vol. 8, no. 5, pp. 245-250.	
Design: Systematic review Country: Australia Aim: To assess the effectiveness of and indications for irradiation of the internal mammary chain (IMC) in the treatment of breast cancer through a review of the literature.	Level 1+
Inclusion criteria Literature search 1966-1998 of the MEDLINE database for English Language articles and a search of reference lists of identified papers, for those assessing the effect of internal mammary chain irradiation in operable breast cancer.	
Exclusion criteria	
Population	
Interventions The effectiveness of IMC irradiation in early stage and locally advanced breast cancer. Irradiation of the axilla, chest wall or breast was also included and taken into consideration. Systemic therapy was not accounted for.	
Outcomes Local control Survival	
Follow up -	
Results	
<i>Methods</i> In most studies the effect of IMC irradiation alone could not be separated from supraclavicular fossa irradiation as the two sites were treated together. Irradiation of the axilla, chest wall or breast was also taken into account. The grading of studies was: Level I Systematic reviews of RCTs Level II At least one RCT Level III Controlled trial with no randomization, cohort, case control studies or multiple time series with and without intervention. Level IV Expert opinion This system differs from NICE grading where Level 1 includes SRs of RCTs and single RCTs.	
<i>Findings</i> Six RCTs and 9 retrospective series in early stage breast cancer.	
RCTs Included RCTs were: Cancer Research Campaign Working Party. Cancer Research Campaign (King's/Cambridge) Trial for early breast cancer. A detailed update at the tenth year. <i>Lancet</i> 1980 July: 55–60. Fisher B, Redmond C, Fisher E R et al. Ten year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. <i>N Engl J Med</i> 1985; 312: 674–681. (NSABP-04). Host H, Brennhord I O, Loeb M. Postoperative radiotherapy in breast cancer – long term results from the Oslo Study. <i>Int J Radiation Oncology Biol Phys</i> 1986; 12: 727–732. Wallgren A, Arner O, Bergstrom J et al. Radiation therapy in operable breast cancer. Results from the Stockholm Trial on adjuvant radiotherapy. <i>Int J Radiat Oncol Biol Phys</i> 1986; 12: 533–537.	

Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. *Radiother Oncol* 1995; 36: 172–176. (Finland).

Ragaz J, Jackson S M, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; 337: 956–962. (Canada).

RCT Intervention	Findings
CRC N=2800 Clinical stage I or II. Simple Mastectomy vs. simple mastectomy + RT to chest wall, IMC, SCF, axilla.	Local recurrence free survival improved in RT group. Overall survival – no significant difference between groups. Medial tumours- no survival benefit with RT.
NSABP-04 N=1665 Node positive randomized to radical mastectomy or simple mastectomy and regional node irradiation (IMC, SCF, axilla). Node negative randomized to radical mastectomy, simple mastectomy, or simple mastectomy and regional node irradiation.	No difference between any of the groups for disease-free survival or overall survival. Regional node irradiation did not provide a benefit over mastectomy alone in women with node negative or positive tumours.
Oslo N=1115 Phase I: All women had radical mastectomy, then randomized to observation or RT (200 kv. x-ray) to axilla, IMC, SCF and chest wall. Phase II: RT delivered with Co-60 and chest wall RT omitted.	A decrease in local recurrence but no effect on overall survival. Subgroup analysis of women with stage II medial and central tumours found a trend of improved survival with Co-60 than x-ray RT. Significant excess of non-breast cancer deaths in Co-60 group.
Stockholm N=960 3 arms Preoperative RT to IMC, SCF, axilla, breast. Postoperative RT to IMC, SCF, axilla, chest wall. Modified radical mastectomy alone.	RT significantly reduced local recurrence, but no difference in overall survival at 10 years. Node positive with RT had a significant reduction in incidence of distant metastases.
Finland N=270 BCS and axillary dissection for Stage I-II breast cancer. RT was given to all but randomized to include the IMC or omit the IMC.	At 2 years no significant difference in relapse between the 2 groups.
Canada N=318 Premenopausal women with positive axillary nodes randomized to RT (IMC, SCF, axilla, chest wall) or observation.	Local recurrences reduced by 56% with RT. Breast cancer specific survival increased by 29% with RT (p=0.05) A non-significant 8% increase in overall survival with RT.
Key: IMC = Internal Mammary Chain RT = Radiotherapy SCF = Supraclavicular Fossa	
Author Summary of RCTs	
<ul style="list-style-type: none"> • The addition of radiotherapy consistently reduced the rate of local recurrence. • The actual benefit of IMC treatment is unknown as sites of relapse were not reported. • No trials found a significant advantage in overall survival, even when the subgroups of medial and central cancers were analysed. • Only one trial reported a cancer specific survival and showed a significant improvement (Ragaz 1997). 	
The authors point out the limitation of the trials in assessing survival since radiotherapy related deaths may negate any overall survival benefit.	
Non-Randomised Studies (NRS)	
9 retrospective studies were identified:	
Arriagada R, Le M G, Mouriessse H et al. Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. Radiother Oncol 1988; 11: 213–222.	
Cappellini M, Ciatto S, Mungai R. Post-operative radiotherapy in node negative breast cancer. A retrospective case-control study. Tumori 1981; 67: 443–445.	

Chahbazian C, del Regato J A, Wilson J F. Postoperative radiation therapy for 'Early' Carcinoma of the Breast. *Cancer* 1978; 42: 1126–1128.

Montague E D, Fletcher G H. The curative value of irradiation in the treatment of nondisseminated breast cancer. *Cancer* 1980; 46: 995–998.

Regnier R, Nguyen T H, Balikdjan D, Lustman-Marechal J, Darquennes H & Henry J. Experience of telecobalt Therapy in operable breast cancer at J. Bordet Institute. *Int J Radiat Oncol Biol Phys* 1982; 8: 1517–1523.

Roseman J M, James A G. The significance of the internal mammary nodes in medially located breast Cancer. *Cancer* 1982; 50: 1426–1429.

Rubin P, Bunyagidj S, Poulter C. Internal mammary lymph node metastases in breast cancer: detection and management. *Am J Roentgenol Radium Ther Nucl Med* 1971; 111: 588–598.

Schmolling J, Maus B, Rezek D et al. Breast preservation versus mastectomy – recurrence and survival rates of primary breast cancer patients at the UFK Bonn. *Eur J Gynaecol Oncol* 1997; 18: 29–33.

Shiba, E, Miyauchi K, Kobayashi T, Takai S, Mori T. Radical mastectomy with parasternal node dissection or radiation to the parasternal region for breast cancer of medial or central location. *Surg Today* 1992; 22: 124–127.

Study Intervention	Findings
<p>Arriagada N=1195 Operative breast cancer (<7cm) and positive axillary nodes treated by modified radical mastectomy and complete axillary dissection. RT to chest wall, SCF and axilla. 4 groups: No IMC treatment (n=135) IMC dissection only (n=102) IMC radiotherapy only (n=523) IMC RT and dissection (n=435)</p>	<p>In the three groups with IMC treatment the risks of death and metastasis were the same. When these groups were combined and compared to the no IMC treatment group there was a trend toward improved survival in the treated arms ($P=0.06$). A subgroup analysis reached statistical significance for medial tumours (10-year survival 58% vs 48%, $P=0.05$) only. Conclusions were that treatment of the IMC was beneficial in improving survival for axillary node-positive medial tumours.</p> <p>These findings are based on subgroup analyses of a retrospective study. Different treatment policies were adopted over sequential time periods and the possibility exists for staging biases.</p> <p><i>This study is included in the observational evidence</i></p>
<p>Regnier N=787 Surgery and postoperative RT to chest wall and regional nodes.</p>	<p>Change in policy of IMC treatment with time. Prior to 1974 the IMC was treated with a single anterior field to a dose of 27.5 Gy. From 1974 onwards the IMC was boosted to 40 Gy for medial cancers.</p> <p>Survival correlated with the higher dose to the IMC, however the distribution of prognostic factors between the two groups was not reported.</p>
<p>Montague N=1111 Radical mastectomy (n=301) Radical mastectomy then RT to SCF and IMC (n=368) Preoperative RT to SCF, IMC and axilla then radical mastectomy (n=442)</p>	<p>Axillary nodal positivity was 12%, 64% and 29% respectively in the 3 groups. There was no difference seen in 10-year survival rates.</p> <p>This was interpreted as being a result of IMC and SCF radiation. This study is limited by use of retrospective data and the omission of prognostic factors between groups that may affect outcomes.</p>
<p>Chahbazian N=225 Node negative operable breast cancer. Radical mastectomy (n=136) Radical mastectomy then RT to SCF and IMC (n=89)</p>	<p>RT group showed a significant survival advantage for medial tumours. No advantage for lateral tumours.</p>
<p>Roseman</p>	<p>RT decreased local recurrences and improved disease-</p>

N=134 Surgery alone (n=118) Surgery and postoperative RT to IMC and SCF (n=17)	free survival in those with medial tumours.
Cappellini (Case –control) N=128 Node negative breast cancer. Post-operative radiotherapy.	No significant difference in recurrence or survival.
Rubin N=230 IMC recurrence identified.	16/230 had an IMC recurrence over 10 years. Of these 32% had received RT.
Shiba N=183 Radical mastectomy with parasternal node dissection or radiation to the parasternal region. Women with medial or central tumours.	No differences in overall survival at 10 years.
Schmolling N=411 Breast preservation versus mastectomy.	IMC RT did not impact on survival rates.
<p>Locally advanced breast cancer 2 RCTs looked at operable locally advanced disease.</p> <p>Rutqvist L, Cedermark B, Glas U et al. Randomised trial of adjuvant tamoxifen combined with postoperative radiation therapy or adjuvant chemotherapy in postmenopausal breast cancer. <i>Cancer</i> 1990; 66: 89–96.</p> <p>Overgaard M, Hansen P S, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. <i>N Engl J Med</i> 1997; 337: 949–955.</p>	
Rutqvist N=427 Postmenopausal women with high risk breast cancer (T>30mm or node positive) randomized postmastectomy to: Radiotherapy alone Radiotherapy and tamoxifen Chemotherapy alone Chemotherapy and tamoxifen RT included chest wall, axilla, SCF and IMC.	The addition of radiotherapy significantly reduced local failure and improved relapse-free survival. There was a trend toward reduced distant metastases ($P=0.06$) but no difference in survival.
Overgaard N=1708 Premenopausal women with T3, T4 or node-positive breast cancer. All patients had mastectomy then randomized: Chemotherapy alone Chemotherapy in combination with radiotherapy to the chest wall, axilla, SCF and IMC.	At 10 years 45% of the chemotherapy alone group and 54% of the radiotherapy group were alive ($P<0.001$).
<p><i>Summary of locally advanced disease</i> Post-mastectomy radiation was delivered to the chest wall and all nodal regions. It is difficult to assess the contribution of IMC radiation alone to these results.</p> <p>Author conclusions In early stage breast cancer some retrospective data suggested that IMC irradiation improved survival in medial or central and axillary node-positive tumours, this was not supported by the randomized data (from one RCT). Two randomized trials were of high risk operable breast cancer. One showed a survival advantage to post-mastectomy irradiation, but the contribution of IMC irradiation could not be delineated. Based on the best current evidence, there is no advantage to elective IMC irradiation. The only indication is for positive IMC nodes where the management aim is palliative.</p> <p>General comments – Many of the trials included in this review have been updated since publication in 1999.</p>	

Randomized controlled trials

Veronesi, U., Orecchia, R., Zurrada, S., Galimberti, V., Luini, A., Veronesi, P., Gatti, G., D'Aiuto, G., Cataliotti, L., Paolucci, R., Piccolo, P., Massaioli, N., Sismondi, P., Rulli, A., Lo, S. F., Recalcati, A., Terribile, D., Acerbi, A., Rotmensz, N., & Maisonneuve, P. 2005, "Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy", *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.*, vol. 16, no. 3, pp. 383-388.

Design: RCT (1995-1998)

Level 1+

Country: Italy, setting: Italian Oncological Senology Group: Multicentre

Aim: To assess the role of axillary radiotherapy (RT) in reducing axillary metastases in patients with early breast cancer who did not receive axillary dissection.

Inclusion criteria

Women aged > 45 years with a unifocal breast carcinoma maximum size of 1.2cm (determined during operation), and no palpable axillary nodes.

Exclusion criteria

Patients with non-invasive carcinoma or a history of previous malignant disease.

Population number of patients = 435

Patients were randomized to either no axillary RT (n=214) or axillary RT (n=221)

The median age was 57 years (interquartile range 52–63) with no difference between the two groups. 41% were < 55 years.

60% of tumours were 0.6-1.0cm.

9% of tumours were 1.2-1.5cm.

Breast tumour was non-palpable in 241 patients (55.4%), and clinically palpable in 194 (44.6%).

No palpable axillary nodes.

Interventions

Wide resection or quadrantectomy (1-2 cm margin of normal tissue) of the primary carcinoma. Quadrantectomy for tumours in the upper outer quadrant were performed without removal of any axillary node. Where lesions were non-palpable, the removed specimen was X-rayed to check that the tumour had been removed completely. The size of the lesion was determined macroscopically in the operating theatre. The final histological size measurement was concordant in most cases. However, in 9.2% of cases (20 in each group), size was in excess of 1.2 cm.

Radiotherapy given by X-Ray photons from a 6MV linear accelerator to produce two opposed tangential fields. The 100% tumour dose was 50 Gy in 25 fractions of 2Gy each. An additional boost to the tumour bed of 6–15MeV electrons (10 Gy in five fractions of 2 Gy each) was given to all patients.

In the intervention arm the axillary region was irradiated with two parallel (non-divergent) opposed fields (antero-posterior postero-anterior). The total dose of 50 Gy in 25 fractions of 2Gy given with a 6MV linear accelerator.

Outcomes

Axillary metastases

Local recurrence

Distant metastases

Breast cancer deaths

Overall deaths

Follow up

All patients received quarterly clinical examination and annual mammography, chest X-ray, liver ultrasound and bone scan. If an enlarged axillary node was found during follow-up, complete axillary dissection was performed. Median follow-up was 63 months (range 2–108 months). Four patients were lost to follow-up (0.7%).

Results

Significantly fewer patients in the no axillary RT arm received no adjuvant treatment of tamoxifen or chemotherapy (11.7% no RT vs 18.5% with RT to axilla, $p=0.046$).

Table of events related to primary tumour:

Events related to primary tumour	No axillary RT	Axillary RT	Log rank test
Appearance of overt axillary metastases	3	1	0.295
Local recurrence	1	1	0.979
Second ipsilateral breast cancer	0	3	0.095
Distant metastases	8	3	0.107
Total events related to primary	12	8	0.305
Other events:			
Contralateral breast cancer	7	4	0.306
Other primary cancer	4	4	0.916
Total first events	23	16	0.185
Deaths due to breast cancer	5	2	0.227
Deaths due to other causes	7	0	0.006
Total deaths	12	2	0.005

Generally, fewer events occurred in the RT arm (exceptions local recurrence, second ipsilateral breast cancer). Additional information reported was that of the 324 patients in both groups with a primary carcinoma less than 1cm in diameter, only one (0.3%) developed overt axillary metastases.

The Log rank test was used to compare survival estimates. Further data are reported in the following table:

INTERVENTION	PATIENTS	Events related to primary tumour	DFS RESULT
Axillary RT	221	8	Kaplan-Meier Log rank test P=0.3039
No axillary RT	214	12	
Total	435	Overall clinically overt axillary metastases: N=4 (0.7%) 95% CI 0.1-2.0%	
	Axillary metastases: RT group n=1 (0.5%) No RT group n=3 (1.5%)		
Outcome	RT	No RT	Overall
5 year DFS	96.9% (95%CI 94.3-99.4)	95.1% (95%CI 92.2-98.1)	96% (95%CI 94.1-97.9)
Hazard ratio (Direction of effect not specified in paper)			1.59 (0.65-3.89)

DFS = any event (axillary metastases, local recurrence, ipsilateral carcinoma or distant metastases) related to primary cancer (excludes contralateral breast cancer and any other cancer).

There were no significant differences between groups for DFS.

The Hazard Ratio for DFS was very wide (0.65-3.89) possibly due to the low number of events.

Author conclusions

The rate of axillary metastases appearing in women treated by breast conservation without any axillary treatment was much lower than expected, leading to the hypothesis that occult axillary metastases might not progress to overt clinical metastases, and secondly, that occult metastases can be kept under control by axillary RT. (For tumours less than 1.2cm).

General comments -

Kaija, H. & Maunu, P. 1995, "Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomised trial", *Radiotherapy & Oncology*, vol. 36, no. 3, pp. 172-176

Design: RCT (1989-1991) Level 1+
Country: Finland, setting: University Centre

Inclusion criteria

Unilateral stage I or II invasive breast cancer

Exclusion criteria

Two patients with distant metastases and two who refused radiotherapy were excluded.

Population number of patients = 270 eligible, 266 entered the trial.

A table of patient, tumour and treatment characteristics from the paper is shown below:

Variable	IMC-RT	No IMC-RT
Age (years)	58.3	57.9
Mean tumour size (cm)	1.4	1.4
Node positive	19	16
Breast left/right	54/48	58/42
Location (%)		
Lateral	75	77
Medial	17	15
Central	8	8
Mean radiation dose	49.7	49.1
Adjuvant systemic therapy (%)	9	7

Interventions

All patients had BCS (segmental resection and axillary dissection) followed by radiotherapy. Randomisation was to a target volume of the ipsilateral parasternal area including the internal mammary chain (group 1, IMC-RT) or omitting the IMC (group 2, no IMC-RT).

The RT dose was delivered using the medial and lateral tangential field technique with 5MV photon beams 4-8 weeks after surgery.

The total radiation dose determined varied during the time period of the study. 50 Gy photons + 10 Gy electron boost or 54 Gy photons or 50 Gy photons, were given in five fractions per week at a daily dose of 2 Gy. The dose variation was due to changing practice in the clinic.

71 patients received 50 Gy photons + 10 Gy electron boost

44 patients received 54 Gy photons

146 patients received 50 Gy photons without boost.

The dose inhomogeneity within the target volume was within 10% in most cases.

Outcomes

Local and distant relapse

Radiation pneumonitis

Radiation fibrosis

Skin reactions

Follow up

Clinical examination 3 monthly and chest X-ray twice a year. Median follow-up 2.7 years.

Data for 263/270 (97.4%) patients were available for analysis.

Results

The main purpose of the study was to follow skin and pulmonary complications.

Skin reactions

These were common in both groups, with 90% of patients having some skin reaction.

Skin reaction	IMC RT N (%)	No IMC RT N (%)	Total N (%)
None	10 (8)	14 (11)	24 (10)
Mild	45 (35)	45 (34)	90 (35)
Moderate	42 (32)	36 (27)	78 (29)
Severe	34 (25)	37 (28)	71 (26)

Total	131 (100)	132 (100)	263 (100)
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Lung reactions

Acute reactions were more common in the IMC-RT group, but the difference was not significant (18 vs. 14%). Lung reactions were mainly mild or moderate, with 2 severe cases in the IMC-RT group. Acute reactions disappeared within 6 months.

11% of patients had lung fibrosis which was more common in the IMC-RT group but not statistically significant ((14 vs. 7%, $p < 0.06$).

15% of patients had respiratory symptoms.

Lung and respiratory events	IMC RT N (%)	No IMC RT N (%)	Total N (%)
Acute lung reactions			
None	107 (82)	112 (86)	219 (84)
Mild	16 (12)	13 (10)	29 (11)
Moderate	5 (4)	6 (4)	11 (4)
Severe	2 (2)	0 (0)	2 (1)
Lung fibrosis			
None	112 (86)	122 (93)	234 (89)
Mild	11 (8)	7 (5)	18 (7)
Moderate	8 (6)	2 (2)	10 (4)
Respiratory symptoms			
No	110 (84)	112 (85)	222 (85)
Yes	21 (16)	19 (15)	40 (15)

There was no significant difference in relapse rates between treatment groups after a median follow-up time of 2.7 years.

Author conclusions

The short observation time in the present study does not as yet allow any conclusions as to the comparative value of internal mammary chain irradiation in preventing breast cancer recurrences. So far there is not any significant difference between treatment groups.

Radiation of internal mammary chain after conservative surgery for early breast cancer did not lead to an increase in clinically important skin or pulmonary complications. Whether it prevents recurrences or increases the cancer risk to the other breast is too early to say in view of the short observation time.

General comments -

Louis-Sylvestre, C., Clough, K., Asselain, B., Vilcoq, J. R., Salmon, R. J., Campana, F., & Fourquet, A. 2004, "Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, vol. 22, no. 1, pp. 97-101

Design: RCT (1982-1987) Level 1+

Country: France, setting: single institution

Aim: To update a study comparing axillary dissection with radiotherapy to the axilla.

Inclusion criteria

Patients \leq 70 years with no history of previous cancer, presenting with a unilateral invasive carcinoma less than 3 cm, no clinically involved axillary lymph nodes, and non-metastatic disease (N0 M0).

Exclusion criteria

Population number of patients = 658

Group A (axillary dissection) n=326

Group B (axillary RT) n=332

Mean age at randomization 52 years in group A and 50.6 years in group B.

19% (126/658) of tumours were \leq 1cm.

48% (314/658) of tumours were 1-2cm.

33% (218/658) of tumours were larger than 2cm.

Interventions

All patients had a wide local excision and breast irradiation. Randomisation was to axillary dissection (group A) or axillary RT (group B).

Axillary dissection (group A) was limited to the Level I and lower Level II nodes (inferior to the axillary vein). After axillary dissection those patients with metastatic nodes received RT to the supraclavicular and internal mammary lymph nodes. Patients with a central or medial tumour also received systematic radiation therapy to the internal mammary lymph nodes.

In group B, no axillary dissection was performed. Irradiation to the breast included radiotherapy to axillary and internal mammary lymph nodes.

All patients received radiotherapy to the breast at a dose of 55 Gy, over 6 weeks.

All patients received a boost of 10 to 15 Gy to the tumour bed.

Axillary nodes received a 50-Gy dose; internal mammary nodes and supraclavicular nodes received a 45-Gy dose.

ER positive postmenopausal women received tamoxifen depending on physician choice.

Patients with more than one metastatic lymph node received adjuvant hormonal or chemotherapy depending on menopausal status.

Outcomes

Overall survival

Disease free survival

Metastases

Local recurrences

Axillary recurrence (isolated) – considered to be lymph node recurrences.

NB Recurrences in the supraclavicular lymph node considered to be metastases.

Follow up

Patients had a physical examination every 3 months for 1 year, then every 6 months for 5 years, and annually thereafter.

Mammography was performed annually.

Median follow-up was 180 months (range 12-221 months).

11 patients lost to follow-up at 5 years, and 58 at 10 years.

Results

There were more patients aged less than 35 years in group B (n=26) than in group A (n=9). More patients in Group A received chemotherapy (19 vs. 9) and hormonal therapy (14 vs. 8) than those in Group B.

322 patients had an axillary dissection (320 in group A, 2 in group B).

Of these 68 had metastatic lymph nodes (21%):

39 patients (57%) had one metastatic node

23 patients (34%) had two or three metastatic nodes

6 patients (9%) had more than three metastatic nodes.

Results at 60, 120 and 180 months are reported in the table below. At six months there was an overall survival advantage in the axillary dissection group, however this was not observed on later follow-up.

Table of outcomes at 60, 120, 180 months

Outcome	Time (months)	Axillary dissection		Axillary RT		P
		Kaplan-Meier estimate [%](SD)		Kaplan-Meier estimate [%](SD)		
Overall survival	60	96.6%	(1)	92.4%	(1.5)	NS
	120	86.6%	(1.9)	83.6%	(2.1)	
	180	75.5%	(2.7)	73.8%	(2.7)	
Disease free survival	60	83.3%	(2)	82.0%	(2.1)	NS
	120	72.6%	(2.5)	72.0%	(2.5)	
	180	64.3%	(2.9)	65.5%	(2.7)	
Metastases	60	10.8%	(1.7)	12.8%	(1.9)	NS
	120	18.3%	(2.2)	21.0%	(2.3)	
	180	25.8%	(2.6)	24.9%	(2.5)	
Local recurrences	60	7.2%	(1.4)	7.1%	(1.4)	NS
	120	12.6%	(1.9)	11.8%	(1.8)	
	180	17.2%	(2.4)	16.3%	(2.3)	
Axillary recurrences (isolated)	60	0.6%	(0.4)	2.2%	(0.8)	0.04
	120	1%	(0.6)	3%	(1)	
	180	1%	(0.6)	3%	(1)	

Key: SD = standard deviation; NS = not significant

The rates of overall survival, disease free survival, ipsilateral local recurrences and distant metastases or supraclavicular node involvement were not statistically different between the two groups at 180 months (15 years).

Isolated axillary recurrences (without concomitant breast recurrence) were lower in group A at 60, 120, and 180 months (5, 10, 15 years respectively): the rate was 1% in group A versus 3% in group B at 180 months (RR, 0.33; 95% CI, 0.11 to 0.98; $P = 0.04$). Seventeen patients developed an axillary recurrence (five in group A and 12 in group B). Five of these had a concomitant breast recurrence. Of the remaining 12 patients with no concomitant breast recurrence, 3 were in group A and 9 in group B. One patient with a lymph node metastasis on initial axillary dissection developed an axillary recurrence.

Author conclusions

At 15-year follow-up axillary dissection and axillary radiotherapy provide identical survival, although local control is better with axillary dissection. The morbidity of the association between sentinel node biopsy and subsequent axillary radiotherapy remains to be evaluated.

General comments -

Wallgren, A., Arner, O., Bergstrom, J., Blomstedt, B., Granberg, P. O., Raf, L., Silfversward, C., & Einhorn, J. 1986, "Radiation therapy in operable breast cancer: results from the Stockholm trial on adjuvant radiotherapy.[erratum appears in Int J Radiat Oncol Biol Phys 1987 Jan;13(1):149]", *International Journal of Radiation Oncology, Biology, Physics*, vol. 12, no. 4, pp. 533-537.

Design: RCT (1971-1976) Level 1+

Country: Sweden, setting: 5 surgical departments in Stockholm

Aim: To update an earlier study of pre- and postoperative radiotherapy in operable breast cancer.

Inclusion criteria

Women aged less than 71 years with Stage I-III operable breast cancer

Exclusion criteria

Not reported.

Population number of patients = 960

Mean age 54.4 years (28-70 years)

Pre-menopausal 38.7%

Postmenopausal 61.3%

Medial tumour 20.7%

Lateral tumour 55.9%

Other site 23.4%

Clinical stage I 11.6%

II 77.1%

III 11.3%

Interventions

Patients were stratified by age (< 50 years or older), node status (N0 or N1), tumour size (≤ 20 , 21-50, or > 50 mm) and randomised to 3 groups:

Preoperative RT

Postoperative RT

Surgery alone (control)

Surgery consisted of a total mastectomy and axillary dissection with preservation of the pectoral muscles (modified radical mastectomy).

Radiotherapy total dose was 45 Gy.

Radiotherapy target volumes for the first 2 years were the chest wall and preoperatively the breast, axillary, supraclavicular and both internal mammary lymph node chains (IMC) (n=327). To decrease the risk of radiation pneumonitis the contralateral IMC were excluded during the remaining period (n=588).

Surgery was delayed for 6 weeks after preoperative RT.

Outcomes

Local and regional recurrence only counted if occurring before or in combination with distant metastases)

Relapse free survival (survival to loco-regional or distant relapse or death from any cause)

Overall survival

Breast cancer deaths (when metastatic disease known)

Time to first event, relapse or death.

Follow up

All patients were followed to death or the end of 1984.

8-14 years, mean 11 years.

Results

Recurrence

An improvement in recurrence free survival was found in the two irradiated groups, this did

not decrease over time (Kaplan-Meier curve).

The ratio of recurrence rates for irradiated patients vs. surgery alone is shown in the table. After 10 years the ratio of 1.04 indicates a similar rate of events between RT and surgery alone groups.

The mean difference in time to first event, relapse or death between RT groups and surgery alone was 15 months (SE 3.6 months).

The frequency and sites of recurrence within the chest wall, nodes or distant recurrences for the first 8 years are shown in the table. More surgery only patients experienced a recurrence than irradiated patients. Although distant metastases were also more frequent in the surgery only group, the difference was not significant (p value not reported).

Cumulative incidence of locoregional disease

The cumulative incidence of locoregional disease in histologically confirmed node negative patients at 11 years was 2.5% in those irradiated postoperatively and 20% in the surgery only group (p<0.001).

In patients with lymph node metastases the corresponding cumulative incidence was 13% after RT and 45% for surgery alone (p<0.001).

The graph of cumulative incidence (in the original paper) for node negative and node positive disease in the 2 groups (postoperative RT vs. surgery alone) showed a higher incidence in node positive patients with no statistically significant difference between postoperative RT and no RT groups (p=0.09). Similarly for node negative patients the cumulative incidence is lower and not statistically significantly different between the 2 groups (p=0.78).

Cumulative incidence of distant metastases

No difference was found between postoperative RT and no RT groups with node negative disease (Approx 20% at 11 years, p=0.82). The cumulative incidence was higher for node positive patients, but a lower rate of distant metastases occurred following postoperative RT (47% at 11 years) than for the no RT group (60% at 11 years, p=0.01).

OUTCOME OF INTEREST	Time period	RT vs. Surgery	
Recurrence rate	Entire period	0.65 (p<0.001)	
	0-5 years	0.63 (p<0.001)	
	5-10 years	0.64 (p=0.002)	
	After 10 years	1.04	

Frequency and site of recurrence at 8 years	RT group n (%) 639 patients	No RT group n (%) 321 patients	
All chest wall	33 (5.2)	62 (19.3)	
All nodes	19 (3.0)	42 (13.1)	
All distant	191 (29.9)	110 (34.3)	
Chest wall + nodes	46 (7)	84 (26)	P<0.001
All recurrences	199 (31.1)	135 (42.1)	

Survival

There were 372 deaths from all causes.

Surgery only 132 deaths

Preoperative RT 121 deaths

Postoperative RT 119 deaths.

The difference of 5% between irradiated and non-irradiated patients at 8 years was not statistically significant.

The cumulative incidence of breast cancer deaths for node negative patients was not statistically significantly different between postoperative RT and surgery alone (approx 7% from survival curve, p=0.78). The survival gain for node positive patients in the postoperative RT group (54%) at 8 years vs. 47% in the surgery only group was also not statistically

significant (p=0.09).

Subgroup analyses

The ratio of death rates was generally lower for the irradiated patients but none of the factors compared reached statistical significance.

Subgroup	N of patients Pre or postoperative RT (n=639). Surgery (n=321)	Ratio of death rates RT/no RT	P value
Clinical stage			
Stage 1	140	0.70	0.43
Stage 2	702	0.79	0.07
Stage 3	118	1.23	0.39
Menopausal status			
Premenopausal	335	0.85	0.44
Postmenopausal	625	0.88	0.35
Site of tumour			
Medial	202	0.69	0.12
Central	229	1.11	0.66
Lateral	529	0.86	0.29
Treatment of internal mammary nodes			
Bilateral	372	0.76	0.10
Ipsilateral	588	0.97	0.85
All patients	960	0.88	0.24

Author conclusions

Preoperative radiotherapy reduced the incidence of local and regional recurrence and of distant metastases (in node positive patients), and also the mortality, as compared with the surgery only group. Postoperative radiotherapy as given in this trial gave almost equal reduction of local and regional recurrence but did not diminish the frequency of distant metastases or the mortality.

General comments -

Fisher, B., Jeong, J. H., Anderson, S., Bryant, J., Fisher, E. R., & Wolmark, N. 2002, "Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation.[see comment]", *New England Journal of Medicine*, vol. 347, no. 8, pp. 567-575.

Design: RCT (1971-1974) Level 1++

Country: USA, setting:

Aim: To determine whether patients with either clinically negative or clinically positive axillary nodes who received local or regional treatments other than radical mastectomy would have outcomes similar to those achieved with radical mastectomy.

This RCT was also included in **Chapter 5.4** (Which groups of patients should receive chest wall radiotherapy after mastectomy?) and is duplicated here.

Inclusion criteria

Women with primary operable breast cancer

Exclusion criteria

Population number of patients = 1665 randomized

A total of 1079 women with clinically negative axillary nodes:

Radical mastectomy (RM) n=362

Total mastectomy (TM) without axillary dissection but with postoperative irradiation (RT) n=352

Total mastectomy plus axillary dissection n=365 (only if they developed positive nodes)

A total of 586 women with clinically positive axillary nodes:

Radical mastectomy n=292

Total mastectomy without axillary dissection but with postoperative regional irradiation (n=294).

About 70% of women in each group were 50 years or older at time of entry. On pathological examination, the mean (SD) diameter of the largest tumour was 3.3 +/- 2.0 cm in women with negative nodes and 3.7 +/- 2.0 cm in women with positive nodes.

Interventions

Radiotherapy was delivered with supervoltage equipment. Women with negative nodes received 50 Gy in 25 fractions; node positive women received an additional boost of 10 to 20 Gy. A dose of 45 Gy in 25 fractions was delivered to both the internal mammary nodes and the supraclavicular nodes. Tangential fields were used to treat the chest wall with 50 Gy in 25 treatments. None of the women received adjuvant systemic therapy.

Outcomes

Disease free survival (DFS)

Relapse free survival

Distant disease free survival

Overall survival

Follow up

87% were followed for at least 25 years. Data collected up to March 2001.

DFS and RFS

Outcomes for disease free survival and recurrence free survival at 25 years follow-up by node status are reported in the Table below. There were no significant differences between treatment groups for either of these outcomes at 25 years in node positive and node negative participants.

OUTCOME OF INTEREST	Radical mastectomy (RM)	Total mastectomy and irradiation	Total mastectomy (TM)	Statistic
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(TM+RT)				
DFS (25 yrs) NO	19% (SE2%)	13% (SE2%)	19% (SE2%)	$p=0.65$
Hazard Ratios (not clear from paper which is the reference set)	RM vs. TM+RT: 1.06 (95% CI 0.90 to 1.25, $p=0.49$) TM vs. RM: 1.07 (95% CI 0.91 to 1.27, $p=0.39$) TM+RT vs. TM: 1.02 (95% CI 0.87 to 1.21, $p=0.78$)			
DFS (25 yrs) Positive nodes	11% (SE2%)	10% (SE2%)		
Hazard Ratio	RM vs. TM+RT: 1.12 (95% CI 0.94 to 1.33, $p=0.20$)			
RFS (25 yrs) NO	53% (SE3%)	52% (SE4%)	50% (SE3%)	$p=0.46$
Hazard Ratios	RM vs. TM+RT: 0.96 (95% CI 0.76 to 1.21, $p=0.74$) TM vs. RM: 1.14 (95% CI 0.91 to 1.42, $p=0.27$) TM+RT vs. TM: 1.18 (95% CI 0.94 to 1.48, $p=0.15$)			
RFS (25 yrs) Positive nodes	36% (SE3%)	33% (SE3%)		
Hazard Ratio	RM vs. TM+RT: 1.09 (95% CI 0.89 to 1.35, $p=0.40$)			

Time to first event

Twenty percent of women with negative nodes and 13% of women with positive nodes were alive and event-free after 25 years of follow-up (See Table below). Most first events were related to distant recurrences of tumour and to deaths unrelated to breast cancer, irrespective of node status. The detection of cancer at other sites was relatively infrequent. There was little difference in the frequency of events either among the groups with negative nodes or between those with positive nodes (no statistical data were provided for these comparisons).

Node negative

There was a statistically significant difference between the 3 groups of women with negative nodes for the cumulative incidence of local or regional recurrence ($p=0.002$ for 3 way comparison). The rate was lowest in the total mastectomy with RT group, indicating a significant benefit of RT in reducing local recurrence. In contrast there were no statistically significant differences between the 3 groups in the cumulative incidence of distant recurrence as a first event ($p=0.61$). [p values were reported in the Figures associated with these findings in the original paper].

Event	Women with negative nodes			Women with positive nodes		All (N=1665)
	RM (n=362)	TM (n=365)	TM+RT (n=352)	RM (n=292)	TM+RT (n=294)	
Any event	281 (78%)	287 (79%)	292 (83%)	254 (87%)	258 (88%)	1372 (82%)
Any recurrence	135 (37%)	156 (43%)	131 (37%)	165 (57%)	168 (57%)	755 (45%)
Local	19 (5%)	26 (7%)	5 (1%)	23 (8%)	8 (3%)	81 (5%)
Regional	15 (4%)	23 (6%)	15 (4%)	22 (8%)	33 (11%)	108 (6%)
Distant	101 (28%)	107 (29%)	111 (32%)	120 (41%)	127 (43%)	566 (34%)
Contralateral breast cancer	19 (5%)	26 (7%)	32 (9%)	13 (4%)	15 (5%)	105 (6%)
2 nd primary cancer	23 (6%)	19 (5%)	28 (8%)	12 (4%)	17 (6%)	99 (6%)
Dead, no evidence of cancer	104 (29%)	86 (24%)	101 (29%)	64 (22%)	58 (20%)	413 (25%)
Alive, event free	81 (22%)	78 (21%)	60 (17%)	38 (13%)	36 (12%)	293 (18%)

KEY:

Any recurrence excludes contralateral breast recurrence

Second primary cancers exclude breast cancers

Positive nodes

Among women with positive nodes, there were no significant differences between the RM and TM + irradiation groups for cumulative incidence of local or regional recurrence ($P=0.67$). Similarly there were no significant differences between the RM and TM + irradiation groups for the incidence of regional recurrence or the incidence of distant recurrence ($P=0.44$). However there was a significant reduction in the incidence of local recurrence after radiation therapy. [p values were reported in the Figures associated with these findings in the original paper].

Distant-Disease-free Survival and Overall Survival

There were no significant differences in distant-disease-free survival among the groups of women

with negative nodes at 25 years ($p = 0.63$ for the three-way comparison). Among women with positive nodes, there was no significant difference in distant-disease-free survival between the radical mastectomy and total mastectomy plus radiation therapy groups (See Table below).

There was no significant difference in overall survival among the groups of women with negative nodes at 25 years ($p=0.68$ for the three-way comparison). In women with positive nodes there was also no significant difference in overall survival between the radical mastectomy and total mastectomy plus radiation therapy groups (See Table below).

OUTCOME OF INTEREST	Radical mastectomy (RM)	Total mastectomy and irradiation (TM+RT)	Total mastectomy (TM)	Statistic
Distant-DFS (25 yrs) NO	46% (SE3%)	38% (SE3%)	43% (SE3%)	$p=0.63$
Hazard Ratios	RM vs. TM+RT: 1.08 (95% CI 0.88 to 1.34, $p=0.44$) TM vs. RM: 1.10 (95% CI 0.89 to 1.35, $p=0.39$) TM+RT vs. TM 1.02 (95% CI 0.83 to 1.25, $p=0.85$)			
Distant-DFS (25 yrs) Positive nodes	32% (SE3%)	29% (SE3%)		
Hazard Ratio	RM vs. TM+RT: 1.07 (95% CI 0.87 to 1.32, $p=0.51$)			
Overall Survival (25 yrs) NO	25% (SE3%)	19% (SE2%)	26% (SE3%)	$p=0.68$
Hazard Ratios	RM vs. TM+RT: 1.08 (95% CI 0.91 to 1.28, $p=0.38$) TM vs. RM: 1.03 (95% CI 0.87 to 1.23, $p=0.72$) TM+RT vs. TM 0.96 (95% CI 0.81 to 1.13, $p=0.60$)			
Overall Survival (25 yrs) Positive nodes	14% (SE2%)	14% (SE2%)		
Hazard Ratio	RM vs. TM+RT: 1.06 (95% CI 0.89 to 1.27, $p=0.49$)			

Positive Axillary Nodes after Total Mastectomy without Radiation Therapy

A total of 68 of 365 women with negative nodes who underwent total mastectomy without radiation therapy (18.6%) subsequently developed pathologically positive ipsilateral nodes. Involved nodes were identified within 2 years after surgery in 51 of the 68 women, > 2 < 5 years after surgery in 10 women, >5 <10 years after surgery in 6 women, and > 10 < 25 years after surgery in 1 woman. The median time from mastectomy to the identification of positive axillary nodes was 14.8 months (range, 3.0 to 134.5).

Author conclusions

The findings validate earlier results showing no advantage from radical mastectomy. Although differences of a few percentage points cannot be excluded, the findings fail to show a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy.

General comments –

In the discussion the authors report that an important finding of the study was that about 40% of women with clinically negative nodes treated with radical mastectomy had pathological confirmation of tumour-positive axillary lymph nodes. Since the women were randomized to treatment groups, an estimate of about 40% of those undergoing total mastectomy alone having positive nodes that were not removed at the time of initial surgery is also assumed. About half of these women subsequently received a diagnosis of positive axillary nodes as a first event. Some investigators suggest that the frequency of delayed occurrence of positive axillary nodes is underestimated because patients with nodes that became positive after a distant recurrence should also have been included in the analysis. They suggest that axillary dissection in all women with clinically negative ancillary nodes is justified. This suggestion may be relevant to achieving local control of disease; however, the data from this trial indicate that leaving positive nodes unremoved did not significantly increase the rate of distant recurrence or breast-cancer-related mortality.

Another point was made about there being no survival advantage for the RT plus total mastectomy group with negative nodes at 25 years follow-up. These findings agree with two other studies at 10 year follow-up (Cancer Research Campaign. Br Med J 1976;1:1035-8;

Cancer Research Campaign Working Party Lancet 1980;2:55-60), but differ from 3 studies reporting a 10% decrease in overall survival (Overgaard *et al* 1997, 1999; Ragaz *et al* 1997). They suggest that the use of systemic therapies in conjunction with postoperative RT may have relevance to these variations.

Ragaz, J., Olivotto, I. A., Spinelli, J. J., Phillips, N., Jackson, S. M., & Wilson 2005, "Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial", *Journal of the National Cancer Institute*, vol. 97, no. 2, pp. 116-126.

Design: RCT (1979-1986) Level 1++
 Country: Canada, setting: Multi-centre
 Aim: To determine the survival impact of locoregional radiation therapy in premenopausal patients with lymph node-positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy.

Inclusion criteria

Premenopausal women with breast cancer and pathologically positive axillary lymph nodes.

Exclusion criteria

Distant metastases, no other concomitant malignant disease. Macroscopic residual tumour.

Population number of patients = 318

Interventions

Modified radical mastectomy and axillary lymph node dissection before randomization
 N=164 received RT and chemotherapy
 N=154 received chemotherapy alone.
 128 ER positive patients were further randomized to oophorectomy or no oophorectomy.
 RT given by 5 field technique:
 Chest wall 37.5Gy in 16 daily fractions for 3-4 weeks
 Mid axilla dose of 35Gy in 16 fractions (supraclavicular/axillary field)
 Internal mammary-chain (bilateral) 37.5Gy in 16 fractions.

Outcomes

Event free survival (interval from date of diagnosis to: locoregional or systemic breast cancer recurrence, second malignancy, death from any cause).
 Disease free survival: (interval from date of diagnosis to date of first breast cancer recurrence-locoregional or systemic).
 Systemic disease-free survival (interval from date of diagnosis to date of first systemic breast cancer recurrence).
 Breast cancer-specific survival.
 Overall survival (diagnosis to date of death from any cause).
 Locoregional recurrence (in chest wall or regional lymph node areas- axillary, supraclavicular, internal mammary areas).

Follow up

20 year follow-up (median follow up for live patients: 249 months)

Results

A median of 11 axillary nodes were removed.
 191/318 had suffered a breast relapse
 190/318 had died (170 from breast cancer and 20 from other causes).

Locoregional recurrence

Isolated locoregional recurrences and any locoregional recurrences before systemic relapse were reduced in the RT arm in comparison to no RT. Consequently survival free of isolated locoregional and locoregional recurrence at any time was significantly improved in the RT arm compared with no RT. (See Table below):

Outcome	RT + chemotherapy	Chemotherapy	Relative Risk (95% CI)
Isolated locoregional recurrence	12/164 (7%)	27/154 (18%)	RR= 0.36 (95% CI, 0.18 to 0.71; P = 0.002) Favours RT
Survival free of isolated locoregional recurrence	90%	74%	
Any locoregional recurrence before systemic relapse	17/164 (10%)	43/154 (28%)	

Survival free of locoregional recurrence at any time	87%	61%	RR= 0.32 (95% CI, 0.18 to 0.57; <i>P</i> < 0.001) Favours RT
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Survival

Survival outcomes at a follow-up of 20 years are shown in the Table below.

Fewer events occurred amongst patients assigned to RT and chemotherapy for all outcomes (upper section of table). All survival Relative Risk values favoured the RT arm compared with no RT.

Outcome	Chemotherapy		RT + chemotherapy		RR (95% CI) p
	Survival (%)	n events/N patients	Survival (%)	n events/N patients	
Event free survival	25	116/154	35	105/164	0.70 (0.54 to 0.92) p=0.009
Breast cancer free survival	30	107/154	48	84/164	0.63 (0.47 to 0.83) p=0.001
Systemic breast cancer free survival	31	104/154	42	84/164	0.66 (0.49 to 0.88) p=0.004
Breast cancer specific survival	38	95/154	53	75/164	0.67 (0.49 to 0.90) p=0.008
Overall survival	37	101/154	47	89/164	0.73 (0.55 to 0.98) p=0.03

Comparison by lymph node status

Event free survival					
N1-3 (n=183)	32	62/92	44	51/91	0.71 (0.49 to 1.03)
N≥ 4 (n=112)	12	47/54	26	44/58	0.68 (0.45 to 1.03) *P=0.8
Breast cancer free survival					
N1-3 (n=183)	41	53/92	57	38/91	0.64 (0.42 to 0.97)
N≥ 4 (n=112)	12	47/54	34	38/58	0.59 (0.38 to 0.91) *P=0.7
Systemic breast cancer free survival					
N1-3 (n=183)	44	50/92	58	38/91	0.68 (0.45 to 1.04)
N≥ 4 (n=112)	11	47/54	33	38/58	0.63 (0.41 to 0.97) *P=0.7
Breast cancer specific survival					
N1-3 (n=183)	53	43/92	64	31/91	0.67 (0.42 to 1.06)
N≥ 4 (n=112)	17	46/54	35	37/58	0.66 (0.43 to 1.01) *P=0.9
Overall survival					
N1-3 (n=183)	50	49/92	57	41/91	0.76 (0.50 to 1.15)
N≥ 4 (n=112)	17	46/54	31	40/58	0.70 (0.46 to 1.06) P=0.7

*P = p value for interaction between subgroups for lymph node status

A further subgroup analysis was conducted by lymph node status (lower section of table): Analysis was by N1-3 vs. N≥4. All survival outcomes were consistently improved with the addition of RT. There were no statistically significant differences between survival outcomes for the N1-3 subgroup compared with N≥4.

The authors suggest that optimal locoregional therapy for high risk breast cancer may involve adequate axillary surgery and RT, but also RT to the internal mammary chain. It is not possible to determine from this study whether the benefit of radiation therapy observed would be compromised if the irradiated fields to the IMC were reduced (ipsilateral vs. bilateral).

Toxicity

The rate of non-breast cancer deaths was 8.5% (14/164) among patients treated with CT and RT, compared to 3.8% (6/154) of patients treated with CT alone (p=0.11).

Three (1.8%) cardiac deaths occurred in the CT+RT group vs. one (0.6%) in the CT group (p=0.622).

Arm oedema occurred in 15 (9.1%) of the CT+RT group, and 5 (3.2%) of the CT group (p=0.035). Six vs. one required intervention.

Limited asymptomatic apical lung fibrosis was seen in all RT treated patients, one (0.6%) developed interstitial pneumonitis.

General comments -

Overgaard, M., Jensen, M.-B., Overgaard, J., Hansen, P. S., Rose, C., Andersson, M., Kamby, C., Kjaer, M., Gadeberg, C. C., Rasmussen, B. B., Blichert-Toft, M., & Mouridsen, H. T. 1999, "Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group", *Lancet*, vol. 353, no. 9165, pp. 1641-1648

Design: RCT (1982-1990)

Level 1++

Country: Sweden, setting: Multi-centre

Aim: To compare adjuvant tamoxifen alone with tamoxifen plus postoperative radiotherapy in a randomised trial among postmenopausal women who had undergone mastectomy.

Inclusion criteria

Postmenopausal women with high-risk breast cancer, younger than 70 years of age. High risk status was defined as node positive, tumour size greater than 5 cm, invasion to skin or pectoral fascia, or any combination of these. Postmenopausal status defined as 5 years or more of amenorrhoea or, for women who had undergone hysterectomy, age over 55 years.

Exclusion criteria

Metastatic distant disease, macroscopic residual tumour.

Population number of patients = 1375 evaluable (1460 randomized)

Median age 62 years (range, 42-69 years).

Median tumour size 2.5cm (range, 0.2-13cm)

N0 n=132 (10%)

N1-3 n=794 (58%)

N>3 n=448 (33%)

Stage I 24%

Stage II 44%

Stage III 16%

Tumour size:

<2.1cm 38%

2.1-5.0cm 49%

>5.0cm 12%

Interventions

Surgery was total mastectomy with axillary-node dissection (removal of the central axillary lymph nodes involving level I and part of level II). The pectoral fascia was stripped leaving the major and minor pectoral muscles. A median of 7 lymph nodes were removed.

Radiotherapy target volume included the surgical scar and regional lymph nodes (the supraclavicular, infraclavicular, and axillary nodes, and internal mammary nodes in the four upper intercostal spaces). The dose was 50.0 Gy in 25 fractions in 35 days, or 48.0 Gy in 22 fractions over 38 days.

Randomization was to adjuvant tamoxifen (30 mg daily for 1 year) alone (689) or with postoperative radiotherapy to the chest wall and regional lymph nodes (686).

Outcomes

Overall survival (all deaths from any cause)

Locoregional recurrence was first site of failure (chest wall, axilla, supra/infraclavicular), alone or together with distant metastases (diagnosed within 1 month).

Disease-free survival was defined as freedom from locoregional or distant recurrence, cancer in opposite breast, other malignant disease, or death without recurrence.

Follow up

Median follow-up 123 months, and for those alive at the time of evaluation 119 months (range 77-166).

Results

Median time to death 46 months (range, 1-160 months).

732/1376 (53%) developed a recurrence.

819 patients had died (59%) at time of analysis.

Local and distant recurrence

Overall frequency of locoregional recurrence as first site of recurrence was 8% in RT + tamoxifen group and 35% in the tamoxifen only group.

Overall survival

There was a 9% absolute benefit in OS for the RT + tamoxifen group (45% [95% CI 41-49] vs. 36% [95% CI 33-40])

Site of first recurrence	RT plus tamoxifen (n=686) (%)	Tamoxifen only (n=689)	All patients (N=1375)
Distant metastases	269 (39%)	169 (25%)	438 (32%)
Locoregional	30 (4%)	203 (29%)	233 (17%) (p<0.001)
Distant metastases and locoregional	22 (3%)	39 (6%)	61 (4%)
All recurrences	321 (47%)	411 (60%)	732 (53%)

Site	(n=637)	(n=444)	(n=1081)
Chest wall	31 (16)	123 (17)	154 (33)
Axillary nodes	9 (2)	73 (8)	82 (10)
Supra/infraclavicular	7 (2)	29 (8)	36 (10)
Axilla and chest wall	3 (1)	9 (2)	12 (3)
Axilla and S/I nodes	0	5 (2)	5 (2)
Chest wall and S/I	2 (1)	3 (2)	5 (3)
All recurrences	52 (22)	242 (39)	294 (61)

Numbers in parentheses = numbers with concurrent distant metastases

The major prognostic factors in primary breast cancer were found to be tumour size, number of affected nodes, and grade of cancer from a multivariate analysis. The addition of RT seemed to be beneficial.

The addition of RT reduced locoregional recurrence. Most recurrences were in the chest wall for both treatment groups. Recurrences at other regional sites were generally lower with RT (test of significance not reported). Supraclavicular and infraclavicular recurrences were associated with distant recurrences in both groups. Axillary and chest wall recurrences more commonly occurred alone.

In patients with less advanced disease (tumours < 5cm) disease-free survival (37% [95% CI 32-42] for RT vs. 25% [21-30] for tamoxifen only; p<0.01) and overall survival (47% [95% CI 42-52] for RT vs. 40% [35-44] for tamoxifen only, p<0.07) were better in the RT group.

The survival analysis results shown in the table below indicate an effect of time since surgery on survival, with the RT group benefiting the most, and those with fewer positive nodes benefiting most in the short term. For long-term effects, the number of positive lymph nodes, and radiotherapy, were the only variables of independent significant importance.

Cox proportional hazard model by time since surgery

Adjusted estimates	Any recurrence after 2 years (n=879)		Death after 4 years (n=877)	
	Relative risk (95% CI)	p	Relative risk (95% CI)	p
Positive nodes				
0-3	1.00		1.00	
>3	2.18 (1.80-2.64)	<0.001	1.97 (1.58-2.45)	<0.001
Radiotherapy				
Tamoxifen alone	1.00		1.00	
RT and tamoxifen	0.64 (0.54-0.77)	<0.001	0.68 (0.55-0.83)	<0.001

Author conclusions

Postoperative radiotherapy decreased the risk of locoregional recurrence and was associated with improved survival in high-risk postmenopausal breast cancer patients after mastectomy and limited axillary dissection, with 1 year of adjuvant tamoxifen treatment. Improved survival in high-risk breast cancer can best be achieved by a strategy of both locoregional and systemic

tumour control.

General comments -

Olivotto, I. A., Chua, B., Elliott, E. A., Parda, D. S., Pierce, L. J., Shepherd, L., Vallow, L. A., White, J. R., & Whelan, T. J. 2003, "A clinical trial of breast radiation therapy versus breast plus regional radiation therapy in early-stage breast cancer: The MA20 trial", *Clinical Breast Cancer*, vol. 4, no. 5, pp. 361-363.

Design: RCT – description of procedures
Country: Multinational, setting: Hospital

Inclusion criteria

Patients with invasive breast cancer who are node positive (if node negative then tumour size > 2.0cm); BCS plus axillary sampling; systemic therapy with chemotherapy, hormones or both; moderate to high risk of regional recurrence; ECOG performance status of 0-2 and life expectancy > 5 years.

Exclusion criteria

Metastatic or locally advanced disease; residual disease in axilla after dissection; pregnancy.

Population number of patients = 784 in Dec 2003, planned accrual 1822.

Interventions

Stratification of patients by number of positive nodes, number of nodes removed, type of chemotherapy and/or hormonal therapy, treatment centre.

Randomization to standard breast RT vs standard breast RT + RT to the regional lymph nodes.

The axilla is treated only if there are < 4 involved nodes or < 10 lymph nodes recovered.

Outcomes

Follow up

Results

Recruitment complete Feb 2007.

General comments -

Ongoing trials

MA20

A Phase III Study of Regional Radiation Therapy in Early Breast Cancer

Eligibility: Pre or post menopausal women with node positive and high risk node-negative breast cancer treated by breast conserving therapy and currently accepted adjuvant chemotherapy and/or hormonal therapy

Objectives: To determine if regional radiation therapy (to the ipsilateral supraclavicular, axillary and internal mammary nodes) in addition to breast radiation prolongs survival in women with early breast cancer compared with breast radiation alone. To compare disease free survival, isolated local regional disease-free survival, and distant disease free survival. To evaluate toxicity. To evaluate quality of life. To determine the cosmetic outcome of these two treatment approaches.

NCT Registration ID (from clinicaltrials.gov): NCT00005957

Participation: Not limited.

Coordination: Intergroup(NCIC CTG)

Status: Closed

Activation Date: December 14, 1999 , Closing Date: February 02, 2007

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Earlier details published in:

Olivotto, I. A., Chua, B., Elliott, E. A., Parda, D. S., Pierce, L. J., Shepherd, L., Vallow, L. A., White, J. R., & Whelan, T. J. 2003, "A clinical trial of breast radiation therapy versus breast plus regional radiation therapy in early-stage breast cancer: The MA20 trial", *Clinical Breast Cancer*, vol. 4, no. 5, pp. 361-363.

Observational Studies (e.g. Prospective Cohort or Retrospective Cohort or Case Series):

Surgery and radiotherapy to the breast (and tumour bed) with or without regional RT to nodes

Livi, L., Paiar, F., Simontacchi, G., Barca, R., Detti, B., Fondelli, S., Bastiani, P., Santini, R., Scotti, V., Bianchi, S., Cataliotti, L., Mungai, V., & Biti, G. 2006, "Loco regional failure pattern after lumpectomy and breast irradiation in 4185 patients with T1 and T2 breast cancer. Implications for nodal irradiation", <i>Acta Oncologica</i> , vol. 45, no. 5, pp. 564-570		
Design: Non-randomised study (NRS) Cohort	(1980-2001)	Level 3
Country: Italy, setting: Single university centre		
Aim: To determine incidence and risk factors for loco regional failure (LRR) (breast, supraclavicular, axillary and internal mammary nodes) and indications for nodal irradiation.		
Inclusion criteria		
Patients without clinical and radiographic evidence of local or distant recurrence after surgery at the time of the first evaluation in the radiotherapy unit.		
No previous malignant disease.		
Exclusion criteria		
Population number of patients = 4185		
Median age 55 years (range 19-86)		
pT1	66.4%	
pT2	33.6%	
N0	69%	
N1-3	20%	
N>3	9%	
ER negative	14%	
ER positive	55%	
Unknown	31%	
Interventions		
Wide excision n=919		
Quadrantectomy n=3266		
Axillary dissection n=3889 (93%)- median 16 nodes removed.		
RT to whole breast with tangential fields (mean dose 50Gy in 2Gy fractions, photons), then tumour bed boost (6-10Gy for negative margins and 14-16Gy positive margins, electrons).		
972 (23.3%) did not receive a boost.		
No RT to nodes.		
924 (21%) received chemotherapy.		
1504 (36%) received tamoxifen.		
Outcomes		
Locoregional recurrence (LRR) –in breast, supraclavicular, axillary and internal mammary nodes. Defined as first site of recurrence and when loco-regional failure was followed by distant metastases not before 6 months.		
Node relapse (NR) any relapse in axilla, internal mammary chain or supraclavicular fossa.		
Supraclavicular relapse (SCR)		
Follow up		
Median 8 years (range 3mths to 20 years)		
Results		
Most of the data were descriptive, however a multivariate analysis was also conducted using variables considered to be of clinical significance as well as statistically significant variables.		
<i>Survival</i>		
Breast cancer deaths	526/4185	(12.5%)
Other deaths	176/4185	(4.2%)
Alive	3512/4185	(83.9%)
Actuarial cause specific survival:		

3 years 96.9% (SE± 0.2%) 5 years 93.1% (SE± 0.4%) 10 years 83.7% (SE± 0.6%)

Locoregional recurrence

LRR median time for all relapses 3.9 years (6 mths-19 years)

224/4185 (5.3%) had locoregional failure.

Median time to node relapse 2.7 years

Site of relapse:

Breast 166/4185 (3.9%)

NR (any relapse in axilla, internal mammary chain or supraclavicular fossa) 58/4185 (1.3%)

SCR (supraclavicular relapse) 33/4185 (0.7%)

The distribution of sites of recurrence in breast and node areas are listed in the table below:

Sites of locoregional recurrences

Site of recurrence	N of patients (n=224/4185)	%
Breast		
Non-operated quadrant	46	17
Index quadrant	110	36
Unknown quadrant	8	3
Multicentric relapse	2	0.7
Supraclavicular	33	15
Axilla	14	6
Internal mammary chain	11	5

(Note- percentage values do not add up to 100)

Rates of locoregional recurrences by site are listed in the following table:

Outcome	3 year actuarial rate	5 year actuarial rate	10 year actuarial rate
LRR	2.3% (SE± 0.2%)	4.3% (SE± 0.4%)	7.4% (SE± 0.5%)
SCR	0.6% (SE± 0.1%)	0.9% (SE± 0.2%)	1% (SE± 0.1%)
NR	1.0% (SE± 0.1%)	2.0% (SE± 0.2%)	2% (SE± 0.2%)

LRR by age group

Less than 40 years at diagnosis LRR (14.4%, 49/339)

40-49 years LRR (8.2%, 83/1006)

50-59 years LRR (4.2% 56/1310)

60-69 years LRR (2.8%, 31/1101)

70-79 years LRR (1.2%, (5/400)

> 80 years LRR (0%, 0/29)

Higher rates of LRR were observed in younger age groups than older age groups (p=0.00001). A further analysis of LRR by site of relapse and age distribution is shown in the following table.

Correlation between age and LRR

Age	N of patients	Breast	Node relapse	SCR
<40 years	339	44 (12%)	5 (1.4%)	2 (0.5%)
40-49	1006	65 (6.4%)	18 (1.7%)	11 (1%)
50-59	1310	36 (2.7%)	20 (1.5%)	10 (0.7%)
60-69	1101	19 (1.7%)	12 (1%)	8 (0.7%)
70-79	400	2 (0.5%)	3 (0.7%)	2 (0.5%)
>80	29	0	0	0

Univariate analyses of LRR, NR and SCR found significantly more recurrences in pT2 tumours than pT1, and in women with N3+ than N0 axillary lymph nodes.

LRR	pT1 4% (110/2779)	pT2 9.1% (114/1406)	P=0.0002
NR	pT1 0.8% (25/2779)	pT2 2.3% (33/1406)	P=0.04
SCR	pT1 0.5% (14/2779)	pT2 1.3% (19/1406)	P=0.02
LRR	N0	N<3	P=0.3
LRR	N0	N3+	P=0.02

LRR	N1-3	N3+	P=0.05
SCR	N0 0.4% (12/2870)	N1-3 0.9% (8/823)	P=0.9
SCR	N0 0.4% (12/2870)	N3+ 3.3% (13/392)	P=0.01
NR	N0 0.8% (24/2870)	N1-3 1.7% (14/823)	N3+ 4.8% (19/392) P=0.007

Similar analyses for patients with positive angiolymphatic invasion found 6% (29/485) of LRR occurred versus 3% (61/2068) for those with negative angiolymphatic invasion ($p=0.001$). When comparing positive angiolymphatic invasion with positive axillary lymph nodes, there was no statistically significant difference for NR in patients with positive lymph nodes ($p=0.6$). The difference was statistically significant ($p=0.0001$) for patients with negative lymph nodes.

A poorer prognosis ($p=0.002$) was found in high grade tumours compared with intermediate and low-grade tumours (LRR rates of 3.1% (24/754), 1.8% (14/775) and 1.2% (7/575) respectively).

Other prognostic factors including site of tumour, extracapsular extension, multifocality and different histological types, did not show any statistical significance on univariate analysis for LRR, NR and SCR.

A multivariate analysis of prognostic factors for LRR found that Grade 3 tumour ($p=0.01$), age at presentation ($p=0.001$), more than three positive lymph nodes ($p=0.004$), pT2 ($p=0.001$) and angiolymphatic invasion ($p=0.02$) were statistically significant parameters. In the multivariate analysis for NR pT2 ($p=0.02$), angiolymphatic invasion ($p=0.002$) and more than three positive lymph nodes ($p=0.001$) were statistically significant. These findings are reported in the following tables.

Multivariate analysis for LRR

Parameter	Hazard ratio (95% CI)	p value
Grade		
G1	1	
G2	1.3 (0.5-3.2)	0.54
G3	2.6 (1.1-5.9)	0.01
Age (years)		
50-59	1	
< 40	2.2 (1.6-3.1)	<0.001
40-49	1.3 (1.0-1.7)	0.003
60-69	0.6 (0.4-0.9)	0.01
70-79	0.4 (0.2-0.8)	0.01
>80	0.4 (0.4-7.0)	0.45
Lymph node status		
Negative	1	
N+ 1-3	0.9 (0.7-1.2)	0.7
N+ >3	1.6 (1.1-2.3)	0.004
Angiolymphatic invasion		
None	1	
Present	1.5 (1.1-2.2)	0.002
pT1	1	
pT2	1.4	<0.001

Multivariate analysis for NR

Parameter	Hazard ratio (95% CI)	p value
Lymph node status		
Negative	1	
N+ 1-3	1.7 (0.8-3.2)	0.11
N+ >3	4.8 (2.5-9.1)	<0.001
Angiolymphatic invasion		
None	1	
Present	3.18 (1.4-6.8)	0.002
pT1	1	
pT2	1.8 (1.07-3.1)	0.002

Author conclusions

It is not necessary to prescribe nodal irradiation to patients with negative or one to three positive axillary nodes. Regarding patients with more than three positive axillary nodes, the number of isolated Nodal Relapse is also small to routinely justify a node irradiation.

General comments -

Fortin, A., Dagnault, A., Blondeau, L., Thuc, T. T., & Larochelle, M. 2006, "The impact of the number of excised axillary nodes and of the percentage of involved nodes on regional nodal failure in patients treated by breast-conserving surgery with or without regional irradiation", *International Journal of Radiation Oncology Biology Physics*, vol. 65, no. 1, pp. 33-39.

Design: NRS Cohort (1972-1997) Level 3

Country: Canada, setting: Single hospital

Aim: After breast-conserving surgery, recommendations for regional nodal radiotherapy are usually based on the number of positive nodes. This number is dependent on the number of nodes removed during the axillary dissection. This study examines whether the percentage of positive nodes may help to select patients for regional radiotherapy.

Inclusion criteria

Node positive, stage T1-T2 invasive breast cancer who had received at least 44Gy RT to the breast.

Exclusion criteria Not reported

Population number of patients = 1372

Median age 53 years (LQ 45, UQ 62)

T1 690 patients

T2 678 patients

Median number of nodes excised 11

N1-3 922 patients

N>3 446 patients (N>7 =156 patients)

472 (34%) patients had regional irradiation:

217 (23.5%) with N1-3

255 (55%) with N>3 nodes

96 (61%) with N>7 nodes

Interventions

Breast conservation surgery usually consisted of a lumpectomy with wide margins.

RT to the whole breast was a dose of either 50 Gy or 45 Gy in 25 or 20 fractions respectively over 4 weeks.

Those receiving regional RT were treated with 44Gy through an anterior supraclavicular-axillary field with a posterior axillary boost. The supraclavicular fossa received a dose of 40 Gy given at 3 centimeters.

Patients receiving regional RT n=477

Patients not receiving regional RT n=904

Nodal irradiation was carried out at the discretion of the radiation oncologist and varied over the years. In the first years of the study, all node-positive patients received locoregional radiotherapy. Later some oncologists only irradiated patients with more than 3 positive nodes.

Outcomes

Regional failure (axilla, supraclavicular)

Percentage of positive nodes was defined as the quotient of positive nodes over nodes removed.

Follow up

Patients were followed at regular intervals of every 3 to 6 months for the first 5 years and then every year. Median follow-up of patients not receiving regional RT was 5.4 years.

Results

The number of positive nodes was directly proportional to the number of nodes removed ($p < 0.00001$).

a) Impact of number of nodes removed (% of involved nodes) on axillary failure in patients not receiving regional radiotherapy

Of 904 patients (no regional RT) 710 had N1-3 and 194 had N>3

Median follow-up 5.4 years.

Negative hormone receptor status (logrank $p= 0.009$) and local failure (logrank $p= 0.008$) were the only factors associated with axillary failure.

The authors reported a trend for patients with extracapsular extension (ECE) to have more axillary failure ($p = 0.1$).

Those factors that were not statistically significant were:

Age <40 vs. > 40 years

T stage T1 vs T2

Number of positive nodes (N1-3, N4-8, N>8)

Histology

Grade 1 vs. grade 2-3

Node size <2cm vs > 2cm

ECE no or not specified vs. yes

Hormone therapy

Chemotherapy

Axillary control vs. number of nodes removed

For patients with > 10 nodes (complete) removed or incomplete axillary dissection there was no difference in axillary control in the overall group or in the subgroups of patients with 1–3 positive nodes or >3 positive nodes.

There was no difference in axillary control when patients were grouped by number of nodes removed (1–6 nodes, 7–10 nodes, 11–16 nodes, and >16 nodes). The number of nodes removed did not influence the axillary failure rate.

Axillary control vs. percentage of positive nodes

Positive nodes were classified into three categories:

For patients with 1–3 positive nodes:

<20%, 20–40%, and ≥40%.

For patients with >3 positive nodes:

<20%, 20–50%, and ≥50%.

Axillary control rates were found to be the same in the lower node groups (<20% and 20–40% for N1–3 or <20% and 20–50% for N>3) and were combined as (<40% for N1–3 and <50% for N > 3). The crude and 10 year axillary control rates are shown in the following table for patients not receiving regional RT.

Axillary control and percentage of involved nodes

Percentage involved nodes	Crude failure rates	10 year axillary control	p value (log-rank)
All patients			
<40	11/753 (1.5%)	97.5	0.007
≥40	7/151 (4.5%)	91.3	
N 1-3			
<40	9/670 (1.3%)	97.5	0.08
≥40	2/43 (4.6%)	93	
N >3			
<50	2/84 (2.4%)	98	0.3
≥50	5/102 (4.7%)	91	

(For “All patients” percentage of involved nodes was ± 40% if N1-3 and ± 50% if N>3)

From the table there were significantly more axillary failures in patients classified as ≥40/50% when all patients were analyzed. The authors suggest that the differences between the percentage of involved nodes in N1-3 and N>3 subgroups were not significant because of low patient numbers.

Cox modelling of all Node positive patients showed that the percentage of positive nodes (hazards ratio = 3.6, $p = 0.02$) and local failure (hazards ratio = 3.1, $p = 0.04$) were associated with axillary failure, whilst the number of nodes removed, T stage, age, grade, and systemic

treatment were not significant.

b) Impact of regional RT by % of involved nodes

477 consecutive node positive patients received axillary RT.

Results for axillary, supraclavicular, regional, and locoregional control in patients receiving regional radiotherapy and those not receiving regional radiotherapy classified by node status are shown in the following table. Confidence intervals for hazard ratios were not reported, significant differences in bold font.

	Group	No regional RT (N and 10 yr control)	Regional RT (N and 10 yr control)	P value (log-rank)	Cox adjusted hazards ratio and p value
Axillary failure	All N+	98% (N=904)	96.5% (N=477)	0.2	0.5 p=0.2
	Ratio <40	97.5% (n=753)	99% (n=234)	0.7	0.5 p= 0.4
	Ratio ≥40	91% (n=150)	98% (n=239)	0.01	0.16 p=0.02
	N1-3	97.5% (N=713)	99% (N=217)	0.2	0.23 p=0.15
	Ratio <40	95% (n=669)	97% (n=152)	0.3	0.36 p=0.3
	Ratio ≥40	93% (n=43)	100% (n=62)	0.08	NA
	N3+	94% (n=191)	97% (n=260)	0.2	0.5 p=0.26
	Ratio <50	97% (n=84)	96% (n=82)	0.98	NA
	Ratio ≥50	91% (n=107)	98% (n=177)	0.06	0.23 p=0.08
Supraclavicular failure	All N+				
	Ratio <40	95%	99%	0.02	0.26 p=0.06
	Ratio ≥40	92%	98%	0.04	0.34 p=0.06
	N1-3	96%	99%	0.08	0.35 p=0.1
	Ratio ≥40	88%	98%	0.1	0.20 p=0.1
	N3+	93%	100%	0.1	NA
Ratio ≥50	94%	98%	0.2	0.40 p=0.1	
Regional failure	All N+				
	Ratio <40	92%	98%	0.01	0.29 p=0.01
	Ratio ≥40	82%	95%	0.0005	0.25 p=0.001
	N1-3	94%	99%	0.01	0.23 p=0.04
	Ratio ≥40	80%	98%	0.01	0.10 p=0.04
	N3+	80%	98%	0.01	0.25 p=0.08
Ratio ≥40	82%	94%	0.01	0.32 p=0.01	

Axillary failure

For all node positive patients regional RT was beneficial for patients classified as ≥40%/50% of positive nodes (p=0.01) from the figure of the probability of axillary control shown in the original paper. It was not beneficial for patients with lower percentages of positive nodes. In patients with N1-3 and N>3 positive nodes, regional RT also reduced axillary failure rates in patients with a high percentage of positive nodes but this was not statistically significant.

Supraclavicular and locoregional failure

For all node positive patients, regional RT reduced the rate of supraclavicular failure in groups of patients with a high percentage and a lower percentage of positive nodes. For N1-3 and N>3 subgroups the decrease was not statistically significant (low statistical power).

RT reduced the locoregional failure rates (axillary or supraclavicular) for all patient subgroups, although there was a tendency for those with higher ratios of involved nodes to receive regional RT (selection bias).

Summary (from paper):

- The number of nodes removed did not have an impact on axillary failure in node-positive patients treated by breast conserving surgery and radiotherapy to the breast alone.
- The percentage of involved nodes was associated with axillary failure. In patients with >40% (for N1–3 positive nodes) and >50% (for N > 3 positive nodes), the rates of axillary failure were significantly increased.
- In patients with a high percentage of involved nodes, regional radiotherapy was

associated with increased axillary control.

- Regional radiotherapy did not increase the rate of axillary control for patients with lower percentages of involved nodes.
- Regional radiotherapy was associated with better regional control (axillary or supraclavicular control), even among patients with lower percentages of involved nodes.

Author conclusions

The percentage of involved nodes should be taken into consideration in selecting patients for regional radiotherapy. Irradiation of the axilla should be reserved for patients with a specific ratio of > 40% involved nodes if N1-3 and $\geq 50\%$ involved nodes if N > 3 nodes.

General comments -

Pejavar, S., Wilson, L. D., & Haffty, B. G. 2006, "Regional nodal recurrence in breast cancer patients treated with conservative surgery and radiation therapy(BCS plus RT)", *International Journal of Radiation Oncology Biology Physics*, vol. 66, no. 5, pp. 1320-1327.

Design: NRS Cohort (1973-2000) Level 3

Country: USA, setting: Single institution

Aim: To review regional lymph node management in a large cohort of conservatively treated breast cancer patients with the aim of describing treatment practices, to identify the incidence and predictors of nodal relapse.

Inclusion criteria

Women with Stage I to II invasive breast cancer treated with conservative surgery followed by RT to the breast.

Exclusion criteria

None reported

Population number of patients = 1920

Mean age 56.4 years, median 57 yrs. 65% ≥ 50 yrs

T1 80%

T2 20%

Negative surgical margins 52%

Unknown margins 32%

Interventions

All patients had conservative surgery followed by RT with tangential fields to the intact breast with 4-6 MeV linear accelerators. A median dose of 48Gy (40-60Gy) was delivered over 5-7 weeks in daily 2Gy fractions. An electron beam boost to the tumour bed of 64Gy (50-72Gy) was also applied.

1330 (69%) of patients had axillary lymph node dissection (more frequently in later years).

Most axillary dissections (AXDs) were Level I and II, and 65% had > 10 nodes sampled.

346/1330 patients (26%) had pathologically involved lymph nodes.

Regional lymph node irradiation was administered to the majority of patients.

- 1) Patients undergoing AXD (1330, 69%) were treated to the breast alone if pathologically node-negative, or to the breast and supraclavicular nodes if pathologically node-positive. There was a general policy to include the supraclavicular fossa (without axillary radiation) in all node-positive patients, including those with 1-3 positive nodes (46Gy, depth 3cm). Radiation treatment to the internal mammary nodes was highly individualized and delivered with alternating photons and 13MeV electrons (median dose 46Gy, depth 3 cm).
- 2) Patients with no AXD (590, 31%).

Supraclavicular and axillary nodes were irradiated, with or without an additional internal mammary field.

Axillary lymph nodes were irradiated by extending the lateral border of the supraclavicular field laterally to include the entire humeral head and clear all axillary contents.

A total median dose of 46 Gy at 3 cm was prescribed.

The patients undergoing SNLB are not reported in the evidence table.

Treatment characteristics reported in the paper are shown below:

Treatment characteristics (n=1920)

	% (n)	Median dose
--	-------	-------------

Axillary dissection		
No	30.7 (590)	
Yes	69.3 (1330)	
Histologically node-positive	26.0 (346)	
Histologically node-negative	74.0 (984)	
Nodes sampled		
None	0.6 (8)	
1-5	14.1 (187)	
6-10	20.4 (272)	
>10	64.9 (863)	
Radiation technique		
Tangents only	46.0 (884)	48 Gy /64 Gy
Tangents + nodal RT	53.4 (1025)	wBoost
SC	23.7 (243)	46 Gy
SC, axilla	27.4 (281)	46 Gy
IM, SC	22.0 (225)	46 Gy
IM, SC, axilla	26.2 (269)	46 Gy
Other	0.7 (7)	
Unknown	0.6 (11)	
Adjuvant chemotherapy		
No	70.2 (1348)	
Yes	29.6 (568)	
Unknown	0.2 (4)	
Adjuvant hormonal therapy		
No	64.7 (1242)	
Yes	34.4 (661)	
Unknown	0.9 (17)	

SC = supraclavicular
IM = internal mammary

Outcomes

Breast failure- histologically confirmed tumour in the ipsilateral breast.

Regional node relapse- clinical failure in the ipsilateral axilla, supraclavicular fossa, infraclavicular fossa, or internal mammary chain as first sight of failure.

Distant failure - any clinical and/or radiographic evidence of metastatic disease.

Patients with recurring carcinoma in the breast and pathologic nodes at the time of breast failure, but without clinical signs of regional nodal failure, were not classified as nodal relapses.

Follow up Median 13 years.

Results

Regional nodal relapses n= 36

5 year and 10 year actuarial nodal recurrence-free rates of 98% and 97%, respectively.

The crude survival and recurrence statistics of the 1920 patients are listed in the table below.

Of these 36 relapses:

18 (50%) occurred in the axilla

14 (39%) in the supraclavicular fossa

2 (5.6%) in the infraclavicular fossa

1 (2.8%) in the internal mammary chain

1 (2.8%) in an unclear location.

More than half (20) were in-field failures.

Pattern of failure	Percentage (n)
Patient status:	
No evidence of disease (alive or dead)	89.6 (1720)
With disease (dead)	10.3 (198)
With disease (alive)	0
Unknown	0.1 (2)
Nodal relapse	1.9 (36)

Breast relapse	8.8 (169)
Distant relapse	13.6 (262)

Patterns of nodal relapse by treatment technique and node status for the 36 nodal relapses are shown in the following table:

Nodal relapse patterns

	% (n)
Nodal status	
No axillary dissection	33.3 (12)
Axillary dissection	66.7 (23)
Node positive	69.6 (16)
Node negative	30.4 (7)
Treatment technique	
Tangents only	25.0 (9)
Tangents + nodal RT	75.0 (27)
SC	37.0 (10)
SC, axilla	11.2 (3)
IM, SC	14.8 (4)
IM, SC, axilla	37.0 (10)

There were no significant differences in the regional nodal control rates when analyzed as a function of regional treatment (AXD vs. regional nodal radiation).

Recurrence free rates between patients undergoing AXD and those receiving nodal irradiation without AXD were similar. The nodal recurrence free rates are reported below:

	5 years	10 years
Patients with AXD (+ SC RT if node +ve)	98.3%	97.4%
Patients with no AXD (+ SC and axillary RT)	98.5%	97.9%

Nodal control rates differed for age, race, pathological node status and systemic treatment regimes.

Node control rates by node status

Pathological Node status	Node control rate
N0	98.7%
N1-3	97.8%
N-4-10	92.4%
N>10	82.9%
Caucasian patients (10 yr)	98.1%
African- American (10yr)	91.8%
Age < 35 yr (10 yr)	92.9%
Age 36-49 yr (10 yr)	95.6%
Age > 50 yr	98.8%
No chemotherapy (10 yr)	98.7%
Chemotherapy treated	94.2%
No hormone therapy	96.8%
Hormone therapy	99.4%

Chemotherapy patients were more likely to be node positive and in the subset of node positive patients, there was no difference in nodal control as a function of chemotherapy.

Possible prognostic factors for nodal recurrence were evaluated including age, race, stage, AXD status, pathologic lymph node status, chemotherapy, hormonal therapy, and oestrogen /progesterone receptor status. A univariate chi-squared analysis found that age <40 years, non Caucasian race, and positive pathologic nodal status significantly correlated with increased risk of nodal relapse. In a multivariate step-wise regression model, age, race, and pathological nodal status remained independent significant predictors of nodal failure. The values are reported in the table.

Prognostic factors for nodal recurrence

Variable	P value
Age < 35 year	<0.0001
Pathological node positive	<0.0001

Non-Caucasian	0.003
Histology	0.055
T stage	0.06
Axillary dissection	NS
Margin status	NS
Family history	NS
ER status	NS
PR status	NS

Actuarial survival rates were poor with patients having axillary relapse only having a better prognosis at 5 years than those failing in the supraclavicular fossa, infraclavicular fossa or internal mammary chain.

Actuarial survival values at 5 and 10 years after nodal relapse are reported below:

	5 year actuarial survival	10 year actuarial survival
Nodal recurrence	31%	12%
Axilla relapse alone	44.2%	NR

Patients failing in the axilla also developed distant metastases less often than patients failing at other sites (5 yr actuarial distant relapse-free rates 13% vs <7%). The numbers were too small to draw firm conclusions.

Author conclusions:

In patients undergoing BCS+RT, both regional nodal irradiation and AXD (including SNB) resulted in equally high rates of regional nodal control. Nodal RT may also be an effective treatment for SN-positive patients.

General comments -

Tai, P., Joseph, K., Sadikov, E., Mahmood, S., Lien, F., & Yu, E. 2007, "Nodal ratios in node-positive breast cancer--long-term study to clarify discrepancy of role of supraclavicular and axillary regional radiotherapy", *International Journal of Radiation Oncology, Biology, Physics*, vol. 68, no. 3, pp. 662-666.

Design: NRS registry data (1981-1995) Level 3

Country: Canada. setting: Single province

Aim: To study the absolute number of involved nodes/the number of nodes examined or the nodal ratio (NR) in breast cancer. The primary study endpoint was to evaluate the role of supraclavicular and axillary radiotherapy (SART) according to the NR.

Inclusion criteria

Node positive patients from register with ≥10 nodes dissected

Exclusion criteria

Not reported

Population number of patients = 1985

1255 had ≥10 nodes dissected

Mean age 62 (range 36-94) years

Other characteristics:

	LNR	MNR	HNR
Patients	667	389	199
Premenopausal	149 (22%)	72 (19%)	39 (20%)
Postmenopausal	501 (75%)	298 (77%)	149 (75%)
Pathological stage:			
T1	334 (50%)	128 (33%)	46 (23%)
T2	269 (40%)	189 (49%)	80 (40%)
T3	26 (3.9%)	37 (9.5%)	32 (16.1%)
T4	21 (3.1%)	30 (7.7%)	35 (17.6%)
N1	661 (99%)	378 (97%)	173 (87%)
N2	3 (0.4%)	9 (2.3%)	22 (11.1%)
N3	1 (0.2%)	0	2 (1.0%)
M0	651 (98%)	369 (95%)	168 (84%)
Involved nodes (n):			
1-3	610 (91.5%)	36 (9.3%)	0 (0%)
4-9	57 (8.5%)	307 (79%)	20 (10%)
>9	0 (0%)	46 (11.8%)	179 (90%)

LNR = Low Node Ratio

MNR= Medium Node Ratio

HNR = High Node Ratio

Interventions

The surgical treatments included lumpectomy (n= 286, 23%) or mastectomy (n= 969, 77%).

Patients undergoing RT had different combinations of fields applied at the discretion of the radiation oncologists and included breast or chest wall, supraclavicular fossa, axilla, and/or internal mammary chain.

Systemic treatments included chemotherapy (461/1255, 37%) with cyclophosphamide, methotrexate and 5-fluorouracil; 5-fluorouracil, adriamycin, and cyclophosphamide; adriamycin and cyclophosphamide; and/or tamoxifen (646/1255, 51%).

Patients were divided into one to three, four to nine, and more than nine involved nodes. The patients were categorized into three NR groups: low (LNR ≤25%), medium (MNR >25% to ≤75%), and high (HNR >75%). This categorization followed previous studies using British Columbia data and American data.

Outcomes

Time to first recurrence
 OS (Overall survival)
 Cause Specific Survival (CSS)

Follow up Not reported

Results

Median number of nodes examined was 14 (range 10-38).
 Median number of positive nodes 3 (1-38)

NR Categories:

LNR = 667

MNR=389

HNR=199

The NR were found to correlate significantly with primary tumour size, clinical stage group, pathological stage group and the risk of any first recurrence as shown in the table below:

Association of NR and tumour characteristics

Characteristic	LNR	MNR	HNR	P (chi-square test)
Primary tumour size (cm)				2.2×10^{-16}
≤ 2	334	128	46	
> 2 to ≤ 5	269	189	80	
> 5	47	67	67	
Clinical stage				5.5×10^{-16}
I	126	36	9	
II	244	165	62	
III	14	22	28	
IV	7	7	4	
Pathological stage				$< 2.2 \times 10^{-16}$
I	5	2	0	
II	591	296	97	
III	48	67	66	
IV	14	17	30	
Recurrence				5.0×10^{-15}
Local	74	53	27	
Regional nodes	58	40	23	
Distant	195	167	115	
None	398	181	49	

Staging according to Fifth American Joint Commission on Cancer

Recurrences were counted for each category, some patients had a combination of recurrences (double counting)

The effects of supraclavicular and axillary radiotherapy (SART) on time to first recurrence, 10 year overall survival (OS) and 10 year cause specific survival (CSS) compared with no SART are shown in the following table and categorized by nodal ratios. The effects of SART were significant in improving outcomes at medium and high node ratios but not at low node ratios.

OUTCOME	LNR	MNR	HNR
Median time to first recurrence (months)			
With SART	191	130	33
Without SART	193	61	24
	P=0.29	P=0.0009	P=0.12
Overall survival (OS) (10 year)			
With SART	57%	48%	19%
Without SART	58%	34%	10%
	P=0.18	P=0.007	P=0.005
Cause Specific Survival (10 year)			
With SART	68%	57%	26%
Without SART	71%	43%	14%
	P=0.32	P=0.002	P=0.005

SART = supraclavicular and axillary RT

A multivariate analysis of data from the 1,255 patients showed that SART ($p < 0.0001$), age ($p < 0.0001$), NR ($p = 0.002$), clinical stage ($p = 0.01$) and pathological stage ($p = 0.0004$) were significant factors for OS. Whilst SART ($p < 0.0001$), Nodal Ratio ($p = 0.005$), clinical stage ($p = 0.02$), pathological stage ($p = 0.0009$), tumour grade ($p = 0.017$) and performance status ($p = 0.03$) were significant factors for CSS.

Radiotherapy to the Internal Mammary Chain field was not significant for OS or CSS ($p = 0.42$, $p = 0.47$ respectively) on multivariate analysis. Similarly RT to the breast or chest wall was also not significant for OS or CSS ($p = 0.79$, $p = 0.69$ respectively) on multivariate analysis.

Effect of regional RT on Cause Specific Survival

For 1,255 patients with ≥ 10 nodes examined from the axilla, supraclavicular fossa and axillary regional RT did not significantly improve cause-specific survival for the LNR group ($p = 0.32$); but was significant for the MNR ($p = 0.002$) and HNR groups ($p = 0.005$).

Effect of regional RT on Overall Survival

For 1,255 patients with ≥ 10 nodes examined from the axilla, supraclavicular fossa and axillary regional RT did not significantly improve overall survival for the LNR group ($p = 0.18$); but was significant for the MNR ($p = 0.007$) and HNR groups ($p = 0.005$).

Author conclusions

Node Ratio is a useful prognostic factor. The study demonstrates that for patients with 10 or more nodes resected, regional RT significantly improves survival for the MNR and HNR groups, but not for the LNR group.

General comments -

Grills, I. S., Kestin, L. L., Goldstein, N., Mitchell, C., Martinez, A., Ingold, J., & Vicini, F. A. 2003, "Risk factors for regional nodal failure after breast-conserving therapy: Regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes", *International Journal of Radiation Oncology Biology Physics*, vol. 56, no. 3, pp. 658-670

Design: NRS Cohort (1980-2000) Level 3
 Country: USA, setting: Single hospital
 Aim: To determine the incidence of, and risk factors for, regional nodal failure (RNF) and to evaluate the effectiveness of, and indications for, regional nodal irradiation (RNI) in patients with Stage I-II breast cancer treated with breast-conserving therapy.

Inclusion criteria

Women with Stage I or II breast cancer

Exclusion criteria

None reported

Population number of patients = 1550

Median age 59 yrs (range 25-92)

40% (604) of patients had complete data available on tumour pathology

1411 (94%) of patients had at least a level I-II axillary lymph node dissection

Median nodes excised for all patients = 14

More than 10 nodes excised in 70% (982) patients

Node status

Nx 89 cases

N0 1076 cases

Pathologically involved lymph nodes in 335 (22%) of patients:

N1-3 in 255/335 (76%) of cases

N4+ in 80/335 (24%) of cases

% positive nodes:

≤ 33% in 83% of cases

34-66% in 11% of cases

≥ 67% in 6% of cases

Size of node metastasis:

< 1.0cm in 116 cases

1.0-1.9cm in 41 cases

> 2.0cm in 18 cases

(Note – size of node metastasis available only in 175 cases)

Extracapsular extension (ECE) in 35% with pathologically positive lymph nodes

Characteristics of patients with 1-3 positive nodes by regional nodal irradiation treatment

There were statistically significant differences for several characteristics between the group receiving regional node irradiation (RNI) (n=67) and the group with no RNI (n=188). These are shown in the table below. There were no significant differences between RNI and no RNI groups for tumour size, oestrogen receptor status, margin status, presence of angiolymphatic invasion, age, menopausal status, or systemic chemotherapy.

In this group of patients with 1-3 positive nodes a smaller proportion with > 10 positive nodes received RNI than no RNI; a larger proportion with > 34% of positive lymph nodes received RNI than no RNI; a larger proportion of ECE positive cases received RNI than no RNI; a larger proportion with large metastases > 1.0 cm received RNI than no RNI.

Characteristic	No RNI (%) (n=188)	RNI (%) (n=67)	p
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Lymph nodes excised (n)			
<6	6 (3)	2 (3)	0.002
6-10	30 (16)	25 (37)	
>10	152 (81)	30 (60)	
Mean	16	14	0.002
Lymph node positive (%)			
≤ 33	183 (98)	58 (87)	0.001
34-66	3 (2)	8 (12)	
≥ 67	1 (1)	1 (2)	
Mean	11	18	0.001
ECE			
LN (+) ECE (-)	146 (82)	40 (61)	<0.001
LN (+) ECE (+)	34 (18)	26 (39)	
Maximal size of LN metastasis (cm)			
<1.0	82 (80)	15 (56)	0.015
1.0-1.9	15 (15)	7 (26)	
≥2.0	5 (5)	5 (18)	
Mean	0.6	1.2	0.002

Characteristics of patients with ≥4 positive nodes by regional nodal irradiation treatment

Statistically significant differences for characteristics between the group receiving regional node irradiation (RNI) (n=59) and the group with no RNI (n=21) were reported for percentage of positive lymph nodes, age and systemic chemotherapy. The other characteristics shown in the previous table and tumour size, oestrogen receptor status, margin status, presence of angiolymphatic invasion and menopausal status were not statistically significantly different between treatment groups.

Characteristic	No RNI (%) (n=21)	RNI (%) (n=59)	p
Lymph node positive (%)			
≤ 33	16 (76)	21 (36)	0.006
34-66	3 (14)	23 (39)	
≥ 67	2 (10)	15 (25)	
Mean	32	48	0.011
Age (years)			
≤ 45	11 (52)	16 (27)	0.036
Systemic chemotherapy	19 (95)	38 (67)	0.016

In this group of patients with ≥ 4 positive nodes a larger proportion of those with > 33 % of positive lymph nodes received RNI than no RNI; larger proportions of patients < 45 years and those receiving chemotherapy did not receive RNI than did receive RNI.

Interventions

Breast Conserving Therapy (BCT)

1411 (94%) had at least Level I or II ipsilateral axillary lymph node dissection. (Level III dissections were not routinely performed).

All patients had external beam RT of photons to the whole breast with tangential fields at a dose of 45 Gy. A tumour bed boost of 61Gy with electrons (19 had photons) was also given.

The breast alone, breast plus supraclavicular nodes and Level III nodes, or breast plus full axilla were treated at the discretion of the radiation oncologist

RT to breast alone n=1309 (87%)

RT to breast and regional nodes n = 191 (13%)

RNI was delivered by a three field technique to the breast and supraclavicular fossa/ axilla. Twenty three percent (n=44) also had a posterior axillary boost. Eight percent (n=16) also received RT to the IMC at a median dose of 50Gy.

Outcomes

Regional Node Failure (RNF) -detection of cancer in the regional site before, or simultaneously with, the diagnosis of local recurrence (LR) or distant metastasis (DM)

Cause-specific survival

Overall survival

DM-free survival

Follow up

Median follow-up 8.1 years

Results

35 patients developed RNF: 12 (6%) received RNI, 23 (2%) had no RNI.

Median time to failure 3.1 years.

Sites of failure are shown in the following table:

Sites of regional nodal failure

Site	Failure (n)				
	Any node	Nx	N0	N 1-3 (+)	N ≥ 4 (+)
Supraclavicular fossa	16	1	8	5	2
Axilla	11	1	3	6	1
Supraclavicular fossa and axilla	2	0	1	0	1
Internal mammary lymph nodes	6	0	3	3	0
Total	35	2	15	14	4

The 5 and 10 year actuarial failure rates by node site are reported in the following table.

Site of relapse	5 Year actuarial rate	10 Year actuarial rate
Any regional nodal failure	1.9%	2.8%
Axillary failure (AF)	0.6%	1.0%
Supraclavicular failure (SCF)	0.9%	1.6%
Internal mammary failure	0.4%	0.4%

RNF and axillary node status

When the 10 year actuarial regional nodal failure rates were related to nodal status and regional node irradiation statistically significant differences between rates with and without RNI were reported for any RNF in patients with 1-3 positive nodes (15% with RNI, 4% without RNI; p=0.003); and patients with ≥ 4 positive nodes (2% with RNI, 11% without RNI; p=0.041). 10 year actuarial failure rates in the axilla were reported as significant in patients with ≥ 4 positive nodes only (0% with RNI, 5% without RNI; p=0.027). However for supraclavicular fossa failure a significant difference was reported in patients with 1-3 positive nodes (8% with RNI, <1% without RNI; p=0.004). No statistically significant differences were reported between patients receiving RNI and no RNI in patients with no positive nodes (N0), unknown node status (Nx) or all N+ patients.

Failure rates by node status and regional node irradiation in subsets of patients are reported in the following table.

Node status	N of patients	+ RNI	-RNI	Site of failure	Characteristics of patients receiving RNI
NX	89 No AXD	42 (47%)	47 (53%)	1 SCF 1AF Both had RNI Not significant	Larger tumours >1cm (69% vs 43%, p=0.02) Angiolymphatic invasion (27% vs 5%, p=0.05)
pN0	1076	23 (2%)	1053 (98%)	15 RNFs SC 8 AF 3 SC+AF 1 IMC 3 1 received RNI 14 did not receive RNI No significant difference between RNI vs no RNI failure	Negative or unknown ER status (p=0.007) Close or positive surgical margins (p=0.004)
N Irradiation (1-3 +ve nodes)	255	67 (26%)	188 (74%)	14 RNFs 8 received RNI: (1 AF, 4 SCF, 3 IMC) 6 no RNI: (5 AF, 1 SCF)	< 6 or < 10 lymph nodes excised Greater % of positive nodes, ECE, or nodal metastasis >1-2cm

N Irradiation (≥ 4 +ve nodes)	80	59 (74%)	21 (26%)	4 RNFs 1 received RNI (2 SCF, 1 AF, 1 AF+SCF)	Higher percentage positive nodes (p=0.006) Age >45 years (p=0.036) Systemic chemotherapy (p=0.008)
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In patients with Nx status RNI was more likely to be delivered to patients with tumour sizes > 1cm or angiolymphatic invasion. Both failures occurred in the RNI group.

In patients with N0 status RNI was more likely to be delivered to patients with negative or unknown oestrogen receptor status or close/positive surgical margins. The rates of RNF, AF, or SCF according to regional nodal treatment were not statistically significant, however the RNI group was very small in comparison to the no RNI group, and this is reflected in the findings (14 failures had no RNI vs. 1 failure had RNI).

In patients with N1-3 positive nodes RNI was more likely to be delivered to patients with <6 or <10 lymph nodes excised, a greater percentage of positive nodes, ECE, or a nodal metastasis >1-2cm. Patients were more likely to develop RNF if they received RNI (15% vs. 3%, p=0.002). SCF was more likely if they received RNI (8% vs. 1%, p=0.005). The rates of AF were similar between groups (2% vs. 4%, p=0.68). Although the number of RNFs was similar between RNI and no RNI groups, again the RNI group was smaller than the no RNI group.

In patients with more than 4 positive nodes RNI was more likely to be delivered to patients with a higher percentage of positive nodes (p=0.006), aged over 45 years (p=0.036), and had received systemic chemotherapy (p=0.008). Three of four RNFs occurred in the no RNI group. In these patients RNI reduced the 10 year actuarial rate of any RNF from 11% to 2% (p=0.041) and the rate of AF from 5% to 0% (p=0.027).

A Cox multiple regression analysis of data from these patients found that RNI was the only significant independent factor predicting a reduced rate of RNF ($p = 0.03$, hazard ratio 0.046). Factors included in the analysis were the percentage of positive nodes, size of lymph node metastasis, age, and angiolymphatic invasion. Independent predictors of AF or SCF were not determined because of the small number of failures.

Extracapsular extension (ECE)

116 (35%) of patients with pathologically involved nodes had ECE.

When ECE-positive patients were stratified by regional nodal treatment, RNI had no impact on the 10-year rate of RNF (6% vs. 7%, $p = 0.690$) or SCF (4% vs. 4%, $p = 0.765$). The rate of AF was lower for RNI patients (0% vs. 4%), but this difference was not statistically significant ($p = 0.109$).

Effect of axillary lymph node dissection

Node negative (N0) patients with <6 nodes excised had a significantly higher rate of RNF. The 10 year rates for patients with <6, 6-10 and >10 nodes excised were 5%, 4% and 1% respectively ($p=0.04$). The rates of failure were higher in node positive patients (N1) but the differences were not statistically significant ($p = 0.427$).

Univariate analysis of RNF

RNI did not affect the rates of regional failure in patients with negative or 1-3 positive nodes. In node-negative patients, the rate of RNF was significantly greater if <6 nodes were removed at the time of axillary dissection. In patients with more than 4 positive lymph nodes RNI significantly reduced RNF. Multiple clinical, pathological, and treatment-related factors were analyzed for association with RNF. On univariate analysis, RNF was associated with the number of nodes excised, number of positive nodes, percentage of positive nodes, size of nodal metastasis, presence of angiolymphatic invasion, oestrogen receptor status, age, systemic chemotherapy, and RNI.

Three subsets of patients had unusually high rates of RNF at 10 years, those with $\geq 67\%$ nodes positive (16%), nodal metastasis ≥ 2.0 cm (44%), or age ≤ 35 years (14%). RNI did not improve the overall survival for any of these subsets.

Multivariate analysis of RNF

A further multivariate analysis of all patients found that the only significant independent predictor of RNF was the maximal size of the nodal metastasis ($p = 0.013$).

Survival analysis

All patients

Data on survival rates are reported in the table below for all 1500 patients (note this figure may be a misprint as 1550 were included in total).

Outcome	5 year rate	10 year rate
Overall survival	90%	78%
Disease Free Survival	84%	70%
Cause-Specific Survival	94%	87%

Rates of survival (DFS and OS) and distant metastases (DM) in relation to regional node treatment are reported in the following table.

Rate	Breast +RNI (%)		Breast alone (%)		p
	5 year	10 year	5 year	10 year	
DFS	68	52	87	73	<0.001
OS	79	61	91	80	<0.001
Distant metastases	13	30	7	11	<0.001

The authors suggest that the poorer survival statistics for RNI patients may be due to the high risk characteristics of these patients (selection bias).

Node status

The number of lymph nodes excised had an impact on overall survival in node-positive patients only. 10-year survival rates were 33%, 65%, and 69% in patients with <6, 6-10, and >10 nodes excised, respectively ($P = 0.05$). Actuarial survival rates at 10 years were not significantly different by number of nodes excised in node negative patients.

The 10 year actuarial rates of DM-free survival, overall survival, and cause-specific survival related to nodal status and RNI are shown in the following table.

Nodal status	Distant metastasis free survival (%)			Overall survival (%)			Cause specific survival (%)		
	RNI	No RNI	P	RNI	No RNI	P	RNI	No RNI	p
N0	82	90	0.042	70	84	0.015	77	92	0.006
Nx	80	89	0.057	51	50	0.234	91	93	0.081
All N+	64	82	0.002	61	70	0.005	69	77	0.039
N+ (1-3)	68	84	0.011	62	72	0.008	71	79	0.040
N+ (≥ 4)	59	64	0.889	58	56	0.941	67	62	0.639

P values in bold font were statistically significant

Node-negative and N1 patients with 1–3 positive nodes receiving RNI had statistically significantly lower survival rates across all three parameters.

NX patients and N1 patients with ≥ 4 positive nodes receiving RNI had survival rates equivalent to those of patients treated to the breast only.

Toxicity

Brachial plexopathy 2/1342 (0.1%), occurred in 2/64 (1.2%) patients treated with RNI.

Pneumonitis 5/1250 (0.4%) (1 patient had RNI, 4 had no RNI)

Arm oedema: mild 6.8% in RNI patients, and 5.8% those not irradiated.

Moderate 3.1% in RNI patients, and 1.4% those not irradiated

3 patients had severe arm oedema, none received RNI.

Breast oedema: 27% with RNI, 42% no RNI

Author conclusions

Failure within the regional lymph nodes as an isolated site of first relapse is uncommon in patients with Stage I–II breast cancer treated with BCT. RNI can significantly reduce the rate of RNF (AF) in patients with ≥ 4 positive lymph nodes. The maximal size of the lymph node metastasis was found to be the only significant independent predictor of RNF, with nodal metastases ≥ 2.0 cm associated with extremely high regional failure rates. Despite this, young age and extent of axillary dissection (particularly as related to the number of positive nodes) also appear to be important and should be considered when evaluating patients for RNI. Inadequate axillary dissection was not only associated with increased regional failure, but also reduced survival.

General comments –

94% of patients received Level I-II axillary dissection as well as node irradiation. The majority of patients with no node irradiation had received axillary surgery only. Extensive subgroup analyses were conducted in this paper. Not all of these analyses are reported in the table since some subgroups were very small (less than 20 patients).

Treatment of the Internal Mammary Node Chain (Dissection or Radiotherapy)

Arriagada, R., Lê, M. G., Mouriessse, H., Fontaine, F., Dewar, J., Rochard, F., Spielmann, M., Lacour, J., Tubiana, M., & Sarrazin, D. 1988, "Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes", *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*, vol. 11, no. 3, pp. 213-222.

Design: NRS Cohort (1958-1978) Level 3

Country: France, setting: Single centre

Aim: To evaluate in a large series of N+ patients the long term effects of treatment of the IMC by IMC dissection (IMCD) or RT on the risk of death or metastasis; and to confirm the beneficial long-term effect of post-operative RT on risk of locoregional recurrence.

Inclusion criteria

Women under 70 years with a primary unilateral infiltrating breast carcinoma (UICC stage T1a, T2a or T3a, N0 or N1 and M0, < 7cm in diameter and histologically invaded axillary nodes.

Exclusion criteria Not reported

Population number of patients = 1195

Interventions

Mastectomy and axillary dissection (Halsted or Patey operation).

From 1958-1963 when axillary nodes were positive IMCD and postoperative RT was administered.

When axillary nodes were negative only patients with medial tumours were treated by IMCD and RT.

When axillary nodes were positive on pathological examination RT was given (standard protocol)

From 1963-1968 IMCD was performed on randomized patients (152 N+ patients did not receive postoperative RT).

From 1968-1972 standard protocol was followed.

From 1972-1978 Patey mastectomy was compared with lumpectomy, axillary dissection and RT to the breast on randomized patients with tumours up to 2cm.

N+ patients were further randomised to postoperative lymph node RT or no further treatment.

For irradiated patients 45Gy in 16 fractions over 32 days was delivered to the chest wall, supraclavicular and axillary nodes and to homolateral IMC.

Outcomes

Mortality

Metastasis

Follow up

Results

Treatment groups are described in the following table.

Characteristics	Group 0 No IMCD	Group 1 IMCD	Group 2 No IMCD	Group 3 IMCD
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	No RT N=135	No RT N=102	RT N=523	RT N=435
Age -years (SD)	53 (9)	52 (10)	52 (10)	50 (9)
Tumour size cm(SD)	34 (13)	39 (12)	33 (13)	37 (13)
% patients with:				
Medial tumour	44	51	38	64
N≥4 +ve axillary nodes	27	40	41	53
Grade 3	39	43	34	36

The risks of death and metastases were similar for groups 1, 2 and 3 indicating that IMCD alone and RT alone have similar effects. These findings are reported in the following table.

Relative risk (adjusted)	Group 1 IMCD no RT	Group 2 No IMCD RT	Group 3 IMCD RT
RR Death	1.0	1.0	1 (ref)
RR Metastasis	1.1	1.1	1 (ref)
10 year rates (Cox):			
Mortality	48%	42%	42%
Metastasis	44%	42%	40%

When pooling the groups (1-3) where treatment was given and comparing to group 0 where no treatment was given, the difference between deaths and metastases was not significant. A significant difference was observed between the subgroups with medial tumours, but not those with lateral tumours. These findings are reported in the following table.

Relative risk (adjusted) of 10 year rates	All patients Gp 0 (n=135) (ref) vs Gp 1-3 (n=1060)	Medial tumours Gp 0 (n=60) (ref) vs Gp 1-3 (n=528)	Lateral tumours Gp 0 (n=75) (ref) vs Gp 1-3 (n=532)
Deaths	1.3 p=0.06	1.6 p=0.01	1.1 NS
Metastases	1.2 NS	1.5 p=0.05	0.9 NS
Mortality %	50 vs 42	52 vs 42	50 vs 42
Metastases %	46 vs 42	56 vs 44	40 vs 40

Multivariate analysis

The long term risk of death at 15 years was assessed in relation to clinical and pathological factors and IMC treatment for the 270 patients still alive:

Characteristic	RR of death	P value
Age (each year)	1.1	0.01
Clinical size (each 2cm)	1.4	NS
Histological grading(each class)	1.2	NS
Positive axillary nodes	0.9	NS
Size of tumour	1.1	NS
Group 0 (n=31)	1 (ref)	
Group 1 (n=43)	1.0	NS
Group 2 (n=75)	0.8	NS
Group 3 (n=121)	0.9	NS

There was no adverse effect of IMC RT or IMCD on long term survival. Age at initial treatment was related to risk of death.

Author conclusions

A beneficial effect of treatment of the internal mammary chain (IMC) on the risks of death and distant metastasis for the patients with medial tumours was found. For these patients, surgical IMC dissection and post-operative irradiation have similar effects on both the risk of death and of distant metastasis. For patients with lateral tumours, no beneficial effect of treatment of the IMC on these two risks was observed. Postoperative irradiation to the IMC, axilla, chest wall and supraclavicular nodes significantly decreases the risk of locoregional recurrences independent of the tumour site and surgical management of the lymph nodes.

General comments –

A recent systematic review by Vinod & Pendlebury (1999) and included earlier in the table commented on the limitations of this study where findings have been based on a subgroup analysis of a retrospective study, and different treatment policies were adopted over sequential time periods, so the possibility exists for staging biases.

Obedian, E. & Haffty, B. G. 1999, "Internal mammary nodal irradiation in conservatively-managed breast cancer patients: Is there a benefit?", *International Journal of Radiation Oncology Biology Physics*, vol. 44, no. 5, pp. 997-1003.

Design: NRS Cohort (1970-1990) Level 3

Country: USA, setting: Single institution

Aim: To evaluate outcome as a function of Internal Mammary Nodal Radiation (IMNR) in a cohort of breast cancer patients treated with CS + RT

Inclusion criteria

Early stage breast cancer with conservative management.

Exclusion criteria None reported.

Population number of patients = 984

Median age 57 years (range 20-86)

T1 690 (73%)

T2 249 (26%)

T3 7 (1%)

Pathologically-negative lymph nodes n= 399 (42%)

Pathologically-involved lymph nodes n=166 (18%):

N1-3 n=113 (12%)

N>4 n=53 (6%)

No lymph node dissection n=381 (40%)

Interventions

All had wide local excision with or without axillary nodal dissection, followed by radiation therapy to the intact breast and regional nodes.

Node-positive patients received adjuvant systemic therapy (94%) and were treated with tangential fields matched to a separate supraclavicular field (95%) with or without IMNR.

Treatment techniques are shown in the following table.

Treatment technique	All patients	IMNR	No IMNR
N	946 (100%)	535 (100%)	411 (100%)
Tangents alone	221 (23%)	1 (0.2%)	220 (54%)
Tangents + supraclavicular	106 (11%)	9 (1.7%)	97 (24%)
Tangents + supraclavicular + axilla	128 (13%)	41 (7.7%)	87 (21%)
Tangents + supraclavicular + IMN	229 (24%)	229 (43%)	0
Tangents + supraclavicular + axilla + IMN	225 (24%)	225 (48%)	0
Median dose (Range, Gy):			
Intact breast	64 (40-96)	64 (40-96)	64 (46-82)
Tangents	50 (20-70)	48 (20-70)	52 (32-64)
Supraclavicular nodal region	46 (0-62)	46 (0-55)	44 (0-62)
Internal mammary nodal region	46 (0-62)	46 (20-54)	0

Outcomes

OS (Overall Survival)

BRFS (Breast Relapse-Free survival)

DMRFS (Distant Metastasis-Free Survival)

Follow up Median follow-up 13 years

Results

At 10 years:

OS=76%

BRFS =88%

DMRFS =81%

Clinical outcomes of node positive patients are shown below:

	Total	IMNR	No IMNR	p-value
Clinical status				P<0.001

Alive with disease	42	27 (5%)	15 (4%)	
Alive, no evidence of disease	693	345 (64%)	348 (85%)	
Dead with disease	123	96 (18%)	27 (7%)	
Dead, no evidence of disease	88	67 (13%)	21 (5%)	
Site of recurrence				P<0.001
None	724	366 (68%)	358 (87%)	
Breast only	82	65 (12%)	17 (4%)	
Nodes only	12	9 (2%)	3 (0.7%)	
Distant only	119	86 (16%)	33 (8%)	
Breast and nodes	1	1 (0.2%)	0 (0%)	
Breast and distant	5	5 (1%)	0 (0%)	
Nodes and distant	3	3 (0.6%)	0 (0%)	

There were no significant differences between the IMC+RT and IMC-noRT groups at 10 years for all patients:

	IMC+RT vs IMC noRT	
OS	72% vs. 84%	p=NS
DMFS	77% vs. 87%	p=NS

Patients in the IMC-noRT group had significantly higher Breast-relapse Free Survival (BRFS) rates at 10 years than patients in the IMC+RT group (84% IMC+RT vs. 94% IMC-noRT, $p < 0.001$).

The authors suggest that the difference in breast relapse rate may be due to increased attention to the status of the surgical margins and increased use of systemic therapy in later years, when internal mammary radiation was less likely to be utilized.

A further subgroup analysis of node positive patients found a trend towards better outcomes in the IMC-noRT group, although there were no significant differences between the IMC+RT and IMC-noRT groups of node positive patients at 10 years for:

OS	68% IMC+RT vs. 76% IMC-noRT	$p > 0.5$
BRFS	85% IMC+RT vs. 96% IMC-noRT	
DMFS	64% IMC+RT vs. 82% IMC-noRT	$p = 0.2$

No benefit of IMC RT was found in further subgroup analyses comparing:

Age <50 vs. >50 years
Number of +ve nodes (1-3 vs. 4 or more)
Location medial vs. lateral
Right vs. left breast

A final subset analysis comparing IMC treatment by a separate field vs. IMC treatment by deep tangent also found no benefit of IMC irradiation.

Author conclusions

No benefit could be attributed to IMNR in conservatively-treated breast cancer patients, even if node-positive or medial in location. Until results of an ongoing EORTC randomized trial addressing this issue are available, these data suggest that it is acceptable to continue to treat node-positive conservatively-managed patients to tangential fields usually matched to a supraclavicular field, but without a separate internal mammary field.

General comments -

Abstracts of other relevant non-randomized studies that were weaker in design or analysis

No node irradiation

Strom, E. A., Woodward, W. A., Katz, A., Buchholz, T. A., Perkins, G. H., Jhingran, A., Theriault, R., Singletary, E., Sahin, A., & McNeese, M. D. 2005, "Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy", *International Journal of Radiation Oncology, Biology, Physics*, vol. 63, no. 5, pp. 1508-1513.

Abstract: PURPOSE: The purpose of this study was to describe regional nodal failure patterns in patients who had undergone mastectomy with axillary dissection to define subgroups of patients who might benefit from supplemental regional nodal radiation to the axilla or supraclavicular fossa/axillary apex.

METHODS AND MATERIALS: The cohort consisted of 1031 patients treated with mastectomy (including a level I-II axillary dissection) and doxorubicin-based systemic therapy without radiation on five clinical trials at M.D. Anderson Cancer Center. Patient records, including pathology reports, were retrospectively reviewed. All regional recurrences (with or without distant metastasis) were recorded. Median follow-up was 116 months (range, 6-262 months).

RESULTS: Twenty-one patients recurred within the low-mid axilla (10-year actuarial rate 3%). Of these, 16 were isolated regional failures (no chest wall failure). The risk of failure in the low-mid axilla was not significantly higher for patients with increasing numbers of involved nodes, increasing percentage of involved nodes, larger nodal size or gross extranodal extension. Only 3 of 100 patients with <10 nodes examined recurred in the low-mid axilla. Seventy-seven patients had a recurrence in the supraclavicular fossa/axillary apex (10-year actuarial rate 8%). Forty-nine were isolated regional recurrences. Significant predictors of failures in this region included > or = 4 involved axillary lymph nodes, >20% involved axillary nodes, and the presence of gross extranodal extension (10-year actuarial rates 15%, 14%, and 19%, respectively, $p < 0.0005$). The extent of axillary dissection and the size of the largest involved node were not predictive of failure within the supraclavicular fossa/axillary apex.

CONCLUSIONS: These results suggest that failure in the level I-II axilla is an uncommon occurrence after modified radical mastectomy and chemotherapy. Therefore, supplemental radiotherapy to the dissected axilla is not warranted for most patients. However, patients with > or = 4 involved axillary lymph nodes, >20% involved axillary nodes, or gross extranodal extension are at increased risk of failure in the supraclavicular fossa/axillary apex and should receive radiation to undissected regions in addition to the chest wall

(Similar study to Livi *et al* (2006) but with fewer patients and stage II-IIIa. Intervention was radical mastectomy or modified radical mastectomy with a Level I and II axillary dissection. No RT was administered after surgery. A crude univariate analysis was performed).

Stranzl, H., Peintinger, F., Ofner, P., Prettenhofer, U., Mayer, R., & Hackl, A. 2004, "Regional nodal recurrence in the management of breast cancer patients with one to three positive axillary lymph nodes - Outcome of patients following tangential irradiation without a separate nodal field", *Strahlentherapie und Onkologie*, vol. 180, no. 10, pp. 623-628.

Abstract: Purpose: To examine the prognosis of breast cancer patients (T1-3, one to three positive axillary Lymph nodes) and loco regional failure rate after breast-conserving therapy/modified radical mastectomy and adequate axillary dissection following tangential radiotherapy without irradiation of the regional lymph nodes.

Patients and Methods: From 1994 to 2002, the medical records of 183 breast cancer patients (T1-3, one to three involved axillary lymph nodes) were examined in order to identify those experiencing regional nodal recurrence, with or without Local recurrence. The median age of the patient population was 58 years (range, 28-86 years). All patients underwent surgical treatment, either breast-conserving therapy ($n = 146$) or modified radical mastectomy ($n = 37$). The median number of Lymph nodes removed was twelve (range, seven to 26 nodes). Irradiation was given to the breast through tangential fields. Chemotherapy was administered to 101 patients (55%), hormonal therapy to 124 (60%), and combined systemic treatment to 47 (26%).

Results: The median observation time was 44.4 months (range, 11-102 months). Of the 14 patients (7.7%) with a relapse, six (3.3%) had a Local recurrence, five (2.8%) a regional relapse, and three (1.6%) a simultaneous recurrence. Nine out of 14 patients with locoregional relapse developed distant failure subsequently and seven of them (78%) died of the disease.

Conclusion: Regional recurrence is uncommon among patients with one to three positive axillary Lymph nodes treated with surgery, adequate axillary dissection, and tangential field irradiation only. The authors conclude that

regional nodal irradiation should not routinely be given following adequate axillary dissection when only one to three Lymph nodes are positive.

(This was a small study of patients treated mainly with BCS (80%) and axillary dissection (the extent varied by individual surgeon) which supports the findings of larger studies for women with N1-3 positive nodes).

Limited node irradiation

Vicini, F. A., Horwitz, E. M., Lacerna, M. D., Brown, D. M., White, J., Dmuchowski, C. F., Kini, V. R., & Martinez, A. 1997, "The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy", *International Journal of Radiation Oncology Biology Physics*, vol. 39, no. 5, pp. 1069-1076.

Abstract: Purpose: To determine the incidence of regional nodal failure (RNF) and indications for regional nodal irradiation (RNI) in patients with Stage I and II breast cancer treated with breast-conserving therapy (BCT),
Methods and Materials: Four hundred fifty-six patients with Stage I/II breast cancer were treated with BCT at William Beaumont Hospital. All patients underwent excisional biopsy and 288 (63%) were reexcised, A Level VII ipsilateral axillary lymph node dissection was performed on 431 patients (95%), Pathologically involved nodes were found in 106 (23%) cases (69 with one to three nodes and 37 with greater than or equal to four nodes involved), All patients received whole breast irradiation (median dose 50 Gy) and 415 (91%) were boosted to the tumor bed (median total dose 60.4 Gy), Three hundred and sixty (79%) patients received breast alone irradiation and 96 (21%) also received RNI, The median axilla/supraclavicular fossa dose was 50 Gy,

Results: With a median follow-up of 83 months, 15 patients developed a RNF for a 5- and 8-year actuarial rate of 3 and 4%, respectively, The 5- and 8-year actuarial rates of axillary failure (AF) were 0.7 and 1.0%, respectively, The incidence of RNF or AF was not affected by the use of RNI in NO or N1 patients with one to three positive nodes, Only in patients with four or more positive nodes was there a trend towards improved regional control with RNI ($p = 0.09$), However, patient numbers were extremely small, and this improvement was limited to a reduction in the rate of failure in the supraclavicular fossa (SCF) (20 vs, 0%, $p = 0.04$), Multiple clinical, pathologic, and treatment related factors were analyzed for an association with AF, On univariate analysis, AF was associated with the number of lymph nodes excised ($p < 0.0001$) estrogen receptor status ($p = 0.0016$), and pathologic node status ($p = 0.0021$),

Conclusions: Regional nodal failure as the first site of failure is uncommon in patients with early-stage breast cancer treated with BCT with less than or equal to three positive lymph nodes and appears unaffected by RNI, For patients with four or more positive lymph nodes, a trend towards improved RNF was noted with RNI, primarily in the SCF, However, patient numbers were extremely small in all subsets analyzed. Additional studies are needed to further define the need for RNI in these patients and help determine other factors associated with RNF.

(Small number of patients had regional node irradiation, the authors' state that conclusions should not be drawn from these findings)

Livsey, J. E., Magee, B., Stewart, A. L., & Swindell, R. 2000, "Axillary recurrence following conservative surgery and radiotherapy in early breast cancer", *Clinical Oncology*, vol. 12, no. 5, pp. 309-314.

Abstract: At the institute, since the late 1980s, there has been a uniform treatment protocol for the management of the regional lymph nodes in patients referred for radiotherapy following breast-conserving surgery. An analysis of 2277 consecutive patients referred for radiotherapy between 1989 and 1992, with particular reference to regional lymph node management, has been undertaken. Axillary surgery alone was used in 517 patients (23%); 1191 (52%) patients had no axillary surgery but had radiotherapy to the axilla, and infraclavicular and supraclavicular fossae by a single anterior field, delivering 40 Gy in 15 daily fractions over 3 weeks; and 474 patients (21%) had axillary surgery followed by radiotherapy. Ninety-five patients (4%) underwent no axillary treatment. There was a total of 155 axillary recurrences with a median follow-up of 5.9 years, giving an actuarial nodal control rate of 94% at 5 years (95% confidence interval (CI) 93.1-95.1). The overall survival at 5 years was 86% (95% CI 84.6-87.5). There was a trend towards improved axillary control with surgery alone compared with radiotherapy alone (4.5% versus 5.9% actuarial axillary failure rate at 5 years). An extremely low incidence of brachial plexus neuropathy secondary to radiotherapy was reported. The multidisciplinary treatment protocol used gave a high rate of regional node control, with minimal recorded morbidity.

(A large study comparing axillary surgery to axillary irradiation including the supraclavicular nodes. The type of axillary surgery was varied and the node status of patients not clear. The independently significant prognostic

factors for nodal recurrence from a univariate Cox's regression analysis were screen-detected referral, grade, age and clinical stage.)

Pierce, L. J., Oberman, H. A., Strawderman, M. H., & Lichter, A. S. 1995, "Microscopic Extracapsular Extension in the Axilla - Is This An Indication for Axillary Radiotherapy", *International Journal of Radiation Oncology Biology Physics*, vol. 33, no. 2, pp. 253-259.

Abstract: Purpose: Although the axilla is often treated with radiotherapy (RT) postoperatively when microscopic extracapsular extension (ECE) of lymph nodal metastases is present, little data are available to assess axillary failure in the absence of such treatment. As it has been the practice at this institution to withhold axillary irradiation in the presence of microscopic extracapsular spread, we retrospectively analyzed our results for axillary recurrence, disease-free survival (DFS), and overall survival (OS).

Methods and Materials: Clinical records were reviewed of 82 women with Stage II node positive breast cancer treated with lumpectomy, axillary dissection, and RT in addition to systemic chemo/hormonal therapy. Axillary surgery consisted of a level I, II, +/-III dissection, with a median of 16.5 nodes removed. Tangential radiotherapy fields were used to treat the breast. All patients were also treated with an abbreviated supraclavicular field with the lateral border medial to the humeral head. Pathological sections were available for review in 72 of the 82 women.

Results: Twenty-seven of 72 (37.5%) had evidence of ECE; 45 of 72 (62.5%) had metastatic carcinoma confined within the nodal capsule. Clinical characteristics were comparable between the patients with and without ECE with the exception of (a) pathologic subtype, with a greater percentage of infiltrating ductal tumors associated with ECE ($p = 0.044$), and (b) number of positive lymph nodes, with 93% of patients without ECE having one to three positive nodes vs. only 56% among patients with ECE ($p < 0.001$). With a median follow-up of 40 months, 1 of 27 patients (4%) with ECE experienced an axillary failure as a component of first failure compared to 0 of 45 patients without ECE ($p = 0.4$). There were no isolated axillary failures. Five-year disease-free survival (72% without ECE vs. 57% with ECE, $p = 0.12$) and overall survival (83% vs. 53%, respectively, $p = 0.068$) suggested a less favorable outcome for patients with ECE.

Conclusions: Microscopic ECE appears to be associated with increased axillary involvement and decreased survival rather than subsequent axillary failure. Our data suggest that radiotherapy to a dissected axilla may be omitted for the sole indication of microscopic extracapsular disease.

[A small study of 82 patients who received BCS and axillary dissection (level I and II, some level III) with tangential irradiation to the breast and a limited supraclavicular field to those with positive nodes. 93% of women had 1-3 positive nodes. A Cox multiple regression analysis of clinical factors was performed for DFS and overall survival. No factors were significant independent predictors (5% level). Trends were observed for each end point, indicating a shorter duration for patients with ECE.

Hazard ratio for survival was 3.3 (95% CI 0.9 to 11.3, $p = 0.06$, adjusted for the number of positive nodes [> 3 vs. 1-3]). The probability of death for patients with ECE was three times that of patients without ECE. Similarly for DFS, the HR was estimated to be 2.6 (95% CI 0.9 to 7.6, $p = 0.07$).

Guidelines

SIGN 2005

The relevant section from the SIGN guideline for radiotherapy to the chest wall and supraclavicular fossa, axilla, and internal mammary node chain is reported below:

RADIOTHERAPY TO THE CHEST WALL AND SUPRACLAVICULAR FOSSA

Recht et al (2001) addressed the question of whether adjuvant radiotherapy should be given to the chest wall and supraclavicular fossa the American Society of Clinical Oncology guideline. Fewer data are available addressing the benefit of PMRT in subgroups of patients with specific numbers of positive axillary nodes. Supraclavicular nodal failures are more common in unirradiated patients with four or more positive axillary nodes.

Level 3

In one series, supraclavicular nodal failure appeared in 17% of unirradiated patients (17/102) compared with 2% of 56 irradiated patients (Kuske 1996 et al abstr). In another series the risk of supraclavicular failure was 13% (6/46) among unirradiated patients with four or more positive nodes, compared with 4% (2/52) for those irradiated (Ewers et al 1992).

Level 1++

An RCT showed improvements in risk of loco-regional failure (LRF) in irradiated patients in the subgroups with either one to three or four or more positive nodes (Ragaz et al 1997). The difference in crude LRF rates for patients with 1-3 positive nodes was of borderline significance between arms (20% in control arm and 8% in the irradiated arm, $p=0.066$), while the difference between arms for patients with 4 or more positive nodes remained highly significant (LRF rates of 51% and 17% respectively, $p=0.004$).

Level 1+

In another trial, patients with one to three positive nodes and those with four or more positive nodes had statistically significant improvements in disease-free survival when given PMRT in addition to chemotherapy, but only patients with 4 or more involved nodes achieved a significant advantage in cancer-specific survival from the addition of PMRT (McArdle et al 1986).

Grade D

The supraclavicular field should be irradiated in all patients with 4 or more positive axillary nodes.

AXILLARY RADIOTHERAPY

The American Society of Clinical Oncology recommends that after adequate surgery by a complete or level I/II axillary dissection, routine adjuvant radiotherapy is not necessary and may add to morbidity (Recht et al 2001).

INTERNAL MAMMARY NODE CHAIN RADIOTHERAPY

There are studies addressing whether radiotherapy to the internal mammary node chain (IMC) is of benefit. The evidence for IMC is conflicting.

Level 1+

Two trials showed no improvement in survival in patients who underwent internal mammary node dissection in addition to standard radical mastectomy (Lacour et al 1983, Veronesi et al 1999).

A trial of 150 patients with internal mammary node involvement randomised individuals to either radical resection of the internal mammary supraclavicular chain, irradiation of the supraclavicular and internal mammary nodes, or no further surgery or deliberate irradiation of these areas. The 5 year disease-free survival rates were similar in the 3 arms (57%, 53% and 51% respectively), although the risk of supraclavicular and/or internal mammary recurrence was lowest in the irradiated group (12%, 0% and 16% respectively) (Yamashita et al 1996 abstr).

Level 4

One overview of case series and RCTs showed no benefit of IMC radiotherapy (Freedman et al 2000). Studies reviewed included patient data from 1938 onwards, raising the possibility that the side effects of antiquated treatments may have influenced the results against IMC irradiation. There is no evidence that IMC irradiation should be performed routinely in any patient group (Recht et al 2001, Freedman et al 2000). The number of screen-detected cancers is increasing and, together with the fact that fewer patients present with locally advanced cancers, should result in a reduction in IMC involvement.

Fodor, J., Polgar, C., Peley, G., & Nemeth, G. 2001, "[Management of the axilla in breast cancer: evidences and unresolved issues]. [Review] [111 refs] [Hungarian]", *Orvosi Hetilap*, vol. 142, no. 36, pp. 1941-1950.

This paper is written in Hungarian so only data provided in the abstract has been reported here.

Computerized searches for publications on the specific treatment of the axilla in breast cancer were run in the MEDLINE database. The level of evidence was graded using standard criteria: 1. meta-analysis of randomized trials, 2. randomized trial, 3. prospective and retrospective studies, 4. reports and opinion of expert committees and working teams. The authors report that the probability of lymph node involvement is related directly to the size of the primary tumour, and even with small tumours (up to 10 mm), the risk of nodal metastases is in the order of 10-20%. The best strategy for determining complete lymph node status (qualitative and quantitative information) was considered to be axillary dissection. At least ten nodes have to be obtained for accurate staging. Formal axillary sampling does not provide all the quantitative data for patients with involved axilla, and sentinel node biopsy is a promising alternative to axillary dissection for staging but at the development stage. Axillary dissection should be omitted in patients with ductal carcinoma in situ since the probability of nodal involvement is less than 1%. In invasive breast cancer, the risk of axillary recurrence in the untreated axilla varies from 10% to 40%. For women with stage I-II breast cancer at least level I and II axillary node dissection should be offered as the standard procedure to reduce the risk of regional recurrence. Women at high risk of axillary recurrence (≥ 4 involved nodes, < 6 nodes obtained from a positive axilla) require axillary irradiation after axillary dissection. However, there is a lack of higher level evidence to support the benefit of post-dissection axillary irradiation. Evidence suggests that axillary irradiation is as effective as axillary dissection in preventing regional recurrence. The following factors have to be considered for decisions regarding dissection or irradiation: patient wishes, general condition, age, the necessity of pathological nodal status for systemic therapy and the risk of post-treatment morbidity. At this time, there is no well defined subgroup of patients in whom axillary intervention can be safely omitted. In selected patients with clinically negative axilla, the decision to observe the axilla rather than use surgery or irradiation should be made jointly between the women and her specialists (surgeon, radiation and medical oncologist). The benefits of axillary treatment in prolonging survival are unclear. Studies have reported different effects on survival. Whilst there is insufficient evidence, the risk of axillary recurrence has to be minimized, and more randomized clinical trials should be conducted. Patients should be fully informed about the benefits and the potential side effects of treatments. A combination of radiotherapy and axillary dissection increases the morbidity rate compared with each individual treatment.

The Australian Clinical Practice Guidelines for the Management of Early Breast Cancer (2001)
NHMRC 2001 includes a section on the potential complication of irradiation to the axilla and supraclavicular fossa. The extracts are reported below:

COMPLICATIONS

Acute radiation pneumonitis

The risk of acute radiation pneumonitis is reported to range from 0.7–7 per cent. When the breast and axilla are irradiated, the risk will be at the upper end of the range because the risk increases with the amount of lung in the radiation field. It is, therefore, a rare complication. Small asymptomatic radiological changes, often referred to as fibrosis, may be noted on the chest X-rays. They may cause confusion and may be mistaken for metastases.

Brachial plexopathy

This is a very rare complication and will only occur when the axilla and supraclavicular fossa are irradiated. The incidence is 0.3 per cent at five years with current doses and fractionation, but has exceeded 5 per cent when hypofractionated regimens have been used.

Second malignancy

Six studies involving about 150,000 women treated with radiotherapy have reported on the development of a second malignancy. These studies have shown a relative risk of 1.17 which was not statistically significant. About half the series quote an increased incidence of colon, uterine and ovarian cancer in patients irradiated for breast cancer. These cancers are unlikely to have been caused by radiotherapy, as the host organ does not lie within the field irradiated. When site-specific associations such as colon, uterus and ovary are excluded, the risk of second malignancy becomes negligible in the clinical context (**Level III**).

In terms of post-radiation sarcoma, only 24 cases have been reported in seven series involving nearly 34,000 patients with follow-up of 5–18 years. The best estimate of risk is of two cases of post-radiation sarcoma per 10,000 women years of follow-up. In the case of breast conservation, perhaps half of these cases will be an angiosarcoma of the breast.

Recht, A., Edge, S. B., Solin, L. J., Robinson, D. S., Estabrook, A., Fine, R. E., Fleming, G. F., Formenti, S., Hudis, C., Kirshner, J. J., Krause, D. A., Kuske, R. R., Langer, A. S., Sledge, G. W., Jr., Whelan, T. J., & Pfister, D. G. 2001, "Postmastectomy radiotherapy: Clinical practice guidelines of the **American Society of Clinical Oncology**", *Journal of Clinical Oncology*, vol. 19, no. 5, pp. 1539-1569.

Extracts from the ASCO guideline are reproduced below:

Axillary node irradiation

Guideline: We suggest that full axillary radiotherapy *not* be given routinely to patients undergoing complete or level I/II axillary dissection. There is insufficient evidence to make suggestions or recommendations as to whether some patient subgroups might benefit from axillary irradiation.

Level of Evidence: III.

Grade of Recommendation: B.

Supraclavicular Nodal Irradiation for patients with Four or more Positive Axillary Lymph Nodes

Guideline: The incidence of clinical supraclavicular failure is sufficiently great in patients with four or more positive axillary nodes that we suggest a supraclavicular field should be irradiated in all such patients.

Level of Evidence: III.

Grade of Recommendation: A.

Supraclavicular Nodal Irradiation for patients with One to Three Positive Axillary Lymph Nodes

Guideline: There is insufficient evidence to state whether a supraclavicular field should or should not be used for patients with one to three positive axillary nodes.

Internal Mammary Nodal Irradiation

Guideline: There is insufficient evidence to make suggestions or recommendations on whether deliberate internal mammary nodal irradiation should or should not be used in any patient subgroup.

Expert Overviews

Grabenbauer, G. G. 2004, "Internal mammary nodes in invasive breast carcinoma. To treat or not to treat? [Review] [37 refs]", *Strahlentherapie und Onkologie*, vol. 180, no. 11, pp. 690-694.

Design: Overview of selected (non-systematic) studies and cohort (1985-1996) Level 4
 Country: Germany setting: Cohort: University Radiation Oncology Department
 Aim: To determine the prognostic impact of radiation therapy (RT) to internal mammary nodes (IMNs) in early breast cancer patients with medial hemisphere tumour location.

Inclusion criteria

Four large recent series of the literature reporting on > 50,000 patients with a special focus on the impact of tumour location, with no systematic RT to IMNs.

Patients with lateral or medial lesions in early breast cancer treated by surgery and RT with or without chemotherapy.

Exclusion criteria

Population

4 recent retrospective studies:

Gaffney 2003 (SEER)

Hammer 2001

Lohrisch 2000

Zucali 1998

Cohort of 822 patients - 492 lateral and 330 medial lesions

T1 or T2 tumour

Primary unilateral breast cancer

Complete surgery with axillary dissection (no residual tumour)

Complete RT

Complete follow-up

Absence of distant metastases at diagnosis

Interventions

Overview: Recent studies with no radiation to the IMN region. No information provided about type or extent of surgery.

Cohort: Surgery and postoperative RT with or without chemotherapy

All patients with medial lesions received RT to IMNs by a mixed-beam approach (50% photons, 50% electrons) with a total dose of 50 Gy.

Patients with lateral lesions received RT directed to the breast alone (50.4 Gy total dose, boost 12-16 Gy).

Outcomes

Overall survival (OS)

Breast cancer specific survival (BCSS)

Disease-free survival (DFS)

Systemic Disease-free survival (SDFS)

Follow up -

Results

Overview

Findings reported in table below. All outcomes were significantly poorer for medial tumours.

Study details	Medial tumours (n)	Lateral tumours (n)	Outcomes (p values indicating lower survival in medial lesions)
Gaffney 2003 N=45880 (1988-1997) All stages M0	10 111	35 769	OS p=0.004 BCSS p= 0.001 DFS NA

Hammer 2001 N=644 (1984-1995) T1-2, N0-2, M0	220	429	OS p=0.0009 BCSS p= 0.009 DFS p= 0.001
Lohrisch 2000 N=5359 T1-3, N0-1, M0	1 511	3 848	OS NA BCSS p= 0.028 DFS p= 0.005 (high risk lesions only)
Zucali 1998 N=2396 (1973-1989) T1-2, N0-1, M0	777	1 619	OS p=0.03 BCSS NA DFS p= 0.0066

Other findings were:

Zucali: A subgroup of 777 women with medial tumours had an excess risk of 30% for distant metastases, and an excess mortality of 20%.

Hazard Ratio (HR) for distant metastases 1.29 with medial tumour vs. lateral tumours.

Lohrisch: in women with low risk cancer there was no effect of tumour location on outcome; in contrast women with high risk factors, e.g. tumour size > 2cm, nodal disease, negative receptors, or invasion of lymphatic or blood vessels, had an excess risk of 50% for both distant metastases and tumour associated death.

HR for BCSS 1.46 for medial tumour vs. lateral tumours.

Gaffney: Both node negative and positive patients, inner vs. outer quadrant tumour location were predictive for OS and breast cancer-specific survival rates. The 5 year BCSS for inner and outer tumour location was 78.9% vs. 82.2% (p=0.002), and the 5 year OS was 72.8% vs. 74.7% (p<0.001).

HR for BCSS 1.31 for medial tumour vs. lateral tumours.

Erlangen Cohort

The findings are reported in the table below.

	Overall survival (10 yrs) RT to IMN			Systemic disease-free survival (10 yrs) No IMN		
	Lateral	Medial	p	Lateral	Medial	p
All patients (n=822)	60.3%	64%	NS	65.5%	70.1%	NS
pT1 (n=458)	73.5%	73.9%	NS	75.8%	75.9%	NS
pT2 (n=364)	45.7%	49.6%	NS	53.0%	60.6%	NS
pN0 (n=432)	75.0%	75.7%	NS	78.4%	82.0%	NS
pN+ (n=390)	46.2%	49.5%	NS	51.9%	55.2%	NS
Premenopausal (n=317)	71.6%	73.4%	NS	70.7%	70.8%	NS
Postmenopausal (n=505)	52.0%	58.9%	0.05	61.6%	69.8%	0.07
Without chemotherapy (n=582)	61.7%	62.8%	NS	70.3%	70.9%	NS
With chemotherapy (n=240)	57.2%	68.9%	NS	54.5%	67.6%	0.02

10 year overall survival was significantly better in patients with medial than lateral tumours (58.9% vs. 52%; p=0.05) in postmenopausal women; and 10 year SDFS was better for those with medial than lateral tumours (67.6% vs. 54.5%; p=0.02) for patients on chemotherapy. These findings are based on non-randomized participants and the univariate statistical comparisons may be affected by confounders.

Kaplan-Meier curves for overall survival were 79.1% and 64% at 5 and 10 years for medial tumours (n=330) with RT to the IMN, and 76.2% and 60.3% for lateral tumours (n=492) (p=0.2) with no IMN irradiation.

SDFS from Kaplan-Meier curves were 72.6% and 70.1% at 5 and 10 years for medial tumours (n=330) with RT to the IMN, and 72.9% and 65.5% for lateral tumours (n=492) (p=0.3) with no IMN irradiation.

Author conclusions

Consistent literature data exist indicating a diminished survival in patients with inner versus

outer quadrant breast cancer. According to our data, RT with a total dose of 50 Gy to IMNs in breast cancer patients with medial lesions was associated with OS and SDFS rates comparable to patients with lateral tumours. RT to IMNs may represent a very effective means to improve survival in patients with medial tumours.

General comments

Other Reviews

- **Freedman, G. M.**, Fowble, B. L., Nicolaou, N., Sigurdson, E. R., Torosian, M. H., Boraas, M. C., & Hoffman, J. P. 2000, "Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist?[see comment]. [Review] [61 refs]", *International Journal of Radiation Oncology, Biology, Physics*, vol. 46, no. 4, pp. 805-814.

The authors analyzed published randomized prospective trials testing the value of elective IMN dissection and/or radiation for patterns of failure for distant metastases and overall survival. Trials need to be carefully examined to draw conclusions that are relevant to present treatment regimes. The Danish and British Columbia trials included a separate internal mammary field in their technique, but attempts to attribute survival benefits to the IMN field is circumstantial. The survival benefit in these studies can be attributed to the reduction of the high rate (30%) of isolated locoregional failure to 10% or less by postmastectomy radiation of the chest wall, supraclavicular and axillary nodes alone. There have been many other postmastectomy trials that failed to show an overall survival benefit to radiation that included the IMN chain. These studies were not designed to assess the impact of IMN irradiation on disease-free or overall survival of patients. The NSABP B-02 trial found that distant metastases as a site of first failure were increased with regional radiation compared to no radiation, as well as other studies. A large reduction in isolated first local-regional (chest wall, supraclavicular or axillary) failures can be associated with a subsequent decrease in secondary late distant metastases and death.

In conclusion the historical reports of IMN positivity in over 25-30% of axillary node positive patients should not be extrapolated to breast cancer patients diagnosed and treated today.

A similar overview examined the postmastectomy RCTs that have been used for earlier topics in this guideline to separate out axillary and IMN metastases.

- **Noguchi, M.** 2002, "Does regional treatment improve the survival in patients with operable breast cancer?. [Review] [78 refs]", *Breast Cancer Research & Treatment*, vol. 76, no. 3, pp. 269-282.

Abstract: **BACKGROUND:** The impact of regional therapy on survival of patients with invasive breast cancer remains controversial. Regional therapies discussed include axillary lymph node dissection (ALND), internal mammary node dissection, and locoregional radiotherapy. **METHODS:** Prospective randomized clinical studies of regional therapy were reviewed using, as a source, Medline, main review articles on the related topic, and statements from consensus conference.

RESULTS: Although a number of randomized clinical studies have failed to demonstrate the benefits of regional treatment for survival, it is still a matter of debate whether ALND or regional radiotherapy alone can have a small but significant beneficial effect on the survival of breast cancer patients. However, recent studies have suggested that survival can be enhanced by interaction of postmastectomy locoregional radiotherapy with adjuvant systemic therapy.

CONCLUSIONS: Locoregional control is important for enhancing survival in the presence of adjuvant systemic therapy. Although only a few randomized controlled trials show conclusively the survival benefit of local therapies, it is expected that in clinical practice, the node-positive or other high-risk breast cancer patients given systemic treatment will be more frequently treated with postmastectomy radiation.

Phase II study

A recent Phase II study of 30 patients (mainly T1-2; N0-N1) requiring a level II/III axillary dissection recommends a change in practice for the localisation of the supraclavicular fossa for radiation therapy.

- Wheatley, D., Adwani, A., Ebbs, S., Hanson, J., Ross, G., Sharma, A. K., Wells, P., & Yarnold, J. 2005, "Matching supraclavicular fields to the extent of axillary surgery in women prescribed radiotherapy for early stage carcinoma of the breast", *Clinical Oncology (Royal College of Radiologists)*, vol. 17, no. 1, pp. 32-38.

The conclusions were that the current standard radiation fields to the supraclavicular fossa, as applied in this study, leave apical axillary lymph nodes untreated in a high proportion of patients. Standard lung shielding, as

applied in this study to patients simulated for axillary radiotherapy, protects medial axillary lymph nodes in a few patients. A change in practice is recommended.

Chapter 7 – Primary systemic therapy

7.1 What is the role of primary medical treatment in patients with early, invasive breast cancer?

Short Summary

The evidence that describes the role of primary systemic treatment in patients with early, invasive breast cancer has been drawn from three systematic reviews (Hind *et al.* 2006; Mieog *et al.* 2007; Trudeau *et al.* 2005) and a review providing updated results of two randomised trials (Rastogi *et al.* 2008). This research question lists two comparisons of interest; the first comparison is related to primary endocrine therapy versus primary surgery in elderly patients while the second comparison relates to primary chemotherapy versus surgery as primary treatment for patients with breast cancer.

Primary Endocrine Therapy

A systematic review of randomised controlled trials provides the most applicable data for the use of endocrine therapy as initial treatment in patients >70 years and reported no significant difference in overall survival between surgery and primary endocrine treatment (Hind *et al.* 2006). There was evidence of a non-significant trend in favour of surgery plus endocrine therapy over primary endocrine therapy (Hind *et al.* 2006). There is a statistically significant effect in favour of surgery plus endocrine therapy over endocrine therapy for breast cancer specific survival (Hind *et al.* 2006).

Primary Chemotherapy

A systematic review (Mieog *et al.* 2007) and a subsequently published review (Rastogi *et al.* 2008) reported no significant difference in overall survival or disease free survival between preoperative and postoperative chemotherapy. A statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy was observed based on pooled estimates from good quality RCTs (Mieog *et al.* 2007).

PICO

Population	Intervention	Comparison	Outcome
Elderly patients: unfit for surgery or who decide not to receive surgery	Primary medical therapy: Endocrine therapy Chemotherapy	No primary medical therapy / surgery Mastectomy	Breast conservation rate Recurrence Survival Cosmesis Patient acceptability Quality of life
Patients who receive primary medical therapy with the aim of breast conserving surgery			

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There is a moderate volume of published evidence for the use of primary chemotherapy or primary hormone therapy in patients with breast cancer. A Cochrane Review of RCTs addresses directly the comparison of primary hormone treatment vs. primary surgery in elderly patients; while a second Cochrane Review has good applicability to the second comparison; namely primary chemotherapy vs. primary surgery. A third systematic review focussed on primary chemotherapy using taxane-containing regimens. A review providing updated results of two randomised trials and an RCT comparing chemotherapy regimens were also identified during update searches.

There are four areas where treatment regimens in the trials do not necessarily coincide with modern clinical practice. Therefore, the appropriateness of the following should be questioned:

- (1) endocrine therapy for women with ER negative tumours;
- (2) surgery without adjuvant endocrine therapy;
- (3) primary endocrine therapy where the individual is fit for and agreeable to surgery;
- (4) new endocrine therapies.

The three systematic reviews reported heterogeneity between the primary randomised studies.

There is no significant difference in overall survival rates when comparing surgery and primary hormone treatment.

There is no significant difference in overall survival or disease free survival between preoperative and postoperative chemotherapy.

Taxane-based primary chemotherapy

In the systematic review of RCTs of taxane-based primary chemotherapy by Trudeau *et al.* 2005, data were reported but have not been cited in this summary for:

- primary taxane regimens versus non-taxane regimens as primary chemotherapy;
- comparisons of different doses/schedules of taxane primary chemotherapy.

However these data are cited in the associated evidence table, but are not the prime concern of topic 26. Data are cited in this summary from Trudeau *et al.* 2005 for primary taxane-based chemotherapy versus adjuvant taxane-based chemotherapy.

In addition to the limitations of study applicability and heterogeneity reported above, the Cochrane Review by Hind *et al.* 2006 reported the following limitations of the data from its included RCTs:

Competing risks

Competing risks apply to outcomes such as local failure in Kaplan-Meier analyses. Censoring patients in whom a competing risk occurs (e.g. death) is not appropriate as it gives an underestimate of the probability of local failure by treating those cases who haven't failed locally and are alive the same as those who have not failed locally but have died (Hind *et al.* 2006).

Informative censoring

Re: time to local or distant recurrence: in one trial patients were censored at the time of their last clinical examination. Assuming that those who have progressed are more likely to attend follow-up clinics and that those who are disease or metastases-free are less likely to attend

clinics, the latter group will be censored earlier, and will stop contributing information to the study. Thus the censoring is potentially dependent on the likelihood of disease progression (that is, related to the outcome). This is another source of potential bias as the rate of censoring does not leave a representative sample of those at risk (Hind *et al.* 2006).

PART 1: PRIMARY HORMONE THERAPY

The Cochrane systematic review of randomised trials by Hind *et al.* (2006) provides the most applicable data for the use of hormone therapy as initial therapy in patients with breast cancer of age >70 years.

1. Primary hormone therapy versus surgery in patients aged over 70 years

Overall survival

The pooled result in the Cochrane Review of three trials based upon a total 495 women demonstrated no statistically significant difference in overall survival between surgery versus primary hormone therapy: hazard ratio (HR) 0.98, 95% CI 0.74 to 1.30, $p=0.9$ (Hind *et al.* 2006).

Progression-free survival

One RCT included in the Cochrane Review provided data on progression-free survival and favoured surgery over primary hormone therapy: HR 0.55, 95% CI 0.39 to 0.77, $p=0.0006$ (Hind *et al.* 2006).

Adverse effects

There were insufficient data for a quantitative analysis of adverse effects. In 1 RCT no patient discontinued treatment with primary endocrine therapy. Eight patients had a total of ten side effects, including hot flushes, skin rash, vaginal discharge, indigestion, breast pain and sleepiness (Hind *et al.* 2006).

Local disease control

No data on local disease control were acceptable for citing due to biases introduced by competing risks, heterogeneity of interventions and informative censoring (Hind *et al.* 2006).

Distant metastasis-free survival

Data from 1 RCT included in the Cochrane Review based upon 164 women demonstrated no statistically significant difference between surgery and primary hormone therapy: HR 0.77, 95% CI 0.37 to 1.58, $p=0.47$ (Hind *et al.* 2006). NB due to the method of calculation, this hazard ratio incorporates distant metastases recorded both as a first event and following or simultaneously with a local progression.

Quality of life

No trials in the Cochrane Review reported any data for quality of life (Hind *et al.* 2006).

2. Surgery plus adjuvant endocrine therapy versus primary endocrine therapy

Overall survival

The pooled overall survival result of three trials in the Cochrane review by Hind *et al.* 2006 based upon 1076 women demonstrated a trend in favour of surgery plus endocrine therapy over primary endocrine therapy, that was not statistically significant: HR 0.86, 95% CI 0.73 to 1.00, $p=0.06$.

Overall survival by ER status

One trial included in the Cochrane Review by Hind *et al.* 2006 provided data based on 147 women, all of whom had ER-positive tumours. There was no significant difference in overall survival arising from surgery plus adjuvant hormone therapy versus primary hormone therapy: HR 0.80, 95% CI 0.28 to 2.32, $p=0.68$.

Overall survival by age

Age-related subgroup analysis in the Cochrane Review was not possible on the basis of published data (Hind *et al.* 2006). In a conference abstract authors reported analyses of combined individual patient data from both trials. They reported that patient age was the most important determinant of survival in patients of age 75 years or more. In patients of age between 70 and 75 years, initial surgery (rather than primary endocrine therapy) was found to determine survival.

Breast cancer specific survival

A published meta-analysis of individual patient data from two RCTs cited by Hind *et al.* 2006 found a statistically significant effect in favour of surgery plus endocrine therapy over primary endocrine therapy: HR 0.7, 95% CI 0.51 to 0.95.

Progression-free survival

Data from 1 RCT cited by Hind *et al.* 2006 found a statistically significant effect in favour of surgery plus endocrine therapy over primary endocrine therapy: HR 0.65, 95% CI 0.53 to 0.81, $p = 0.0001$).

Adverse effects

There were insufficient data to justify any quantitative analysis of adverse effects (Hind *et al.* 2006).

Local disease control

A pooled estimate based on data from 2 RCTs (929 women) included in the Cochrane Review by Hind *et al.* 2006 demonstrated a statistically significant difference in favour of surgery plus endocrine therapy over primary endocrine therapy: HR 0.28, 95% CI 0.23 to 0.35, $p < 0.00001$. There were insufficient data to justify any quantitative analysis of prospectively identified subsets. However, one trial which recruited only patients with ER-positive tumours reported better local control in the surgery plus endocrine arm.

One trial which contributed data to the hazard ratio quoted above reported this outcome by type of surgery, comparing both mastectomy (52 of 225 women) and breast-conserving surgery (159 of 225) against the same population of primary endocrine therapy (230 women). The trialists reported better local disease control for both mastectomy and breast-conserving surgery than primary endocrine therapy.

Distant metastasis-free interval

Although data were available from one trial they were not used by the review authors because data quality was suspect (Hind *et al.* 2006).

Quality of life

There were insufficient data to justify any quantitative analysis of this outcome (Hind *et al.* 2006). However, in one published trial included in the Cochrane Review by Hind *et al.* 2006

authors used the General Health Questionnaire 28, designed to detect psychiatric morbidity, and a socio-demographic questionnaire, which investigated levels of domestic support and social isolation. At three months after start of treatment the surgery group had more psychosocial morbidity than the primary hormone therapy group (p value 0.03). However, there was no difference between the surgery and primary hormone therapy groups at two years.

3. Main results of randomised trials not included in the cited systematic reviews

Three additional RCTs evaluate primary hormone therapy in patients with breast cancer either compared to primary chemotherapy (Tan *et al.* 2001) or in combination with primary chemotherapy (Cocconi *et al.* 1990; Von *et al.* 2001b).

The small (n=49) and possibly underpowered RCT by Cocconi *et al.* 1990 compared primary CMF chemotherapy followed mastectomy and adjuvant CMF chemotherapy, versus primary chemoendocrine therapy (CMF plus tamoxifen) followed by mastectomy and the same chemoendocrine combination as adjuvant treatment in patients with locally advanced breast cancer. There was no statistically significant difference in median time to progression or recurrence in the CMF group (58.3 months) compared to the CMF plus tamoxifen group (29.1 months; p=0.38, Cox-Mantel test). Respective values of median overall survival were 79.7 months and 41.5 months; this difference was of borderline statistical significance (p=0.05, Cox-Mantel test).

The RCT by Von *et al.* 2001 also evaluated the addition of tamoxifen to a primary chemotherapy regimen (docorubicin-docetaxel), versus primary chemotherapy alone, studying short-term outcomes. There was no evidence of a difference in the rate of pathological complete response between the randomised arms: 10.3% in the primary chemotherapy arm versus 9.1 in the primary chemotherapy plus tamoxifen arm (difference - 1.2%; 95% CI -8.6 to +6.2) There was little difference in toxicity between the two groups (numerous variables tabulated; no statistical testing of differences performed). There was a higher incidence of severe infections associated with the higher rate of grade 3/4 neutropenia in the primary chemotherapy plus tamoxifen arm. However, the incidences of febrile neutropenia were similar, at 8.3% in the primary chemotherapy plus tamoxifen arm and 8.7% in the primary chemotherapy group. The most common severe forms of toxicity, apart from alopecia, were fatigue and loss of appetite. All other toxicities occurred in less than 5% of the cycles. The rate of breast-conserving surgery did not vary significantly between randomised arms, at 68.6% in the primary chemotherapy plus tamoxifen arm and 69.0% in the primary chemotherapy arm (difference -0.4; 95% CI -12.0% to +11.1%) (Von *et al.* 2001a).

The RCT by Tan *et al.* 2001 compared primary hormone therapy versus primary chemotherapy as initial therapies in patients with locally advanced breast cancer. The time to first locoregional failure was significantly shorter in the initial hormone therapy group when compared with the multimodal therapy group (P<0.01). There was no difference in the number of patients who developed distant metastases (n=29 and n=30 for those treated with initial hormone therapy and multimodal therapy, respectively), nor in the time to distant metastases between the two groups (p=0.84). There was no statistically significant difference in overall survival between the randomised groups (p=0.22) (Tan *et al.* 2001).

An RCT by Eirmann *et al.* 2001 evaluated preoperative treatment of postmenopausal breast cancer patients with letrozole compared to tamoxifen.

PART 2: PRIMARY CHEMOTHERAPY

1. Primary chemotherapy versus adjuvant (following surgery) chemotherapy

NB: In The Cochrane Review by Mieog *et al.* 2007 which is the best quality source of data for primary chemotherapy, median follow-up in each of the 14 included RCTs had range 18-124 months.

Overall survival

The Cochrane Review by Mieog *et al.* 2007 provided a pooled estimate of overall survival based on data from 10 RCTs (4620 women). There was no statistically significant difference in overall survival between preoperative and postoperative chemotherapy: HR 0.98 (95% CI, 0.87 to 1.09; $p=0.67$).

Disease-free survival

The Cochrane Review by Mieog *et al.* 2007 provided a pooled estimate of disease-free survival based on data from 10 RCTs (4510 women). There was no statistically significant difference between preoperative and postoperative chemotherapy: HR 0.97 (95% CI, 0.89 to 1.07; $p=0.58$).

Time to loco-regional recurrence

The Cochrane Review by Mieog *et al.* 2007 provided a pooled estimate of time to loco-regional recurrence based on data from 11 RCTs (5041 women). There was a statistically significant difference in favour of postoperative chemotherapy: HR 1.21 (95% CI, 1.02 to 1.43; $p=0.03$).

Rate of loco-regional recurrence reported in Cochrane Review by Mieog *et al.* 2007 (preoperative versus postoperative chemotherapy) by subgroup for loco-regional treatment

1. Breast conserving surgery (4 RCTs, 1830 women): relative risk (RR), 1.13; 95% CI, 0.82 to 1.54; $p=0.5$
2. Mastectomy (4 RCTs, 1427 women, 82 recurrences): RR, 1.14; 95% CI, 0.74 to 1.75; $p=0.6$
3. Exclusive RT: no data
4. Total (3257 women, 225 recurrences): HR 1.13; 95% CI, 0.88 to 1.46; $p=0.35$; risk difference, 2.3; 95% CI, 0.9 to 3.6; control group risk, 5.9%; $p=0.3$.

There was no statistically significant difference in loco-regional recurrence between women treated with BCT and those treated with mastectomy (Chi^2 for difference, 0.01; $p, 0.92$).

Nodal involvement revealed by surgery

The systematic review by Trudeau *et al.* 2005 reported data from one RCT in which there were significantly different rates of nodal involvement at surgery; 61% of patients who received primary chemotherapy with paclitaxel and doxorubicin were node-negative at surgery compared with 38% of patients who received no primary chemotherapy ($p=0.0001$).

2. Tumour response to preoperative chemotherapy

Tumour response to primary chemotherapy is described below and summarised in the table below.

In the Cochrane Review by Mieog *et al.* 2007, eleven studies reported a complete clinical response rate in the preoperative chemotherapy arm for 1761 assessable patients. The complete clinical response rate ranged from 0 to 64.7%.

Twelve studies reported an overall clinical response rate in the preoperative chemotherapy arm for 2032 assessable patients. The overall clinical response rate ranged from 11.1 to 83.3% (Mieog *et al.* 2007).

Seven studies reported a pathological complete response rate in the preoperative chemotherapy arm for 1972 assessable women. The pathological complete response rate ranged from 4.0 to 29.2% (Mieog *et al.* 2007).

In the systematic review of primary taxane chemotherapy by Trudeau *et al.* 2005 the proportion of cases in which a tumour pathological complete response (pCR) was achieved was reported for 36 randomised arms across 18 RCTs. This value had mean 15.6%, median 15.0% and range 0% to 31%.

In the same systematic review eight randomised arms provided data for the proportion of cases in which a tumour pathological partial response (pPR) was achieved. This value had mean 28%, median 28.5% and range 0% to 57% (Trudeau *et al.* 2005).

21 randomised arms provided data for the proportion of cases in which a tumour clinical complete response (cCR) was achieved. This value had mean 24%, median 20% and range 0% to 84% (Trudeau *et al.* 2005).

25 randomised arms provided data for the proportion of cases in which a tumour clinical partial response (cPR) was achieved. This value had mean 53.8%, median 56% and range 3% to 96% (Trudeau *et al.* 2005).

Table: summary of tumour responses to primary chemotherapy

Study	(Mieog <i>et al.</i> 2007)	(Trudeau <i>et al.</i> 2005)
Overall clinical response (%)		
mean		
median		
range	11.1-83.3	
Partial clinical response (%)		
mean		53.8
median		56
range		3-96
Complete clinical response (%)		
mean		24
median		20
range	0-64	0-84
Pathological partial response (%)		
mean		28
median		28.5
range		0-57

Pathological complete response (%)		
mean		15.6
median		15
range	4-29.2	0-31

Association of pathological complete response with clinical outcome

The Cochrane Review by Mieog *et al.* 2007 compared overall and disease-free survival between patients with a pathological complete response and those who had residual disease at pathological examination.

Four RCTs reported overall survival data for 1290 assessable patients involving 381 estimated deaths. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.33 to 0.69) (Mieog *et al.* 2007).

Five studies reported disease-free survival data for 1741 assessable patients. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.37 to 0.63) (Mieog *et al.* 2007).

3. Primary chemotherapy and rates of breast conserving treatment

The Cochrane Review by Mieog *et al.* 2007 provided a pooled estimate of the rate of mastectomy following preoperative versus postoperative chemotherapy based upon 10 RCTs (5292 women, of which 2395 underwent mastectomy¹⁷). There was a statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy: RR 0.71 (95% CI, 0.67 to 0.75; $p < 10^{-5}$), representing a risk difference of 16.6% (95% CI, 15.1 to 18.1; control group risk, 52.9%; NNT = 6). For this result there was considerable heterogeneity between studies.

Sensitivity analysis did not account for the study heterogeneity relating to this pooled estimate. The authors excluded two studies from the analysis due to clinical heterogeneity¹⁸ and re-analysed using data from 8 RCTs (3709 women, of which 1452 underwent mastectomy). There was a statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy: RR 0.82 (95% CI, 0.76-0.89; $p < 10^{-5}$), representing a risk difference of 8.0% (95% CI, 6.3-9.7; control group risk, 43.1%; NNT = 13); with moderate heterogeneity across studies (Mieog *et al.* 2007).

¹⁷ In three of these studies the reported conservative treatment rate was that achieved after subsequent follow-up i.e. taking account of mastectomy as a second operation to treat local recurrence (Bordeaux 1991, Institut Curie 1994; Royal Marsden 1998).

¹⁸ One study involved an intensive chemotherapy regimen including taxane and anthracycline drugs and reached a high pCR rate, allowing ^{more} conservative treatment (ECTO 2005). The second study treated all patients in the control arm with mastectomy since one of the inclusion criteria was patients with tumours not suitable for conservative treatment (Bordeaux 1991).

In the systematic review of taxane primary chemotherapy by Trudeau *et al.* 2005, the proportion of patients who received breast conserving surgery was reported for 21 randomised arms in 14 RCTs. This proportion had mean 54%, median 56% and range 20% to 85%.

Changes to originally planned locoregional treatment (5 RCTs)

In the Cochrane Review by Mieog *et al.* 2007 five studies reported changes of loco-regional treatment to those planned originally in the preoperative chemotherapy arm (1549 assessable women). Across studies, 397 women had their originally planned surgical treatment altered due to down staging (25.6%; 95% CI, 23.5 to 27.8), 1086 women had no change to planned treatment (70.1%; 95% CI, 67.8 to 72.4), and 66 women required more radical surgery than originally planned (4.3%; 95% CI, 3.3 to 5.3).

In the same review two RCTs compared outcomes between patients who received down staged breast conserving therapy compared to those who received planned breast conserving therapy in the preoperative chemotherapy arm. There was no statistical significant difference in either overall survival (odds ratio (OR) 1.33; 95% CI 0.67-2.63) or loco-regional recurrence (RR 1.34; 95% CI 0.85-2.13). However the review authors concluded that direct evidence concerning long-term prognosis and risk of local recurrence after downstaging of surgical treatment following preoperative chemotherapy is still lacking (Mieog *et al.* 2007).

4. Adverse events

In the Cochrane Review by Mieog *et al.* 2007, seven RCTs provided data on adverse effects. There was no statistically significant difference between preoperative and postoperative chemotherapy for postoperative complications, nausea/ vomiting, and alopecia. Events of cardiotoxicity were less frequent in women receiving preoperative chemotherapy, but not statistically significantly so (RR 0.74; 95% CI, 0.53-1.04; $p=0.08$). The four studies reporting on leucopenia/ neutropenia/ infections involving 2799 women demonstrated a statistically significant difference in favour of preoperative chemotherapy: RR 0.69 (95% CI, 0.56 to 0.84; $p=0.0003$); risk difference 4.2% (95% CI, 2.3 to 5.6; control group risk, 13.8%; NNT, 24).

The systematic review of taxane primary chemotherapy by Trudeau *et al.* 2005 reported a large amount of data on adverse effects: haematologic toxicity, cardiotoxicity, neurotoxicity, gastrointestinal toxicity and other toxicities. The authors concluded that general, haematologic toxicity, in particular neutropenia and febrile neutropenia, was more common with a taxane-containing regimen compared to non taxane-comparing regimens. Neurotoxicity may be associated with primary paclitaxel and hand-foot syndrome may be associated with primary docetaxel. There was little evidence to suggest that other adverse events occur more frequently with a primary taxane (Trudeau *et al.* 2005).

5. Quality of life

In the Cochrane Review by Mieog *et al.* 2007, no data were available for this outcome.

6. Main results of randomised trials not included in the cited systematic reviews

The RCT by Avril *et al.* 1998 compared primary chemotherapy (followed by locoregional treatment) with mastectomy (followed by adjuvant chemotherapy). At 10 years follow-up, estimated overall survival was 60% both in the primary chemotherapy group and in the mastectomy group. Also at 10 years follow-up, estimated recurrence-free survival was 50% in the primary chemotherapy group and 57% in the mastectomy group.

The RCT by Ragaz *et al.* 1986 reported on an early step towards primary chemotherapy, comparing a regimen in which one cycle of CMF chemotherapy was given before surgery followed by eight further cycles adjuvant to surgery, versus all nine cycles of CMF adjuvant to surgery. There was no statistically significant difference between randomised arms in disease-free survival at 2 years follow up ($p > 0.1$).

The RCT by Scholl *et al.* 1991 compared primary chemotherapy versus multimodal therapy based mostly on RT, but also involving surgery and adjuvant chemotherapy. Over the entire follow-up period (median 54 months) there was no statistically significant difference in disease-free survival between randomised groups (primary versus adjuvant chemotherapy); $p = 0.4$. Over the same follow-up period there was no statistically significant difference in overall survival between randomised groups (primary versus adjuvant chemotherapy); $p = \text{NS}$; log-rank test. The rate of local recurrence between randomised groups was similar: 18% for the primary chemotherapy group and 20% for the adjuvant chemotherapy group (no p value reported). The rate of breast conserving surgery was 56% in the primary chemotherapy group versus 35% in the adjuvant chemotherapy group.

Update evidence:

- From an RCT (von Minckwitz *et al.* 2008) that compared 6 cycles of doxorubicin, docetaxel and cyclophosphamide (two 3-week cycles of docetaxel at 75 mg/m², doxorubicin at 50 mg/m², and cyclophosphamide at 500 mg/m²)(TAC) with 8 cycles of TAC in patients with previously untreated unilateral or bilateral primary breast cancer.
- The rates of pathological complete response were not statistically significantly different between the arms.
- The clinical complete responses at surgery were not statistically different with 8 TAC cycles than with 6 TAC cycles.
- The sonographic complete responses at surgery were statistically more with 8 TAC cycles than with 6 TAC cycles.
- There was no statistical significant difference in the rate of breast-conserving surgery in both arms.
- Grade 3 or 4 leukopenia and edema and various grade 1 or 2 adverse events were more frequent in patients receiving 8 TAC cycles than in those receiving 6 cycles.
- There were statistically more treatment discontinuations were due to adverse reactions reported in the 8 cycle arm than in the 6-cycle arm.
- Negative hormonal receptor status; nonlobular histology; undifferentiated grade; age younger than 50 years were statistically significantly independently associated with pathological complete response.

A review by Rastogi 2008, provided updated results from two randomised controlled trials, B-18 and B-27; trial B-18 compared preoperative chemotherapy with doxorubicin and cyclophosphamide with postoperative chemotherapy. Trial B-27 compared 3 groups; 4 cycles of preoperative AC plus docetaxel vs. 4 cycles of preoperative AC chemotherapy and postoperative docetaxel vs. 4 cycles of preoperative AC chemotherapy alone.

The updated results provide evidence that there is no statistically significant difference in overall survival (OS) or disease free survival (DFS) when comparing preoperative chemotherapy with post-operative chemotherapy in either trial.

		Hazard Ratio, 95% CI (p)
B-18	Overall Survival	HR=0.99, 95% CI, 0.85 to 1.16 (p=0.90)
	Disease Free Survival	HR=0.93, 95% CI, 0.81 to 1.06 (p=0.27)
B-27	Overall Survival	No HR or CI given (p=0.76)
	Disease Free Survival	No figures given

In trial B-18, individuals who achieved a pathological complete response (pCR) had superior DFS and OS outcomes when compared with patients not achieving a pCR (DFS HR =0.47, p<0.0001; OS HR =0.32, p<0.0001).

In trial B-27 pCR was a significant predictor of improved DFS (HR=0.49, p<0.0001) and OS (HR=0.36, p<0.0001).

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Evidence Tables

Systematic reviews of RCTs

Citation
Hind, Wyld, Beverley & Reed . Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). [Review] [43 refs]. Cochrane.Database.of Systematic.Reviews. [1], CD004272. 2006.
Design
Systematic review of RCTs, evidence level: 1 + Country: Various
Inclusion criteria
Aim: to systematically review the evidence for the clinical effectiveness of surgery (with or without adjuvant endocrine therapy) in comparison to primary endocrine therapy in the treatment of operable breast cancer in women aged 70 years and over, both in terms of local progression and mortality. Eligible studies: RCTs
Exclusion criteria
No eligible studies were excluded.
Population
Women aged 70 years or over with clinically-defined operable primary breast cancer, that is, primary tumour not fixed to underlying structures (including the TNM classification T1-3 and T4b where there is only minor skin involvement, N0-1, mobile lymph nodes (UICC 1987)). The following age-based subgroups were planned: 70 to 79 years; 80 years and over.
Interventions
1) Surgery alone versus primary endocrine therapy. 2) Surgery plus adjuvant endocrine therapy versus primary endocrine therapy.
Outcomes
Primary outcome measures 1) Survival - overall (interval between start of treatment and patient's death; cause of death where available). 2) Progression-free survival (interval between start of treatment and need for second-line treatment/palliative treatment/recurrence/death from any cause). Secondary outcome measures 1) Adverse effects (number of surgical complications/primary endocrine therapy related side effects, including hot flushes, nausea, vomiting, vaginal discharge, vaginal bleeding, thrombosis, endometrial carcinoma, visual

problems, skin rashes).

2) Local disease control (interval between start of treatment and need for second-line treatment/palliative treatment/recurrence; specified whether local disease has recurred in the breast/mastectomy scar or axilla).

3) Distant metastasis-free interval (interval between start of treatment and the development of metastatic disease).

4) Quality of life (however measured).

Follow up

Variable across primary studies but adequate; commonly approximately 10 years.

Results

Ratios of treatment effects are reported so that HRs less than 1.0 favour surgery or surgery plus adjuvant endocrine therapy and values greater than 1.0 favour primary endocrine therapy.

7 RCTs were eligible of which 6 provided usable data. In each trial the endocrine therapy used was tamoxifen

1. Surgery versus primary endocrine therapy

Overall survival

Pooled result of three trials (495 women). There was no statistically significant difference between interventions (HR 0.98, 95% CI 0.74 to 1.30, $p=0.9$).

Progression-free survival

Data from 1 RCT favours surgery (HR 0.55, 95% CI 0.39 to 0.77, $p=0.0006$).

Adverse effects

There were insufficient data for a quantitative analysis. In 1 RCT no patient discontinued treatment with primary endocrine therapy. Eight patients had a total of ten side effects, including hot flushes, skin rash, vaginal discharge, indigestion, breast pain and sleepiness.

Local disease control

No data were acceptable for citing due to biases introduced by competing risks, heterogeneity of interventions and informative censoring.

Distant metastasis-free survival

Data from 1 RCT (164 women) shows no statistically significant difference between interventions (HR 0.77, 95% CI 0.37 to 1.58, $p=0.47$). NB due to the method of calculation, this hazard ratio incorporates distant metastases recorded both as a first event and following or simultaneously with a local progression.

Quality of life

No trials reported any data for this outcome.

2. Surgery plus adjuvant endocrine therapy versus primary endocrine therapy

Overall survival

Pooled result of three trials (1076 women): There was a trend in favour of surgery plus endocrine therapy that was not statistically significant (HR 0.86, 95% CI 0.73 to 1.00, $p=0.06$).

Overall survival by ER status

One trial provided data based on 147 women, all of whom had ER+ tumours. There was no significant difference between the interventions (HR 0.80, 95% CI 0.28 to 2.32, $p=0.68$).

Overall survival by age

Age-related subgroup analysis was not possible on the basis of published data. In a conference abstract authors from two trials reported analyses of combined individual patient data from both trials. They reported that patient age was the most important determinant of survival in later years (75 years plus). In those between 70 and 75 years, initial surgery (rather than primary endocrine therapy) determined survival.

Breast cancer specific survival

A published meta-analysis of individual patient data from two RCTs found a statistically significant effect in favour of surgery plus endocrine therapy (HR 0.7, 95% CI 0.51 to 0.95).

Progression-free survival

Data from 1 RCT found a statistically significant effect in favour of surgery plus endocrine therapy (HR 0.65, 95% CI 0.53 to 0.81, P value 0.0001).

Adverse effects

There were insufficient data to justify any quantitative analysis of this outcome.

Local disease control

Pooled estimate based on data from 2 RCTs (929 women): this analysis showed a statistically significant difference in favour of surgery plus endocrine therapy (HR 0.28, 95% CI 0.23 to 0.35, $p < 0.00001$). There were insufficient data to justify any quantitative analysis of prospectively identified subsets. However, one trial which recruited only patients with ER+ tumours reported better local control in the surgery plus endocrine arm.

One trial which contributed data to the hazard ratio quoted above reported this outcome by type of surgery, comparing both mastectomy (52 of 225 women) and breast-conserving surgery (159 of 225) against the same population of

primary endocrine therapy (230 women). The trialists reported better local disease control for both mastectomy and breast-conserving surgery than primary endocrine therapy.

Distant metastasis-free interval

Although data were available from one trial they were not used by the review authors because data quality was suspect.

Quality of life

There were insufficient data to justify any quantitative analysis of this outcome. However, in one published trial authors used the General Health Questionnaire 28, which detects psychiatric morbidity, and a socio-demographic questionnaire, which investigated levels of domestic support and social isolation. At three months after start of treatment the surgery group had more psychosocial morbidity (p value 0.03). However, there was no difference between the surgery and PET groups at two years.

Authors' summary and conclusions

This study has demonstrated that primary endocrine therapy is inferior to surgery with endocrine therapy for the local control of breast cancer in medically fit older women who are not selected on the basis of ER status. This is independent of the type of surgery, with both mastectomy and wide excision (without adjuvant radiotherapy) achieving superior local control. However, the surgery does not result in significantly better overall survival.

Primary endocrine therapy should only be offered to women with oestrogen receptor (ER) positive tumours who are unfit for or who refuse surgery. In women with significant co-morbid disease and ER positive tumours it is possible that primary endocrine therapy may be a superior option to surgery. Trials are needed to evaluate the clinical effectiveness of aromatase inhibitors as primary therapy for an infirm older population with ER positive tumours.

General comments

In some cases the strength of evidence was affected by competing risks, informative censoring and study heterogeneity between trials, in terms of interventions and outcome assessment. Therefore only reliable data were used. The authors describe these limitations as follows:

Competing risks

Applies to outcomes such as local failure in Kaplan-Meier analyses: censoring patients in whom a competing risk occurs (e.g. death) is not appropriate as it gives an under-estimate of the probability of local failure by treating those cases who haven't failed locally and are alive the same as those who have not failed locally but have died.

Informative censoring

Re: time to local or distant recurrence: in one trial patients were censored at

the time of their last clinical examination. Assuming that those who have progressed are more likely to attend follow-up clinics and that those who are disease or metastases-free are less likely to attend clinics, the latter group will be censored earlier, and will stop contributing information to the study. Thus the censoring is potentially dependent on the likelihood of disease progression (that is, related to the outcome). This is another source of potential bias as the rate of censoring does not leave a representative sample of those at risk.

Heterogeneity of populations and interventions

Whilst all studies met the inclusion criteria for the review, there was heterogeneity between studies in terms of tumour size, and use of either breast conserving surgery or mastectomy.

Heterogeneity of outcome assessments

Studies differed with regard to classification of distant metastatic events either as those occurring after local events or as those occurring as first events.

Applicability of results

The authors report that the results of their review need to be read bearing in mind that they are derived from a small number of individually underpowered studies. Additionally, there are four areas where treatment regimens in the trials do not necessarily coincide with modern clinical practice. Therefore, the appropriateness of the following should be questioned:

- (1) endocrine therapy for women with ER negative tumours;
- (2) surgery without adjuvant endocrine therapy;
- (3) primary endocrine therapy where the individual is fit for and agreeable to surgery;
- (4) new endocrine therapies.

Literature search strategy

The Cochrane Breast Cancer Group Specialised Register was searched on 21st August 2003. Details of the search strategy applied by the Group to create the register, and the procedure used to code references, are described in the Group's module on The Cochrane Library. Studies coded as "EARLY BREAST CANCER", "ENDOCRINE THERAPY", "PSYCHOSOCIAL" or "SURGERY" on the specialised register were extracted for consideration.

Assessment of primary study quality

This is evident and considers randomisation method, concealment and intention-to-treat analysis. It was not possible to accurately assess the quality of all studies (including the quality of the randomisation process) due to lack of information in the published articles. The quality of three trials was graded as A (CRC; EORTC 10851; GRETA) with the rest being graded as B (Naples; Nottingham 1; Nottingham 2; St Georges).

Citation
Mieog, van der Hage & van d . Preoperative chemotherapy for women with operable breast cancer. Cochrane Database of Systematic Reviews. [2], CD005002. 2007.
Design
Systematic review of RCTs (therapy), evidence level: 1 ++ Country: Various, setting: Tertiary care
Inclusion criteria
RCTs of primary (preoperative) chemotherapy in women with operable breast cancer: TNM stage T1c, T2, T3, N0 to 2, and M0 (AJCC stage I-IIIa).
Exclusion criteria
5 RCTs were excluded for the following reasons: 1. Randomised controlled trial consisting of 101 women with operable locally advanced disease (T4b, N0-2, M0) 2. Abstract of conference proceeding. Reported a subset of patients part of NSABP B-18 study. 3. Abstract of conference proceeding. No data available. Publication pending. 4. Randomised controlled trial comparing preoperative with postoperative chemotherapy. Relevant data stratified to apoptotic index. No response from authors. 5. Abstract of conference proceeding. Not properly randomised (of the 98 analysed patients only 87 were included in a randomised prospective fashion)
Population
Number of patients = 5500.
Interventions
Aim: to systematically identify and assess all of the available evidence from RCTs as to the effectiveness of preoperative chemotherapy on treatment-related outcomes in women with operable breast cancer.
Eligible comparisons
i) Preoperative chemotherapy versus postoperative chemotherapy. ii) Preoperative and postoperative chemotherapy versus postoperative chemotherapy.
All included trials compared preoperative chemotherapy with a postoperative regimen (see also Appendix AAtable). In six trials patients in the preoperative arm received all cycles prior to loco-regional treatment. In the remaining eight trials, patients in the preoperative arm received some of the cycles after loco-regional treatment. A variety of chemotherapeutic regimens were administered to patients across the included trials; all regimens were made up

of multiple chemotherapeutic agents.

Hormone therapy in eligible studies

Endocrine treatment was administered instead of chemotherapy to patients with tumours expressing high estrogen receptor levels in two studies (Edinburgh 1995, London 2001). Non-responders to endocrine treatment in the preoperative arm of London 2001 crossed over to an anthracycline containing chemotherapeutic regimen after loco-regional treatment. Tamoxifen was administered to eligible patients in seven studies (ECTO 2005, EORTC 2001, Japan 1998; Lithuania 1998; NSABP 1998, Royal Marsden 1998; USA 2003) and was mostly started after loco-regional treatment; in one study patients in the preoperative arm started tamoxifen treatment along with chemotherapy and thus before surgery (Royal Marsden 1998).

Loco-regional therapy

Loco-regional treatment varied across studies. Five studies applied the same local treatment to all included patients (Edinburgh 1995, Japan 1998; Lithuania 1998, St. Petersburg 1994). In other studies treatment varied according to patients' individual requirements (e.g. tumour size, nodal involvement). Three studies administered radiotherapy before surgery (Institut Curie 1991; Institut Curie 1994, St. Petersburg 1994). Three studies treated some of the participants exclusively with radiotherapy (Bordeaux 1991; Institut Curie 1991; Institut Curie 1994).

Outcomes

Primary outcomes:

1. Overall survival
2. Disease-free survival
3. Loco-regional recurrence as first event

Secondary outcomes:

1. Tumour response rate to primary chemotherapy as follows:
 - i) Clinical complete response (cCR): complete disappearance of all clinically detectable malignant disease at the time of surgery
 - ii) Overall clinical response (OR): defined as $\geq 50\%$ decrease in total tumour size after chemotherapy compared to the pre-treatment size
 - iii) Pathological complete response (pCR): defined as the complete disappearance of invasive carcinoma on histological examination
2. Association of pathological complete response with clinical outcome
3. Type of loco-regional treatment
4. Changes of originally planned loco-regional treatment
5. Adverse effects (WHO grades III and IV events of postoperative complications, cardiotoxicity, leukopenia or neutropenia or infection, nausea and vomiting, and alopecia).
6. Quality of life

Follow up
In 14 RCTs median follow-up had range 18-124 months
Results
<p>14 RCTs met the inclusion criteria.</p> <p>Unless stated otherwise, ratios of treatment effects are reported so that values less than 1.0 favour primary chemotherapy and values greater than 1.0 favour adjuvant chemotherapy.</p> <p>Overall survival 10 RCTs, 4620 randomised women, 1139 estimated deaths. See appended table below for survival rates of the research and control arm for each study after 5 and 10 years median follow-up. There was no statistically significant difference in overall survival between preoperative and postoperative chemotherapy: HR 0.98 (95% CI, 0.87 to 1.09; p=0.67); without heterogeneity.</p> <p>Disease-free survival 10 RCTs, 4510 randomised women, 1596 estimated events. There was no statistically significant difference between preoperative and postoperative chemotherapy: HR 0.97 (95% CI, 0.89 to 1.07; p=0.58); moderate heterogeneity.</p> <p>Time to loco-regional recurrence 11 RCTs, 5041 randomised women, 558 estimated recurrences. There was a statistically significant difference in favour of postoperative chemotherapy: HR 1.21 (95% CI, 1.02 to 1.43; p=0.03), without heterogeneity.</p> <p>Rate of loco-regional recurrence (preoperative versus postoperative chemotherapy) by subgroup for loco-regional treatment</p> <ol style="list-style-type: none"> 1. Breast conserving surgery (4 RCTs, 1830 women, 143 recurrences): RR, 1.13; 95% CI, 0.82 to 1.54; p=0.5 2. Mastectomy (4 RCTs, 1427 women, 82 recurrences): RR, 1.14; 95% CI, 0.74 to 1.75; p=0.6 3. Exclusive RT: no data 4. Total (3257 women, 225 recurrences): HR 1.13; 95% CI, 0.88 to 1.46; p=0.35; risk difference, 2.3; 95% CI, 0.9 to 3.6; control group risk, 5.9%; p=0.3. <p>There was no statistically significant difference in loco-regional recurrence between women treated with BCT and those treated with mastectomy (Chi² for difference, 0.01; p, 0.92).</p> <p>Tumour response to preoperative chemotherapy Eleven studies reported a complete clinical response rate in the preoperative chemotherapy arm for 1761 assessable patients involving 653 complete</p>

clinical responses. The complete clinical response rate ranged from 0 to 64.7%.

Twelve studies reported an overall clinical response rate in the preoperative chemotherapy arm for 2032 assessable patients involving 1384 overall clinical responses. The overall clinical response rate ranged from 11.1 to 83.3%.

Seven studies reported a pathological complete response rate in the preoperative chemotherapy arm for 1972 assessable women involving 278 pathological complete responses. The pathological complete response rate ranged from 4.0 to 29.2%.

Association of pathological complete response with clinical outcome

The authors compared overall and disease-free survival between patients with a pathological complete response and those who had residual disease at pathological examination.

Four studies reported overall survival data for 1290 assessable patients involving 381 estimated deaths. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.33 to 0.69).

Five studies reported disease-free survival data for 1741 assessable patients involving 606 estimated events. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.37 to 0.63).

Primary chemotherapy and rates of breast conserving treatment

10 RCTs, 5292 randomised women, of which 2395 underwent mastectomy¹⁹. There was a statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy: RR 0.71 (95% CI, 0.67 to 0.75; $p < 10^{-5}$), representing a risk difference of 16.6% (95% CI, 15.1 to 18.1; control group risk, 52.9%; NNT, 6) and with substantial heterogeneity across studies.

Sensitivity analysis did not account for the study heterogeneity relating to this pooled estimate. The authors excluded two studies from the analysis due to clinical heterogeneity²⁰ and re-analysed with the following result:

¹⁹ In three of these studies the reported conservative treatment rate was that achieved after subsequent follow-up i.e. taking account of mastectomy as a second operation to treat local recurrence (Bordeaux 1991, Institut Curie 1994; Royal Marsden 1998).

²⁰ One study involved an intensive chemotherapy regimen including taxane and anthracycline drugs and reached a high pCR rate, allowing ^{more} conservative treatment (ECTO 2005). The second study treated all patients in the control arm with mastectomy since one of the inclusion criteria was patients with tumours not suitable for conservative treatment (Bordeaux 1991).

8 RCTs, 3709 randomised women, of which 1452 underwent mastectomy. There was a statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy: RR 0.82 (95% CI, 0.76-0.89; $p < 10^{-5}$), representing a risk difference of 8.0% (95% CI, 6.3-9.7; control group risk, 43.1%; NNT, 13) and with moderate heterogeneity across studies.

Changes to originally planned locoregional treatment (5 RCTs)

Five studies reported changes of loco-regional treatment that had been originally planned in the preoperative chemotherapy arm (1549 assessable women; see appendix: table). Across studies, 397 women had their originally planned surgical treatment altered due to down staging (25.6%; 95% CI, 23.5 to 27.8), 1086 women had no change to planned treatment (70.1%; 95% CI, 67.8 to 72.4), and 66 women required more radical surgery than originally planned (4.3%; 95% CI, 3.3 to 5.3).

Table: relationship between treatment intended and treatment performed

Study	BCT - BCT	MAST - MAST	MAST - BCT	MAST - RT	BCT - RT	BCT - MAST	Total
Bordeaux 1991	-	49	40	44	-	-	133
EORTC 2001	60	190	60	-	-	14	324
Institut Curie 1994	-	36	62	102	-	-	200
NSABP 1998	435	187	69	-	-	52	743
Royal Marsen 1998	113	16	19	-	1	-	149
Total	608	478	250	146	1	66	1549

Two RCTs compared outcomes between patients who received down staged breast conserving therapy compared to those who received planned breast conserving therapy in the preoperative chemotherapy arm. There was no statistical significant difference in loco-regional recurrence or overall survival between these groups:

Table: Effect on outcome of downstaging: ratio outcomes for downstaged vs planned breast conserving surgery in primary chemotherapy arms of two RCTs

Outcome	No. of studies	No. of participants	Statistical method	Effect size
Overall	1	120	Peto Odds Ratio	1.33 [0.67,

survival			[95% CI]	2.63]
Loco-regional recurrence	2	623	Relative Risk (Fixed) [95% CI]	1.34 [0.85, 2.13]

Authors conclude that direct evidence concerning long-term prognosis and risk of local recurrence after downstaging of surgical treatment following preoperative chemotherapy is still lacking. Indirectly derived data suggest no intrinsic risk amplification associated with downstaged breast-conserving surgery. However, evidence from direct comparison is needed to draw valid conclusions.

Adverse events

7 RCTs provided data. There was no statistically significant difference between preoperative and postoperative chemotherapy for postoperative complications, nausea/ vomiting, and alopecia. Events of cardiotoxicity were less frequent in women receiving preoperative chemotherapy (RR 0.74; 95% CI, 0.53-1.04; p=0.08); without heterogeneity. The four studies reporting on leucopenia/ neutropenia/ infections involving 2799 women and 327 events demonstrated a statistically significant difference in favour of preoperative chemotherapy: RR 0.69 (95% CI, 0.56 to 0.84; p=0.0003); with low heterogeneity; risk difference 4.2% (95% CI, 2.3 to 5.6; control group risk, 13.8%; NNT, 24).

Quality of life

No data were available for this outcome.

General comments

Most outcomes are reported as hazard ratios for primary (preoperative) versus postoperative chemotherapy arms.

The studies vary in their primary chemotherapy regimens, use of axillary surgery, hormone therapy and, in primary chemotherapy arms, whether adjuvant chemotherapy was also given.

Literature search:

Cochrane Breast Cancer Group Specialist Register of RCTs searched on 4.8.05; includes published and unpublished trials; no language restrictions. Keywords: 'early' and 'chemo' and 'locally advanced' and 'chemo'. In addition the authors searched reference lists of related literature reviews.

Study selection:

Two review authors independently applied the selection criteria on the methods sections of the selected trials. The review authors were blinded to all but the methods section. Any disagreements were resolved by consensus.

Quality assessment:

Two review authors independently reviewed each included study based on:

- concealment of the allocation sequence
- generation of the allocation sequence
- comparability between groups at the baseline
- inclusion of all randomised participants in the analysis (Intention to treat)
- loss to follow-up

Allocation concealment was graded as follows:

- Grade A - clearly adequate
- Grade B - possibly adequate,
- Grade C - clearly inadequate
- Grade D - not used.

Data extraction:

At least two individuals independently extracted data from the studies identified for inclusion. Any disagreements were resolved by consensus.

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Appendix: table of eligible RCTs of primary chemotherapy; from Cochrane Review, including survival data where reported

NB estimated 5-year and 10-year survival values read from bar graph

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
ABCSG 2001	Receptor -ve tumours (n=301); receptor +ve tumours, size >3cm (n=122)	Preop and postop vs postop CMF/EC Arm A: 3 cycles of preoperative Cyclophosphamide, Methotrexate, Fluorouracil. Followed by 3 cycles of postoperative CMF (same as above) for node-negative pts or 3 cycles of Epirubicin, Cyclophosphamide for node-positive pts. Arm B: idem as for A, all postoperative.	Surgery given (including breast conservation; otherwise not specified)	-	-		
Bordeaux 1991	T2>3cm, T3, N0-1, M0	Preop vs postop EVM + MTV Arm A: 3 cycles of preoperative Epirubicin -Vincristine - Methotrexate every 3 weeks followed by 3 cycles of preoperative Mitomycin C - Thiotepa - Vindesine every 3 weeks. Arm B: mastectomy then adjuvant chemotherapy as for arm A if histological axillary node involvement or negative ER/PR, otherwise no adjuvant chemotherapy.	Arm A i) Complete regression: exclusive RT of breast (50 Gy + 20-24 Gy boost) and axilla, internal mammary, supraclavicular node areas (50 Gy + 10 Gy boost on axilla if positive prechemotherapy). ii) Residual < 2cm: lumpectomy + breast irradiation (50 Gy + 10 Gy boost). iii) Residual > 2cm: modified radical mastectomy (Patey) without RT. Arm B mastectomy	80	80	62	59
ECTO 2005	T size >2cm; (20%>4cm)	3 Arms: Preop AT-CMF vs postop AT-CMF vs postop A-CMF Arm A: 4 cycles of preoperative Doxorubicin - Paclitaxel every 3 weeks followed by 4 cycles of Cyclophosphamide - Methotrexate -Fluorouracil on days 1 and 8 every 4 weeks. Arm B: idem as for A, all postoperative. Arm C: 4 cycles of postoperative Doxorubicin 75 mg/m ² IV every 3 weeks followed by 4 cycles of CMF IV on days 1 and 8 every 3 weeks.	Mastectomy or BCT + radiotherapy RT for mastectomy-treated patients with pT4 tumours.	87	90	-	-
EORTC 2001	T1c-T3, T4b, N0-1, M0	Preop vs postop FEC Arm A: 4 cycles of preoperative Fluorouracil - Epirubicin - Cyclophosphamide every 3 weeks. Arm B: idem as for A, all postoperative	Mastectomy or BCS + RT (50 Gy in 5 weeks). Chest wall/parasternal: pts with initial tumour of 5 cm or more. Infra and supraclavicular fossa: pts with positive infraclavicular node after LN dissection. Tamoxifen: pts >50 yrs (regardless of ER/nodal status) received 20 mg daily for at least 2 yrs.	77	82	64	66

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
Edinburgh 1995	Operable tumours >4cm in size; no metastases.	<p>Arm A: ER -ve pts and non-responding ER+ve pts: 4 cycles of preoperative Cyclophosphamide, Doxorubicin, Prednisolone every 3 weeks. Followed by 2 cycles of postoperative cycles of CAP. Responding ER+ve pts: endocrine treatment: * Premenopausal: Goserelin monthly for 12 weeks. Followed by oophorectomy. * Postmenopausal: Tamoxifen for 12 weeks and continued postoperatively.</p> <p>Arm B: appropriate adjuvant therapy: NFS.</p>	Modified radical mastectomy with level III axillary clearance for all pts within 3 weeks after last cycle of chemotherapy or after study entry.	-	-		
Institut Curie 1991	T2-3, N0, 1b, M0	<p>Preop and postop vs postop FAC/AMVT</p> <p>Arm A: 2 cycles of preoperative 5-Fluorouracil, Doxorubicin and Cyclophosphamide every 4 wks. Good responders received a following 4 cycles of FAC as above after loco regional treatment. Non-responders received 4 cycles of Doxorubicin, Methotrexate, Vindesine and Thiotepa.</p> <p>Arm B: 6 cycles of postoperative FAC as above.</p>	<p>Primary radiation therapy: 55 Gy in 6 weeks to breast and inferior axillary nodes + 45 Gy to supraclavicular nodes and internal mammary chain. A boost to tumour bed (totalling 75-80 Gy) was given to pts who had a regression of the tumour at 55 Gy.</p> <p>Surgery (mastectomy or lumpectomy) was limited to pts presenting with a persisting mass after RT.</p>	-	-		
Institut Curie 1994	T2-3, N0-1, M0 (T size 3-7cm)	<p>Preop vs postop FAC</p> <p>Arm A: 2 cycles of preoperative 5-Fluorouracil on days 1, 3, 5, 8, Doxorubicin and Cyclophosphamide on day 1 and 8 every 4 wks. Followed by response assessment: Good responders: 2 additional cycles of preoperative FAC. Non-responders: loco-regional treatment</p> <p>Arm B: 4 cycles of adjuvant FAC within 2 weeks of ending loco-regional treatment.</p>	<p>Primary RT: 54 Gy in 6 weeks to breast and axillary nodes + 45 Gy to supraclavicular nodes and internal mammary chain. Patients with CR or near CR received a boost to tumour bed (totalling 75-80 Gy) and had no surgery. N+ patients received a 10-15 Gy boost to inferior axilla if no surgery was performed.</p> <p>Surgery (mastectomy or lumpectomy) was limited to patients presenting with a persisting mass after 54 Gy. A total of 24 patients underwent mastectomy without RT.</p>	84	77	64	60
Japan 1998	Stage II with tumour size >4cm and stage III.	<p>Preop and post op vs postop EC and UFT</p> <p>Arm A: 2 cycles of preoperative Epirubicin, Cyclophosphamide every 3 weeks followed by 3 cycles of postoperative EC. Daily administration of 400 mg UFT.</p> <p>Arm B: idem as for A, all postoperative.</p>	Surgery: mastectomy for all patients. Tamoxifen for 2 yrs.	-	-		

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
Lithuania 1998	Stage II (T2, N0-1)	Preop and postop vs postop CMF Arm A: 2 cycles of preoperative Cyclophosphamide, Methotrexate, Fluorouracil: NFS. Arm B: idem as for A, all postoperative.	Conservative surgery (plastic quadraneotomy), RT, adjuvant chemo/hormonotherapy (NFS).	-	-		
London 2001	T1-4, N0-1, M0 (24% T3-4)	Preop and postop vs postop treatment. Either chemo- or endocrine therapy based on ER-status: Arm A: ER+ pts (47): endocrine treatment Premenopausal: Goserelin monthly for 12 weeks. Postmenopausal: Formestane every 2 weeks for 12 weeks. ER - pts: 4 cycles in 12 weeks of preoperative Mitozantrone every 3 weeks, Mitomycin C every 6 weeks, Methotrexate every 3 weeks with fonic acid rescue 4 times for 24 hours, starting 24 hrs after chemotherapy. After clinically assessing tumour response and surgery/radiotherapy: Responders: received a total of 8 cycles MMM or 18 months Goserelin or Formestane (doses as above). Non-responders: ER + pts: 8 cycles of MMM (as above) ER - pts: 8 cycles of 5-Fluorouracil - Epirubicin - Cyclophosphamide every 3 weeks. Arm B: ER+ pts: endocrine therapy Premenopausal: Goserelin as above for 18 months. Postmenopausal: Formestane as above for 18 months. ER - pts: 8 cycles of MMM as above.	Primary surgery (mastectomy or BCS + RT to breast + boost to scar) or primary RT. Pts with involved axillary nodes: RT to axilla and supraclavicular fossa. Pts with tumours in medial half of breast: RT to ipsilateral mammary chain. When primary RT did not produce a response, a mastectomy was performed.	77	87	-	-
NSABP 1998	T1-3, N0-1, M0 (no locally advanced disease)	Preop vs postop AC Arm A: 4 cycles of preoperative Doxorubicin - Cyclophosphamide every 3 weeks. Women with progressive disease before completion of all 4 courses received the remaining courses after surgery. Arm B: idem as for A, all postoperative.	Mastectomy or BCS + RT. Tamoxifen: pts >50 yrs (regardless of ER/nodal status) received 10 mg twice daily for 5 yrs	80	82	68	70

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
Royal Marsden 1998	T1-4, N0-1, M0 (7% T3-4)	Preop and postop vs postop MM(M) Arm A: 4 cycles of preoperative Mitomycin C every 6 weeks, Mitoxantrone every 3 weeks, Methotrexate every 3 weeks or 2M (same as 3M, with the exclusion of Mitomycin C and increased dose of Mitoxantrone) followed by 4 cycles postoperative of 3M or 2M. Arm B: idem as for A, all postoperative.	Mastectomy or BCT + RT (54 Gy to breast + 10 Gy boost to scar). Clinically involved lymph nodes: Level II axillary lymph node dissection. No axillary dissection for clinically node negative pts. RT to axilla and supraclavicular fossa was only given to those pts with palpable nodes at presentation, who did not have axillary dissection. Tamoxifen: 20 mg daily for 5 years simultaneously started with chemotherapy.	77	77	70	64
St Petersburg 1994	Stage IIb-IIIa: T3, N0-1; T2, N1; T1-2, N2, M0	Preop and postop vs postop TMF Arm A: 1 or 2 cycle(s) of preoperative Thiotepa on days 1,3,5,7,9,11, Methotrexate - 5-Fluorouracil on days 1 and 8 every 4 weeks. Followed, starting during mastectomy, by 4-5 cycles of TMF. Arm B: 6 cycles of postoperative TMF.	Preoperative RT: 60 Gy (2 Gy daily) to breast + 40 Gy to axillary area, supra- and subclavicular areas followed after 3-4 weeks by modified radical mastectomy.	87	78	-	-
USA 2003	Stage II: T1, N1; T2, N0; T2, N1	Preop vs postop FLAC + G(M)-CSF Arm A: 5 cycles of preoperative 5-Fluorouracil - Leucovorin - Doxorubicin on days 1,2,3 and Cyclophosphamide on day 1 every 3 wks + Granulocyte-macrophage colony stimulation factor Arm B: idem as for A, all postoperative (2-3 wks after surgery)	Mastectomy or BCS + RT. RT 50.4 Gy to the breast and, in cases with N stage disease, axilla. Patients with extranodal extension received 50.4 Gy to the posterior axillary field. All pts received an additional 10-Gy boost to the surgical bed. Tamoxifen for ER+/PR+ pts: 10 mg twice daily for 5 yrs.	93	84	87	72

Trudeau, Sinclair & Clemons . Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: A systematic review. Cancer Treat.Rev. 31[4], 283-302. 2005.
Design
Systematic review of RCTs (therapy), evidence level: 1 - Country: Various, setting: Secondary care
Inclusion criteria
For eligible studies: <ul style="list-style-type: none"> • A primary taxane-containing regimen was evaluated using any of the publication types listed in the search strategy (randomised controlled trials or systematic reviews/metaanalyses). • Reported outcomes included rates of clinical response, pathologic response, breast conservation, DFS, or overall survival. • Clinical trial results were reported in either full papers or abstracts.
Exclusion criteria
Non English language papers
Population
Number of patients = 6225.
Interventions
Aim: to review RCT evidence on the role of primary taxane chemotherapy in patients with non-metastatic breast cancer. All patients underwent primary chemotherapy; at least one arm receiving primary taxane chemotherapy. All randomised arms planned surgery in addition, and some, radiotherapy and hormone therapy in addition.
Outcomes
Response to primary chemotherapy (tumour and lymph nodes) Proportion of patients who underwent breast conserving surgery Disease-free survival (DFS) Overall survival (OS)
Follow up
See table below
Results
17 RCTs were included, presented in 18 papers, one of which provided further analysis between subgroups for different primary taxane doses/schedules. In all trials the randomised comparison is either primary taxane chemotherapy versus non-taxane primary chemotherapy, primary taxane versus adjuvant taxane, or different

doses/schedules of primary taxane chemotherapy.

Of 17 included RCTs only four provide data on DFS or OS (appendicised table 2). Due to heterogeneity in terms of follow-up extent for assessing survival, no concise summary statement is possible.

The majority (12) of studies were available only in abstract at the time of completion of the literature search (September 2004), suggesting that follow-up is immature.

Locoregional treatment

Of 17 RCTs, nine omitted radiotherapy altogether and eight used radiotherapy in all randomised arms. In contrast all RCTs used surgery in all of their randomised arms. Some studies report the proportion of patients in whom breast conserving surgery was performed; the complement of this proportion represents patients who received mastectomy.

Primary tumour response to primary chemotherapy

Across the 18 included trials, the proportion of cases in which a tumour pathological complete response (pCR) was achieved was reported for 36 randomised arms. This value had mean 15.6%, median 15.0% and range 0% to 31%.

Eight randomised arms provided data for the proportion of cases in which a tumour pathological partial response (pPR) was achieved. This value had mean 28%, median 28.5% and range 0% to 57%.

21 randomised arms provided data for the proportion of cases in which a tumour clinical complete response (cCR) was achieved. This value had mean 24%, median 20% and range 0% to 84%.

25 randomised arms provided data for the proportion of cases in which a tumour clinical partial response (cPR) was achieved. This value had mean 53.8%, median 56% and range 3% to 96%.

Breast conserving surgery after primary chemotherapy

In all 17 RCTs surgery was performed in every randomised arm. In total the proportion of patients who received breast conserving surgery was reported for 21 randomised arms in 14 RCTs. This proportion had mean 54%, median 56% and range 20% to 85%.

NB See Appendix A below for table of primary study details reported in systematic review.

1. Primary taxane regimens vs. other primary regimens

The smallest paclitaxel trial (n = 30, accrual ongoing) reported a statistically significant improvement in pathologic complete response (pCR) with paclitaxel and epirubicin

therapy compared to 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) therapy (25% vs. 0%; p-value not reported) but no difference in pathologic partial response (pPR) (Malamos et al. 1998).

Two trials reported rates of breast-conserving surgery that appeared to favour primary paclitaxel; however, p-values for the differences were not reported (Budzar et al. 1999, Pouillart 1999). DFS was assessed in one trial; no significant difference between paclitaxel alone or 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) was detected. (Budzar et al. 1999) Overall survival was not reported in any of the paclitaxel trials.

While not quite significant at the 5% level, the Aberdeen trial results (n = 97) suggested improved pCR with CVAPr followed by docetaxel vs. CVAPr followed by CVAPr (31% vs. 15%; p=0.06). Overall clinical response was also higher in the first arm (85% vs. 64%; p = 0.001) (Hutcheon et al. 2003).

The ACCOG trial detected a trend towards improved clinical overall response with doxorubicin and docetaxel vs. doxorubicin and cyclophosphamide (AC) (71% vs. 61%; p = 0.06), but equivocal rates of pCR (Evans et al. 2004).

In the NSABP B-27 trial (n = 2,411), a pCR occurred in 26% of patients who received primary docetaxel in addition to AC (arm i) compared to 15% in the AC followed by surgery and adjuvant docetaxel group (arm ii) and 13% in the AC followed by surgery alone group (arm iii) (p < 0.001 for arm i vs. arms ii and iii) (Bear et al. 2003). Clinical overall response followed the same pattern, with improved rates in the primary docetaxel arm (p < 0.001 for arm i vs. arms ii and iii).

Of the docetaxel trials that measured and reported axillary lymph node involvement, only the NSABP B-27 trial reported significant differences. Women who received primary docetaxel after AC were more likely to be node negative at the time of surgery compared with women who received AC alone (58% vs. 51%; p < 0.001) (Bear et al. 2003).

In the Aberdeen trial, patients with tumours that responded to four cycles of CVAPr and who were randomised to docetaxel were more likely to undergo breast conservation compared with patients who were randomised to receive further CVAPr (67% vs. 48%; p < 0.01) (Smith et al. 2002).

Two of the four remaining trials reported rates of breast conservation that appeared to favour the docetaxel treatment arm; however, p-values were not reported (GEPAR-TRIO: von Minckwitz et al. 2003, Luporsi et al. 2000).

At 38 months, the Aberdeen trial detected higher overall survival rates in CVAPr-responders who received docetaxel compared with those who received further CVAPr (97% vs. 84%; p=0.02) (Hutcheon et al. 2001). At a median follow-up of 65 months, the difference was still statistically significant (93% vs. 78%; p = 0.04) (Hutcheon et al. 2003). DFS was also significantly higher among CVAPr-responding women who received primary docetaxel (90% vs. 77%; p=0.03) (Hutcheon et al. 2001).

At a median follow-up of 32 months, the ACCOG trial detected no significant differences in DFS (75% vs. 69%, $p = \text{NS}$) or overall survival (86% vs. 84%, $p = \text{NS}$) with docetaxel and doxorubicin vs. AC, respectively (Evans et al. 2004). Similarly, Bouzid et al. 2001 reported no significant difference between the median number of months progression free in the doxorubicin and docetaxel arm compared with the FAC arm (8.3 months vs. 6.9 months; p -value not reported).

2. Primary taxane regimens vs. adjuvant taxane regimens

The ECTO trial ($n = 892$) found significantly different rates of nodal involvement at surgery; 61% of patients who received primary paclitaxel and doxorubicin were node-negative at surgery compared with 38% of patients who received no primary chemotherapy ($p=0.0001$) (ECTO; Gianni et al. 2002). Breast conservation was more likely in women who received primary paclitaxel and doxorubicin compared with no primary chemotherapy (71% vs. 35%; $p < 0.0001$) (ECTO; Gianni et al. 2002).

3. Taxane dose and/or schedule comparisons

The SICOG 9908 trial ($n = 130$) reported significantly higher rates of pCR (16% vs. 4%, $p=0.03$) and cCR (29% vs. 15%, $p = 0.05$) with 12 cycles of lower-dose weekly cisplatin, epirubicin, and paclitaxel combination therapy vs. four cycles of higher-dose three-weekly epirubicin and paclitaxel (Cormella et al. 2004). Similarly, the M.D. Anderson trial by Green et al. 2002 ($n = 118$) found significantly improved pCR rates, defined according to the Chevallier classification system, in weekly vs. three-weekly paclitaxel followed by FAC (29% vs. 14%, $p<0.01$).

The AGO trial ($n = 475$; accrual ongoing) detected significantly higher rates of pCR in the dose-dense sequential docetaxel therapy arm compared to the standard therapy arm (18% and 10%, respectively; $p = 0.03$) (Untch 2002). Romieu et al. 2002 ($n = 232$) reported pCR rates of 17% vs. 24% (Sataloff classification) and 11% vs. 16% (Chevallier classification) in patients who received four and six cycles of doxorubicin and paclitaxel, respectively (p -values not reported). Clinical response was 32% vs. 20% in the six-cycle group and four cycle groups, respectively (p -value not reported).

Node response was reported in two trials (Cormella et al. 2004, Untch et al. 2002). Untch et al. 2002 reported rates of 51% and 42% at the time of surgery in their dose-dense sequential and standard dose arms, respectively ($p = 0.098$).

Two trials reported comparative breast conservation data. The AGO trial detected a higher rate in women who received dose-dense sequential epirubicin and paclitaxel compared with standard-dose epirubicin and docetaxel (66% vs. 55%; $p = 0.016$) (Untch et al. 2002).

In the ABCSG-14 trial ($n = 288$), the rate of pCR was higher in the six-cycle epirubicin–docetaxel arm vs. the three-cycle arm (19% vs. 8%; $p = 0.0045$). More women in the six vs. three three-weekly cycles of epirubicin and docetaxel were node-negative at the time of surgery (57% vs. 43%; $p = 0.02$) (Steger et al. 2004).

In the Miller et al. 1999 trial, 19% of women who received combination therapy were node negative at surgery compared with 53% of women who received sequential therapy (p-value not reported). On average, 2.17 vs. 4.81 nodes were positive in the combination and sequential groups, respectively ($p = 0.037$).

While there was a slight trend towards improved rates of breast conservation in the ABCSG-14 trial, the rates of breast conservation in the six- and three-cycle groups were not significantly different at the 5% level (76% vs. 67%; $p = 0.1$) (Steger et al. 2004). In the Miller et al. 1999 trial, 19% of women who received doxorubicin and docetaxel in combination underwent breast conservation compared with 37% of women who received sequential therapy ($p = \text{NS}$).

4. Adverse effects associated with primary taxanes

Hematologic toxicity

Primary paclitaxel therapy appeared to be associated with higher rates of grade 3 and/or 4 febrile neutropenia in two trials; however, p-values were not reported (Budzar et al. 1999, Gianni et al. 2002). In the M.D. Anderson trial (Budzar et al. 2002), 53% of women receiving paclitaxel ($250 \text{ mg/ m}^2 \text{ q3wx4}$) vs. 21% of those receiving FAC experienced neutropenic fever. Granulocyte colony-stimulating factor (G-CSF) was administered if patients had neutropenic fever in a previous cycle or was used prophylactically. Women receiving paclitaxel were more likely than those receiving FAC to receive G-CSF (56% vs. 25%; p-value not reported).

In the ECTO trial, 9% of women receiving doxorubicin and paclitaxel ($200 \text{ mg/ m}^2 \text{ q3wx4}$) followed by CMF experienced febrile neutropenia compared with 5% in those receiving doxorubicin alone followed by CMF (Gianni et al. 2002).

Six of nine docetaxel trials reported differential rates of neutropenia. Lee et al. 2004 detected less grade 3 or 4 neutropenia in the docetaxel (75 mg/ m^2) and capecitabine arm (77%) than in the AC arm (94%) p-values not reported.

In the NSABP B-27 trial, febrile neutropenia was significantly more frequent in the primary docetaxel and AC arm compared with the AC-only arm (21% vs. 7%, p-value not reported). Rates of G-CSF support were approximately the same (21 vs. 18% respectively, p-value not reported) (Bear et al. 2003).

In the Aberdeen trial, Grade 3 or 4 granulocytopenia ($p = 0.006$) was more common in patients who received eight cycles of CVAPr compared with those who received CVAPr followed by four cycles of docetaxel ($100 \text{ mg/ m}^2 \text{ q3wx4}$) (Smith et al. 2002).

In the GEPAR-TRIO trial, grade 3 or 4 neutropenia seemed to occur more frequently in the non-responders who received TAC followed by vinorelbine and capecitabine compared with non-responders who received vinorelbine and capecitabine alone (76% vs. 33%; p-value not reported) (Bouzid et al. 2001).

Bouzid et al. 2001 reported higher rates of grade 3 or 4 neutropenia (71% vs. 25%; p-value not reported) and febrile neutropenia (10% vs. 0%; p-value not reported) with doxorubicin and docetaxel (75 mg/ m² q3wx4) than with FAC.

Miller et al. 1999 reported significantly more granulocytopenia in their combination doxorubicin and docetaxel arm (100 mg/ m²) than in their sequential doxorubicin and docetaxel arm (75 mg/ m²) (grade 3: 10% vs. 37% and grade 4: 76% vs. 37%, respectively; p < 0.05 for grade 3 and 4 events) In both arms, G-CSF was administered once daily on days 2–11 of both treatment cycles.

Anaemia data were reported in three paclitaxel trials: Only one trial reported a differential between arms: the SICOG 9908 trial reported “substantially more frequent” severe anemia in the lower dose cisplatin–epirubicin–paclitaxel (120 mg/ m² q1wx12) arm than in the higher-dose three-weekly epirubicin–paclitaxel (175 mg/ m² q3wx4) arm.

Two docetaxel trials reported leukopenia rates: the Aberdeen trial reported more grade 3 or 4 leukopenia in patients who received CVAPr for eight cycles compared with those who switched to docetaxel (100 mg/ m² q3wx4) after four cycles (p = 0.029) (Smith et al. 2002).

In the Miller et al. 1999 trial, leukopenia was more common with the combination arm (docetaxel 100 mg/ m² q3wx4) than with the sequential arm (docetaxel 75 mg/ m² q2wx3) (grade 3: 43% vs. 32% and grade 4: 38% vs. 11%, respectively; p < 0.05 for grade 3 and 4 events combined).

Cardiotoxicity

One of four paclitaxel trials reporting cardiotoxicity data detected a slight trend towards more adverse cardiac events with primary taxane therapy. Pouillart et al. 1999 reported abnormal left ventricular fraction values in 8% and 5% of the women receiving a primary doxorubicin and paclitaxel (200 mg/ m² q3wx4) combination vs. those receiving AC, respectively. One patient in the doxorubicin–cyclophosphamide arm experienced congestive heart failure.

Neurotoxicity

Three of six trials reported different rates of neurotoxicity between randomised arms (p-values not reported). The M.D. Anderson trial (Buzdar et al. 1999) reported grade 2 paresthesias in 46% of women receiving paclitaxel (250 mg/ m² qw3x4) vs. 8% of those receiving FAC. Severe neurotoxicity was less common, with only 5% and 1% experiencing grade 3 paresthesias, respectively.

Similar to the M.D. Anderson trial findings, grade 2 neurotoxicity occurred in 23% and 5% of women in the ECTO trial who received doxorubicin and paclitaxel (200 mg/ m² q3wx4) followed by CMF or doxorubicin alone followed by CMF therapy (Gianni et al. 2002). Grade 3 neurotoxicity rates were 2% and 0%, respectively.

Peripheral neuropathy was “substantially more frequent” in the SICOG 9908 lower-dose

weekly cisplatin–epirubicin–paclitaxel (120 mg/ m² q1wx12) arm than in the higher-dose three weekly epirubicin–paclitaxel (175 mg/ m² q3wx4) arm (Comella et al. 2004).

The NSABP B-27 was the only docetaxel trial to report rates of neurotoxicity (Bear et al. 2003). Grade 3 neurosensory and neuromotor events and grade 4 neuromotor and neurocortical events were very infrequent and not different among groups.

Gastrointestinal toxicity

Two of three trials that reported on gastrointestinal toxicity noted differences in one or more of this class of adverse events. In the M.D. Anderson trial (Buzdar et al. 2002), rates of grade 3 stomatitis (16.9% vs. 13%), nausea (21% vs. 10%), vomiting (7% vs. 2%), and diarrhoea (16% vs. 3%) appeared to be higher in the FAC group than in the paclitaxel (250 mg/ m², q3wx4) group, respectively.

Conversely, gastrointestinal toxicity was “substantially more frequent” in the SICOG 9908 cisplatin–epirubicin–paclitaxel (120 mg/ m² q1wx12) arm than in the higher-dose threeweekly epirubicin–paclitaxel (175 mg/ m²q3wx4) arm (Comella et al. 2004).

Four docetaxel trials reported gastrointestinal toxicity data (Lee et al. 2004, Bear et al. 2003, Smith et al. 2002, Bouzid et al. 2001). Nausea, vomiting, diarrhoea and stomatitis were infrequent, and toxicity rates were similar between groups in each trial.

Other toxicities

The M.D. Anderson trial (Buzdar et al. 2002) reported grade 3 infection rates of 9% and 5% in the paclitaxel (250 mg/ m², q3wx4) and FAC arms, respectively. The M.D. Anderson trial found lower rates of overall toxicity in the 80 mg/ m² weekly arm compared with the 150 mg/ m² weekly arm (personal communication: Green et al. 2002). No trials reported any incidents of death due to toxicity.

Lee et al.2004 reported the occurrence of hand–foot syndrome in 8% of women receiving docetaxel and capecitabine. No women receiving AC experienced hand–foot syndrome. Miller et al. 1999 reported a trend towards more grade 3 and 4 hand–foot syndrome (21% vs. 0%, p-value not reported) with sequential doxorubicin and docetaxel (75 mg/ m² q2wx3) than in their combination doxorubicin and docetaxel arm (75 mg/ m² q3wx4), respectively.

In the NSABP B-27 trial, more women receiving primary docetaxel in addition to AC required more dose reductions (19%) compared with those receiving AC alone (2%) (Bear et al. 2003). Deaths were more frequent in the primary docetaxel arm (0.4% vs. 0.1%; p-value not reported).

In the Aberdeen trial, two women in the CVAPr followed by docetaxel arm died of neutropenic sepsis. Women who switched to docetaxel after CVAPr were more likely to receive a higher percentage of the total intended drug dose than were patients who continued to receive CVAPr (p = 0.002) (Smith et al. 2002).

Authors' conclusions

The RCTs reviewed suggest that primary taxane chemotherapy is both efficacious and safe. The addition of a taxane (paclitaxel or docetaxel) to standard primary FAC or AC chemotherapy regimen has been shown to be superior in terms of clinical response, pathologic response, and disease free and overall survival to the anthracycline-based regimen alone.

There is no evidence at this time to suggest that one taxane is superior to the other in the primary setting.

In general, haematologic toxicity, in particular neutropenia and febrile neutropenia, was more common with a taxane-containing regimen. Neurotoxicity may be associated with primary paclitaxel and hand-foot syndrome may be associated with primary docetaxel. There was little evidence to suggest that other adverse events occur more frequently with a primary taxane.

General comments

Well-conducted systematic review; sparse DFS/OS data. High clinical and methodological heterogeneity between studies; results presented with tabulated data/narrative. Evidence grade applied reflects these shortcomings, and also that the majority of primary data were available only in abstract form.

Study quality assessment evident e.g. considering publication as peer-reviewed paper or abstract, complexity of randomised comparison(s) method of randomisation and concealment, stratification for confounding variables, intention-to-treat analysis, power calculation.

Criticisms of the studies in general include failing to describe methods of randomisation, lack of blinding to allocation, not adjusting p values or 95% confidence intervals to account for the effects of multiple comparisons, lack of power calculations, exclusion of patients who did not complete chemotherapy.

Re: reporting of adverse effects, often trials administered supportive agents, such as antibiotics, antiemetics or G-CSF to prevent or alleviate adverse events due to chemotherapy.

Re: reporting of tumour response rates, the definitions of pathologic and clinical response of the primary tumour varied. Across the 18 trials, three different definitions of clinical response and two different definitions of pathologic response involving the primary tumour were used. This is likely to affect the validity of the results.

The authors also note that these results are preliminary since the evidence on taxanes as primary chemotherapy is evolving rapidly.

Literature search strategy:

MEDLINE and EMBASE databases to September 2004. Search terms reported e.g.

MEDLINE: Breast neoplasms[MeSH], Induction chemotherapy OR primary chemotherapy OR primary chemotherapy OR preoperative chemotherapy[Title/Abstract] Taxoids[MeSH] Meta-analysis[pt] OR randomised controlled trial[pt] OR practice guideline [pt]. Also the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium were searched.

Updated 2018

Table1: Primary tumour response rates to primary chemotherapy reported in systematic review by Trudeau et al. 2005.

RCT	Treatment arms	Patient characteristics	Primary tumour response			
			pCR (%)	pPR (%)	cCR (%)	cPR (%)
Primary taxane versus other primary chemotherapy regimens						
Paclitaxel						
M.D. Anderson (Buzdar, 1999)	i [T q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy ii [FAC q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy	T1-3, N0-1, M0 (17% stage III)	8 16	NR	27 24	53 55
Pouillart, 1999	i [AT q3wx4] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy	T2-3,N0-1,M0 (38% T3)	16 10	NR	NR	14* 9*
Malamos, 1998	i [ET q3wx3] then local surgical treatment then [ET q3wx3] then radiotherapy then hormone therapy ii [FEC q3wx3] then local surgical treatment then [FEC q3wx3] then radiotherapy then hormone therapy	Operable breast cancer	25 0	56 57	31 0	56 50
Docetaxel						
ACCOG (Evans, 2004)	i [AT q3wx6] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx6] then local surgical treatment then radiotherapy then hormone therapy	8% locally advanced, inoperable, 15% inflammatory, 77% large, operable	21 24	NR	20 17	50 44
Lee, 2004	i [TX q3wx4] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy	Stage II/III, N+ (44% stage III)	15 6	NR	3 3	85 72
NSABP B-27	i [AC q3wx4] + hormone therapy then [Tq3wx4] then local surgical treatment then radiotherapy ii [AC q3wx4] + hormone therapy then local surgical treatment then [Tq3wx4] then radiotherapy iii [AC q3wx4] + hormone therapy then local surgical treatment then radiotherapy	T1-3,N0-1,M0 (45% >=T4)	26 15 13	NR	NR	91* 85* 96*

Aberdeen	i [CVAPr q3wx4] (R-) then [Tq3wx4] then local surgical treatment (patients not randomised) ii [CVAPr q3wx4] (R+) then [T q3wx4] then local surgical treatment iii [CVAPr q3wx4] (R+) then [CVAPr q3wx4] then local surgical treatment	T _≥ 3cm or T3-4, N2 (41% stage III)	31 15	42 40	NR	85* 64*
GEPAR-TRIO	i [TAC q3wx2] (R+) then [TAC q3wx4] then local surgical treatment ii [TAC q3wx2] (R-) then [TAC q3wx4] then local surgical treatment iii [TAC q3wx2] (R-) then [NX q3wx4] then local surgical treatment	T _≥ 2cm or locally advanced (89% operable)	7 3	NR	NR	25* 25*
Bouزيد, 2001	i [AT q3wx4] then local surgical treatment ii [FAC q3wx4] then local surgical treatment	Stage IIIa or b	NR	NR	11 9	61 55
Luporsi, 2000	i [ET q3wx6] then local surgical treatment ii [FEC q3wx6] then local surgical treatment	T2-4 Non-IBC	24 24	NR	84 72	NR
Primary taxane versus adjuvant taxane regimens						
ECTO (Gianni, 2002)	i [AT q3wx4] then [CMF q4wx4] then local surgical treatment ii local surgical treatment then [A q3wx4] then [CMF q4wx4] iii local surgical treatment then [AT q3wx4] then [CMF q4wx4]	T>2 cm	23 NA	NR	52 NR	NR
Different doses/schedules of primary taxane regimens						
Paclitaxel						
SICOG 9988 (Comella, 2004)	i [cis+ET q1wx12] then local surgical treatment ii [ET q3wx4] then local surgical treatment	T4 and/or N3 ≤70 yrs	16 4	NR	29 15	59 62
Stearns, 2003	i [A q2wx3] then [T q2wx3] then local surgical treatment then CT then hormone therapy then radiotherapy ii [T q2wx3] then [A q2wx3] then local surgical treatment then CT then hormone therapy then radiotherapy	T3-4 Stage IIIa: 48% Stage IIIb: 35% Stage IV: 17%	10 7	7 17	10 3	3 17

AGO (Untch, 2002)	i [Eq2wx3] then [T q2wx3] then local surgical treatment then [CMF q4wx3+radiotherapy] ii [ET q3wx4] then local surgical treatment then [CMF q4wx3 +radiotherapy]	T>3 cm or inflammatory	18 10	NR	NR	NR
Romieu, 200232a	i [AT q3wx6] then local surgical treatment ii [AT q3wx4] then local surgical treatment	T2-3,N0-1,M0 (T2: 50%, T,3: 49%, N0: 43%, N1: 57%)	24 17	NR	32 20	NR
M.D. Anderson (Green, 2002)	i N+ [T q1w for 3wks, 1wk break x4] then [FACx4] then local surgical treatment ii N- [T wx12] then [FACx4] then local surgical treatment iii N- [T 3wx4] then [FACx4] then local surgical treatment iv N+ [T 3wx4] then [FACx4] then local surgical treatment	T1-3,N0-1,M0	28 29 13 14	NR	NR	NR
Docetaxel						
ABCSG-14 (Steger, 2004)	i [ETq3wx6] then local surgical treatment ii [E+D q3wx3] then local surgical treatment	T1-4a-c, N+/- M0	19 8	NR	NR	NR
Miller, 1999	i [AT q3wx4] then local surgical treatment ii [A q2wx3] then [T q2wx3] then local surgical treatment	>=2 cm and Stage II or III N+: 57%	5 16	5 0	10 32	71 58

NB: * denotes values reported as 'clinical response' i.e. no differentiation between cCR and cPR. Re-classified for tabulation here as cPR, to give a conservative estimate of response.

Abbreviations:

A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynakologische Onkologie; C, cyclophosphamide; cCR, clinical complete response; cis, cisplatin; cPR, clinical partial response; cm, centimetre(s); CT, chemotherapy; D, docetaxel; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; F, fluorouracil; GEPAR German Pre-operative Adriamycin Docetaxel Trial; M, methotrexate; N, vinorelbine; NR, not reported; N+, node positive; N-, node negative; NSABP National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel; pCR, pathologic complete response; pPR, pathologic partial response; Pr, prednisolone; R+, responders; R-, non-responders; SICO Southern Italy Cooperative Oncology Group; T taxane; V, vincristine-; w, wks, week(s); X, capecitabine.

Table2: Survival data reported in systematic review by Trudeau et al. 2005.

RCT	Treatment arms	Patient characteristics	Follow-up (months)	BCS (%)	DFS (%)	OS (%)
Primary taxane versus other primary chemotherapy regimens						
Paclitaxel						
M.D. Anderson (Buzdar, 1999)	i [T q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy ii [FAC q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy	T1-3, N0-1, M0 (17% stage III)	23	i 46 ii 35	i 94 ii 89	NR
Pouillart, 1999	i [AT q3wx4] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy	T2-3,N0-1,M0 (38% T3)	NR	56	i NR ii 45	NR
Malamos, 1998	i [ET q3wx3] then local surgical treatment then [ET q3wx3] then radiotherapy then hormone therapy ii [FEC q3wx3] then local surgical treatment then [FEC q3wx3] then radiotherapy then hormone therapy	Operable breast cancer	NR	NR	NR	NR
Docetaxel						
ACCOG (Evans, 2004)	i [AT q3wx6] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx6] then local surgical treatment then radiotherapy then hormone therapy	8% locally advanced, inoperable, 15% inflammatory, 77% large, operable	32	i 20 ii 20	i 75 ii 69	i 86 ii 84
Lee, 2004	i [TX q3wx4] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy	Stage II/III, N+ (44% stage III)	NR	i 64 ii 56	NR	NR
NSABP B-27	i [AC q3wx4] + hormone therapy then [Tq3wx4] then local surgical treatment then radiotherapy ii [AC q3wx4] + hormone therapy then local surgical treatment then [Tq3wx4] then radiotherapy iii [AC q3wx4] + hormone therapy then local surgical treatment then radiotherapy	T1-3,N0-1,M0 (45% >=T4)	NR	i 64 ii 62 iii NR	NR	NR

Aberdeen	<p>i [CVAPr q3wx4] (R-) then [Tq3wx4] then local surgical treatment (patients not randomised)</p> <p>ii [CVAPr q3wx4] (R+) then [T q3wx4] then local surgical treatment</p> <p>iii [CVAPr q3wx4] (R+) then [CVAPr q3wx4] then local surgical treatment</p>	<p>T_≥3cm or T3-4, N2 (41% stage III)</p>	38/65	<p>i NR</p> <p>ii 67</p> <p>iii 48</p> <p>p<0.05</p>	<p>i NR</p> <p>ii 90</p> <p>iii 77</p> <p>p<0.05</p>	<p>i NR</p> <p>ii 97% at 38 months; 93% at 65 months</p> <p>iii 84% at 38 months, 78% at 65 months</p> <p>p<0.05</p>
GEPAR-TRIO	<p>i [TAC q3wx2] (R+) then [TAC q3wx4] then local surgical treatment</p> <p>ii [TAC q3wx2] (R-) then [TAC q3wx4] then local surgical treatment</p> <p>iii [TAC q3wx2] (R-) then [NX q3wx4] then local surgical treatment</p>	<p>T_≥2cm or locally advanced (89% operable)</p>	NR	<p>i 61</p> <p>ii 56</p>	NR	NR
Bouzid, 2001	<p>i [AT q3wx4] then local surgical treatment</p> <p>ii [FAC q3wx4] then local surgical treatment</p>	Stage IIIa or b	8.3	NR	NR	NR
Luporsi, 2000	<p>i [ET q3wx6] then local surgical treatment</p> <p>ii [FEC q3wx6] then local surgical treatment</p>	<p>T2-4 Non-IBC</p>	NR	<p>i 85</p> <p>ii 69</p>	NR	NR
Primary taxane versus adjuvant taxane regimens						
ECTO (Gianni, 2002)	<p>i [AT q3wx4] then [CMF q4wx4] then local surgical treatment</p> <p>ii local surgical treatment then [A q3wx4] then [CMF q4wx4]</p> <p>iii local surgical treatment then [AT q3wx4] then [CMF q4wx4]</p>	T>2 cm	NR	<p>i 61</p> <p>ii 38</p>	NR	NR
Different doses/schedules of primary taxane regimens						
Paclitaxel						
SICOG 9988 (Comella, 2004)	<p>i [cis+ET q1wx12] then local surgical treatment</p> <p>ii [ET q3wx4] then local surgical treatment</p>	<p>T4 and/or N3 <=70 yrs</p>	NR	NR	NR	NR
Stearns, 2003	<p>i [A q2wx3] then [T q2wx3] then local surgical treatment then CT then hormone therapy then radiotherapy</p> <p>ii [T q2wx3] then [A q2wx3] then</p>	<p>T3-4 Stage IIIa: 48% Stage IIIb: 35%</p>	24	44	NR	NR

	local surgical treatment then CT then hormone therapy then radiotherapy	Stage IV: 17%				
AGO (Untch, 2002)	i [Eq2wx3] then [T q2wx3] then local surgical treatment then [CMF q4wx3+radiotherapy] ii [ET q3wx4] then local surgical treatment then [CMF q4wx3+radiotherapy]	T>3 cm or inflammatory	NR	i 66 ii 55 p<0.05	NR	NR
Romieu, 200232a	i [AT q3wx6] then local surgical treatment ii [AT q3wx4] then local surgical treatment	T2-3,N0-1,M0 (T2: 50%, T,3: 49%, N0: 43%, N1: 57%)	NR	64	NR	NR
M.D. Anderson (Green, 2002)	i N+ [T q1w for 3wks, 1wk break x4] then [FACx4] then local surgical treatment ii N- [T wx12] then [FACx4] then local surgical treatment iii N- [T 3wx4] then [FACx4] then local surgical treatment iv N+ [T 3wx4] then [FACx4] then local surgical treatment	T1-3,N0-1,M0	NR	NR	NR	NR
Docetaxel						
ABCSG-14 (Steger, 2004)	i [ETq3wx6] then local surgical treatment ii [E+D q3wx3] then local surgical treatment	T1-4a-c, N+/- M0	NR	i 76 ii 67	NR	NR
Miller, 1999	i [AT q3wx4] then local surgical treatment ii [A q2wx3] then [T q2wx3] then local surgical treatment	≥2 cm and Stage II or III N+: 57%	i 98 ii 105	i 19 ii 37	NR	NR

Abbreviations:

A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynakologische Onkologie; C, cyclophosphamide; cis, cisplatin; cm, centimetre(s), CT, chemotherapy; D, docetaxel; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; F, fluorouracil; GEPAR German Pre-operative Adriamycin Docetaxel Trial; M, methotrexate; N, vinorelbine; NR, not reported; N+, node positive; N-, node negative; NSABP National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel; Pr, prednisolone; R+, responders; R-, non-responders; SICO Southern Italy Cooperative Oncology Group; T taxane; V, vincristine-; w, wks, week(s); X, capecitabine.

Randomised controlled trials

<p>Avril, Faucher, Bussieres, Stockle, Durand, Mauriac, Bonichon, Dilhuydy & Campo . [Results of 10 years of a randomized trial of neoadjuvant chemotherapy in breast cancers larger than 3 cm.]. [French]. Chirurgie 123[3], 247-256. 1998.</p>		
<p>Design</p>		
<p>Design: RCT, evidence level: 1 - Country: France</p>		
<p>Inclusion criteria</p>		
<p>272 women of age ≤ 70 years with operable breast cancer tumours larger than 3 cm (stage T2-3/N0-1/M0) treated between January 1, 1985 to April 30, 1989.</p> <p>Distribution of disease stage:</p>		
Stage	Group A (n=136)	Group B (n=134)
T2	119	106
T3	19	29
N0	56	64
<p>Mean tumour diameter: 43mm</p>		
<p>Exclusion criteria</p>		
<p>Age > 70 years, bilateral cancer, other associated cancer, Also patients were excluded from analysis due to refusal of treatment, or contraindication of treatment e.g. poor anaesthetic risk.</p>		
<p>Population</p>		
<p>N=270</p>		
<p>Interventions</p>		
<p>Aim: to evaluate the use of neo-adjuvant chemotherapy in patients with operable breast cancers of T size > 3 cm.</p> <p>Group A (n = 138): received mastectomy and axillary node dissection. Adjuvant chemotherapy (3 cycles of epirubicine, vincristine and methotrexate followed by 3 cycles of mitomycine, thiotepa and vindesine) was indicated for 104 patients with axillary node involvement (n = 82) or negative oestrogen and progesterone receptors (n = 22).</p> <p>Group B (n = 134): received primary chemotherapy (identical regimen as in group A) followed by locoregional treatment according to the response: RT alone in cases of complete tumour remission (n=44), BCS + RT in cases of residual tumour ≤ 2cm in size (n=40) and mastectomy in cases of residual</p>		

tumour >2cm in size (n=49).

Outcomes

Locoregional recurrence
Recurrence-free survival
Overall survival

Follow up

Median 124 months (range 87-148 months)

Results

In group B (primary chemotherapy), 49 patients (36.5%) were resistant to chemotherapy, warranting mastectomy. In the remaining 84 patients BCS was performed (62.6%). In this last subgroup, 19 (22.6%) needed a secondary mastectomy because of locoregional recurrence.

10-year crude data for recurrence:

Recurrence type	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
Locoregional recurrence alone	1	14
Locoregional and distant recurrence	19	27
Distant recurrence alone	37	26

Estimated overall survival:

Analysis point	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
5-year	80%	80%
10-year	60%	60%

Estimated recurrence-free survival:

Analysis point	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
5-year	65%	58%
10-year	57%	50%

General comments

Data extracted from English language abstract and French language paper. Study reports survival analysis by Kaplan-Meier, but reports no p values for differences in survival between randomised groups.

Randomisation was stratified by ER-PR status.

Citation		
Cocconi, di, Bisagni, Alberti, Botti & Anghinoni . Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. A prospective, randomized study 164. American Journal of Clinical Oncology 13[3], 226-232. 1990.		
Design		
Design: Randomized controlled trial (therapy), evidence level: 1 - Country: Italy, setting: Secondary care		
Inclusion criteria		
49 patients with locally advanced (T3b-T4; any T,N2; M0) breast cancer, treated within the years 1978-1983 with disease characteristics as follows:		
TABLE		
Factor	CMF group	CMF + T group
Stage		
T2-3a	1	2
T3b	5	5
T4a, b, c	16	16
T4 inflammatory	2	2
N2	6	6
ER status		
Unknown	7	5
Known	17	20
ER+	13	12
ER-	4	8
Exclusion criteria		
Patients with clinical stage N3 supraclavicular nodes or positive bone scans.		
Population		
N=49		
Interventions		
Aim: to compare the efficacy of two treatment regimens in patients with locally advanced breast cancer, as follows:		
<p>CMF group (n= 24): received four courses of primary cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy, followed by mastectomy and then four courses of the same chemotherapy in the adjuvant setting.</p> <p>CMF + T group (n= 25): received four courses of primary CMF chemotherapy</p>		

with concurrent tamoxifen, followed by mastectomy and then four courses of the same chemotherapy/hormone therapy in the adjuvant setting. Tamoxifen was ceased at the end of the adjuvant regime.

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Outcomes		
Adherence to primary chemotherapy regime (all 8 cycles) Response to primary chemotherapy (see reference below); Median time to progression or recurrence (from initiation of primary chemotherapy) Median overall survival Median survival from time progression or recurrence		
Follow up		
Median 6 years		
Results		
Adherence to primary chemotherapy regime (all 8 cycles): CMF: 21/24 = 87.5% CMF+T: 20/25 = 80%		
Response to primary chemotherapy		
Response	CMF	CMF+T
Total n patients	24	25
Progression	2	1
No change	5	8
Partial remission	16	13
Complete remission	1	3
Complete and partial remission	17	16
Median time to progression or recurrence (from initiation of primary chemotherapy, months) CMF: 58.3 CMF+T: 29.1 (p=0.38, Cox-Mantel test)		
Median overall survival (months) CMF: 79.7 CMF+T: 41.5 (p=0.05, Cox-Mantel test)		
Median overall survival (months) by subgroup for response (R) and no response (NR) to primary systemic therapy CMF (R): 74.7 CMF (NR): 48.1 (p=0.89, Cox-Mantel test)		
CMF+T (R): 54.1 CMF+T (NR): 30.1 (p=0.12, Cox-Mantel test)		
Median survival from time progression or recurrence (months) CMF: 17.3 CMF+T: 7.5 (p=0.09, Cox-Mantel test)		

General comments

Study evaluates a putative synergistic effect of primary/adjuvant CMF chemotherapy and tamoxifen, and not tamoxifen continued as long term hormone therapy.

Response to primary chemotherapy was assessed according to the UICC criteria reported in: Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer: a project of the Programme on Clinical Oncology of the International Union Against Cancer, Geneva, Switzerland. *Cancer*. 1977 Mar;39(3):1289-94. No abstract available.

ER testing was not consistently available during this study; the authors report the limitation that they'd have preferred to exclude patients with ER- tumours. There were slightly more patients with ER- tumours in the CMF+T group.

Randomisation method: randomly permuted blocks of three with stratification for T stage (any T versus inflammatory breast cancer), node stage (N0-1b versus N2) and menopausal status (premenopausal versus postmenopausal <5 years versus post menopausal >=5 years)

Wording of paper is ambiguous on whether all patients underwent mastectomy, or only those who responded to primary chemotherapy. On balance it appears that all patients underwent mastectomy.

Analysis appears to be by intention-to-treat, but the study is neither blinded, nor placebo-controlled. The study is further limited by small size and may be underpowered to detect meaningful differences; the study was stopped prior to the target accrual point of 130 patients in total owing to less favourable outcome in the CMF+T arm.

Citation
Ragaz . Preoperative (neoadjuvant) chemotherapy for breast cancer: outline of the British Columbia Trial. Recent Results Cancer Res. 103, 85-94. 1986.
Design
RCT Evidence level: 1-
Inclusion criteria
68 premenopausal patients with newly diagnosed breast cancer. 50% of patients in each arm had N0 nodal status and tumour size <2cm.
Exclusion criteria
Not reported
Population
N=68
Interventions
<p>Patients were randomised to two treatment groups:</p> <p>Primary chemotherapy group (n=34): received the first cycle of CMF chemotherapy before surgery, and where indicated, eight further cycles of CMF chemotherapy, adjuvant to surgery, where indicated (see below).</p> <p>Adjuvant chemotherapy group: (n=34): received surgery, then nine cycles of CMF chemotherapy where indicated (see below).</p> <p>Patients received modified radical mastectomy (42 patients) or lumpectomy (26 patients)</p> <p>RT was given to patients with disease-positive axillary nodes, those with tumours located in the medial and central quadrants and those who underwent lumpectomy. RT dose was 37.5 Gy in 15 fractions.</p>
Outcomes
Disease-free survival
Follow up
2 years
Results
There was no statistically significant difference in disease-free survival at 2 years follow up (p>0.1).
General comments
Study appears to evaluate an early regimen of primary chemotherapy, as a

small proportion of the total systemic therapy given.

Due to the date of the paper applicability may be limited because of factors such as whether these tumours were screen detected etc. Also for patients randomised to either arm, adjuvant chemotherapy was not necessarily indicated, but reserved for patients with disease-positive axillary nodes, or tumour LVI. In any event only one of nine cycles of chemotherapy was given prior to surgery in the primary chemotherapy arm.

Of all patients with nodal status N0, 100% of those randomised to primary chemotherapy received 1 cycle or more of chemotherapy, compared with 24% of those randomised to the adjuvant chemotherapy arm ($p < 0.0001$); representing a bias for more systemic therapy in the primary chemotherapy arm.

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Citation				
Scholl, Asselain, Palangie, Dorval, Jouve, Garcia, Vilcoq, Durand & Pouillart . Neoadjuvant chemotherapy in operable breast cancer 13106 13398. European Journal of Cancer 27[12], 1668-1671. 1991.				
Design				
Design: Randomized controlled trial, evidence level: 1 - Country: France				
Inclusion criteria				
196 patients with T2-3, N0-1b operable breast cancer treated within the period: November 1983 to March 1986.				
Table: disease stage				
Stage	Primary chemotherapy group (n=95)		Adjuvant chemotherapy group (n=86)	
	n	%	n	%
T2 N0	0	0%	3	3%
T2 N1b	43	45%	26	30%
T3 N0	24	23%	24	28%
T3 N1b	28	29%	33	38%
Total	95	100%	86	100%
Mean T size: Primary chemotherapy group: 5.4 cm Adjuvant chemotherapy group: 5.0 cm				
Exclusion criteria				
Prior cancer; Concomitant serious illness; Age >65 years.				
15 patients were excluded after randomisation due to randomisation errors, poor compliance or receipt of treatment in a non-participating centre.				
Population				
N=181				
Interventions				
Aim: to compare the effects of two treatment strategies: one based on primary				

chemotherapy and the other based on primary RT with adjuvant chemotherapy.

Primary chemotherapy group (n=100): received 2 cycles of doxorubicin, cyclophosphamide and fluorouracil (ACF), followed by assessment of tumour response and locoregional treatment (see below). Patients with a good initial response to primary chemotherapy received adjuvant chemotherapy consisting of 4 further cycles of ACF, whereas patients with a poor response received 4 cycles of doxorubicin, methotrexate, vindesine and thiotepa as adjuvant chemotherapy

Adjuvant chemotherapy group (n=96): received locoregional treatment (see below) followed by 6 cycles of ACF as adjuvant chemotherapy.

All patients received steroid drugs.

Table: locoregional treatment:

Treatment	Primary chemotherapy group (n=95)		Adjuvant chemotherapy group (n=86)	
	n	%	n	%
Mastectomy	22	23%	31	36%
Lumpectomy	32	34%	26	30%
No surgery	41	43%	29	34%
RT	95	100%	86	100%

RT consisted of 55Gy to the whole breast with boost to the tumour bed to make a total dose of 75-80Gy. 45-55Gy were applied to the node bearing tissues.

In the primary chemotherapy group, only patients with residual tumour after primary chemotherapy underwent surgery, with surgical procedure determined according to individual patients' needs.

Outcomes

Local recurrence (defined as tumour presence at or after 9 months from the start of treatment, because not all patients underwent surgery)

Disease-free survival

Follow up

Median 54 months (range 35-70 months).
Two patients were lost to follow-up at 35 and 38 months

Results

Relationship between tumour response to primary chemotherapy and

dose received

In patients in the primary chemotherapy arm, there was a statistically significant relationship between tumour response and the total *dose* (dose/m² as an average for all drugs) received, as the proportion of the planned dose. This was true for the subgroup of patients who completed all planned *cycles* of primary chemotherapy (n=77; p=0.003; see tabulated data below) and also for all patients in the primary chemotherapy arm (n=95; p=0.002; no data shown).

Table: tumour response by dose of chemotherapy as % of planned dose in 77 patients who completed all planned cycles of primary chemotherapy

	Dose received as % of planned dose		
	<50%	50-75%	75-100%
CR	0	0	10
PR<50%	0	4	20
PR>50%	2	12	20
Stable disease	0	3	4
Progressive disease	0	1	0
Total	2	20	54

Chi² = 8.82; p=0.003

Overall survival (all patients; intention-to-treat)

Over the entire follow-up period there was no statistically significant difference in overall survival between randomised groups (primary versus adjuvant chemotherapy); p=NS; log-rank test.

Disease-free survival (all patients; intention-to-treat)

Over the entire follow-up period there was no statistically significant difference in disease-free survival between randomised groups (primary versus adjuvant chemotherapy); p=0.4; log-rank test.

Disease-free survival in primary chemotherapy arm by subgroup for tumour response of regimen

In the subgroup of patients within the primary chemotherapy arm who completed all planned chemotherapy (n=77; 81% of the randomised arm) disease-free survival at 36 months follow-up was as follows:
80% in patients with >50% tumour regression when assessed after 2 cycles of primary chemotherapy;
68% in patients with ≤ 50% tumour regression when assessed after 2 cycles of primary chemotherapy (figures read from chart).
This difference by tumour response was not statistically significant over the entire follow-up period (median 54 months; p=0.058; log-rank test).

The same analysis including the 18 patients randomised to primary chemotherapy, but who ceased treatment (e.g. due to stage N0 nodes, or toxicity) also indicated no significant difference in disease-free survival (median follow-up 54 months, n=95; p=0.3, log-rank test).

Overall survival in primary chemotherapy arm by subgroup for completion of regimen

There was no statistically significant difference in overall survival in patients treated with primary chemotherapy and who completed all cycles (n=77) between the subgroup with >50% tumour regression and the subgroup with ≤50% tumour regression (median follow-up 54 months; p=0.07; log-rank test).

The same analysis including the 18 patients randomised to primary chemotherapy, but who ceased treatment (e.g. due to stage N0 nodes, or toxicity) also indicated no significant difference in overall survival (median follow-up 54 months, n=95; p=0.2, log-rank test).

Local recurrence

For all randomised patients, the rate of local recurrence (defined as tumour presence at or after 9 months from the start of treatment) between randomised groups was similar: 18% for the primary chemotherapy group and 20% for the adjuvant chemotherapy group (no p value reported).

Rate of breast conserving surgery (all randomised patients)

Primary chemotherapy group: 56%
Adjuvant chemotherapy group: 35%

General comments

In both randomised arms a subgroup arises of patients with N0 status revealed by surgery for whom chemotherapy (primary or adjuvant) was discontinued. This occurred in 18 patients in the primary chemotherapy group and 21 patients in the adjuvant chemotherapy group; these subgroups represent 'better prognosis' patients.

No mention of randomisation method. Blinding is unlikely to have been feasible. Not all analyses are by intention to treat.

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Citation		
Tan, Cheung, Willsher, Blamey, Chan & Robertson . Locally advanced primary breast cancer: medium-term results of a randomised trial of multimodal therapy versus initial hormone therapy 118. European Journal of Cancer 37[18], 2331-2338. 2001.		
Design		
Design: Randomized controlled trial (therapy), evidence level: 1 - Country: UK, setting: Tertiary care		
Inclusion criteria		
108 patients with locally advanced primary breast cancer (i.e. T size \geq 5cm, inflammatory breast cancer and/or with skin involvement or chest wall/axillary node fixity but with no distant metastases), treated between January 1989 and December 1994.		
Table: patient characteristics		
Variable	Primary hormone therapy	Multimodal therapy
n	52	56
Median age (range) (years)	62 (36-73)	58 (32-71)
Mean T size	6.2 cm	6.5 cm
Inflammatory breast cancer	6 (12%)	5 (9%)
T2, N2 tumour	12 (23%)	7 (13%)
T3 tumour	34 (64%)	44 (79%)
Proportion of patients with ER+ tumours (NB: not assessed for all patients): Minimal therapy arm: 35/49 = 71% Multimodal therapy arm: 28/53 = 53% (Chi square=3.0; p=0.09)		
Exclusion criteria		
Not reported; defined by inclusion criteria		
Population		
N = 108, age range 32 to 73 years.		
Interventions		
Aim: to compare, in patients with locally advanced/inflammatory breast cancer, primary hormone therapy with multimodal therapy consisting of primary chemotherapy, Patey mastectomy, post-operative radiotherapy and adjuvant hormone therapy.		
Patients were randomised to two groups:		

1. Primary hormone therapy group (n=52): treated as follows:
 Post-menopausal patients (n=45): tamoxifen i.e. sole hormone therapy
 Pre-menopausal patients (n=7): tamoxifen plus goserelin i.e. sole hormone therapy
 On discovery of progressive disease (PD): hormone therapy ceased; and either surgery, RT, or adjuvant chemotherapy given.
 On discovery of further PD: the next appropriate therapy was given.
 NB one treatment modality was given at a time

2. Multimodal therapy group (n=56): treated as follows:
 Primary chemotherapy with mitoxantrone, methotrexate and mitomycin (n=55); followed by either breast RT (n=2) or Patey mastectomy (n=53) followed by RT: 40 Gy to the chest wall (n=50) and hormone therapy (n=53): tamoxifen for post-menopausal patients and tamoxifen plus goserelin for pre-menopausal patients.
 On discovery of locoregional failure or distant metastases, the most appropriate treatment was given.

Outcomes

Initial response to primary chemotherapy:

- Complete response: resolution of tumour;
- Partial response: >50% reduction in bidimensional product of tumour;
- Static disease: <50% reduction, or <25% increase in bidimensional product of tumour;
- Progressive disease: >25% increase in bidimensional product of tumour.

Locoregional failure
 Distant metastasis
 Overall survival

Follow up

Median (range):
 Primary hormone therapy: 45 (7-113) months
 Multimodal therapy: 52 (6-120) months

Results

Table: initial response to primary chemotherapy

Response	Primary hormone therapy (n=52)	Multimodal therapy (n=56)
Complete response	2 (4%)	5 (9%)
Partial response	17 (33%)	26 (47%)
Stable disease	16 (31%)	22 (40%)
Progressive disease	17 (33%)	2 (4%)

1. Outcomes by randomised group

Locoregional failure

The time to first locoregional failure was significantly shorter in the initial hormone therapy group when compared with the multimodal therapy group ($P < 0.01$).

Distant metastases

There was no difference in the number of patients who developed distant metastases ($n=29$ and $n=30$ for those treated with initial hormone therapy and multimodal therapy, respectively), nor in the time to distant metastases between the two groups ($p=0.84$).

Number of therapies

When compared with the multimodal therapy group, patients in the initial hormone therapy required fewer therapies to achieve disease control (mean 3.6 therapies) compared to patients in the multimodal therapy group (mean 4.9 therapies).

16 patients (31%) in the initial hormone therapy group eventually underwent mastectomy for locoregional control of their tumour, although over 80% required a 'local' therapy (i.e. either surgery (31%) or radiotherapy (52%)).

Overall survival

There was no statistically significant difference in overall survival between the randomised groups ($p=0.22$).

2. Outcomes by randomised group with subgroups based on tumour ER status

Patients with ER+ tumours

In patients with ER+ tumours there was no statistically significant difference in time to distant metastasis ($p=0.52$) nor overall survival ($p=0.14$). However time to locoregional failure was statistically significantly shorter in the initial hormone therapy group ($p=0.001$).

Patients with ER- tumours

In patients with ER- tumours there was no statistically significant difference in time to distant metastasis ($p=0.74$) nor overall survival ($p=0.74$). However time to locoregional failure was statistically significantly shorter in the initial hormone therapy group ($p=0.001$).

General comments

1 patient in the multimodal therapy arm refused primary chemotherapy, surgery and RT and received Megestrol acetate.

Analysis appears to be by intention-to-treat; patients who refused particular

therapies are reported, and 100% of randomised patients completed the trial. The authors acknowledge that no prospective power calculation was performed, and that the sample size is small, and that the rates of late-occurring events are based on small numbers.

Patient/investigator blinding not reported, but unlikely to be feasible due to multimodal nature of therapy.

Patients were randomised irrespective of ER status, which was known for 103 patients.

Updated 2018

Citation				
Von, Costa, Raab, Blohmer, Eidtmann, Hilfrich, Merkle, Jackisch, Gademann, Tulusan, Eiermann, Graf & Kaufmann . Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: A randomized, controlled, open phase IIb study. Journal of Clinical Oncology 19[15], 3506-3515. 2001.				
Design				
Randomised controlled trial. Evidence grade: 1- Country: Germany				
Inclusion criteria				
250 patients recruited during the period April 1998-June 1999 with unilateral primary carcinoma of the breast, with primary tumor size ≥ 3 cm in largest diameter with no evidence of distant metastases. Eligible age range was between 18 and 70 years; life expectancy had to be at least 10 years (disregarding the diagnosis of cancer) for eligibility and Karnofsky index $\geq 70\%$.				
Exclusion criteria				
Locally advanced cancer (stage T4); Bilateral, metastatic, or inflammatory breast cancer; Previous treatment for breast cancer (surgical diagnostic procedures were allowed).				
Population				
N=250. Median age: 48 years (range 27-67 years)				
Median palpable tumour diameter: 4cm (range 0-19cm)				
Characteristic	ADoc + T		ADoc	
	No.	%	No.	%
N status (palpation)				
Negative	59	48.4	67	53.2
Positive	63	51.6	59	46.8
Histology				
Ductial invasive	91	75.2	97	77.6
Lobular invasive	19	15.7	15	12.0
Other/mixed	11	9.1	13	10.4
Not assessed	1		1	
Histologic grade				
I	6	5.4	4	3.8
II	50	44.6	57	53.8
III	56	50.0	45	42.4
Not assessed	10		20	

ER status				
Negative	41	41.8	39	39.8
Positive	57	58.2	59	60.2
Not assessed	24		28	
PR status				
Negative	44	44.9	44	45.4
Positive	54	55.1	53	54.6
Not assessed	24		29	

Interventions

Aim: to determine whether the addition of tamoxifen to preoperative dose-dense doxorubicin and docetaxel combination chemotherapy improves the rate of pCRs.

Patients were randomly allocated to two groups:

1. Primary chemotherapy group (n=128): received doxorubicin and docetaxel every 14 days for four cycles (ADoc) as primary chemotherapy.

2. Primary chemoendocrine therapy group (n=122): received ADoc primary chemotherapy plus tamoxifen taken daily commencing on day 1 of the first cycle of ADoc and continued for 5 years for patients with a partial or complete tumour response, irrespective of ER status. Patients with no response or with progression were treated with other chemotherapy or endocrine therapy at the discretion of the treating clinicians but were followed up according to the protocol and all therapies received were documented. Patients in this group could receive black cohosh, clonidine or medroxyprogesterone acetate for symptoms of oestrogen withdrawal.

All patients received steroid, anti-emetic and G-CSF with primary chemotherapy. Patients in either group could receive antibiotic prophylaxis.

Therapy could be postponed for a maximum of 1 week only if severe hematologic or nonhematologic toxicities occurred (definition provided in paper). If toxicity did not improve during this period, chemotherapy had to be discontinued and surgery was recommended. No dose reduction was permitted.

Locoregional treatment

All patients underwent surgery between 14 and 28 days after the last chemotherapy cycle, as follows:

- i) modified radical mastectomy for large tumours; patients were offered autologous or heterologous reconstructive surgery.
- ii) breast-conserving surgery (BCS), in cases with clear (≥ 1 mm) surgical margins where an adequate cosmetic result was anticipated; and where cosmetically acceptable, the whole previously involved area could be excised.

All patients who underwent BCS received radiotherapy. Radiotherapy to the chest wall or regional lymph nodes was performed according to local procedures at each participating center.

Outcomes

Compliance with protocol (not cited)
Toxicity
pCR rate
Rate of breast conserving surgery

Follow up

Not reported; outcomes relate to peri-operative period.

Results

Pathological complete response rate

There was no evidence of a difference in rate of pCR between the randomised arms:

No. of pCRs:

ADoc + T: 11/121 = 9.1%

ADoc: 13/126 = 10.3% (difference -1.2%; 95% CI -8.6 to +6.2)

Toxicity

Toxicity was analyzed according to the treatment actually given; 120 patients received ADocT and 128 received ADoc alone. There was little difference in toxicity between the two groups (numerous variables tabulated; no statistical testing of differences performed). There seemed to be a higher incidence of severe infections associated with the higher rate of grade 3/4 neutropenia in the ADoc + T group. However, the incidences of febrile neutropenia were similar, at 8.3% in the ADoc + T group and 8.7% in the ADoc group. The most common severe forms of toxicity, apart from alopecia, were fatigue and loss of appetite. All other toxicities occurred in less than 5% of the cycles.

Rate of breast-conserving surgery.

Rate of BCS

ADoc + T: 68.6%

ADoc: 69.0% (difference -0.4; 95% CI -12.0% to +11.1%).

The chances of being able to conserve the breast in larger tumors were highly dependent on the clinical response to preoperative chemotherapy. Patients with tumors larger than 4 cm had a higher rate of breast conservations if they achieved a favorable remission.

Re-excisions had to be performed in 51 (20.6%) of 247 patients. A further three patients refused re-excision. The second operation consisted of mastectomy in 58.8% of cases and of BCS in 41.2% of cases.

General comments

Non blinded study. Randomisation was carried out centrally with stratification for participating centre. Sample size is based upon a statistical power calculation. Analysis is by intention-to-treat.

Patient and tumour characteristics were evenly distributed between the randomised groups (statistically tested).

Toxicity was analyzed according to the treatment actually given; 120 patients received ADocT and 128 received ADoc alone (non ITT, but with only small likely impact on results).

Authors have not performed statistical testing of observed differences for the majority of variables.

Updated 2018

UPDATE EVIDENCE:

von Minckwitz, Kummel, S., Vogel, P., Hanusch, C., Eidtmann, H., Hilfrich, J., Gerber, B., Huober, J., Costa, S. D., Jackisch, C., Loibl, S., Mehta, K., Kaufmann, M. & German Breast Group. (2008) Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. *Journal of the National Cancer Institute*, 100: 552-562.

Design: RCT, Evidence level 1-

Country: Germany

Aim: To evaluate the effect of extended chemotherapy on pathological complete response at surgery (the GeparTrio trial).

Inclusion criteria

- Breast cancer diagnosis had to be confirmed histologically from a core biopsy specimen. Patients needed to have at least one of the following risk factors: age younger than 36 years, clinical tumour size > than 5 cm, estrogen receptor – and progesterone receptor – negative tumour, clinical involvement of axillary lymph nodes, or undifferentiated tumor grade.
- For bilateral disease, the investigator had to prospectively choose one side for evaluation (ie, the breast with the tumor that was most easily measured) on the registration form.
- Patients with locally advanced disease that included clinical involvement of skin and/or muscle, clinical evidence of inflammatory breast cancer (T4a – T4d), or N3 stage that included supraclavicular lymph nodes were eligible for this study but were randomly assigned to treatment in a separate stratum.
- For patients with inflammatory disease, the area of inflammation was used for evaluation and was measured clinically.
- For multifocal or multicentric disease, the lesion with the largest diameter was chosen for followup.
- Other inclusion criteria were age 18 years or older, Karnofsky performance status of at least 80%, normal left ventricular ejection fraction, and sufficient hematopoietic (neutrophil count of $\geq 2.0 \times 10^9$ cells per liter, platelet count of $\geq 100 \times 10^9$ platelets per liter, and hemoglobin of ≥ 10 g/dL), liver (total bilirubin of 1X upper normal limit; aspartate aminotransferase and alanine aminotransferase, each of $\leq 2.5X$ upper normal limit; and alkaline phosphatase of $\leq 5X$ upper normal limit), and renal (creatinine of $\leq 175 \mu$ mol/L) function.
- Patients were excluded if they had evidence of distant metastases, previous chemotherapy or radiation therapy, previous serious illnesses, concurrent treatment with sex hormones or experimental drugs, or a known hypersensitivity reaction to the study compounds or if they were male.

Exclusion criteria

Population

- Patients with previously untreated unilateral or bilateral primary breast cancer.

- 2090 eligible patients and 2072 were included in the GeparTrio trial: 1390 (66.5%) were randomly assigned as responders after 2 initial TAC cycles to receive an additional 4 (n = 704) or 6 (n = 686) TAC cycles.

NOTE: approx 88% of the included population fall into the EBC scope (tumour stage T1-3)

Interventions

- Untreated breast cancer patients received two 3-week cycles of docetaxel at 75 mg/m², doxorubicin at 50 mg/m², and cyclophosphamide at 500 mg/m² (TAC).
- Those whose tumor size decreased by 50% or more by sonographic measurement (i.e. a reduction in the product of the two largest perpendicular diameters by at least 50%) were classified as responders and randomly assigned to receive 4 (for a total of 6 TAC cycles) or 6 more cycles of TAC (for a total of 8 TAC cycles)
- Only the TAC cycle outcomes are presented in this paper

Outcomes

Sonographic response rates and rates of breast-conserving surgery and adverse effects

Results

- Details of the early responders: 1390 (67.1%, or 66.5% of the 2090 patients enrolled) responded to treatment with a decrease in tumour size of 50% or more; 622 (30.0%) did not respond to treatment (ie, their tumours decreased in size by <50% or increased in size by <25%), and 60 (2.9%) terminated treatment early.
- Rates of pathological complete response were not statistically significantly different between the arms (21.0% with 6 TAC cycles and 23.5% with 8 TAC cycles; difference = 2.5%, 95% CI = -1.8% to 6.8%; P = 0.27).
- Assessment by physical examination: The clinical complete responses at surgery were not statistically different with 8 TAC cycles than with 6 TAC cycles (52.9% vs 48.2% respectively, difference = 4.7%; 95% CI = -0.55% to 9.95%; P = 0.08)
- Sonographic assessment showed a statistically different complete response to surgery with 6 TAC cycles than with 8 TAC cycles (22.6% vs 27.6%, difference = 5%; 95% CI = 0.45% to 9.55%; P = 0.033)
- The rate of breast-conserving surgery was similar in both arms, with no statistically significant difference (67.5% vs 68.5%, respectively, P = 0.68).
- Grade 3 or 4 leukopenia and edema and various grade 1 or 2 adverse events were more frequent in patients receiving 8 TAC cycles than in those receiving 6 cycles.
- Treatment discontinuations were due to adverse reactions were reported in 2.4% of the patients in the 6-cycle arm and 7.7% of the patients in the 8 cycle arm (P<0.001).
- In the multivariable model, negative hormonal receptor status (odds ratio [OR] = 5.5, 95% CI = 3.8 to 8.0), nonlobular histology (OR = 2.5, 95% CI = 1.2 to 5.4), undifferentiated grade (OR = 1.6, 95% CI = 1.1 to 2.4), and age younger than 50 years (OR = 1.5, 95% CI = 1.0 to 2.1) were statistically significantly independently associated with pathological complete response.

General comments

Authors' conclusions: Patients receiving 8 TAC cycles had statistically significantly higher sonographic response rates but not pathological complete response rates than those receiving 6 TAC cycles. However, they also had more toxic effects. So far, 8 cycles of TAC cannot be recommended for the whole group of patients responding to two initial cycles of TAC.

Limitations: The power of the study to detect a statistically significant difference between arms was reduced because of the small sample size. More patients in the 8-cycle arm than in the 6-cycle arm discontinued treatment. There was a high level of interobserver variability in the assessment of sonographic and clinical responses.

Rastogi, P. et al. (2008) Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *Journal of Clinical Oncology* 26;5:778-785

Design: Review of Randomised Controlled Trials B-18 and B-27

Country:

Aim: To provide and update of extended outcomes of two preoperative chemotherapy trials of NSABP through 16 years of follow-up for B-18 and 8.5 years of follow-up for B-27.

B-18: to determine whether preoperative chemotherapy with doxorubicin and cyclophosphamide would result in better OS and DFS when compared with post operative adjuvant chemotherapy. (This trial was reviewed as part of a Cochrane Review which was included in the original evidence (Mieog 2007)).

B-27: to determine whether adding docetaxel to preoperative AC would increase DFS and OS in patients with operable breast cancer (This trial was included in a systematic review which was included in the original evidence (Trudeau 2005)).

Inclusion criteria

Detailed eligibility and inclusion criteria were reported elsewhere.

B-18: Women with operable, palpable breast cancer diagnosed by core needle biopsy or FNA.

B-27: Women with primary operable breast cancer diagnosed by core biopsy or FNA.

Exclusion criteria

Reported in previous publications.

Population

B-18: N=1,523

B-27: N=2,411

Interventions

B-18:surgery (lumpectomy or ALND) followed by four cycles of AC Chemotherapy (doxorubicin 60mg/m² and cyclophosphamide 600mg/m² every 21 days vs. AC Chemotherapy (doxorubicin 60mg/m² and cyclophosphamide 600mg/m² followed by surgery.

B-27:Four cycles of AC chemotherapy every 21 days before surgery followed by surgery, vs. Four cycles of AC chemotherapy every 21 days before surgery and preoperative docetaxel (T), followed by surgery vs. Four cycles of AC chemotherapy every 21 days before surgery followed by surgery and postoperative docetaxel.

Outcomes

Tumour Response

Overall Survival (OS)

Disease Free Survival (DFS)

Relapse Free Interval (RFI)

Results

Overall Survival

B-18:

No significant difference was observed between the two groups (HR=0.99; 95% CI, 0.85 to 1.16; p=0.90)

Survival estimates were as follows:

Estimated Survival	Preoperative	Postoperative
5 year	80%	81%
8 year	72%	72%
16 year	55%	55%

B-27:

No statistically significant differences in overall survival according to treatment (p=0.76).

Survival estimates were as follows:

Estimated Survival	Group 1	Group 2	Group 3
5 year	82%	83%	82%
8 year	74%	75%	75%

Disease Free Survival

B-18:

No significant difference in DFS between the two groups (HR=0.93; 95% CI, 0.81 to 1.06; p=0.27)

Survival estimates were as follows:

Estimated Survival	Preoperative	Postoperative
--------------------	--------------	---------------

5 year	80%	67%
8 year	72%	55%
16 year	55%	39%

B-27:

No statistically significant difference in DFS was observed according to treatment group.

Survival estimates were as follows:

Estimated Survival	Group 1	Group 2	Group 3
5 year	68%	71%	70%
8 year	59%	62%	62%

Relapse Free Interval

B-18:

No significant difference was observed between the two treatment groups (HR=0.98; 95% CI, 0.83 to 1.15; p=0.78)

B-27:

Survival estimates as follows:

Estimated Survival	Group 1	Group 2	Group 3
5 year	71%	76%	74%
8 year	66%	71%	69%

Treatment by Covariate Interactions and Subset Analysis

B-18:

There was a significant treatment-age interaction for OS (p=0.01).

There was no significant difference in DFS between treatment groups for women >50 years at entry.

B-27:

No significant effect of treatment heterogeneity was observed for age categories or other variables.

Association between Pathological Response and Outcome

B-18:

Individuals achieving a pCR have superior DFS and OS outcomes when compared with patients not achieving a pCR (DFR HR = 0.47, p<0.0001; OS HR = 0.32, p<0.0001).

B-27:

pCR was a significant predictor of improved DFS (HR = 0.49, p<0.0001)) and OS (HR = 0.36, p<0.0001).

General comments

Author's Conclusions:

These data demonstrate that the achievement of pCR in the breast and negative axillary nodes following preoperative therapy predict favourable outcomes. Although most patients

will not achieve pCR and significant heterogeneity exists in relation to outcomes among non pCR patients following preoperative therapy.

Preoperative Chemotherapy is equivalent to adjuvant chemotherapy with respect to OS and DFR; although it may be beneficial for patients who want breast conservation surgery but for whom this may not be an option on initial presentation.

Updated 2018

7.2 For patients with inflammatory of locally advanced breast cancer who are treated with primary cytotoxic chemotherapy, what is the role of surgery and/or radiotherapy?

Short Summary

There is a considerable body of high quality evidence that has evaluated the role of primary chemotherapy in patients with locally advanced breast cancer, inflammatory breast cancer, or operable breast cancer. Patients also received loco-regional treatment, the effect of which was not the main focus of the study resulting in little direct evidence on the individual effects of surgery or radiotherapy following primary chemotherapy.

In patients with locally advanced breast cancer who receive primary chemotherapy, findings from a Cochrane review and two systematic reviews suggest that better tumour response is associated with better outcomes (Mieog *et al* 2007; Shenkier *et al* 2004; Pouillart *et al* 1981). The applicability of this evidence is limited however because the majority of patients had operable breast cancer of stage I-II.

No difference in overall survival was observed when comparing different radiotherapy regimens (Bucholz *et al.* 2006, Shenkier *et al.* 2004), however there was also evidence of a higher rate of loco-regional recurrence in patients who received radiotherapy without surgery after primary chemotherapy (Mieog *et al.* 2007, Mauri *et al.* 2005). Veyret *et al.* 2006 evaluated the outcomes after primary chemotherapy. Some patients underwent surgery or received radiotherapy. The univariate analysis conducted in this study showed the following factors were statistically significantly associated with recurrence: no surgery, no overall pathological complete response, no breast pathological complete response, no lymph node pathological complete response and diffuse inflammatory signs. However no variable remained statistically significant in multivariate analysis and the use of radiotherapy was not included in the model. A retrospective study by Huang *et al.* 2004 examined the effect of radiotherapy on outcomes in patients treated for locally advanced breast cancer with primary chemotherapy and mastectomy. Radiotherapy was found to reduce loco-regional recurrence and improve survival for patients. Another retrospective study by McGuire *et al.* (2007) investigated the role of post-mastectomy radiotherapy in women with breast cancer who achieved a pathologic complete response to neo-adjuvant chemotherapy. In patients initially presenting with stage III disease; those receiving radiotherapy had statistically significantly lower rates of locoregional response; higher distant metastatic survival rates; higher cause specific survival rates and higher overall survival rates.

PICO

Population	Intervention	Comparison	Outcomes
Patients with <ul style="list-style-type: none"> • inflammatory breast cancer • stage III/T3-4 (locally advanced breast cancer) who have received primary chemotherapy. 	<ul style="list-style-type: none"> • Surgery • Radiotherapy 	<ul style="list-style-type: none"> • Surgery • Radiotherapy • Surgery with WLE+XRT • Radiotherapy with WLE+XRT • Nothing 	<ul style="list-style-type: none"> • Recurrence • Disease Free Survival • Overall Survival • Patient Acceptability • Quality of Life • Cost Effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

The evidence body for this question consisted of a Cochrane Review, a number of systematic reviews and RCTs and an observational study although there is little direct evidence from randomised studies on the individual effects of surgery or RT following treatment with primary chemotherapy.

Some of the included studies have limited applicability due to the majority of patients having operable breast cancer of stage I-II (Mieog *et al.* 2007; Trudeau *et al.* 2005; Mauri *et al.* 2005; Avril *et al.* 1998; Scholl *et al.* 1991).

There is evidence that in patients with locally advanced breast cancer that are treated with primary chemotherapy, better tumour response is associated with better outcomes (Mieog *et al.* 2007; Shenkier *et al.* 2004; Pouillart *et al.* 1981).

There is indirect evidence that 5 and 10 year overall survival is poorer in patients with locally advanced or inflammatory breast cancer whom are treated with primary chemotherapy and loco-regional therapy when compared with those with stage I-II disease ((Baldini *et al.* 2003; Tan *et al.* 2001; Veyret *et al.* 2006; Mieog *et al.* 2007).

There is evidence that radiation therapy was significantly associated with a higher 10 year overall survival in the irradiated group compared with the non-irradiated group (McGuire *et al.* 2007).

The effect of response to primary chemotherapy

In a Cochrane Review of RCTs (Mieog *et al.* 2007) the rate of pathological complete response to primary chemotherapy in 7 trials ranged from 4.0% to 29.2%. From four RCTs a statistically significant difference in overall survival in patients with a pathological complete response was observed compared with those patients with residual disease (HR = 0.48; 95% CI, 0.33 to 0.69). From five RCTs there was a statistically significant difference in disease free survival in patients with a pathological complete response to primary chemotherapy compared to those with residual disease (HR = 0.48; 95% CI, 0.33 to 0.69).

Changes to intended loco-regional therapy and achievement of breast conserving surgery

A Cochrane systematic review of RCTs (Mieog *et al.* 2007) estimated that in patients with operable breast cancer who are treated with primary chemotherapy, loco-regional treatment is changed to a less radical strategy due to down-staging in 25.6% (95% CI 23.5%-27.8%) of patients and in 4.3% (95% CI 3.3%-5.3%) of patients more radical loco-regional treatment was given. In the remaining 70.1% (95% CI 67.8%-72.4%) there was no change to planned treatment.

Two RCTs in the same review (Mieog *et al.* 2007) found that there was no significant difference in loco-regional recurrence (RR 1.34; 95% CI 0.85-2.13) or overall survival (OR 1.33; 95% CI 0.67-2.63) according to whether breast conserving surgery was planned from the outset or made feasible by the effect of primary chemotherapy.

From a systematic review of RCTs (Trudeau *et al.* 2005), the mean proportion of patients receiving breast conserving surgery was 54%, the median was 56% and the range was 20% to 85%.

The applicability of this evidence is limited due to the fact that the majority of patients were Stage I-II in both reviews.

The effect of loco-regional surgery of radiotherapy in patients with locally advanced or inflammatory breast cancer treated with primary chemotherapy

Four RCTs provide randomised comparisons of loco-regional therapies in patients with locally advanced or inflammatory breast cancer who are treated with primary chemotherapy (Bucolz *et al.* 2006, Perloff *et al.* 1998, Murali *et al.* 1993 and DeLena *et al.* 1981).

An RCT (Bucolz *et al.* 2006) compared hyperfractionated RT with standard RT in patients with locally advanced breast cancer showing an acceptable response to primary chemotherapy and who had mastectomy and adjuvant chemotherapy. No significant difference was observed at 15 year follow-up between the hyperfractionated and standard arms for loco-regional recurrence free survival (12% and 7% respectively, $p=0.36$), overall survival (33% and 45% respectively, $p=0.54$), late toxicity (11% and 6% respectively, $p=0.54$).

A systematic review (Shenkier *et al.* 2004) included three RCTs (Perloff *et al.* 1998, Murali *et al.* 1993 and DeLena *et al.* 1981) comparing mastectomy alone with loco-regional RT alone following primary chemotherapy in patients with locally advanced or inflammatory breast cancer. The results suggest that both treatments are equally effective in terms of recurrence and survival, after primary chemotherapy in inoperable disease.

In contrast the Cochrane Review (Mieog *et al.* 2007) and a systematic review (Mauri *et al.* 2005) suggest higher rates of loco-regional recurrence in patients who received RT without surgery after primary chemotherapy. Three RCTs included in the Cochrane Review (Mieog *et al.* 2007) a substantial number of patients received RT alone after primary chemotherapy; the combined rate of loco-regional recurrence for all patients was 19.3% as compared to a combined rate of 9.7% in the remaining RCTs in which all patients had surgery. A single RCT reported a rate of loco-regional recurrence of 29.5% in the subgroup of patients who received RT alone following primary chemotherapy.

A similar association was reported in a systematic review ((Mauri *et al.* 2005) based on the same three primary studies. Patients treated with primary systemic therapy were at 22% increased risk of loco-regional recurrence when compared with those who received adjuvant chemotherapy following primary loco-regional treatment (RR primary:adjuvant 1.22 (95% CI, 1.04-1.43), $p=0.015$). This increased risk of loco-regional recurrence associated with primary systemic treatment was driven largely by three trials in which radiotherapy only was adopted more often in the primary systemic arm than in the adjuvant arms (RR primary:adjuvant 1.53; 95% CI 1.11 to 2.10; $p=0.009$) whereas no association with loco-regional recurrences was found in other trials (RR 1.10; 95% CI 0.87 to 1.38; $p=0.44$).

In one small RCT (Pouillart *et al.* 1981) of patients with inflammatory breast carcinoma treated with primary chemotherapy, subsequent loco-regional therapy was RT without surgery. The randomised comparison was live BCG vaccine in one arm and no vaccine in the other arm. In

all patients the mean overall survival was 34 months and mean disease-free survival was 26 months.

The high degree of heterogeneity of RCTs (Table 1) in terms of initial disease stage, distribution of loco-regional therapies, extent of follow-up (or time of assessment of outcome) and primary chemotherapeutic regimens does not permit a concise summary of their results.

Five year overall survival data are available for three randomised arms in 2 trials of patients with locally advanced or inflammatory breast cancer who are treated with primary chemotherapy followed by loco-regional therapy. The values are 52%, 54% and 50% (Baldini *et al.* 2003; Tan *et al.* 2001) (Table 1). This suggests that overall survival is poorer in patients with stage III or inflammatory disease, than in similarly treated patients with predominantly stage I-II disease: 5 year survival range 77%-93% (Mieog *et al.* 2007).

Similar data for 10 year overall survival in patients with inflammatory breast cancer comes from a single RCT in which patients received primary chemotherapy, surgery and RT (Veyret *et al.* 2006). 10 year overall survival was 41% (table 1), whereas 10-year survival in similarly treated patients with predominantly stage I-II disease reported in the Cochrane Review had range 62% to 87% (Mieog *et al.* 2007).

Multivariate analyses of factors to predict outcomes in patients with locally advanced breast cancer treated with primary chemotherapy

The RCT by Veyret *et al.* 2006 (Table 2) evaluated in its randomised comparison, the addition of granulocyte colony stimulating factor to primary chemotherapy. After primary chemotherapy, 85% of patients underwent surgery and 95% received RT. At a median follow-up period of 120 months the rate of recurrence by subgroup for loco-regional therapy was: No surgery: 10 cases (55.6%), no mastectomy: 15 cases (33.3%), breast conserving surgery: 5 cases (18.5%) and RT as only adjuvant treatment: (12 cases) 84.6%. In univariate analysis the following factors were statistically significantly associated with recurrence: No surgery, no overall pathological complete response, no breast pathological complete response, no lymph node pathological complete response and diffuse inflammatory signs. However no variable remained statistically significant in multivariate analysis. The use of RT was not included in the model (Veyret *et al.* 2006).

A retrospective study by Huang *et al.* 2004 examined the effect of RT on outcomes in 676 patients treated for locally advanced breast cancer with primary chemotherapy and mastectomy. 542 patients received in addition, adjuvant RT and 134 patients did not. The 10-year rate of loco-regional recurrence was 11% in patients who received RT versus 22% in patients who did not receive RT ($p=0.0001$; log-rank test). There were no statistically significant differences in 10-year overall survival (54% versus 47% respectively; $p=0.063$; log-rank test) and in 10-year cause-specific survival (58% and 55% respectively, $p=0.85$; log-rank test). In a multivariate analysis of factors, the following variables were statistically significantly associated with loco-regional recurrence: No RT, $\geq 20\%$ sampled nodes positive, stage \geq IIIB, no tamoxifen, minimal (or less) clinical response to primary chemotherapy and ER negative tumour. Of these variables, the most strongly associated with local recurrence was not having RT (HR 4.68; 95% CI 2.70-8.13; $p<0.0001$). Although this study was retrospective and excluded patients with recurrence within 2 months of surgery and those who received breast conserving surgery, the effect in favour of RT was observed despite patients who received RT

tending to have more advanced initial disease stage, a poorer response to primary chemotherapy and close or positive surgical margins (Huang *et al.* 2004).

On updating the evidence, a retrospective study by McGuire *et al.* (2007) investigated the role of post-mastectomy radiotherapy in women with breast cancer who achieved a pathologic complete response to neo-adjuvant chemotherapy. 106 patients without inflammatory breast cancer were included in the study (radiation therapy n=72; non-irradiated n=34). The 10 year actuarial rates of local regional recurrence (LRR) did not differ significantly between the two groups (p=0.40).

In patients initially presenting with stage III disease;

- Radiation therapy was significantly associated with a lower 10 year rate of LRR in the irradiated group compared with the non-irradiated group; 7.3% \pm 3.5% vs. 33.3% \pm 15.7% (p=0.040)
- 10 year distant metastasis survival rate was 87.9% \pm 4.6% in the irradiated group and 40.7% \pm 15.5% in the non-irradiated group (p = 0.0006)
- 10 year cause specific survival (CSS) rate was 87% \pm 5% for the irradiated group and 40% \pm 16% for the non-irradiated group (p=0.0014)
- 10 year overall survival (OS) rate was 77.3% \pm 6% for the irradiated group and 33.3% \pm 14% for the non-irradiated group (p=0.0016)

Table 1: Recurrence and survival outcomes from trials that were not included in the Cochrane Review by Mieog et al. (2007): patients with locally advanced or inflammatory breast cancer treated with primary chemotherapy then loco-regional therapy

RCT	n	Population (stage)	Loco-regional therapy (following primary chemotherapy); % of patients where applicable	Follow-up	Results	Notes
(Avril <i>et al.</i> 1998)	134	Stage T2-3/N0-1/M0	RT alone: 33% BCS + RT: 30% Mastectomy: 37%	5 years 10 years	DFS: 58% OS: 80% DFS: 50% OS: 60%	Included in SR by Mauri et al. (2005) Limited applicability (stage) 1 arm relevant (n=134)
(Baldini <i>et al.</i> 2003)	146	Stage III or IBC	Mastectomy: 125 (86%) BCS: 12 (8%) RT alone: 11 (8%)	5 years	DFS: 48%; 60% PFS: 52%; 56% OS: 52%; 54%	Two values for each outcome represent two randomised arms.
(Buchholz <i>et al.</i> 2006)	108	Stage II: 19.5% Stage III: 79% Other: 2%	Mastectomy, RT and adjuvant chemotherapy (all patients). Randomised comparison: hyperfractionated versus standard RT.	15 years	LRFS: 7%; 12% OS: 45%; 33% No difference in outcome by randomised RT regimen	Two values for each outcome represent two randomised arms. Applicable randomised comparison. Patients were also randomised to 1 of 2 adjuvant chemotherapy regimens and to 1 of 2 adjuvant RT regimens. The distribution of treatment arising from one randomisation relative to the other is not known.
(Cocconi <i>et al.</i> 1990)	49	LABC	Mastectomy + adjuvant chemotherapy + adjuvant RT (all patients)	Median 6 years	Median OS: 6.6 years; 3.5 years	50% of patients received tamoxifen as the randomised comparison (for the duration of primary and adjuvant chemotherapy). Two values for OS outcome represent two randomised arms

RCT	n	Population (stage)	Loco-regional therapy (following primary chemotherapy); % of patients where applicable	Follow-up	Results	Notes
(De Lena <i>et al.</i> 1981)	132	LABC	Randomised comparison: 1. Mastectomy + adjuvant chemotherapy 2. RT + adjuvant chemotherapy	Minimum 6 months	No difference in OS (percentages and p value not reported). Median duration of remission 15 months in surgical group, 22 months in RT group (p=0.58). Total incidence of loco-regional recurrence 29.6% in surgical group, 31.1% in RT group (no p value reported). Total incidence of treatment failure in distant sites 43% in surgical group, 26.2% in RT group (p = 0.25).	Cited from systematic review by Shenkier <i>et al.</i> (2004) Applicable randomised comparison
(Evans <i>et al.</i> 2005)	363	LABC: 8% IBC: 15% Operable; T>3cm: 77%	BCS: 20% Mastectomy: 74% RT: 80% HT: 63%	Median 32 months	Recurrence: 28% (95% CI 23%-32%) Distant recurrence: 17% (95% CI 14%-21%) Mortality: 15% (95% CI 11%-19%)	Anglo-Celtic II Poor applicability (stage) Immature follow-up
(Mourali <i>et al.</i> 1993)	68	IBC	Randomised comparison: 1. Mastectomy + adjuvant chemotherapy 2. RT + adjuvant chemotherapy	Minimum 10 years	DFS and OS not reported. No difference in disease-free interval between treatment groups (percentages and p value not reported).	Cited from systematic review by Shenkier <i>et al.</i> (2004) Applicable randomised comparison

RCT	n	Population (stage)	Loco-regional therapy (following primary chemotherapy); % of patients where applicable	Follow-up	Results	Notes
(Perloff <i>et al.</i> 1988)	87	Stage III breast cancer	Randomised comparison: 1. Mastectomy + adjuvant chemotherapy 2. RT + adjuvant chemotherapy	Median 37 months	Median OS 39.3 months in mastectomy group, 39.0 months in RT group (p value not reported). Local recurrence rate 42% in mastectomy group, 55% in RT group (p=0.43).	Cited from systematic review by Shenkier <i>et al.</i> (2004) Applicable randomised comparison
(Pouillart <i>et al.</i> 1981)	77	IBC	RT + adjuvant chemotherapy	34 months	Mean OS: 34 months Mean DFS: 26 months	50% of patients received live BCG vaccination as the randomised comparison.
(Rainer <i>et al.</i> 1993)	76	LABC	Mastectomy + adjuvant chemotherapy or adjuvant RT	See results	Median DFS: 2.9 years Estimated 3-year OS: 70%	1 arm relevant (n=76) 38% of patients received adjuvant RT.
(Scholl <i>et al.</i> 1991)	77	Stage T2-3/N0-1b	Mastectomy: 23% BCS: 34% RT alone: 43% RT: 100%	3 years	DFS: 80%; 68%	Included in SR by Mauri <i>et al.</i> (2005) Limited applicability (stage); also results are based only on 77 patients who completed all planned chemotherapy out of an initial 100. 1 arm relevant (n=100) Two values for DFS outcome are for >50% tumour regression and ≤50% tumour regression respectively, after primary chemotherapy.
(Tan <i>et al.</i> 2001)	56	LABC: 91% IBC: 9%	RT alone: 4% Mastectomy + HT: 5% Mastectomy + RT + HT: 89%	5 years	OS: 50% Rate of loco-regional failure: 26%	1 arm relevant (n=56)
(Veyret <i>et al.</i> 2006)	120	IBC	Mastectomy: 63% BCS: 26% RT (chest wall): 93% RT (IMC): 81% RT (SCF): 89%	10 years	DFS: 36% OS: 41%	BCS was followed in addition by a RT boost

RCT	n	Population (stage)	Loco-regional therapy (following primary chemotherapy); % of patients where applicable	Follow-up	Results	Notes
(Willsher <i>et al.</i> 1990)	55	LABC	Mastectomy + tamoxifen: 95% RT: 89%	Median 30 months	Median OS: 3.6 years Rate of loco-regional recurrence: 22% Rate of uncontrollable loco-regional recurrence: 4%	1 arm relevant (n=55)

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Evidence Tables

Systematic reviews of RCTs

Mauri, Pavlidis & Ioannidis . Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis.[see comment]. J.Natl.Cancer Inst. 97[3], 188-194. 2005.

Design

Systematic review of RCTs (therapy), evidence level: 1 +
Country: Various, setting: Secondary care

Inclusion criteria

1. RCTs that compared primary systemic with adjuvant systemic treatment (chemotherapy or endocrine therapy) for breast cancer, in which the same regimen was given preoperatively to one group and postoperatively to another group, regardless of what additional surgery or radiation treatment was used.
2. RCTs where one arm received exclusively postoperative therapy while the other arm received some cycles of the same regimen preoperatively and some other cycles postoperatively.

11 RCTs were included, of patients with disease stage as follows:

RCT	Stage
Avril et al. (1998) Mauriac et al. (1999)	T2-3 N0-1
Semiglazov et al. (1994)	IIB IIIA
Scholl et al. (1991)	T2-3 N0-1b
Scholl et al. (1994); Broet et al. (1999)	T2-3 N0-1b
Makris et al. (1998)	T0-4 N0-1
NSABP B-18 (1998; 2001)	T1-3 N0-1
Gazet et al. (2001)	T1-4 N0-2
van der Hage et al. (2001)	T1 c – 4 b N0-1
Danforth et al. (2003)	II

Exclusion criteria

Meeting abstracts, escalation dose studies, and pseudorandomised trials (e.g., those with alternate allocation of subjects). If other concomitant anticancer nonsurgical treatments were also used (e.g., hormone therapy and radiation therapy), these treatments should not have differed systematically between the two arms.

Population

number of patients = 3861.

Interventions

Aim: to review evidence from RCTs to assess whether primary systemic therapy is associated with any advantage compared with the same adjuvant systemic therapy for the treatment of breast cancer.

All patients underwent a chemotherapy regimen (and some regimens included hormone therapy); randomised comparisons were between primary systemic therapy and adjuvant systemic therapy.

Local treatment consisted of surgery and RT (full details not reported).

Outcomes

Primary outcomes:

Death (from any cause), disease progression, loco-regional disease recurrence, and distant disease recurrence (metastasis). Disease progression was defined as locoregional or distant recurrence, occurrence of contralateral cancer, or death. Loco-regional recurrence was defined as recurrence in the ipsilateral breast or in the ipsilateral regional lymph nodes or chest wall.

Secondary outcomes:

Local clinical response to primary systemic treatment (three categories: complete versus partial versus none or progressive disease), the pathologic response (complete versus noncomplete) in the primary systemic arm, and the surgical approaches adopted (no surgery needed [radiotherapy only], breast-conserving surgery [e.g., lumpectomy or quadrantectomy], or mastectomy) in each arm. After preoperative chemotherapy, the absence of clinical evidence of tumor in the breast was defined as a clinically complete response and a reduction in the clinical tumor size of 50% or more was defined as a partial response. A complete pathologic response was defined as the absence of tumor in the surgical specimen (primary tumor and lymph node metastasis); this response was pertinent only for women who had surgery after primary systemic treatment.

Follow up

Median follow-up in 9 RCTs had mean 80 months (range 53-124 months)

Results

The pooled relative risks (RR) of death, disease progression and distant recurrence revealed no statistically significant difference in risk of event arising from primary systemic therapy compared to adjuvant systemic therapy. However primary systemic therapy was associated with a 22% increased risk of locoregional recurrence (RR primary:adjuvant 1.22 (95% CI 1.04-1.43), $p=0.015$).

There was statistically significant heterogeneity across studies in the rates of conservative local treatment in the adjuvant arms (ranging from 0% to 92%; P for heterogeneity of $<.001$) and in the primary systemic arms (ranging from 28% to 89%; P for heterogeneity of $<.001$).

Overall, there was a statistically significant higher rate of conservative local treatment in the primary systemic arms than in the adjuvant arms of five studies, a borderline difference in another trial ($P = .06$), and no difference between arms in three studies.

RT only, without surgery, was administered statistically significantly more often in the primary systemic arms than in the adjuvant arms in three trials.

Increased risk of loco-regional recurrence associated with primary systemic treatment was driven largely by the three trials in which radiotherapy only without surgery was adopted more often in the primary systemic than in the adjuvant arms (RR by random effects = 1.53, 95% CI = 1.11 to 2.10; $P = .009$; and RR by fixed effects = 1.53, 95% CI = 1.17 to 2.00; $P = .002$; no statistically significant between-study heterogeneity), whereas no association with loco-regional recurrences was found in other trials (RR by both fixed and random effects = 1.10, 95% CI = 0.87 to 1.38; $P = .44$).

The strongest association between primary systemic treatment and increased risk of loco-regional recurrence was observed in the study in which the patients in the primary systemic arm with a complete clinical response received radiotherapy alone without any surgical treatment. Patients who were treated only with radiotherapy had statistically significantly higher rates of loco-regional recurrence (20 of 44 patients) than patients who were treated with breast-conserving surgery (nine of 40 patients).

General comments

Patient population includes those with stage III disease, but also patients with less advanced disease; true applicability not known.

The authors warn that the principle subgroup data cited for this question (i.e. risk of locoregional recurrence following primary medical treatment with RT and no surgery) should be interpreted cautiously because of multiple comparisons.

Literature search:

MEDLINE and EMBASE databases. Keywords: breast cancer AND (neoadjuvant OR neo-adjuvant OR preoperative OR preoperative OR induction) AND (clinical trial OR randomised controlled trial OR double-blind OR single-blind OR random OR randomised OR placebo). Cochrane Central Register of Controlled Trials also searched for randomised trials that compared primary systemic with adjuvant systemic treatment for breast cancer.

No language restrictions.

Search cut-off date: October 2003.

Oncology journals hand-searched for the years 1995 through 2003

The reference list of retrieved papers was further screened for additional

publications, and several investigators were contacted and asked to provide clarifications and, potentially, additional data.

Study quality assessment:

Data were collected for each study based on the following: authors' names, journal and year of publication, country of origin of patients, inclusive dates of patient enrollment, number of centers involved, study design items (including whether there was a description of the mode of randomisation, allocation concealment, number of withdrawals per arm, and blinding).

Patient data were collected as follows: number of patients randomly assigned to treatment and analyzed per arm, their age, their tumor stage, their menopausal status, regimens used (including type of therapy [endocrine therapy and/or chemotherapy], timing, number of courses for each arm, and additional treatments given to both arms), and number of outcome events per arm.

Two individuals extracted and checked the data, checking discrepancies with the primary study authors.

Mieog, van der Hage & van, V . Preoperative chemotherapy for women with operable breast cancer. Cochrane.Database.of Systematic.Reviews. 2007.

Design

Systematic review of RCTs (therapy), evidence level: 1 ++
Country: Various, setting: Tertiary care

Inclusion criteria

RCTs of primary (preoperative) chemotherapy in women with operable breast cancer: TNM stage T1c, T2, T3, N0 to 2, and M0 (AJCC stage I-IIIa).

Exclusion criteria

5 RCTs were excluded for the following reasons:

1. Randomised controlled trial consisting of 101 women with operable locally advanced disease (T4b, N0-2, M0)
2. Abstract of conference proceeding. Reported a subset of patients part of NSABP B-18 study.
3. Abstract of conference proceeding. No data available. Publication pending.
4. Randomised controlled trial comparing preoperative with postoperative chemotherapy. Relevant data stratified to apoptotic index. No response from authors.
5. Abstract of conference proceeding. Not properly randomised (of the 98 analysed patients only 87 were included in a randomised prospective fashion)

Population

number of patients = 5500.

Interventions

Aim: to systematically identify and assess all of the available evidence from RCTs as to the effectiveness of preoperative chemotherapy on treatment-related outcomes in women with operable breast cancer.

Eligible comparisons:

- i) Preoperative chemotherapy versus postoperative chemotherapy.
- ii) Preoperative and postoperative chemotherapy versus postoperative chemotherapy.

(For details see Appendix ATable)

Outcomes

Primary outcomes:

Overall survival

Disease-free survival

Loco-regional recurrence as first event

Secondary outcomes:

Tumour response rate

Association of pathological complete response with clinical outcome

Type of loco-regional treatment

Changes of originally planned loco-regional treatment

Adverse effects

Quality of life

Follow up

In 14 RCTs median follow-up had range 18-124 months

Results

Study characteristics

14 RCTs were included (5500 patients; 2748 of whom received preoperative chemotherapy and 2748 of whom received chemotherapy after locoregional treatment).

All included trials compared preoperative chemotherapy with a postoperative regimen (see also Appendix A table). In six trials patients in the preoperative arm received all cycles prior to loco-regional treatment. In the remaining eight trials, patients in the preoperative arm received some of the cycles after loco-regional treatment. A variety of chemotherapeutic regimens were administered to patients across the included trials; all regimens were made up of multiple chemotherapeutic agents.

Loco-regional treatment varied across studies. Five studies applied the same local treatment to all included patients (Edinburgh 1995, Japan 1998; Lithuania 1998, St. Petersburg 1994). In other studies treatment varied according to patients' individual requirements (e.g. tumour size, nodal involvement). Three studies administered radiotherapy before surgery (Institut Curie 1991; Institut Curie 1994, St. Petersburg 1994). Three studies treated some of the participants exclusively with radiotherapy (Bordeaux 1991; Institut Curie 1991; Institut Curie 1994).

Tumour response to preoperative chemotherapy

Eleven studies reported a complete clinical response rate in the preoperative chemotherapy arm for 1761 assessable patients involving 653 complete clinical responses. The complete clinical response rate ranged from 0 to 64.7%.

Twelve studies reported an overall clinical response rate in the preoperative chemotherapy arm for 2032 assessable patients involving 1384 overall clinical responses. The overall clinical response rate ranged from 11.1 to 83.3%.

Seven studies reported a pathological complete response rate in the preoperative chemotherapy arm for 1972 assessable women involving 278

pathological complete responses. The pathological complete response rate ranged from 4.0 to 29.2%.

Association of pathological complete response with clinical outcome

The authors compared overall and disease-free survival between patients with a pathological complete response and those who had residual disease at pathological examination.

Four studies reported overall survival data for 1290 assessable patients involving 381 estimated deaths. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.33 to 0.69).

Five studies reported disease-free survival data for 1741 assessable patients involving 606 estimated events. There was a statistically significant difference in favour of pathological complete response: HR (pCR versus residual disease) 0.48 (95% CI 0.37 to 0.63).

Changes to originally planned locoregional treatment (5 RCTs)

Five studies reported changes of loco-regional treatment that had been originally planned in the preoperative chemotherapy arm (1549 assessable women; see appendix: table). Across studies, 397 women had their originally planned surgical treatment altered due to down staging (25.6%; 95% CI, 23.5 to 27.8), 1086 women had no change to planned treatment (70.1%; 95% CI, 67.8 to 72.4), and 66 women required more radical surgery than originally planned (4.3%; 95% CI, 3.3 to 5.3).

Table: relationship between treatment intended and treatment performed

Study	BCT - BCT	MAST - MAST	MAST - BCT	MAST - RT	BCT -RT	BCT - MAST	Total
Bordeaux 1991	-	49	40	44	-	-	133
EORTC 2001	60	190	60	-	-	14	324
Institut Curie 1994	-	36	62	102	-	-	200
NSABP 1998	435	187	69	-	-	52	743
Royal Marsen 1998	113	16	19	-	1	-	149
Total	608	478	250	146	1	66	1549

Two RCTs compared outcomes between patients who received down staged breast conserving therapy compared to those who received planned breast

conserving therapy in the preoperative chemotherapy arm. There was no statistical significant difference in loco-regional recurrence or overall survival between these groups:

Table: Effect on outcome of downstaging: ratio outcomes for downstaged vs planned breast conserving surgery in primary chemotherapy arms of two RCTs

Outcome	No. of studies	No. of participants	Statistical method	Effect size
Overall survival	1	120	Peto Odds Ratio [95% CI]	1.33 [0.67, 2.63]
Loco-regional recurrence	2	623	Relative Risk (Fixed) [95% CI]	1.34 [0.85, 2.13]

Authors conclude that direct evidence concerning long-term prognosis and risk of local recurrence after downstaging of surgical treatment following preoperative chemotherapy is still lacking. Indirectly derived data suggest no intrinsic risk amplification associated with downstaged breast-conserving surgery. However, evidence from direct comparison is needed to draw valid conclusions.

Overall survival following primary chemotherapy and then locoregional treatment

Nine studies reported estimated overall survival at 5 years and six studies at 10 years in patients treated with primary chemotherapy and then locoregional therapy (RT alone, BCS plus RT, mastectomy, mastectomy plus RT; see Appendix A table).

Overall survival at 5 years had mean value 82.4%, median 80% and range 77% to 93%.

Overall survival at 10 years had mean value 69.2%, median 66% and range 62% to 87%.

Radiotherapy without surgery following primary chemotherapy

In three studies, the loco-regional treatment for a substantial number of patients consisted of exclusive radiotherapy and no surgery. In Bordeaux 1991, 44 (33%) women in the primary chemotherapy arm received exclusive radiotherapy, and none in the control arm. In Institut Curie 1991, 41 (43%) women received exclusive radiotherapy after primary chemotherapy compared with 30 (35%) women in the control arm. In Institut Curie 1994, 102 (51%) women received exclusive radiotherapy after primary chemotherapy compared with 87 (46%) women in the control arm. Although these studies did not separately report loco-regional recurrence rates for these patients,

except for Bordeaux 1991 (13/44=29.5%), they did show an increased overall loco-regional recurrence rate compared to the remaining eight studies: 163/843 (19.3%) and 407/4198 (9.7%), respectively.

General comments

Applicability to this question is limited due to inclusion of studies of patients with disease stages I-II.

Most outcomes are reported as hazard ratios for primary (preoperative) versus postoperative chemotherapy arms and are therefore not relevant to this question. Selected outcomes of relevance are cited.

Overall survival data are of limited applicability to this question because the data are not reported by the individual locoregional therapies (combinations of surgery and/or RT), but combined (see Appendix AAtable). In the primary chemotherapy arms of the RCTs, surgery and/or RT were often given according to the response to primary chemotherapy. In addition the studies vary in their primary chemotherapy regimens, use of axillary surgery, hormone therapy and, in primary chemotherapy arms, whether adjuvant chemotherapy was also given.

Re: Tabulated data on 'Effect on outcome of downstaging: ratio outcomes for downstaged vs planned breast conserving surgery in primary chemotherapy arms of two RCTs': the direction of effect is in favour of planned breast conserving surgery after primary chemotherapy versus breast conserving therapy achieved by down-staging by primary chemotherapy, but the 95% confidence intervals for the pooled results cited (and also the results of the primary studies) include the null hypothesis value of 1; therefore the effect is not statistically significant. The result may be nevertheless, clinically important.

Literature search:

Cochrane Breast Cancer Group Specialist Register of RCTs searched on 4.8.05; includes published and unpublished trials; no language restrictions. Keywords: 'early' and 'chemo' and 'locally advanced' and 'chemo'. In addition the authors searched reference lists of related literature reviews.

Study selection:

Two review authors independently applied the selection criteria on the methods sections of the selected trials. The review authors were blinded to all but the methods section. Any disagreements were resolved by consensus.

Quality assessment:

Two review authors independently reviewed each included study based on:

- concealment of the allocation sequence
- generation of the allocation sequence
- comparability between groups at the baseline

- inclusion of all randomised participants in the analysis (Intention to treat)
- loss to follow-up

Allocation concealment was graded as follows:

Grade A - clearly adequate

Grade B - possibly adequate,

Grade C - clearly inadequate

Grade D - not used.

Data extraction:

At least two individuals independently extracted data from the studies identified for inclusion. Any disagreements were resolved by consensus.

Table of survival data from RCTs of primary chemotherapy; from Cochrane Review by Mieog et al. 2007

NB estimated 5-year and 10-year survival values read from bar graph

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
Bordeaux 1991	T2>3cm, T3, N0-1, M0	<p>Preop vs postop EVM + MTV</p> <p>Arm A: 3 cycles of preoperative Epirubicin - Vincristine - Methotrexate every 3 weeks followed by 3 cycles of preoperative Mitomycin C - Thiotepa - Vindesine every 3 weeks.</p> <p>Arm B: mastectomy then adjuvant chemotherapy as for arm A if histological axillary node involvement or negative ER/PR, otherwise no adjuvant chemotherapy.</p>	<p>Arm A</p> <p>i) Complete regression: exclusive RT of breast (50 Gy + 20-24 Gy boost) and axilla, internal mammary, supraclavicular node areas (50 Gy + 10 Gy boost on axilla if positive prechemotherapy).</p> <p>ii) Residual < 2cm: lumpectomy + breast irradiation (50 Gy + 10 Gy boost).</p> <p>iii) Residual > 2cm: modified radical mastectomy (Patey) without RT.</p> <p>Arm B mastectomy</p>	80	80	62	59
ECTO 2005	T size >2cm; (20%>4cm)	<p>3 Arms: Preop AT-CMF vs postop AT-CMF vs postop A-CMF</p> <p>Arm A: 4 cycles of preoperative Doxorubicin - Paclitaxel every 3 weeks followed by 4 cycles of Cyclophosphamide - Methotrexate - Fluorouracil on days 1 and 8 every 4 weeks.</p> <p>Arm B: idem as for A, all postoperative.</p> <p>Arm C: 4 cycles of postoperative Doxorubicin 75 mg/m² IV every 3 weeks followed by 4 cycles of CMF IV on days 1 and 8 every 3 weeks.</p>	Mastectomy or BCT + radiotherapy RT for mastectomy-treated patients with pT4 tumours.	87	90	-	-

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
EORTC 2001	T1c-T3, T4b, N0-1, M0	Preop vs postop FEC Arm A: 4 cycles of preoperative Fluorouracil - Epirubicin - Cyclophosphamide every 3 weeks. Arm B: idem as for A, all postoperative	Mastectomy or BCS + RT (50 Gy in 5 weeks). Chest wall/parasternal: pts with initial tumour of 5 cm or more. Infra and supraclavicular fossa: pts with positive infraclavicular node after LN dissection. Tamoxifen: pts >50 yrs (regardless of ER/nodal status) received 20 mg daily for at least 2 yrs.	77	82	64	66
Institut Curie 1994	T2-3, N0-1, M0 (T size 3-7cm)	Preop vs postop FAC Arm A: 2 cycles of preoperative 5-Fluorouracil on days 1, 3, 5, 8, Doxorubicin and Cyclophosphamide on day 1 and 8 every 4 wks. Followed by response assessment: Good responders: 2 additional cycles of preoperative FAC. Non-responders: loco-regional treatment Arm B: 4 cycles of adjuvant FAC within 2 weeks of ending loco-regional treatment.	Primary RT: 54 Gy in 6 weeks to breast and axillary nodes + 45 Gy to supraclavicular nodes and internal mammary chain. Patients with CR or near CR received a boost to tumour bed (totalling 75-80 Gy) and had no surgery. N+ patients received a 10-15 Gy boost to inferior axilla if no surgery was performed. Surgery (mastectomy or lumpectomy) was limited to patients presenting with a persisting mass after 54 Gy. A total of 24 patients underwent mastectomy without RT.	84	77	64	60

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
London 2001	T1-4, N0-1, M0 (24% T3-4)	<p>Preop and postop vs postop treatment. Either chemo- or endocrine therapy based on ER-status:</p> <p>Arm A: ER+ pts (47): endocrine treatment Premenopausal: Goserelin monthly for 12 weeks. Postmenopausal: Formestane every 2 weeks for 12 weeks. ER - pts: 4 cycles in 12 weeks of preoperative Mitozantrone every 3 weeks, Mitomycin C every 6 weeks, Methotrexate every 3 weeks with fonic acid rescue 4 times for 24 hours, starting 24 hrs after chemotherapy. After clinically assessing tumour response and surgery/radiotherapy: Responders: received a total of 8 cycles MMM or 18 months Goserelin or Formestane (doses as above). Non-responders: ER + pts: 8 cycles of MMM (as above) ER - pts: 8 cycles of 5-Fluorouracil - Epirubicin - Cyclophosphamide every 3 weeks.</p> <p>Arm B: ER+ pts: endocrine therapy Premenopausal: Goserelin as above for 18 months. Postmenopausal: Formestane as above for 18 months. ER - pts: 8 cycles of MMM as above.</p>	Primary surgery (mastectomy or BCS + RT to breast + boost to scar) or primary RT. Pts with involved axillary nodes: RT to axilla and supraclavicular fossa. Pts with tumours in medial half of breast: RT to ipsilateral mammary chain. When primary RT did not produce a response, a mastectomy was performed.	77	87	-	-

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
NSABP 1998	T1-3, N0-1, M0 (no locally advanced disease)	Preop vs postop AC Arm A: 4 cycles of preoperative Doxorubicin - Cyclophosphamide every 3 weeks. Women with progressive disease before completion of all 4 courses received the remaining courses after surgery. Arm B: idem as for A, all postoperative.	Mastectomy or BCS + RT. Tamoxifen: pts >50 yrs (regardless of ER/nodal status) received 10 mg twice daily for 5 yrs	80	82	68	70
Royal Marsden 1998	T1-4, N0-1, M0 (7% T3-4)	Preop and postop vs postop MM(M) Arm A: 4 cycles of preoperative Mitomycin C every 6 weeks, Mitoxantrone every 3 weeks, Methotrexate every 3 weeks or 2M (same as 3M, with the exclusion of Mitomycin C and increased dose of Mitoxantrone) followed by 4 cycles postoperative of 3M or 2M. Arm B: idem as for A, all postoperative.	Mastectomy or BCT + RT (54 Gy to breast + 10 Gy boost to scar). Clinically involved lymph nodes: Level II axillary lymph node dissection. No axillary dissection for clinically node negative pts. RT to axilla and supraclavicular fossa was only given to those pts with palpable nodes at presentation, who did not have axillary dissection. Tamoxifen: 20 mg daily for 5 years simultaneously started with chemotherapy.	77	77	70	64
St Petersburg 1994	Stage IIb-IIIa: T3, N0-1; T2, N1; T1-2, N2, M0	Preop and postop vs postop TMF Arm A: 1 or 2 cycle(s) of preoperative Thiotepa on days 1,3,5,7,9,11, Methotrexate - 5-Fluorouracil on days 1 and 8 every 4 weeks. Followed, starting during mastectomy, by 4-5 cycles of TMF. Arm B: 6 cycles of postoperative TMF.	Preoperative RT: 60 Gy (2 Gy daily) to breast + 40 Gy to axillary area, supra- and subclavicular areas followed after 3-4 weeks by modified radical mastectomy.	87	78	-	-

RCT	Population (stage)	Randomised comparison	Surgery/other treatment	5-year survival (%)		10-year survival (%)	
				Pre-op	Post-op	Pre-op	Post-op
USA 2003	Stage II: T1, N1; T2, N0; T2, N1	<p>Preop vs postop FLAC + G(M)-CSF</p> <p>Arm A: 5 cycles of preoperative 5-Fluorouracil - Leucovorin -Doxorubicin on days 1,2,3 and Cyclophosphamide on day 1 every 3 wks + Granulocyte-macrophage colony stimulation factor</p> <p>Arm B: idem as for A, all postoperative (2-3 wks after surgery)</p>	<p>Mastectomy or BCS + RT.</p> <p>RT 50.4 Gy to the breast and, in cases with N stage disease, axilla. Patients with extranodal extension received 50.4 Gy to the posterior axillary field. All pts received an additional 10-Gy boost to the surgical bed.</p> <p>Tamoxifen for ER+/PR+ pts: 10 mg twice daily for 5 yrs.</p>	93	84	87	72

Trudeau, Sinclair & Clemons . Neoadjuvant taxanes in the treatment of non-metastatic breast cancer: A systematic review. *Cancer Treat.Rev.* 31[4], 283-302. 2005.

Design

Systematic review of RCTs (therapy), evidence level: 1 ++
Country: Various, setting: Secondary care

Inclusion criteria

For eligible studies:

A neoadjuvant taxane-containing regimen was evaluated using any of the publication types listed in the search strategy (randomized controlled trials or systematic reviews/metaanalyses).

Reported outcomes included rates of clinical response, pathologic response, breast conservation, DFS, or overall survival.

Clinical trial results were reported in either full papers or abstracts.

Exclusion criteria

Non English language papers

Population

number of patients = 6225.

Interventions

Aim: to review RCT evidence on the role of primary taxane chemotherapy in patients with non-metastatic breast cancer.

All patients underwent primary chemotherapy; at least one arm receiving primary taxane chemotherapy. All randomised arms planned surgery in addition, and some, radiotherapy and hormone therapy in addition.

Outcomes

Response to primary chemotherapy (tumour and lymph nodes)

Proportion of patients who underwent breast conserving surgery

Disease-free survival (DFS)

Overall survival (OS)

Follow up

See table below

Results

17 RCTs were included, presented in 18 papers, one of which provided further analysis between subgroups for different primary taxane doses/schedules. In all trials the randomised comparison is either primary taxane chemotherapy versus non-taxane primary chemotherapy, primary

taxane versus adjuvant taxane, or different doses/schedules of primary taxane chemotherapy.

The studies provide some information on subsequent treatment, including surgery and radiotherapy, administered within RCT protocols.

Of 17 included RCTs only four provide data on DFS or OS, although the majority (12) were available only in abstract at the time of completion of the literature search (September 2004), suggesting that follow-up is immature.

Of 17 RCTs, nine omitted radiotherapy altogether and eight used radiotherapy in all randomised arms. In contrast all RCTs used surgery in all of their randomised arms. Some studies report the proportion of patients in whom breast conserving surgery was performed; the complement of this proportion represents patients who received mastectomy.

Primary chemotherapy, surgery, radiotherapy and hormone therapy

In one trial (M. D. Anderson) patients were randomised to either paclitaxel or FAC primary chemotherapy, and then received surgery, adjuvant FAC, radiotherapy and hormone therapy. The respective proportions of patients who received breast conserving surgery were 46% and 35%. Respective DFS at 23 months was 94% and 89%. 17% of patients had initial stage III disease.

A second trial (Pouillart, 1999) randomised patients to either doxorubicin-paclitaxel or doxorubicin-cyclophosphamide primary chemotherapy. All patients then received surgery, radiotherapy and hormone therapy. DFS data are summarised for the latter arm only: 45% with unknown follow-up duration. 56% of patients underwent breast conserving surgery and 38% of patients had initial stage T3 tumours.

In a similar trial (ACCOG) patients were randomised to either doxorubicin-docetaxel or doxorubicin-cyclophosphamide primary chemotherapy. All patients then received surgery, radiotherapy and hormone therapy. 20% of patients in each arm received breast conserving surgery. At 32 months follow-up DFS was 75% and 69%, respectively, and OS was 86% and 84%, respectively. At outset 8% of patients had locally advanced disease and 15% inflammatory breast cancer. The remainder of patients had large, operable tumours.

Primary chemotherapy and surgery

A fourth RCT treated patients initially with primary cyclophosphamide, vincristine, doxorubicin and paclitaxel (CVAP). Patients with complete response were randomised to either the same repeated primary chemotherapy regimen, or to docetaxel. After primary chemotherapy all patients underwent surgery. 41% of patients had initial stage III disease. Breast conserving surgery was performed in 67% of the CVAP group and

48% of the docetaxel group ($p < 0.05$). Respective values for DFS at 38 months follow-up were 90% and 77% ($p < 0.05$). Respective values for OS at 65 months follow-up were 93% and 78% ($p < 0.05$).

Breast conserving surgery after primary chemotherapy

In all 17 RCTs surgery was performed in every randomised arm. In total the proportion of patients who received breast conserving surgery was reported for 21 randomised arms in 14 RCTs. This proportion had mean 54%, median 56% and range 20% to 85%.

NB See Appendix A below for table of primary study details reported in systematic review.

General comments

Well-conducted systematic review; limited applicability to this question owing to inclusion of patients with stage I-II breast cancer and sparse DFS/OS data. High clinical and methodological heterogeneity between studies; results presented with tabulated data/narrative.

Literature search strategy:

MEDLINE and EMBASE databases to September 2004. Search terms reported e.g. MEDLINE: Breast neoplasms[MeSH], Induction chemotherapy OR primary chemotherapy OR neoadjuvant chemotherapy OR preoperative chemotherapy[Title/Abstract] Taxoids[MeSH] Meta-analysis[pt] OR randomized controlled trial[pt] OR practice guideline [pt]. Also the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium were searched.

Study quality assessment evident e.g. considering publication as peer-reviewed paper or abstract, method of randomisation and concealment, stratification for confounding variables, intention-to-treat analysis, power calculation.

Table of primary study details reported in systematic review by Trudeau et al. 2005.

RCT	Treatment arms	Patient characteristics	Follow-up (months)	BCS (%)	DFS (%)	OS (%)
Primary taxane versus other primary chemotherapy regimens						
Paclitaxel						
M.D. Anderson (Buzdar, 1999)	<p>i [T q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy</p> <p>ii [FAC q3wx4] then local surgical treatment then [FAC q3wx4] then radiotherapy then hormone therapy</p>	T1-3, N0-1, M0 (17% stage III)	23	<p>i 46</p> <p>ii 35</p>	<p>i 94</p> <p>ii 89</p>	NR
Pouillart, 1999	<p>i [AT q3wx4] then local surgical treatment then radiotherapy then hormone therapy</p> <p>ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy</p>	T2-3,N0-1,M0 (38% T3)	NR	56	<p>i NR</p> <p>ii 45</p>	NR
Malamos, 1998	<p>i [ET q3wx3] then local surgical treatment then [ET q3wx3] then radiotherapy then hormone therapy</p> <p>ii [FEC q3wx3] then local surgical treatment then [FEC q3wx3] then</p>	Operable breast cancer	NR	NR	NR	NR

	radiotherapy then hormone therapy					
Docetaxel						
ACCOG (Evans, 2004)	i [AT q3wx6] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx6] then local surgical treatment then radiotherapy then hormone therapy	8% locally advanced, inoperable, 15% inflammatory, 77% large, operable	32	i 20 ii 20	i 75 ii 69	i 86 ii 84
Lee, 2004	i [TX q3wx4] then local surgical treatment then radiotherapy then hormone therapy ii [AC q3wx4] then local surgical treatment then radiotherapy then hormone therapy	Stage II/III, N+ (44% stage III)	NR	i 64 ii 56	NR	NR
NSABP B-27	i [AC q3wx4] + hormone therapy then [Tq3wx4] then local surgical treatment then radiotherapy ii [AC q3wx4] + hormone therapy then local surgical treatment then [Tq3wx4] then radiotherapy iii [AC q3wx4] + hormone therapy then local surgical treatment then radiotherapy	T1-3,N0-1,M0 (45% >=T4)	NR	i 64 ii 62 iii NR	NR	NR

Aberdeen	<p>i [CVAPr q3wx4] (R-) then [Tq3wx4] then local surgical treatment (patients not randomised)</p> <p>ii [CVAPr q3wx4] (R+) then [T q3wx4] then local surgical treatment</p> <p>iii [CVAPr q3wx4] (R+) then [CVAPr q3wx4] then local surgical treatment</p>	T _≥ 3cm or T3-4, N2 (41% stage III)	38/65	<p>i NR</p> <p>ii 67</p> <p>iii 48</p> <p>p<0.05</p>	<p>i NR</p> <p>ii 90</p> <p>iii 77</p> <p>p<0.05</p>	<p>i NR</p> <p>ii 97% at 38 months ; 93% at 65 months</p> <p>iii 84% at 38 months , 78% at 65 months</p> <p>p<0.05</p>
GEPAR-TRIO	<p>i [TAC q3wx2] (R+) then [TAC q3wx4] then local surgical treatment</p> <p>ii [TAC q3wx2] (R-) then [TAC q3wx4] then local surgical treatment</p> <p>iii [TAC q3wx2] (R-) then [NX q3wx4] then local surgical treatment</p>	T _≥ 2cm or locally advanced (89% operable)	NR	<p>i 61</p> <p>ii 56</p>	NR	NR
Bouزيد, 2001	<p>i [AT q3wx4] then local surgical treatment</p> <p>ii [FAC q3wx4] then local surgical treatment</p>	Stage IIIa or b	8.3	NR	NR	NR
Luporsi, 2000	<p>i [ET q3wx6] then local surgical treatment</p> <p>ii [FEC q3wx6] then local surgical treatment</p>	T2-4 Non-IBC	NR	<p>i 85</p> <p>ii 69</p>	NR	NR
Primary taxane versus adjuvant taxane						

regimens						
ECTO (Gianni, 2002)	<p>i [AT q3wx4] then [CMF q4wx4] then local surgical treatment</p> <p>ii local surgical treatment then [A q3wx4] then [CMF q4wx4]</p> <p>iii local surgical treatment then [AT q3wx4] then [CMF q4wx4]</p>	T>2 cm	NR	<p>i 61</p> <p>ii 38</p>	NR	NR
Different doses/schedules of primary taxane regimens						
Paclitaxel						
SICOG 9988 (Comella, 2004)	<p>i [cis+ET q1wx12] then local surgical treatment</p> <p>ii [ET q3wx4] then local surgical treatment</p>	T4 and/or N3 <=70 yrs	NR	NR	NR	NR
Stearns, 2003	<p>i [A q2wx3] then [T q2wx3] then local surgical treatment then CT then hormone therapy then radiotherapy</p> <p>ii [T q2wx3] then [A q2wx3] then local surgical treatment then CT then hormone therapy then radiotherapy</p>	T3-4 Stage IIIa: 48% Stage IIIb: 35% Stage IV: 17%	24	44	NR	NR
AGO (Untch, 2002)	i [Eq2wx3] then [T q2wx3] then local surgical treatment then [CMF q4wx3+radiotherap	T>3 cm or inflammatory	NR	<p>i 66</p> <p>ii 55</p> <p>p<0.0</p>	NR	NR

	y) ii [ET q3wx4] then local surgical treatment then [CMF q4wx3 +radiotherapy]			5		
Romieu, 200232a	i [AT q3wx6] then local surgical treatment ii [AT q3wx4] then local surgical treatment	T2-3,N0-1,M0 (T2: 50%, T,3: 49%, N0: 43%, N1: 57%)	NR	64	NR	NR
M.D. Anderson (Green, 2002)	i N+ [T q1w for 3wks, 1wk break x4] then [FACx4] then local surgical treatment ii N- [T wx12] then [FACx4] then local surgical treatment iii N- [T 3wx4] then [FACx4] then local surgical treatment iv N+ [T 3wx4] then [FACx4] then local surgical treatment	T1-3,N0-1,M0	NR	NR	NR	NR
Docetaxel						
ABCSG-14 (Steger, 2004)	i [ETq3wx6] then local surgical treatment ii [E+D q3wx3] then local surgical treatment	T1-4a-c, N+/- M0	NR	i 76 ii 67	NR	NR
Miller, 1999	i [AT q3wx4] then local surgical treatment ii [A q2wx3] then [T q2wx3] then local surgical treatment	>=2 cm and Stage II or III N+: 57%	i 98 ii 105	i 19 ii 37	NR	NR

Abbreviations:

A, doxorubicin; ABCSG Austrian Breast Cancer Study Group; ACCOG Anglo-Celtic Cooperative Oncology Group; AGO Arbeitsgemeinschaft Gynakologische Onkologie; C, cyclophosphamide; cis, cisplatin; cm, centimetre(s), CT, chemotherapy; D, docetaxel; E, epirubicin; ECTO European Cooperative Trial in Operable Breast Cancer; F, fluorouracil; GEPAR German Pre-operative Adriamycin Docetaxel Trial; M, methotrexate; N, vinorelbine; NR, not reported; N+, node positive; N-, node negative; NSABP National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel; Pr, prednisolone; R+, responders; R-, non-responders; SICO Southern Italy Cooperative Oncology Group; T taxane; V, vincristine-; w, wks, week(s); X, capecitabine.

Randomised controlled trials

Baldini, Gardin, Giannessi, Evangelista, Roncella, Prochilo, Collecchi, Rosso, Lionetto, Bruzzi, Mosca & Conte . Accelerated versus standard cyclophosphamide, epirubicin and 5-fluorouracil or cyclophosphamide, methotrexate and 5-fluorouracil: a randomized phase III trial in locally advanced breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 14[2], 227-232. 2003.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 +
Country: Italy, setting: Secondary care

Inclusion criteria

150 patients with histologically documented stage IIIA/B breast cancer [including ipsilateral supraclavicular metastases], no distant disease, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and normal baseline organ function blood tests. Patients were treated between June 1992 and March 1997.

Stage IIIA: 19 (Group A) 15 (Group B)
Stage IIIB: 37 (Group A) 34 (Group B)
IBC: 18 (Group A) 18 (Group B)

Exclusion criteria

Four of 150 patients were ineligible: one in arm A (metastatic disease) and three in arm B (two metastatic disease and one stage IIB).

Population

number of patients = 150, age range 30 to 70 years, median age = 51 years.

Interventions

Aim: to examine the effect of accelerated primary chemotherapy on the rate of pathological complete response in patients with locally advanced breast cancer.

Patients were randomised as follows:

Arm A (standard treatment; n=76). Both primary and adjuvant chemotherapy were given at 3-week intervals. Patients received three courses of primary CEF (cyclophosphamide 600 mg/m², epirubicin 60 mg/m² and 5-fluorouracil 600 mg/m², day 1), followed by local therapy (surgery or radiotherapy) and subsequent adjuvant chemotherapy consisting in one course of CEF alternated with one course of CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m², day 1) for a total

of six courses.

Arm B (dose-dense treatment; n=70). Both primary and adjuvant chemotherapy were given at 2-week intervals. Patients received three courses of primary CEF plus GM-CSF (300 micrograms total dose subcutaneously days 4-13), followed by local therapy and subsequent adjuvant chemotherapy consisting in one course of CEF plus GM-CSF alternated with one course of CMF plus GMCSF for a total of six courses. Doses of drugs were the same in both arms.

In cases of clinical remission or stable disease, with operable lesions, patients underwent surgery (radical mastectomy or segmental mastectomy with axillary node dissection) within 3 weeks after the completion of induction chemotherapy (ICT). Inoperable cases or patients refusing surgery (with no evidence of distant metastasis) received radiotherapy.

At the end of adjuvant chemotherapy (ACT), in both arms, patients with T4 tumours received radiotherapy for a total dose of 50-60 Gy to the breast or chest wall, internal mammary lymph nodes and supraclavicular fossa. Patients with hormonal receptor-positive tumours received tamoxifen for 5 years.

Outcomes

Chemotherapy toxicity (not cited)

Primary outcome: clinical complete response (cCR): complete disappearance of the tumour mass and adenopathy; Other categories of response:

Partial response (PR): >50% reduction in the product of the two largest perpendicular diameters of the breast mass and adenopathy;

Stable disease (SD), <50% reduction in the product of the two largest perpendicular dimensions of the breast mass and adenopathy.

Progressive disease (PD): >25% increase in the sum of the products of the two perpendicular diameters of all measurable lesions, or the appearance of new lesions or distant metastases

Pathological complete response (pCR): no residual invasive tumour in the breast and axillary nodes (includes DCIS, N0; excludes any cases of positive axillary nodes).

Disease-free survival (DFS): from the date of complete response (whether this was achieved with chemotherapy or surgery) to first relapse or last observation/death.

Progression-free survival (PFS): from the date of randomisation to evidence of relapse or last observation/death.

Overall survival (OS): from the date of randomisation to death or last observation

relapse or last observation/death

Follow up

Time-to-event outcomes reported at 5 years (range 1-96 months)

Results

Response to primary chemotherapy

The overall response rate to primary CEF was 62.3% (95% CI 51% to 73%) in arm A and 61.6% (95% CI 49% to 73%) in arm B; two cCRs were obtained in arm A and one in arm B.

Twenty-six (33.8%) and 24 (32.9%) stabilizations were reported in arms A and B, respectively. Seven patients were not evaluable for response: two patients were missing data and one was ineligible in arm A; one patient was missing data and three were ineligible in arm B. No patient progressed during induction chemotherapy.

Two pCRs (2.6%) (95% CI 0.32% to 9.07%) were observed in arm A and three (4.1%) (95% CI 0.86% to 11.5%) in arm B ($P = 0.95$); three additional patients in arm B achieved a primary tumour pCR only (no invasive breast tumour with positive axillary nodes).

Surgery and radiotherapy

Local treatments were as follows: radical mastectomy, 65 (84.4%) patients in arm A and 60 (82.2%) patients in arm B; conservative surgery, five (6.5%) patients in arm A and seven (9.6%) patients in arm B; radiotherapy alone, six (7.8%) and five (6.8%) patients in arms A and B, respectively.

After primary CEF and loco-regional therapy 137 of 150 patients (91%) were disease-free: subsequent adjuvant chemotherapy was completed, as planned, for 63 patients (81.8%) in arm A and 60 patients (82.1%) in arm B. Main reasons for earlier discontinuation was patient refusal (arm A, 12 patients and arm B, 9 patients).

Recurrence and survival

Five year disease-free survival rates were 48% and 60% in arms A and B, respectively ($P = 0.18$); 5-year progression-free survivals were 52% in the standard arm and 56% in the experimental arm ($P = 0.3$) while 5-year overall survival rates were 52% and 54% in arms A and B, respectively ($P = 0.64$).

General comments

Centralised randomisation: stratified by participating institutions.

The randomised groups were visibly well-balanced for patient/tumour characteristics.

Power calculation performed. No mention of blinding to allocated treatment or

analysis by intention-to-treat; 4 patients with ineligible disease stage excluded after randomisation.

Buchholz, Strom, Oswald, Perkins, Oh, Domain, Yu, Woodward, Tereffe, Singletary, Thomas, Buzdar, Hortobagyi & McNeese . Fifteen-year results of a randomized prospective trial of hyperfractionated chest wall irradiation versus once-daily chest wall irradiation after chemotherapy and mastectomy for patients with locally advanced noninflammatory breast cancer. *Int.J.Radiat.Oncol.Biol.Phys.* 65[4], 1155-1160. 2006.

Design

RCT (therapy), evidence level: 1 -
Country: USA, setting: Secondary care

Inclusion criteria

108 patients with stage III histologically proven breast cancer who underwent randomisation to one of two radiotherapy regimens between the years 1985-1989.

Initial stage:

IIB: 39 (19.5%)

IIIA: 87 (43.5%)

IIIB: 58 (29%)

IIIC: 13 (6.5%)

Other: 4 (2%)

Exclusion criteria

Congestive heart failure
Abnormal blood markers for systemic disease

NB published results exclude patients who did not respond to initial primary chemotherapy.

Population

number of patients = 179, age range 15 to 75 years.

Interventions

Aim: to investigate whether hyperfractionated chest wall RT is safe for patients treated with primary chemotherapy, mastectomy and adjuvant chemotherapy for locally advanced breast cancer.

200 patients were treated with primary chemotherapy (vincristine, doxorubicin, cyclophosphamide and prednisolone (VACP) in 3 cycles).

Patients who responded (no definition provided) underwent mastectomy.

Patients with $\geq 1\text{cm}^3$ residual tumour underwent randomisation to one of two

adjuvant chemotherapy regimens (either continued VACP until 500 mcg/m² of doxorubicin attained or 6 cycles of a regimen of methotrexate, 5-fluorouracil, leukovorin and vinblastine). Patients with residual tumour of size <1cm³ continued VACP until 500 mcg/m² of doxorubicin was attained.

Patients were also offered randomisation to one of two adjuvant chest wall and supraclavicular fossa radiotherapy regimens as follows:

Standard radiotherapy group: received 60Gy in 30 fractions, once daily (2Gy) to the chest wall and 50Gy in 25 fractions once daily (2Gy) to the supraclavicular fossa

Hyperfractionated radiotherapy group: received 72Gy in 60 fractions twice daily (1.2Gy) to the chest wall and 50Gy in 25 fractions once daily (2Gy) to the supraclavicular fossa.

Outcomes

Locoregional recurrence-free survival (Kaplan-Meier method)

Overall survival (Kaplan-Meier method)

Late toxicity (Kaplan-Meier method)

Acute toxicity (crude rate)

Follow up

Estimated 15-year rates of outcome presented.

Results

Non-response rate to primary chemotherapy = 21/200 = 10.5% (no definition of 'response' reported).

15-year estimated rate of locoregional recurrence-free survival:

Standard radiotherapy group: 7%

Hyperfractionated radiotherapy group: 12% (p=0.36, log-rank test)

15-year estimated rate of overall survival:

Standard radiotherapy group: 45%

Hyperfractionated radiotherapy group: 33% (p=0.54, log-rank test)

15-year estimated rate of moderate-to-severe late toxicity, potentially related to radiotherapy:

Standard radiotherapy group: 6%

Hyperfractionated radiotherapy group: 11% (p=0.54, log-rank test)

The crude rate of severe acute toxicity was similar between randomised arms:

Standard radiotherapy group: 4%

Hyperfractionated radiotherapy group: 5% (no p value reported).

Authors conclude that no benefit was achieved through the hyperfractionated

radiotherapy regimen.

General comments

The distribution of patients within the radiotherapy randomised comparison by randomised group for comparison of adjuvant chemotherapy is not known. Patients were similar in terms of many patient/disease-related variables (by statistical testing), but adjuvant chemotherapy group was not one of the factors investigated for similarity, and may confound the results. Reportedly, outcomes did not differ according to the allocated adjuvant chemotherapy (results published separately).

Assessment of outcome was in part retrospective, by review of medical records (re: acute and late toxicity attributed to radiotherapy). For this reason it is difficult to correctly define an adverse effect from radiotherapy. Study was not blinded.

Analysis was by intention-to-treat; one patient switched from the hyperfractionated arm to the standard arm; 2 patients in the standard arm ceased radiotherapy due to distant metastases; 1 patient in the hyperfractionated arm switched to a palliative dose due to local recurrence.

Power calculation related to assessment of effect of adjuvant chemotherapy, not adjuvant radiotherapy.

The role of the subgroup of patients with residual tumour of size $<1\text{cm}^3$ after mastectomy who were non-randomly allocated to continue VACP until 500 mcg/m² of doxorubicin was attained, is not clear.

Evans, Yellowlees, Foster, Earl, Cameron, Hutcheon, Coleman, Perren, Gallagher, Quigley, Crown, Jones, Highley, Leonard & Mansi . Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: an anglo-celtic cooperative oncology group study. J.Clin.Oncol. 23[13], 2988-2995. 2005.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 +
Country: Europe, setting: Tertiary care

Inclusion criteria

363 women with histologically proven (core biopsy) breast cancer with large primary (>3 cm) tumours, inflammatory breast cancer, or locally advanced disease who were considered to be candidates for primary chemotherapy before surgical intervention. All patients were required to have adequate performance status (Eastern Cooperative Oncology Group performance status ≤ 1); adequate hematologic, renal and liver function; and to have no evidence of metastatic disease.

Patients were treated between 1999 and 2001 in 25 centers in the United Kingdom, Ireland, and Belgium.

Table: tumour operability (pre-primary chemotherapy)

Subgroup	AC (n=180)	AD (n=183)	All patients (n=363)
Operable by mastectomy	140 (78%)	140 (77%)	280 (77%)
Inflammatory breast cancer	26 (14%)	28 (15%)	54 (15%)
Locally advanced tumour	14 (8%)	15 (8%)	29 (8%)

Exclusion criteria

Patients were excluded from the study if there was any evidence of active cardiac disease, prior history of malignancy other than basal cell carcinoma of the skin, or in situ cancer of the cervix.

Population

number of patients = 363, age range 25 to 74 years, median age = 48 years.

Interventions

Aim: to compare two combinations of primary chemotherapy drugs in patients with large or locally advanced breast cancer tumours.

AC group (n=180): received doxorubicin and cyclophosphamide as primary chemotherapy

AD group (n=183): received doxorubicin and docetaxel as primary chemotherapy plus dexamethasone and prophylactic ciprofloxacin.

In both arms on completion of chemotherapy, surgery was intended, including axillary node dissection, with the choice of surgical procedure for local control of the primary breast lesion at the discretion of the surgeons at the participating centers:

Table: interventions

Treatment	AC (n=180)	AD (n=183)	All patients (n=363)
BCS	36 (20%)	37 (20%)	73 (20%)
Mastectomy	136 (76%)	133 (73%)	269 (74%)
RT	148 (82%)	143 (78%)	291 (80%)
Endocrine therapy	106 (59%)	121 (66%)	227 (63%)

NB not all patients received surgery.

Postoperative radiotherapy and tamoxifen were administered according to existing management guidelines. Some patients received conventional-dose chemotherapy (six cycles of cyclophosphamide, methotrexate, and fluorouracil) or high-dose chemotherapy with peripheral stem-cell support as part of a different study.

Outcomes

Relapse-free survival

Overall survival

(Kaplan-Meier survival analysis and log-rank test)

Follow up

Median 32 months

Results

Table: disease-related events (median follow-up 32 months)

Event	AC (n=180)			AD (n=183)			All patients (n=363)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Recurrence	55	30.6%	24%-37%	45	24.6%	18%-31%	100	27.5%	23.2%-32.4%
Distant recurrence	36	20%	14%-26%	26	14%	9%-19%	62	17.1%	13.6%-21.3%

Death	28	16%	10%- 21%	25	14%	9% to 19%	53	14.6%	11.3%- 18.6%
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There was no significant difference in the recurrence-free survival ($p=0.17$) or in overall survival ($p=0.57$) between the two groups, although authors acknowledge that follow-up is immature.

Table: recurrence by site

Site of relapse	AC (n=55)	AD (n=45)	All patients (n=100)
Local relapse only	14	17	31
Contralateral breast cancer	1	0	1
Local + distant recurrence	10	7	17
Distant recurrence only	26	19	45
Site of distant relapse	AC (n=36)	AD (n=26)	All patients (n=62)
Bone	13	9	22
Liver	5	7	12
Lung	4	8	12
Pleura	5	0	5
Other	10	4	14

Summary: 363 patients with breast cancer with large primary (>3 cm) tumours, inflammatory breast cancer, or locally advanced disease received primary chemotherapy with either AC or AD regimens. 74% of patients underwent subsequent mastectomy, 20% BCS, 80% RT and 63% endocrine therapy. In all patients at a median follow-up of 32 months the rate of recurrence was 27.5% (95% CI 23.2%-32.4%) and the mortality rate was 14.6% (95% CI 11.3%-18.6%).

General comments

Applicability to this question is limited since only 23% of patients had locally advanced or inflammatory breast cancer.

Randomisation was stratified according to tumour operability at baseline and participating centre. Baseline characteristics were well balanced between randomised arms (tabulated data).

Data collection was performed by statistical staff, not investigators, but the study does not specify concealment of allocation nor blinding to allocation.

6 patients (1.9%) were withdrawn from the study; 5 due to chemotherapy toxicity and one due to protocol violation.

Analysis was by intention-to-treat.

Tan, Cheung, Willsher, Blamey, Chan & Robertson . Locally advanced primary breast cancer: medium-term results of a randomised trial of multimodal therapy versus initial hormone therapy. Eur.J.Cancer 37[18], 2331-2338. 2001.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 +
Country: UK, setting: Tertiary care

Inclusion criteria

108 patients with locally advanced primary breast cancer (i.e. T size \geq 5cm, inflammatory breast cancer and/or with skin involvement or chest wall/axillary node fixity but with no distant metastases), treated between January 1989 and December 1994.

Table: patient characteristics

Variable	Primary hormone therapy	Multimodal therapy
n	52	56
Median age (range) (years)	62 (36-73)	58 (32-71)
Mean T size	6.2 cm	6.5 cm
Inflammatory breast cancer	6 (12%)	5 (9%)
T2, N2 tumour	12 (23%)	7 (13%)
T3 tumour	34 (64%)	44 (79%)

Exclusion criteria

Not reported; defined by inclusion criteria

Population

number of patients = 108, age range 32 to 73 years.

Interventions

Aim: to compare, in patients with locally advanced/inflammatory breast cancer, primary hormone therapy with multimodal therapy consisting of primary chemotherapy, Patey mastectomy, post-operative radiotherapy and adjuvant hormone therapy.

Patients were randomised to two groups:

1. Primary hormone therapy (n=52): treated as follows:

Post-menopausal patients (n=45): tamoxifen i.e. sole hormone therapy

Pre-menopausal patients (n=7): tamoxifen plus goserelin i.e. sole hormone therapy

On discovery of progressive disease (PD): hormone therapy ceased; and either surgery, RT, or adjuvant chemotherapy given.

On discovery of further PD: the next appropriate therapy was given.

NB one treatment modality was given at a time

2. Multimodal therapy group (n=56): treated as follows:

Primary chemotherapy with mitoxantrone, methotrexate and mitomycin (n=55); followed by either breast RT (n=2) or Patey mastectomy (n=53) followed by RT: 40 Gy to the chest wall (n=50) and hormone therapy (n=53): tamoxifen for post-menopausal patients and tamoxifen plus goserelin for pre-menopausal patients.

On discovery of locoregional failure or distant metastases, the most appropriate treatment was given.

Outcomes

Initial response to primary chemotherapy

Locoregional failure

Distant metastasis

Overall survival

Follow up

Median (range):

Primary hormone therapy: 45 (7-113) months

Multimodal therapy: 52 (6-120) months

Results

NB Results are cited for multimodal therapy arm only.

Initial response to primary chemotherapy:

Complete response: 5 (9%)

Partial response: 26 (47%)

Stable disease: 22 (40%)

Progressive disease: 2 (4%)

Recurrence and survival:

Estimated 5-year proportion of patients free of locoregional failure: 74%

Estimated 5-year proportion of patients free of distant metastasis: 50%

Estimated 5-year overall survival: 50%

General comments

Only the multimodal therapy arm of this RCT is applicable to this question.

1 patient in the multimodal therapy arm refused primary chemotherapy, surgery and RT and received Megestrol acetate.

Analysis appears to be by intention-to-treat; patients who refused particular therapies are reported, and 100% of randomised patients completed the trial. The authors acknowledge that no prospective power calculation was performed, and that the sample size is small, and that the rates of late-occurring events are based on small numbers.

Patient/investigator blinding not reported, but unlikely to be feasible due to multimodal nature of therapy.

Patients were randomised irrespective of ER status, which was known for 103 patients.

Time-to-event outcomes are read from graphs in paper.

Veyret, Levy, Chollet, Merrouche, Roche, Kerbrat, Fumoleau, Fargeot, Clavere & Chevallier . Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: Ten-year results from the French Adjuvant Study Group GETIS 02 trial. *Cancer* 107[11], 2535-2544. 2006.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 +
Country: France, setting: Tertiary care

Inclusion criteria

120 patients with nonmetastatic, unilateral, inflammatory breast cancer, treated between February 1990 and September 1992 in 9 centres.

Exclusion criteria

Not reported

Population

number of patients = 120.

Interventions

Aim: to evaluate the role of G-CSF to support patients with inflammatory breast cancer who receive high dose primary chemotherapy.

120 patients received primary chemotherapy consisting of high dose fluorouracil, epirubicin and cyclophosphamide and were randomised to receive in addition, G-CSF (n=61) or placebo (n=59).

Of the whole study population 115 patients successfully completed primary chemotherapy and 5 stopped treatment due to disease progression, toxicity or protocol violation. Thereafter 102 patients received surgery (quadrantectomy; n=27; mastectomy; n=75) and 114 patients received RT (60 Gy to the chest wall (n=112) and axilla (n=77), 50 Gy to the internal mammary chain (n=97), and 46 Gy to the supraclavicular fossa (n=107). From 4 to 6 weeks after the first irradiation, a 20-Gy boost was delivered to the breast in patients who underwent breast-conserving surgery (n=31).

109 patients received adjuvant chemotherapy consisting of standard dose fluorouracil, epirubicin and cyclophosphamide, including 83 patients before RT and 36 patients after RT. 102 patients successfully completed adjuvant chemotherapy and 7 stopped treatment due to neutropenia, infection, reduction in cardiac output, patient refusal or other reasons.

Outcomes

Response to primary chemotherapy

Disease-free survival (Kaplan-Meier method)
 Factors to predict recurrence (univariate and multivariate analysis)
 Overall survival (Kaplan-Meier method)

Follow up

Median 120 months (range 30-140 months)

Results

Overall clinical response rate to primary chemotherapy: 91.1%.
 Overall pCR rate: 14.7%.

Estimated 10-year disease-free survival: 35.7%
 Median time to recurrence: 39 months (95% CI 25-53 months)

Pattern of recurrence: local recurrence (26.3%), soft tissues (9.2%), lymph nodes (9.2%), bone (36.8%), lung (17.1%), liver (26.3%), and other sites (17.1%).

Table: rate of recurrence by locoregional treatment

Treatment	N	n (recurrence)	Rate n/N (%)
No surgery	18	10	55.6%
No mastectomy	45	15	33.3%
Breast conserving surgery	27	5	18.5%
RT only	14	12	84.6%

Among the patients who underwent modified mastectomy, 5 patients developed local chest wall recurrences (6.7%).

Sixty-eight of 76 patients (89.5%) developed recurrent disease during the first 4 years after diagnosis. In the patients who were treated according to the protocol (n=108 patients), the recurrence rate was similar between those who received maintenance chemotherapy before radiotherapy or after radiotherapy (59.8% vs. 53.8%, respectively); however, this rate increased dramatically in patients who received only radiotherapy as locoregional treatment (84.6%; table, above).

Univariate analysis for prognostic factors showed that no surgery (HR 2.02; 95% CI 1.45-2.59; p=0.01), diffuse inflammatory signs, or no pCR were correlated significantly with disease recurrence. In multivariate analysis (Cox proportional hazards model), there was no significant prognostic factor for recurrence.

Table: Prognostic Factors for Recurrence

Factor	Univariate analysis	Multivariate analysis
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	HR (95% CI)	p	HR (95% CI)	p
G-CSF (no vs. yes)	0.92 (0.47–1.37)	0.7		NS
Menopausal status (premenopausal vs. postmenopausal)	1.01 (0.55–1.47)	0.98		NS
Surgery (no vs. yes)	2.02 (1.45–2.59)	0.01	1.40 (0.00–3.48)	0.75
Quadrantectomy vs. modified mastectomy	0.58 (0.00–1.20)	0.08	1.20 (0.36–2.04)	0.67
Inflammatory signs (limited vs. diffuse)	0.48 (0.00–0.97)	0.003	0.73 (0.12–1.34)	0.31
Breast pCR (no vs. yes)	2.36 (1.68–3.04)	0.01	1.79 (0.32–3.26)	0.44
Lymph nodes pCR (no vs. yes)	2.52 (1.91–3.13)	0.003	1.93 (1.09–2.77)	0.12
Overall pCR (no vs. yes)	3.03 (2.12–3.94)	0.02	1.04 (0.00–2.89)	0.97

Seventy patients died (58.3%), and the estimated 10-year overall survival rate was 41.2%.

Median survival: 61 months (95% CI, 43-79 months).

General comments

No differences in outcome were observed for the randomised comparison; results are reported for all 120 patients together.

Analysis is by intention-to-treat.

Authors do not define criteria for pathological complete response (pCR)

Avril, Faucher, Bussieres, Stockle, Durand, Mauriac, Bonichon, Dilhuydy & Campo . [Results of 10 years of a randomized trial of neoadjuvant chemotherapy in breast cancers larger than 3 cm.]. [French]. Chirurgie 123[3], 247-256. 1998.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: France, setting: Tertiary care

Inclusion criteria

272 women of age ≤ 70 years with operable breast cancer tumours larger than 3 cm (stage T2-3/N0-1/M0) treated between January 1, 1985 to April 30, 1989.

Table: distribution of disease stage:

Stage	Group A (n=136)	Group B (n=134)
T2	119	106
T3	19	29
N0	56	64

Mean tumour diameter: 43mm

Exclusion criteria

Age > 70 years, bilateral cancer, other associated cancer, Also patients were excluded from analysis due to refusal of treatment, or contraindication of treatment e.g. poor anaesthetic risk.

Population

number of patients = 272.

Interventions

Aim: to evaluate the use of neo-adjuvant chemotherapy in patients with operable breast cancers of T size > 3 cm.

Group A (n = 138): received mastectomy and axillary node dissection. Adjuvant chemotherapy (3 cycles of epirubicine, vincristine and methotrexate followed by 3 cycles of mitomycine, thiotepa and vindesine) was indicated for 104 patients with axillary node involvement (n = 82) or negative oestrogen and progesterone receptors (n = 22).

Group B (n = 134): received primary chemotherapy (identical regimen as in group A) followed by locoregional treatment according to the response: RT alone in cases of complete tumour remission (n=44), BCS + RT in cases of residual tumour ≤ 2 cm in size (n=40) and mastectomy in cases of residual tumour > 2 cm in size (n=49).

Outcomes

Locoregional recurrence
Recurrence-free survival
Overall survival

Follow up

Median 124 months (range 87-148 months)

Results

In group B (primary chemotherapy), 49 patients (36.5%) were resistant to chemotherapy, warranting mastectomy. In the remaining 84 patients BCS was performed (62.6%). In this last subgroup, 19 (22.6%) needed a secondary mastectomy because of locoregional recurrence.

Table: 10-year crude data for recurrence:

Recurrence type	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
Locoregional recurrence alone	1	14
Locoregional and distant recurrence	19	27
Distant recurrence alone	37	26

Table: estimated overall survival:

Analysis point	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
5-year	80%	80%
10-year	60%	60%

Table: estimated recurrence-free survival:

Analysis point	Group A (mastectomy; n=136)	Group B (primary chemotherapy; n=134)
5-year	65%	58%
10-year	57%	50%

General comments

Data extracted from English language abstract and French language paper. Study reports survival analysis by Kaplan-Meier, but reports no p values for differences in survival between randomised groups. Study has limited applicability to this question since not all patients had stage III disease (see

stage data in 'inclusion criteria').

Randomisation was stratified by ER-PR status.

Cocconi, di, Bisagni, Alberti, Botti & Anghinoni . Neoadjuvant chemotherapy or chemotherapy and endocrine therapy in locally advanced breast carcinoma. A prospective, randomized study. Am.J.Clin.Oncol. 13[3], 226-232. 1990.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: Italy, setting: Secondary care

Inclusion criteria

49 patients with locally advanced (T3b-T4; any T,N2; M0) breast cancer, treated within the years 1978-1983 with disease characteristics as follows:

Table: patient characteristics

Factor	CMF group	CMF + T group
Stage		
T2-3a	1	2
T3b	5	5
T4a, b, c	16	16
T4 inflammatory	2	2
N2	6	6
ER status		
Unknown	7	5
Known	17	20
ER+	13	12
ER-	4	8

Exclusion criteria

Patients with clinical stage N3 supraclavicular nodes or positive bone scans.

Population

, age range 41 to 76 years.

Interventions

Aim: to compare the efficacy of two treatment regimens in patients with locally advanced breast cancer, as follows:

CMF group (n= 24): received four courses of primary cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy, followed by mastectomy and then four courses of the same chemotherapy in the adjuvant setting, then adjuvant RT.

CMF + T group (n= 25): received four courses of primary CMF chemotherapy with concurrent tamoxifen, followed by mastectomy and then four courses of the same chemotherapy/hormone therapy in the adjuvant setting, then

adjuvant RT.. Tamoxifen was ceased at the end of the adjuvant regime.

Outcomes

Adherence to primary chemotherapy regime (all 8 cycles)
Response to primary chemotherapy (see reference below);
Median time to progression or recurrence (from initiation of primary chemotherapy)
Median overall survival
Median survival from time progression or recurrence

Follow up

Median 6 years

Results

Adherence to primary chemotherapy regime (all 8 cycles):
CMF: 21/24 = 87.5%
CMF+T: 20/25 = 80%

Table: response to primary chemotherapy

Response	CMF (n=24)	CMF+T (n=25)
Progression	2	1
No change	5	8
Partial remission	16	13
Complete remission	1	3
Complete and partial remission	17	16

Median time to progression or recurrence (from initiation of primary chemotherapy, months)
CMF: 58.3
CMF+T: 29.1 (p=0.38, Cox-Mantel test)

Median overall survival (months)
CMF: 79.7
CMF+T: 41.5 (p=0.05, Cox-Mantel test)

Median survival from time progression or recurrence (months)
CMF: 17.3
CMF+T: 7.5 (p=0.09, Cox-Mantel test)

General comments

Response to primary chemotherapy was assessed according to the UICC criteria reported in: Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer: a project of the Programme on Clinical Oncology of the International Union Against Cancer, Geneva, Switzerland. Cancer. 1977

Mar;39(3):1289-94. No abstract available.

ER testing was not consistently available during this study; the authors report the limitation that they'd have preferred to exclude patients with ER- tumours. There were slightly more patients with ER- tumours in the CMF+T group.

Randomisation method: randomly permuted blocks of three with stratification for T stage (any T versus inflammatory breast cancer), node stage (N0-1b versus N2) and menopausal status (premenopausal versus postmenopausal <5 years versus post menopausal \geq 5 years)

Wording of paper is ambiguous on whether all patients underwent mastectomy, or only those who responded to primary chemotherapy. On balance it appears that all patients underwent mastectomy.

Analysis appears to be by intention-to-treat, but the study is neither blinded, nor placebo-controlled. The study is further limited by small size; the study was stopped prior to the target accrual point of 130 patients in total owing to less favourable outcome in the CMF+T arm.

Pouillart, Palangie, Jouve, Garcia-Giralt, Vilcoq, Bataini, Calle, Fenton, Mathieu, Rousseau & Asselain . [Inflammatory breast carcinoma treated with a combination of chemotherapy and radiation therapy. Results of a randomized trial studying the therapeutic role of an immunotherapy with BCG (author's transl)]. [French]. Bull.Cancer (Paris) 68[2], 171-186. 1981.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: France, setting: Tertiary care

Inclusion criteria

77 patients with either primary (n=41) or secondary (n=36) inflammatory breast carcinoma treated between march 1977 and september 1979.

Nodal stage:

N0-N1a: 14

N1b-N2: 46

N3: 17

Hormone receptor status (known for 31 patients):

ER+PR+: 2

ER+PR-: 1

ER-PR+: 1

ER-PR-: 27

Exclusion criteria

Not known

Population

number of patients = 77, age range 25 to 70 years, median age = 49 years.

Interventions

All patients were treated with the same primary chemotherapy (adriamycin, vincristine, cyclophosphamide and 5-fluorouracil (AVCF)) plus RT (70 Gy over 7 weeks) schedule. Each course of chemotherapy was repeated every 28 days for one year. Patients were then given a maintenance course of chemotherapy for one year (cyclophosphamide, melphalan and methotrexate). Patients were randomised as follows:

Group 1 (n=36): patients received chemotherapy and RT alone

Group 2 (n=41): patients received chemotherapy and RT plus live BCG vaccinations.

Outcomes

Actuarial disease-free and overall survival

Follow up

Maximum: 36 months; median: not known.

Results

Table: objective response to treatment

Response	No.	%
Initial response to chemotherapy		
Complete regression of inflammatory disease	29	51
Partial regression of inflammatory disease	18	31.5
Persistence/progression of inflammatory disease	10	17.5
Total evaluable	57	100
Response to chemotherapy + RT		
Complete regression of tumour	38	50.6
Tumour remaining	37	49.4
Total evaluable	75	100

In all patients actuarial survival at 34 months follow-up was 50% (i.e. mean overall survival 34 months), with no statistically significant difference between randomised arms. There was a statistically significant difference in actuarial survival according to initial response to chemotherapy, with longest survival in the complete response subgroup and shortest survival in the persistence/progression group ($p=0.002$; no further data reported). In all patients mean disease-free survival was 26 months.

General comments

Data extracted from French language paper and English language abstract; some detail may be lost. It is difficult to determine whether this trial was blinded or had concealment of allocation or analysis by intention-to-treat. Median follow-up not known. Study has small size, with no apparent power calculation.

Rainer, Denck, Fritsch, Spitzky, Alth, Dinstl, Depisch, Haider, Jakesz, Kolb, Mader, Reiner, Schennach, Schuller, Smola, Steger, Steindorfer, Tuchmann & Wildauer . Prospective randomized clinical trial of primary treatment in breast cancer stages T3/4, N+/-, MO: Chemotherapy vs. radiotherapy. Anticancer Res. 13[5 C], 1917-1923. 1993.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: Austria, setting: Tertiary care

Inclusion criteria

151 patients with T3/4, N+/-, M0 locally advanced breast cancer, treated in 52 centres.

Exclusion criteria

31 patients with inflammatory breast cancer (not included in survival analysis, since these patients were non-randomly allocated to the chemotherapy arm)

Population

number of patients = 151.

Interventions

The RCT compared two treatment regimens as follows:

Primary chemotherapy group (n=76): received primary chemotherapy comprising fluorouracil, methotrexate, cyclophosphamide, vincristine and mitoxantrone; followed by mastectomy; followed by the same regimen of chemotherapy as adjuvant therapy.

Primary RT group (n=75): received 40Gy RT as primary therapy; followed by mastectomy; followed by 20Gy RT as adjuvant therapy.

Outcomes

Rates of delayed mastectomy wound healing
Relapse-free survival
Overall survival

Follow up

Data are based on 1900 days of study enrollment; i.e. maximum follow-up of 5.2 years.

Results

29/76=38% of patients in the primary chemotherapy group did not respond to primary chemotherapy and following mastectomy were crossed over to adjuvant RT instead of adjuvant chemotherapy, as permitted in the study

protocol.

Rates of delayed mastectomy wound healing:

Chemotherapy group: 36%

RT group: 47%

Median relapse-free survival:

Chemotherapy group: 2.9 years

RT group: 2.4 years

Over the entire follow-up period, relapse free survival was statistically significantly better in the chemotherapy group than the RT group ($p=0.018$).

Overall survival:

In the chemotherapy group, the median overall survival was not reached; 3-year estimated overall survival in the chemotherapy group was 70%, and in the RT group, 56%.

Over the entire follow-up period, overall survival was statistically significantly better in the chemotherapy group than the RT group ($p=0.047$).

General comments

Paper reports poorly the number of included/excluded patients.

Randomisation was stratified according to patient age, tumour size, localisation and lymph node involvement.

The two groups were comparable with regard to patient/tumour variables; statistically tested (although only data from the chemotherapy arm inform this question).

Study does not report whether there was concealment of allocation, blinding of subjects or investigators, analysis by intention-to-treat, nor whether patients dropped out of the study.

Scholl, Asselain, Palangie, Dorval, Jouve, Garcia, Vilcoq, Durand & Pouillart . Neoadjuvant chemotherapy in operable breast cancer. Eur.J.Cancer 27[12], 1668-1671. 1991.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: France, setting: Tertiary care

Inclusion criteria

196 patients with T2-3, N0-1b operable breast cancer treated within the period: November 1983 to March 1986.

Table: disease stage

Stage	Primary chemotherapy group (n=95)		Adjuvant chemotherapy group (n=86)	
	n	%	n	%
T2 N0	0	0%	3	3%
T2 N1b	43	45%	26	30%
T3 N0	24	23%	24	28%
T3 N1b	28	29%	33	38%
Total	95	100%	86	100%

Mean T size:

Primary chemotherapy group: 5.4 cm

Adjuvant chemotherapy group: 5.0 cm

Exclusion criteria

Prior cancer;

Concomitant serious illness;

Age >65 years.

15 patients were excluded after randomisation due to randomisation errors, poor compliance or receipt of treatment in a non-participating centre.

Population

number of patients = 181.

Interventions

Aim: to compare the effects of two treatment strategies: one based on primary chemotherapy and the other based on primary RT with adjuvant chemotherapy.

Primary chemotherapy group (n=100): received 2 cycles of doxorubicin, cyclophosphamide and fluorouracil (ACF), followed by assesment of tumour response and locoregional treatment (see below). Patients with a good initial response to primary chemotherapy received adjuvant chemotherapy consisting of 4 further cycles of ACF, whereas patients with a poor response received 4 cycles of doxorubicin, methotrexate, vindesine and thiotepa as adjuvant chemotherapy

Adjuvant chemotherapy group (n=96): received locoregional treatment (see below) followed by 6 cycles of ACF as adjuvant chemotherapy.

All patients received steroid drugs.

Table: locoregional treatment:

Treatment	Primary chemotherapy group (n=95)		Adjuvant chemotherapy group (not applicable; n=86)	
	n	%	n	%
Mastectomy	22	23%	31	36%
Lumpectomy	32	34%	26	30%
No surgery	41	43%	29	34%
RT	95	100%	86	100%

RT consisted of 55Gy to the whole breast with boost to the tumour bed to make a total dose of 75-80Gy. 45-55Gy were applied to the node bearing tissues.

In the primary chemotherpay group, only patients with residual tumour after primary chemotherapy underwent surgery, with surgical procedure determined according to individual patients' needs.

Outcomes

Local recurrence (defined as tumour presence at or after 9 months from the start of treatment, because not all patients underwent surgery)

Disease-free survival

Follow up

Median 54 months (range 35-70 months).

Two patients were lost to follow-up at 35 and 38 months

Results

Local recurrence rate in all patients in the primary chemotherapy arm at a median follow-up of 54 months: 18%.

In the subgroup of patients within the primary chemotherapy arm who completed all planned chemotherapy (n=77; 81% of the randomised arm) disease-free survival at 36 months follow-up was as follows:
80% in patients with >50% tumour regression when assessed after 2 cycles of primary chemotherapy;
68% in patients with ≤ 50% tumour regression when assessed after 2 cycles of primary chemotherapy (figures read from chart).
This difference by tumour response was not statistically significant over the entire follow-up period (median 54 months; p=0.058).
No data are available for patients randomised to primary chemotherapy, but who ceased treatment (e.g. due to stage N0 nodes, or toxicity).

General comments

Only results from the primary chemotherapy group are applicable to this question.

All patients had RT, but surgery is considered by the authors as an outcome (BCS rate) and is not a randomised treatment.

The disease-free survival result reported for the primary chemotherapy arm is based only on patients who completed all chemotherapy (i.e. not an intention-to-treat analysis).

In all patients in either group with N0 status revealed by surgery, any chemotherapy was discontinued. This occurred in 18 patients in the primary chemotherapy group and 21 patients in the adjuvant chemotherapy group.

No mention of randomisation method or blinding. Not all analyses are by intention to treat.

Willsher, Robertson, Chan, Jackson & Blamey . Locally advanced breast cancer: early results of a randomised trial of multimodal therapy versus initial hormone therapy. *European journal of cancer* (Oxford, England.: 33[1], 45-49. 1990.

Design

Design: Randomized controlled trial (therapy), evidence level: 1 -
Country: UK, setting: Tertiary care

Inclusion criteria

108 patients with locally advanced breast cancer treated between January 1989 and December 1994. Locally advanced breast cancer was defined as T size > 5cm or gross skin involvement, chest wall fixity or fixed axillary nodes.

Mean maximal diameter of primary tumour (primary chemotherapy arm): 6.5cm

Exclusion criteria

Not reported.

Population

number of patients = 55.

Interventions

Aim: to compare two treatment strategies for patients with locally advanced breast cancer as follows:

1. Minimal therapy arm (n=53): received initial hormone therapy (tamoxifen +/- goserelin) with assessment of response after 6 months of treatment; patients continued with hormone therapy until evidence of recurrence emerged. At recurrence, therapy was chosen by clinicians and patients and included RT (n=24), hormone therapy (n=18), mastectomy (n=9), chemotherapy (n=7) and excision of local recurrence (n=2).

Multimodal therapy arm (n=55): received four cycles of primary chemotherapy with mitoxantrone, methotrexate and mitomycin. Patients were then assessed for response. Subsequent therapy consisted of mastectomy (n=52) and 40 Gy RT to the chest wall in 15 fractions (n=49). All patients who underwent mastectomy received adjuvant tamoxifen (n=52) and in 10 cases, goserelin.

Outcomes

Response to primary chemotherapy (assessed after 6 months) defined as:

Complete response: resolution of tumour;

Partial response: >50% reduction in bidimensional product of tumour;

Static disease: <50% reduction, or <25% increase in bidimensional product of tumour;

Progressive disease: >25% increase in bidimensional product of tumour.

Rate of distant metastases, locoregional recurrence, survival.

Follow up

Median 30 months

Results

All cited results are for patients in the primary chemotherapy arm

Response to primary chemotherapy (n):

Complete response: 5

Partial response: 26

Static disease: 21

Progressive disease: 2

Objective response rate (primary chemotherapy arm): $31/54 = 57\%$

Rate of distant metastases: 45%

Rate of locoregional recurrence: $12/55 = 22\%$

Rate of uncontrollable local recurrence: $2/55 = 3.6\%$

Median overall survival: 43 months.

General comments

Only data from the multimodal therapy arm (n=55) is applicable to this question; results from other arm not cited.

Patients were randomised irrespective of ER status, which was not routinely assessed at enrolment.

Small trial, with no reporting of blinding (unlikely to be feasible); adherence to planned therapy reported, analysis appears to be by intention-to-treat (not reported).

Systematic reviews of combined study designs

Shenkier, Weir, Levine, Olivotto, Whelan, Reyno & Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer.[see comment]. [Review] [73 refs]. CMAJ.Canadian.Medical.Association.Journal 170[6], 983-994. 2004.

Design

Design: Systematic review of combined study designs (therapy), evidence level: 2 +

Country: Canada, setting: Tertiary care

Inclusion criteria

Studies of patients with locally advanced breast cancer (LABC), considered stage III disease, defined as:

1. large breast tumours (> 5 cm in diameter) associated with either skin or chest-wall involvement or with fixed (matted) axillary lymph nodes or with disease spread to the ipsilateral internal mammary or supraclavicular nodes.
2. Inflammatory breast cancer

Exclusion criteria

Not made explicit: all identified, English language studies were included, but also relevant non-randomised studies, as reflects the nature of the evidence base.

Population

-

Interventions

Aim: To define the optimal treatment for women with LABC.

Treatments include primary chemotherapy and locoregional treatment (surgery and RT).

Outcomes

Locoregional control (defined as freedom from recurrence in the breast, chest wall or regional lymph nodes)

Disease-free survival (DFS; defined as survival free of breast cancer recurrence)

Overall survival (OS).

Follow up

Not reported.

Results

a) Operable tumours (NB as reported in the subsequent Cochrane Review by Mieog et al. 2007)

Data was from 1 retrospective study and 5 RCTs that compared preoperative and postoperative chemotherapy. These studies involved patients mainly with stage I or stage II disease and included a small proportion of women with tumours greater than 5 cm in diameter. No difference in DFS and OS was detected between the preoperative and postoperative chemotherapy groups. Preoperative chemotherapy often caused shrinkage of the tumour and permitted the performance of breast-conserving surgery (BCS) when a mastectomy was originally planned. However, results from 2 trials suggested that patients whose tumours were down-staged so that BCS could be performed when it was not initially planned were at higher risk of local recurrence and had worse survival (NB: in the Cochrane Review these results were not statistically significant; but may be clinically important).

b) Inoperable tumours (NB the majority of these studies were not included in the subsequent Cochrane Review by Mieog et al. 2007)

Multivariate analyses in 1 RCT and 3 observational studies have shown that the primary tumour response is correlated with patient outcome and that patients who have pathological evidence of a complete response following primary therapy have a superior DFS and OS compared with those who do not have such a response. Clinical response is seen in about 80% of patients who receive primary chemotherapy.

Three small RCTs compared mastectomy alone with locoregional RT alone following primary chemotherapy. The results of these studies suggest that both treatments are equally effective after primary chemotherapy in inoperable disease. No RCTs were found that compared mastectomy plus RT with mastectomy alone following primary chemotherapy, but 2 observational studies demonstrated that locoregional control was better if both mastectomy and RT were performed.

There was insufficient evidence on the importance of sequence of surgery and RT, or on breast conserving surgery, in patients with inoperable tumours who are treated with primary chemotherapy. No evidence was found to guide locoregional management of patients with stage IIIC disease who respond to primary chemotherapy.

General comments

The systematic review informs a Canadian clinical practice guideline. Only the findings of primary studies are cited, and not authors' recommendations for practice. Results presented as narrative. Study selection criteria and quality consideration are adequate.

Literature search strategy:

English-language literature retrieved from MEDLINE (1984 to June 2002) and CANCERLIT (1983 to June 2002). Search terms used were "breast neoplasms," "locally advanced breast cancer," "stage III breast cancer," "drug therapy," "neo-adjuvant," "primary systemic therapy," "radiotherapy or irradiation," "surgery," "randomised trials" and "high-dose therapy." A nonsystematic review of the literature was continued through December 2003. Additional data were identified by reviewing references in retrieved reports and by monitoring major conferences on breast cancer.

Study quality assessment:

A 5-level hierarchy of evidence was applied, based on: Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1989;95(Suppl):2S-4S.

Observational studies

Huang, Tucker, Strom, McNeese, Kuerer, Buzdar, Valero, Perkins, Schechter, Hunt, Sahin, Hortobagyi & Buchholz . Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy.[erratum appears in J Clin Oncol. 2005 Jan 1;23(1):248]. J.Clin.Oncol. 22[23], 4691-4699. 2004.

Design

Design: Retrospective comparative study (therapy), evidence level: 3
Country: USA, setting: Tertiary care

Inclusion criteria

676 patients with locally advanced breast cancer treated within 6 trials of doxorubicin-based primary chemotherapy between the years 1974 and 2000.

Table: clinical stage:

Clinical stage	No RT (n=134)		RT (n=542)		p
	n	%	n	%	
I	1	1	0	0	<0.001
IIA	21	16	8	1	
IIB	45	34	83	15	
IIIA	29	22	164	30	
IIIB	32	24	233	43	
IV	6	4	54	10	

Exclusion criteria

31 patients who experienced recurrence within 2 months of mastectomy or completion of adjuvant therapy (15 in the RT group and 16 in the no RT group; this was done to remove from the analysis patients who received RT due to recurrence, rather than as planned therapy).

Patients with distant metastases.

Patients treated with breast conserving surgery after primary chemotherapy.

Population

number of patients = 676.

Interventions

Aim: to retrospectively examine outcomes in patients treated for locally advanced breast cancer with primary chemotherapy and mastectomy; comparing those who received adjuvant RT with those who did not. Two groups were retrospectively defined:

1. RT group (n=542): patients received primary chemotherapy, mastectomy and RT: typically 50 Gy to chest wall/axilla with 10 Gy boost to chest wall.

2. No RT group (n=134): patients received primary chemotherapy and mastectomy.

In the whole study population primary chemotherapy was as follows:
Fluorouracil, doxorubicin and cyclophosphamide (FAC), or high-dose FAC: n=351
Vincristine, doxorubicin, cyclophosphamide and prednisolone: n=160
FAC or paclitaxel: n=101
Doxorubicin and docetaxel: n= 64

640 patients (95%) received also adjuvant chemotherapy and 233 patients (34%), tamoxifen.

Outcomes

Local recurrence rate (defined as disease recurrence on the ipsilateral chest wall or in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. Any other site of recurrence was considered distant metastasis).

Local recurrence rate as first site of failure

Overall survival

Cause-specific survival (rates estimated by Kaplan-Meier method)

Factors associated with locoregional recurrence and cause-specific survival

Follow up

Median values:

RT group: 73 months

No RT group: 66 months

All patients: 69 months

Results

10-year estimated rate of locoregional recurrence:

RT group: 11%

No RT group: 22% (p=0.0001; log-rank test)

Table: multivariate (Cox regression) analysis of factors associated with locoregional recurrence

Factor	HR	95% CI	p
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No radiation	4.68	2.70 to 8.13	<0.0001
>= 20% sampled nodes positive	3.58	2.11 to 6.08	<0.0001
Stage >= IIIB	2.38	1.42 to 4.02	0.001
No tamoxifen	2.19	1.19 to 4.06	0.012
Minimal or worse clinical response to neoadjuvant chemotherapy	1.88	1.10 to 3.23	0.021
ER negative	1.69	1.04 to 2.76	0.033
Clinical complete response	No data	No data	NS
Pathological complete response	No data	No data	NS

10-year estimated rate of overall survival:
RT group: 54%
No RT group: 47% (p=0.063; log-rank test)

10-year estimated rate of cause-specific survival:
RT group: 58%
No RT group: 55% (p=0.85; log-rank test)

Table: multivariate (Cox regression) analysis of factors associated with cause-specific survival

Factor	HR	95% CI	p
Stage >= IIIB	2.35	1.77-3.11	<0.0001
Residual tumour (positive pathology) after primary chemotherapy	2.13	1.27-3.57	0.004
No RT	2.03	1.41-2.92	<0.0001
>= 4 positive lymph nodes	1.67	1.20-2.31	0.002
Minimal or worse clinical response to neoadjuvant chemotherapy	1.62	1.21-2.17	0.001
<10 lymph nodes sampled	1.53	1.15-2.06	0.004
No tamoxifen	1.40	1.03-1.90	0.030
ER negative	1.39	1.06-1.82	0.19
Clinical complete response	No data	No data	NS
Pathological complete response	No data	No data	NS

General comments

Retrospective study with post-hoc analyses and several groups of patients excluded. Patients were not randomly allocated to RT or mastectomy, but on the basis of clinician/patient choice; the authors acknowledge this possible selection bias.

The patients with recorded stage IV disease had disease-positive

supraclavicular lymph nodes but no distant metastases.

Comparability of groups:

A greater percentage of RT group patients had more advanced clinical T-stage, clinical N-stage, combined clinical stage, poorer clinical response to primary chemotherapy, higher numbers of pathologically positive nodes and close or positive surgical margins ($p < .01$ for all comparisons). There were no differences between the two groups with respect to age, use of tamoxifen, use of adjuvant chemotherapy, pathological tumor size, number of dissected axillary nodes, or percentage of ER negative tumours.

Update Evidence

McGuire, Gonzalez-Angulo, Huang, Tucker, Kau, Yu, Strom, Oh, Woodward, Tereffe, Hunt, Keurer, Sahin, Hortobagyi, & Buchholz. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve pathological response to neoadjuvant chemotherapy.
Design: Retrospective Analysis Evidence Level: 3
Country: USA
Aim: To investigate the role of postmastectomy radiation therapy in women with breast cancer who achieved a pathological complete response to neoadjuvant chemotherapy.
Inclusion criteria Patients with primary breast cancer who had a pathologic complete response (pCR) following receipt of neoadjuvant chemotherapy. Treated with mastectomy following neoadjuvant chemotherapy.
Exclusion criteria Inflammatory breast cancer
Population N=106
Interventions Postmastectomy radiation therapy
Outcomes Rates of LRR in radiated group vs. irradiated group. Rates of LRR according to clinical and pathological factors in patients with Stage III disease. 10 year survival rates.
Results 10 year actuarial rates of LRR did not significantly differ between the irradiated and radiated

groups ($p=0.40$) despite a significantly greater percentage of patients in the irradiated group having more advanced clinical disease stages at presentation ($p<0.001$).

Radiation therapy was significantly associated with a lower 10 year rate of LRR in patients who initially presented with Stage III disease - $7.3\% \pm 3.5\%$ in the irradiated group vs. $33.3\% \pm 15.7\%$ in the non-irradiated group ($p=0.040$).

In patients presenting with Stage III disease survival rates were as follows:

10 year distant metastasis free survival (DMFS) rate was $87.9\% \pm 4.6\%$ in the irradiated group and $40.7\% \pm 15.5\%$ in the non-irradiated group ($p = 0.0006$).

10 year cause specific survival (CSS) rate was $87\% \pm 5\%$ for the irradiated group and $40\% \pm 16\%$ for the non-irradiated group ($p=0.0014$).

10 year overall survival (OS) rate was $77.3\% \pm 6\%$ for the irradiated group and $33.3\% \pm 14\%$ for the non-irradiated group ($p=0.0016$).

General comments

92% of patients received anthracycline as a component of neoadjuvant chemotherapy, 38% received a taxane either pre or post operatively.

The decision regarding whether or not to have postmastectomy radiation was made by the patient and physician.

Chapter 8 - Complications of local treatment, menopausal symptoms and psychological support

8.1 What strategies are effective in preventing lymphoedema in patients with breast cancer?

Short Summary

The quality of the evidence for this question is varied, including few randomised controlled trials (RCTs) and several observational studies. There appear to be few studies of interventions aimed to prevent lymphoedema in the population of patients with breast cancer (including patients who have received surgery and adjuvant treatment) who are at risk of developing the condition.

Evidence from recent RCTs suggests that arm or shoulder exercise interventions after surgery for breast cancer do not affect subsequent rates of lymphoedema and that their effect upon shoulder mobility is inconsistent. An earlier systematic review of studies with mixed design found that shoulder exercise therapy does improve shoulder mobility. It should be noted that there is high heterogeneity across the studies: the interventions investigated differed considerably in their design, time of commencement and intensity. Control groups were also treated differently across studies. (Bendz and Fagevik 2002; Box *et al.* 2002a, 2002b; Cave and Jones 2006; Cheema *et al.* 2008)

Evidence from one RCT and a systematic review supports the role of aerobic exercise in patients treated for breast cancer, with some demonstrable benefit in terms of shoulder mobility and quality of life, but not consistently. Evidence from observational studies suggests that aerobic exercise is beneficial both physically and in terms of psychological well being. (Karki *et al.* 2001; Lane 2005; Sandel *et al.* 2005).

There was very limited evidence for the effectiveness of cognitive-behavioural interventions and arm massage. A poor quality RCT by Forchuk *et al.* (2004) found that an intervention whereby patients' partners were instructed to perform distal-to-proximal circular arm massage had no demonstrable effect on shoulder range of motion at four months postoperatively. The intervention group experienced significantly greater arm swelling than the control group at 14 weeks and four month postoperatively. An RCT by Braden and Badger (2000) found that patients who received an intervention designed to help them manage uncertainty arising from breast cancer reported better coping with arm swelling than patients in the control group, over a seven month period of follow-up. This result should be interpreted with caution as full trial details are not currently available.

Observational evidence suggests that where information is provided to patients on lymphoedema, it is done so by different healthcare professionals, with no apparent dominant group. (Cordero *et al.* 2003; Coward 1999; Karki *et al.* 2004; Yik *et al.* 2001)

PICO

Population	Intervention	Comparison	Outcome
Patients with breast cancer who have received surgery, radiotherapy or no treatment	Any strategy with the aim of preventing lymphoedema e.g.: <ul style="list-style-type: none"> • Education • Exercise • Compression Garments • Pneumatic Devices • Skin Care • Simple Lymph drainage massage • Advice on interventions to avoid • Pharmaceuticals • Physiotherapy • Psychological support 	Any or no strategy	<ul style="list-style-type: none"> • Risk of developing lymphoedema • Incidence of lymphoedema • Measures of lymphoedema • Anxiety/Depression measures/psychological morbidity associated with lymphoedema • Subsequent use of healthcare services • Cost effectiveness

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There appear to be few studies of interventions aimed to prevent lymphoedema in the population of patients with breast cancer (including patients who have received surgery and adjuvant treatment) who are at risk of developing the condition. Some of the studies reviewed touch on wider issues in the same population i.e. interventions for earlier diagnosis, prevalence and time of onset of lymphoedema, risk factors, provision of education to patients and extent of patients' knowledge subsequently.

Applicability is reasonable since the study populations are in European or Western countries with the exception of Yik *et al.* (2000) (Hong Kong). The study by Braden and Badger (2000) specified that the population studied was Mexican American women.

In general the degree of consistency of the findings across the studies is poor for the primary focus of interventions to prevent lymphoedema. Prevalence data for lymphoedema is also very variable (as discussed below). There is high heterogeneity across the studies: the interventions investigated differed considerably in their design, time of commencement and intensity. Control groups were also treated differently across studies.

Evidence suggests that arm or shoulder exercise interventions after surgery for breast cancer do not affect subsequent rates of lymphoedema and that their effect upon shoulder mobility is inconsistent. An earlier systematic review of studies with mixed design found that shoulder exercise therapy does improve shoulder mobility.

Evidence supports the role of aerobic exercise in patients treated for breast cancer, with some demonstrable benefit in terms of shoulder mobility and quality of life, but not consistently.

Evidence suggests that where information is provided to patients on lymphoedema, it is done so by different health professionals, with no apparent dominant group

Effectiveness of interventions

Exercise/physiotherapy to the shoulder/arm

Four RCTs reviewed do not provide evidence that interventions consisting of arm/shoulder exercise or physiotherapy in patients at risk of lymphoedema affect subsequent rates of lymphoedema. Two RCTs found that such interventions improved shoulder function (Bendz and Fagevik 2002, Cave and Jones 2006) whereas the RCT by Box *et al.* (2002a, 2002b) found no significant effect in shoulder function as a result of their interventions.

- Box *et al.* (2002a and 2002b) evaluated a physiotherapy/exercise intervention initiated preoperatively and found no significant difference between intervention and control groups in rates of lymphoedema as defined *a priori*, or shoulder function at two years after surgery.
- Bendz and Fagevik (2002) evaluated a shoulder exercise programme initiated on the first post-operative day and found no significant differences in changes in arm volume between intervention and control groups at two years following surgery, nor in incidence of lymphoedema as defined *a priori*. At two years, the intervention group had significantly better shoulder mobility in two of four movements measured.
- Cave and Jones (2006) demonstrated that a shoulder physiotherapy/exercise intervention commenced at 6-8 weeks after surgery improved shoulder function at post-operative weeks 12 and 26.
- Kosir *et al.* (2002) found that an intervention consisting of structured patient education in shoulder exercises resulted in similar rates of lymphoedema compared to standard care, when assessed after 33 months of study accrual.

An earlier systematic review of 31 studies (including non randomised studies) by Karki *et al.* (2001) found no evidence that early shoulder exercise (immediately after surgery) was beneficial to delayed shoulder exercise in terms of shoulder mobility. However exercise therapy was found to improve shoulder mobility at 1-3 months post-operatively, compared to no exercise therapy.

A systematic review which included mixed study designs summarised the efficacy of prescribed progressive resistance training (PRT) following breast cancer surgery (Cheema *et al.* 2008). The included studies reported unilateral, upper extremity lymphoedema was an entry criterion and cases of lymphoedema were reported in other studies and did not preclude participation in these trials. One trial prescribed the use of compression sleeves during exercise in each enrolled participant while the use of compression sleeves was a decision made in conjunction with a lymphoedema specialist in other trials. Lymphoedema incidence, secondary to exercise was tracked as an adverse effect in three RCTs and in three uncontrolled trials. No incidence or exacerbation of lymphoedema, either quantified or self-reported was attributed to the training regime. No improvements in lymphoedema were reported.

De Rezende *et al.* (2006) conducted a small RCT to compare two schemes of exercise, directed or free, following modified radical mastectomy or quadrantectomy with axillary dissection, evaluating postoperative complications such as shoulder dysfunction and lymphatic disturbance. There was no difference between the directed and free groups in the average range of motion for adduction, extension and internal rotation between preoperative and 42nd day postoperative when analysing the groups individually. There was a statistically significant difference in the average range of motion for abduction, flexion and external rotation when analysed individually. There was significant differences between the directed and free groups in the average range of motion for abduction ($p=0.0077$), flexion ($p=0.0087$), extension ($p=0.0447$) and external rotation ($p=0.0403$) between preoperative and 42nd day postoperative when analysed in relation to the exercise groups. There was no statistically significant difference between the two groups in relation to lymphatic disturbance and no clinically significant difference in the groups in relation to arm circumference. Statistically significant increases in the arm circumference at 7.5cm above the humeroradial joint were observed in the free group.

An observational study with methodological flaws by Gordon *et al.* (2005a) found that health related quality of life, measured by four instruments, improved from 6-12 months following diagnosis in patients who received two different shoulder rehabilitation programmes and also in a control group. There were no statistically significant differences between the three groups as measured on any instrument.

Generalised or aerobic exercise

- A cross-over RCT by Sandel *et al.* (2005) found that quality of life measured by the FACT-B scale significantly improved in response to a 13 week movement and dance programme, compared to a control group. However the effect was not consistent across different quality of life scales. Shoulder range of movement increased significantly in both groups over a 26 week period and there were no significant changes in arm circumference in either group over the same period.

- The systematic review by Karki *et al.* (2001) cited above found that aerobic exercise after breast cancer surgery was beneficial in terms of psychological well-being.
- An observational study by Lane (2005) found that a 20 week, structured exercise programme for women treated for breast cancer, with dragon boat racing as its focus, resulted in a significant increase in upper body strength. Whilst arm circumference and arm volume significantly increased, there were no significant changes in the affected arm relative to the contralateral arm during the programme. A qualitative study by Unruh and Elvin (2004) of women with breast cancer who participate in dragon boat racing found that the women reported benefits from participation including physical and emotional well-being.

A poor quality RCT by Forchuk *et al.* (2004) found that an intervention whereby patients' partners were instructed to perform distal-to-proximal circular arm massage had no demonstrable effect on shoulder range of motion at four months post-operatively. The intervention group experienced significantly greater arm swelling than the control group at 14 weeks and four month post-operatively.

Cognitive-behavioural interventions

An RCT by Braden and Badger (2000) found that patients who received an intervention designed to help them manage uncertainty arising from breast cancer reported better coping with arm swelling than patients in the control group, over a seven month period of follow-up. This result should be interpreted with caution as full trial details are not currently available.

Diagnostic interventions

A small, non-randomised study by Campisi *et al.* (2006) studied the utility of lymphoscintigraphy as a test to select patients at risk of lymphoedema, combined with early intervention with microsurgery. Patients in the intervention group experienced a significantly lower incidence of lymphoedema than those in the control group, up to five years after initial surgery.

A diagnostic study of multiple frequency bioelectrical impedance analysis (MFBI) to predict early onset of lymphoedema with clinical diagnosis as gold standard was undertaken by Cornish *et al.* (2000) and presented as an interim report. Although the data reported look promising (representing sensitivity 100%, specificity 97.6%, positive predictive value 90.5%, negative predictive value 100%) they should be interpreted with caution due to problems including short follow up and fallible gold standard.

Prevalence of lymphoedema

Evidence from the studies identified suggests that prevalence of lymphoedema is between 13.8% to 49% of patients at risk due to treatment for breast cancer. Possible explanations for this large range include different methods to define lymphoedema and variable extent of follow-up between studies (Table 1). The longest follow-up period of is the retrospective cohort

study by Petrek et al. (2001) which reports the highest prevalence at 49% using objective arm measurements. Considering only the studies where all patients are followed up for at least 5 years, prevalence range becomes 20% to 49%.

Evidence from two studies that graded lymphoedema for severity (based on objectively assessed extent of arm swelling) suggests that the swelling is severe in 13% of this patient group (Petrek *et al.* 2001, Berlin *et al.* 1999).

Time of lymphoedema onset

Evidence from the studies identified suggests that lymphoedema incidence is higher within 3 years of baseline: usually diagnosis or definitive surgery. (Petrek *et al.* 2001, Berlin *et al.* 1999, Yik *et al.* 2001, Coward 1999) The retrospective cohort study by Petrek *et al.* (2001) found that 77% of cases occurred within 3 years of diagnosis and in the remaining 30 patients the rate of onset was gradual at approximately 10 patients per 5 year interval. The observational study by Berlin *et al.* (1999) found that 37% of patients who developed lymphoedema did so within 6 months of surgery and 63% within 1 year of surgery. The risk of developing lymphoedema was highest during the first year following surgery.

Table 1. Sources of lymphoedema prevalence data

Study	Prevalence	Assessment method	Follow up
Box et al. (2002)	21%	Objective	2 years
Bendz and Fagevik (2002)	13.8%	Objective	2 years
Petrek et al. (2001)	49%	Objective	20 years
Campisi et al. (2006)	22	Clinical diagnosis (subjective)	5 years
Cornish et al. (2000)	18.6%	Clinical diagnosis (subjective)	88% of patients were followed up for >18 months.
Berlin et al. (1999)	20%	Objective	5 years
Loerzel et al. (2005)	22%	Patient reported (subjective)	2-12 months
Yik et al. (2001)	45.6%	Patient reported (subjective)	In the order of 3 months to 3 years (approximately)
Coward (1999)	37.5%	Patient reported (subjective)	median 2.6 years, range 2 months to 17

			years
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Risk factors for developing lymphoedema

NB: Questions 2a and 2b address the risk of lymphoedema after different surgical axillary staging procedures and their data is expected to supplement the data presented here.

Some of the studies identified reported factors associated with lymphoedema, but the focus of the research question towards interventions to prevent lymphoedema will not have identified all of the prognostic evidence and so the results should be interpreted with caution.

There is some observational study evidence to implicate radiotherapy, particularly to the axilla as also a risk factor for subsequent lymphoedema (Yik et al. 2001, Coward 1999, Cordero et al. 2003), but the studies do not consistently single out the role of radiotherapy from other treatments applied. However all studies except Yik (2001) state that patients underwent axillary surgery.

There is some evidence from one RCT (as a secondary finding) and from one retrospective cohort study to suggest that weight gain following treatment may also be a risk factor for lymphoedema (Box et al. 2002, Petrek et al. 2001) as may injury or infection to the arm on the treated side (Box et al. 2002).

- The RCT by Box et al. (2002) found that of numerous treatment and patient factors explored, only increasing BMI in the two years following surgery was found to be a risk factor for the presence of lymphoedema at 2 years follow up: OR 1.21 (95% CI 1.04-1.41, p=0.01).
- The retrospective cohort study by Petrek et al. (2001) examined many demographic, disease-related and treatment-related variables for their relationship with lymphoedema prevalent at 20 years following treatment. Only history of arm infection /injury and weight gain since treatment were found to be associated with the presence of lymphoedema.
- The observational study by Berlin et al. (1999) found that significantly more patients with severe or moderate lymphoedema had received radiotherapy (anatomical site not specified, p<0.01, no further details provided).
- The observational study by Yik et al. (2001) found that of 16 different treatment combinations examined, the combination of mastectomy, lymph node dissection, chemotherapy and radiotherapy had a statistically higher than expected rate of lymphoedema (83/171=48.5%, Chi square=6.305, p=0.043).
- The observational study by Coward (1999) found that women reporting lymphoedema were more likely to have received radiotherapy to the axilla (Chi square=5.486, df=1, p=0.02) and to the breast (Chi square=4.192, df=1, p=0.04).
- The observational study by Cordero et al. (2003) found that 98.5% of patients with lymphoedema had received axillary clearance and 75.4% radiotherapy (site of treatment not specified).

Anxiety/ depression measures/psychological morbidity associated with lymphoedema

These outcomes have been reported above, according to the interventions evaluated in the studies.

Subsequent use of healthcare services e.g. out patients appointments, primary care consultations – to be summarised.

None of the studies identified provided information on these outcome measures.

Cost effectiveness

Very little data was identified on the cost-effectiveness of interventions to prevent lymphoedema. The poor quality RCT by Forchuk et al. (2004) described above which evaluated an intervention whereby patients' partners performed post-operative arm massage, found no significant differences between randomised groups in subsequent health utilisation related costs.

Provision of information on lymphoedema to patients and patients' adherence to preventive strategies

Evidence from observational studies suggests that the information provided to patients with breast cancer at or near the time of their surgery is very variable. Different studies estimate the proportion of patients reporting that they received health education on lymphoedema (or that they have some knowledge of the condition) to be between 3% and 82.5%. The study designs are generally susceptible to recall bias and assess patients at different follow-up points. All studies originate from outside of the UK. However the same level of evidence suggests that length of hospital stay does not affect the education given to patients and that older patients receive less information than younger patients (Karki et al. 2004). Two studies that measured patient knowledge of arm care following breast cancer treatment using numerical scores demonstrated that patients' knowledge is relatively low (Yik et al. 2001, Coward 1999). In the studies reviewed the proportion of patients reporting that they use at least one lymphoedema prevention strategy was between 40.3% and 76%.

- The observational study by Loerzel et al. (2005) found that 79.3% of patients reported that they received lymphoedema information when evaluated within one year of diagnosis. Of these, 40.3% used taught strategies to prevent lymphoedema and 58.8% did not use the strategies at all.
- The observational study by Yik et al. (2001) found the mean score for knowledge of lymphoedema (of a possible range of 0-9, 9 representing most knowledge) in a sample of patients to be 4.07 (SD=2.35, mode=2) The authors reported this as a low value. 82.5% of patients reported that they knew they were at risk of lymphoedema. The level of knowledge did not vary significantly according to whether patients had developed lymphoedema, nor whether patients had attended a talk on lymphoedema.
61.4% of patients reported that they performed arm exercises on the advice of a health professional, with a reported frequency of once daily

to less than once weekly. Only 6.4% patients performed manual lymphatic massage on the instruction of a health professional.

- An observational study Coward (1999) measured patients' knowledge of lymphoedema using a numerical scale (possible range 0-18, 18 reflecting most knowledge), based on based on knowledge of 18 recommendations used in clinical practice. Patients' scores had mean 8.6 (SD 4.3), median 9 and mode 8. Thus, patients typically reported being told of 8 or 9 of the 18 strategies to prevent/manage lymphoedema. 76% of respondents reported using at least one lymphoedema prevention/management strategy.
- The observational study by Cordero et al. (2003) found that only 24.6% of patients reported receiving any information after surgery on lymphoedema. Of these, 3% reported a discussion of risk factors for lymphoedema whereas 87.5% were taught basic arm exercises and 87.5% were told to avoid exertion.
- The observational study by Karki et al. (2004) found that length of hospital stay did not have any statistically significant effect on the education provided for shoulder mobility, oedema prevention/treatment, strength training and use of the upper limb. However older patients were significantly more likely to report less instruction for oedema prevention/treatment than younger patients. Of all patients who received modified radical mastectomy, 67% received sufficient information on shoulder movement, 33% received sufficient instruction for strength training and 38% received sufficient information for use of the upper limb.
- The observational study by Yik et al. (2001) found that nurses were the most frequently cited source of education on lymphoedema, followed by doctors, physiotherapists and friends/relatives.
- The observational study by Coward (1999) found that surgeons were the most frequent source of information followed by reading material and other survivors. However advice on blood pressure measurement and venepuncture was most commonly reported as coming from nurses.
- In the observational study by Cordero et al. (2003), patients reported that information on lymphoedema was given by (in descending order) oncologists, medical rehabilitation professionals and 'others', family doctors and surgeons.

In the observational study by Karki et al. (2004), 57.1% of patients reported that physiotherapists and physiotherapy assistants were the individuals providing the most information.

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Randomized controlled trials

Box, Reul-Hirche, Bullock-Saxton & Furnival . Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. Breast cancer research and treatment. 75[1]. 2002.

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: Australia, setting: Secondary care

Inclusion criteria Women scheduled to undergo breast conserving surgery (complete local excision and axillary dissection) or modified radical mastectomy at two hospitals in Brisbane between 1996 and 1997.

Exclusion criteria Confused mental state or inability to follow the exercise guidelines (n=5)

Concurrent reconstructive surgery (n=3)

Residence beyond 50km radius of either hospital and no monitoring as an outpatient (n=20)

Refusal of random allocation (n=9)

Insufficient time to obtain consent/perform preoperative assessment (n=8)

Absence of principal investigator at time of recruitment (n=5)

Population number of patients = 65, mean age = 56 years.

Interventions Aim: To measure the effect of a physiotherapy management care plan (PMCP) for women undergoing breast cancer surgery.

Intervention group (n=32):

Provision of an exercise programme and lymphoedema awareness education which started preoperatively and continued post-operatively. The PMCP also included therapeutic intervention with exercise when secondary lymphoedema was detected.

Control group (n=33):

Provision of exercise instruction booklet only (but physiotherapy intervention was initiated when lymphoedema was detected: see comment on ITT analysis).

Outcomes Difference in arm circumference (CIRC) between operated arm and non-operated arm.

Difference in volume (VOL) between operated arm and non-operated arm.

Ratio of extra-cellular water content between operated arm and non-operated arm, determined by multi-frequency bioimpedance analysis (MFBIA) i.e. impedance spectroscopy.

The threshold for lymphoedema was set at:

>=5cm difference in CIRC from the preoperative measurement;

>=200ml difference in VOL from the preoperative measurement;

MFBIA ratio (operated arm:non-operated arm) below the 95% CI determined from preoperative data.

Follow up 2 years, with assessment at following stages:

Pre-operative

Prior to randomisation

Post-operatively at day 5, 1 month, 3 months, 6 months, 12 months and 24 months.

Results Of 57 patients who were assessed at 24 months, 12 (21%) had lymphoedema using the VOL criteria: incidence was 3 (11% [95% CI 0.7-22.9%]) in the intervention group compared to 9 (30% [95% CI 13.6-46.4%]) in the control group ($p=0.08$).

Only the VOL method of lymphoedema measurement was found to accurately assess the presence of lymphoedema (presumably using clinical examination as the gold standard: see comment).

By log regression, only increasing BMI was found to be a risk factor for the presence of lymphoedema at 24 months follow up: OR 1.21 (95% CI 1.04-1.41, $p=0.01$). No other variable explored was found to be a risk factor (axillary dissection level, no. lymph nodes removed, wound infection, cording, wound drainage volume, seroma, age, dominant operated arm, radiotherapy, occupation). However these results should be considered with the low event rate.

General comments Randomisation was performed after informed consent and stratified by planned surgical procedure.

Single blind design: participants were blinded, physiotherpists were not entirely blind to allocation.

No specific power calculation performed for lymphoedema outcomes. Low event rate observed therefore results are mostly descriptive.

Two patients received bilateral procedures and were excluded from the analysis. At 24 months follow up 57 patients provided data.

Lymphoedema measurement was objective, based upon difference in measurements between operated and non operated arms, at preoperative and subsequent follow up points.

Subjective clinical examination was used as a gold standard to assess diagnostic consistency of the three measures of lymphoedema.

This paper does not report the incidence of lymphoedema after the 2 year follow up point.

Box, Reul-Hirche, Bullock-Saxton & Furnival . Shoulder movement after breast cancer surgery: results of a randomised controlled study of postoperative physiotherapy. Breast Cancer Research and Treatment 75[1]. 2002.

Design: Randomized controlled trial (therapy), evidence level: 1 +
Country: Australia, setting: Secondary care

Inclusion criteria Women scheduled to undergo breast conserving surgery (complete local excision and axillary dissection) or modified radical mastectomy at two hospitals in Brisbane between 1996 and 1997. 49% of patients received breast conserving surgery. According to local practice, patients did not receive axillary radiotherapy (but may have received breast radiotherapy).

Exclusion criteria Confused mental state or inability to follow the exercise guidelines (n=5).

Concurrent reconstructive surgery (n=3).

Residence beyond 50km radius of either hospital and no monitoring as an outpatient (n=20)

Refusal of random allocation (n=9)

Insufficient time to obtain consent/perform preoperative assessment (n=8)

Absence of principal investigator at time of recruitment (n=5)

Population number of patients = 65, mean age = 56 years.

Interventions Aim: To measure the effect of a physiotherapy management care plan (PMCP) for women undergoing breast cancer surgery.

Intervention group (n=32):

Provision of an exercise programme and lymphoedema awareness education which started preoperatively and continued post-operatively. The PMCP also included therapeutic intervention with exercise when secondary lymphoedema was detected.

Control group (n=33):

Provision of exercise instruction booklet only (but see comments on ITT analysis).

Outcomes Recovery of active shoulder movement on the operated arm:

Abduction, flexion, extension, internal rotation, external rotation.

Functional status assessment

Wound drainage, incidence of postoperative complications and lymphoedema

Factors that may contribute to delayed recovery.

Follow up 2 years, with assessment at following stages:

Pre-operative

Prior to randomisation

Post-operatively at day 5, 1 month, 3 months, 6 months, 12 months and 24 months.

Results Two years after surgery, 80% of all patients reported no residual problems with shoulder stiffness or functional actions.

The rate of residual problems at two years were not significantly different between groups: 14% [95% CI 1-28%] of the intervention group reported residual problems compared with 26% [95% CI 9.9-40%] of the control group.

The intervention group demonstrated greater abduction compared to the control group at 3 months follow-up [156 degrees versus 142 degrees respectively (values read from graph), $p < 0.05$] which was maintained to 2 years follow-up 150 degrees versus 143 degrees respectively, $p < 0.01$].

No significant differences were found for flexion, internal rotation or external rotation, but significant associations were found by ANOVA between limitations in these movements and difficulties with 6 of 12 assessed functional tasks:

Back scratching: abduction, flexion and external rotation [$p < 0.02$]

Putting on a shirt: abduction and flexion [$p < 0.01$]

Brushing hair: abduction [$p < 0.01$]

Doing up a bra: extension and internal rotation [$p < 0.05$]

Zippering a back fastening dress: extension and internal rotation [$p < 0.02$]

Making a double bed: abduction [$p < 0.022$]

Authors conclude that the PMCP intervention resulted in greater recovery of shoulder range of movement during the first two years following breast cancer surgery.

General comments Randomisation was performed after informed consent and stratified by planned surgical procedure.

Single blind design: participants were blinded, physiotherapists were not entirely blind to allocation.

Range of movement measurements objectively performed.

Power calculation performed.

All analyses were controlled for age, number of lymph nodes excised, level of axillary dissection, history of previous shoulder problem, radiotherapy, chemotherapy and wound infection. Analysis was by ITT: 3 patients in the control group received physiotherapy as per the intervention group according to a rule set a priori due to poor recovery at a specified level.

59 of the 65 recruited patients were fully evaluated.

Bendz & Fagevik . Evaluation of immediate versus delayed shoulder exercises after breast cancer surgery including lymph node dissection - A randomised controlled trial. Breast 11[3]. 2002.

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: Sweden, setting: Secondary care/home

Inclusion criteria Women patients undergoing radical mastectomy or quadrantectomy, including those with axillary dissection for breast cancer between November 1994 and December 1996.

Exclusion criteria Age >80 years, senility, bilateral surgery or co-morbidity affecting the outcome e.g. rheumatoid arthritis, stroke.

Population number of patients = 230, mean age = 58 years.

Interventions Intervention group: patients were given preoperatively a shoulder/arm exercise programme of to be started on the first post-operative day.

Control group: patients were advised to use the arm as much as was comfortable but to avoid lifting/carrying/forced movements for 14 post-operative days.

After 14 days patients in both groups received an exercise programme to perform (no 'stopping date' reported) i.e. comparison is immediate post-operative versus delayed (14 days) shoulder/arm exercise.

Outcomes Lymphoedema: percentage change in arm volume as measured by water displacement: lymphoedema was defined as a 10% increase in volume on the operated arm compared to the non-operated arm, corrected for preoperative differences and the dominant arm.

Arm flexion, abduction and external/internal rotation using a goniometer. Hand grip strength using a vigorimeter.

Subjective estimation of pain, heaviness and tension in the operated arm using a visual analogue scale (mild, moderate, severe).

Follow up Patients were seen at the preoperative, 2 week, 1 month, 6 month and 2 year post-operative points.

A total of 49/230 patients were lost to follow up due to death (n=16), moving away (n=12), comorbidity (n=5), contralateral surgery (n=4) and personal reasons (n=12).

Results There were no significant differences in changes in arm volume between randomised groups at any follow up point up to 2 years post-operatively. At 2 years follow up there was no significant difference between randomised groups in the proportion of patients with lymphoedema as defined a priori: intervention group (13%) versus control group (12%), $p>0.05$. The overall incidence of lymphoedema was 6.5% at 6 months and 13.8% at 2

years.

All measured movements in both randomised groups were reduced at 2 weeks and 1 month post-operatively.

At 2 weeks post-operatively arm elevation was 73% of its preoperative level in the intervention group compared to 55% of its preoperative level in the control group ($p < 0.001$).

At 2 years follow up the intervention group had statistically significantly better movement than the control group for:

flexion (167 degrees versus 164 degrees respectively, $p < 0.05$)

abduction (154 versus 145 degrees respectively, $p < 0.05$).

At 2 years follow up there were no statistically significant differences between groups for:

external rotation (88 degrees in both groups, $p > 0.05$)

internal rotation (70 degrees in both groups, $p > 0.05$)

There were no statistically significant differences in volume change or arm mobility between patients who received radiotherapy and those who did not receive radiotherapy (NB all radiotherapy was to the chest wall only, not the axilla).

There were no statistically significant differences between randomised groups for hand grip strength at any follow up point.

There were no statistically significant differences between randomised groups for subjectively assessed pain, heaviness and stiffness at any follow up point. Where symptoms were reported they were mild or moderate.

Authors conclude that the early exercise start does not affect the incidence of lymphoedema compared to a delayed (14 days) exercise start, but is of value in avoiding deterioration of shoulder mobility.

General comments NB: From the data provided, 47% of all patients in this study appear to have received either mastectomy only or quadrantectomy only i.e. no axillary surgery, which could be expected to bring about a lower incidence of lymphoedema.

No statistically significant differences existed between groups at outset for age, dominant hand, mastectomy only, quadrantectomy only and treatment with radiotherapy. There were statistically significantly more operations on the right hand side in the control group, but volume measurements were corrected for dominance.

Uncertain whether analysis by whether radiotherapy was received was a sub-group analysis (by randomised group) or a separate analysis, by radiotherapy status alone. Approximately 50% of patients in the study received radiotherapy.

Units of measurement not always reported: range of movement units assumed to be degrees. Confusion arises on the outcomes reported: 'elevation' is cited in results although not stated in the methods section. Methods of reporting are variable.

Small differences between groups may have arisen since the control group were also 'fairly mobile' with regard to their arms. However patients were discharged early with drains in situ as standard.

Cave & Jones . Physiotherapy improves shoulder function after treatment in women with early breast cancer. Cancer Treatment Reviews 32. 2006.

Design: Randomized controlled trial (therapy), evidence level: 1+
Country: Denmark, setting: Secondary care

Inclusion criteria 139 women scheduled for unilateral surgery for breast cancer at the Aarhus University Hospital, Denmark.

All women underwent modified radical mastectomy (including level I and II axillary dissection) or breast conserving surgery plus level I and II axillary dissection.

Exclusion criteria Pre-operative illness affecting upper limbs

Population number of patients = 139.

Interventions This study aimed to determine whether physiotherapy in the immediate post-operative period improves shoulder function in women treated for breast cancer.

Intervention group:

Standard immediate post operative treatment (daily instruction in shoulder and vein pump exercises in the first week after surgery) plus physiotherapy (two 60 minute sessions per week for 6 weeks) commenced in 6th-8th post-operative week.

Control group:

Standard immediate post-operative treatment as above, with physiotherapy commenced as standard i.e. after the 26th post-operative week.

Outcomes Shoulder function assessed by constant shoulder score (based upon pain, range of movement and strength; range 0-100); includes subjective and objective parameters.

Follow up Assessment of outcome was made at 6, 12 and 26 weeks post-operatively.

Results At 6 weeks post-operatively there was no significant difference in change in constant shoulder score: 21 in the intervention group versus 17 in the control group (Mann-Whitney U-test, p=NS).

Physiotherapy improved shoulder function compared with no physiotherapy at 12 and 26 weeks after surgery (median change [in constant shoulder score from preoperative value] = 4 in intervention group versus 9 in control group at 12 weeks, Mann-Whitney U-test, p=0.001; median change = 2 versus 7 respectively at 26 weeks, Mann-Whitney U-test, p=0.001).

Authors state that careful case selection must be made for early physiotherapy as evaluated here, based upon treatment and patient factors.

General comments Study does not measure shoulder function in the longer

term e.g. 12-18 months, where the control group would also have received physiotherapy as per standard treatment.

It is not reported how many patients received radiotherapy, nor to which site, but authors state that some patients in the intervention received radiotherapy prior to the intervention, which may underestimate the treatment effect.

Braden & Badger . Side effects experienced by women receiving treatment for breast cancer: depression by self-help intervention by time effects on arm swelling side effect... 33rd Annual Communicating Nursing Research Conference/14th Annual WIN Assembly, "Building on a Legacy of Excellence in Nursing Research," held April 13-15, 2000 at the Adam's Mark Hotel, Denver, Colorado. Communicating Nursing Research 33. 2000.

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United States, setting: Secondary care

Inclusion criteria Two studies contributed data with a total of 600 women treated for operable invasive breast cancer in North Carolina and Arizona. The women in Arizona were younger (≤ 49 years) than those in North Carolina (≥ 50 years).

Participants had low financial income and represented Mexican-American women, African American women and Anglo American women.

NB Only the Mexican-American women from Arizona ($n = 79$) who provided objective arm measurement data across all time points are represented in this analysis (i.e. low income women of age ≤ 49 years).

Participants were divided into high and low risk groups for depression based upon the Centre for Epidemiological Studies Depression Scale (CES-D) score.

The majority of women received axillary dissection and a minority, sentinel lymph node biopsy. Women did not receive axillary radiotherapy.

Exclusion criteria None reported.

Population number of patients = 79, age range 0 to 49 years.

Interventions

Intervention group:

Patients received a cognitive-behavioural intervention. Although addressing arm problems was not the focus of the intervention, information about protecting the arm on the operated side and support for discussing any concerns with their physician was provided to women who indicated uncertainty about management of arm problems.

Control group:

Patients received standard care.

Outcomes Arm circumference measured objectively at 4 points, based on an assessment protocol from a rehabilitation centre;

Patient-reported pain and weakness in the arm on the operated side (frequency, ability to manage and a measure of 'how much it bothered the

patient').

Follow up Data were collected at three points over a follow-up period of 7 months.

Results Over the seven month period of follow-up:

Patients in the intervention group reported significantly more ability in terms of the 'managing arm swelling' item in the self-report measure, compared to patients in the control group ($F=7.3$, $2/73$, $p=0.01$). This result was observed regardless of level of depression.

Patients in the intervention group experienced significantly less arm swelling as measured objectively at the forearm point ($F=5.74$, $2/73$, $p=0.004$). This result was observed regardless of level of depression.

General comments Results cited are from published abstract and correspondence with first author.

Statistics reported are by repeated measures MANOVA.

Apart from the results shown (i.e. those abstracted) it is not fully known what factors were explored, but found to have no statistically significant effect on outcome; it appears that a large number of patient-reported factors were reported e.g. 'difficulty sleeping, fatigue, quality of life, psychosocial adjustment). For this reason, which arises from an incomplete set of results in abstract form, the results cited should be taken with caution. Caution also arises due to the focus of the intervention, which was not to address arm problems; advice on arm care was given only to 'patients who indicated uncertainty about management of arm problems'.

The cited significant result for 'managing arm swelling' may arise in part, because specific arm care advice was given to patients in the intervention group who 'indicated uncertainty about management of arm problems', and where blinding was not likely to have been feasible; it is not surprising that these patients might report their ability to manage arm swelling favourably when asked at a later date.

Forchuk, Baruth, Prendergast, Holliday, Bareham, Brimner, Schulz, Chan & Yamine . Postoperative arm massage: a support for women with lymph node dissection. Cancer Nursing 27[1]. 2004.

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: Canada (federal state, Commonwealth Realm), setting: Secondary care

Inclusion criteria Patients 18 years of age or older, scheduled for lymph node dissection as part of surgery for breast cancer. Patients had to plan on having their significant other present (within 1 hour of leaving post anaesthesia care) after surgery, and both patient and significant other needed to consent to participate and be fluent in English.

The significant others included spouses (n=49, 83.1%), parents (n=4, 6.8%), other relatives (n=2, 3.4%), firends (n=1, 1.7%) and others (n=3, 5.1%).

Exclusion criteria Organic brain disease;
Pre-existing disorder affecting arm function or the lymphatic system.

Population number of patients = 59, age range 21 to 78 years, mean age = 56 years.

Interventions Intervention group (n=30):

Patients' significant others were taught how to perform a distal to proximal arm massage in circular pattern and encouraged to do so from the immediate post-operative period. No set parameters for frequency and duration of massage were set other than a suggested 10 minute duration.

Control group (n=29)

Patients received standard post-operative care.

Outcomes Pain, measured on numeric rating scale (0-10), reported at it's most, least and average each day.

Pain control achieved by analgesia, measured on the same scale as above.

Stress experienced by patients' families, measured using the family stressor inventory.

Shoulder function, measured subjectively, using the disability section of the shoulder pain and disability index (SPADI).

Shoulder range of motion (ROM) measured objectively by a single, trained individual.

Arm volume, estimated by circumferential measurements at 4 inch intervals.

Health related costs, based upon patient reported episodes (e.g. physician visits); ascertained at 10-14 days and 4 month post-operative points, and

projected to a yearly rate, based on an Ontario health utilisation instrument.

Follow up Outcomes were measured preoperatively and at 24 hours, 10-14 days and 4 months post-operatively.

Pain and frequency of massage were recorded daily by patients and significant others.

Results Pain control data not shown, as reporting is incomplete and suspicious (see comments).

In the intervention group the mean number of massages performed on days 1, 2 and 3 post-operatively was 1.72, 2.28 and 2.44 respectively. This value peaked on day 4 at 2.69 and then progressively tailed off.

No results shown for family stressor inventory data: Different subsets of data are reported at different follow-up points i.e. whole data set not reported in paper, just selected results.

Prior to surgery there were no significant differences within the SPADI scale for shoulder mobility between randomised groups. At 10-14 days post surgery the intervention group reported statistically significantly less difficulty than the control group in the following tasks (with $p < 0.05$ by t test):

Washing their back;

Putting on a shirt;

Placing an object on a high shelf;

Placing an object in a back pocket.

There was no significant difference between randomised groups for ROM at the 10-14 days and 4 months post-operative follow up points (No assessment was made at the 24 hour post-operative point).

The intervention group experienced statistically significantly more swelling at the 10-14 day post-operative follow-up point (e.g. proximal girth measurements 16.95 versus 16.20 respectively, $t=53$, $p < 0.05$) and also the 4 month follow up point (no statistics reported). These differences ceased to be statistically significant when outliers were removed from the analysis (no details shown).

There were no significant differences between randomised groups in health utilisation related costs, (e.g. based on consultations with nurses, post-operative tests, medication).

General comments Study lacks a standard regime of massage as an intervention; frequency and compliance may have faltered with no prescribed regime (authors report poor compliance after 4 days post-operatively) 10-14 days as second follow-up point represents a variable follow-up point between patients.

Entire SPADI criteria shown (Nonsignificant results may not be reported in

paper).

Study had a large amount of incomplete data.

ROM was measured by two individuals and not the intended sole individual.

Findings for pain control appear very suspicious: suggestive that authors summed pain relief from two sources, implying independent efficacy. Authors contacted for clarification.

Overall this appears to be a flawed RCT. No details of random allocation are given and the validity is otherwise questionable.

Kosir, Rymal, Du, Koppolu, Smith, Mood, Rice, Northouse, Aref, Brown & Youseef . Lymphedema prophylaxis utilizing perioperative education. Era of Hope, Department of Defence Breast Cancer research program meeting. 2002.

Design: Randomized controlled trial (therapy), evidence level: 1-
Country: United States, setting: Secondary care

Inclusion criteria Patients treated for breast cancer with surgery including axillary dissection and/or radiotherapy at the Karmanos Cancer Institute, Detroit.

Of 173 enrolled patients (target 176) 154 were randomised. A total of 20 patients died or dropped out leaving 153 evaluable patients of which 113/158=71.5% yielded a full data set.

Exclusion criteria No details available.

Population number of patients = 113.

Interventions Intervention group (n=51 fully evaluable):
Received standard care (written breast rehabilitation materials and preoperative counselling by the breast surgeon) plus structured education in breast surgery rehabilitation including range of motion exercises, lymphoedema arm precautions and management of complications).

Control group (n=62 fully evaluable):
Received standard care alone.

Outcomes Incidence of lymphoedema and infection (lymphoedema was determined on the basis of a 10% volume increase or a >1cm arm circumference increase, with verification by a lymphoedema specialist); Quality of life (QOL) measured by the functional assessment of cancer therapy-breast (FACT-B) survey and the medical outcome study short form health survey (MOS SF-36) and sexuality subscales of the cancer rehabilitation evaluation system (CARES); Patient knowledge and practice of lymphoedema protective skills, measured by testing.

Follow up Data are reported at the interim stage after 33 months of accrual. Mean follow-up period not known.

Results Interim results within the first 33 months of accrual:

52.9% (27/51) of evaluable patients in the intervention group had lymphoedema versus 46.8% (29/62) of evaluable patients in the control group.

49.6% (56/113) of all evaluable patients developed lymphoedema within the first 33 months of accrual, including acute lymphoedema (described as occurring within one year of surgery) and chronic lymphoedema.

Authors report that the lymphoedema rate observed is higher than that reported in the literature.

General comments RCT appears to be ongoing: unpublished interim material cited ('Year III report', identified by standard search methods).

Results are only shown for 113 fully evaluable patients: no 'worst case' or 'best case' analyses performed.

Sandel, Judge, Landry, Faria, Ouellette & Majczak . Dance and movement program improves quality-of-life measures in breast cancer survivors. Cancer Nursing 28[4]. 2005.

Design: Randomized controlled trial, evidence level: 1-
Country: United States, setting: Community

Inclusion criteria Patients treated for breast cancer MidState Medical Center, Conneticut, having undergone surgery at least one month previous, but within the preceding 5 years.

The mean time since surgery was 11 months.

Of 38 included participants, 35 completed measurements at 26 weeks.

Exclusion criteria Patients with metastatic breast cancer or the inability to stand unaided for 3 minutes.

Population number of patients = 35, age range 38 to 82 years, mean age = 61 years.

Interventions This trial aimed to measure the effect of a dance and movement programme on quality of life, body image, shoulder function and arm circumference in patients treated for breast cancer.

Intervention group (n=19):

Underwent a 12 week dance exercise program of a planned 18 sessions. At week 14 patients resumed their normal activities.

Control group (n=16):

Maintained normal activity until week 14, when they undertook the dance programme as above, from weeks 14-25.

The dance programme included warm up, core exercises (to shoulder, elbow and wrist), dance movements and stretching.

Outcomes The following outcomes were assessed using a patient-administered questionnaire:

Functional Assessment of Cancer Therapy-Breast (FACT-B) quality of life instrument, which has physical, social, functional and emotional domains plus 9 questions that are breast cancer specific;

Health related quality of life using the SF-36 instrument;

The Body Image Scale;

Shoulder range of movement (ROM) in abduction, flexion, rotation and extention (as a sum [degrees] of all measurements);

Arm circumference, summed from measurements at 3 points and compared to the untreated arm.

Follow up Outcome measures were obtained at baseline, 13 weeks and 26 weeks.

Results FACT-B significantly improved in the intervention group at 13 weeks from 102.0 (SD15.8) to 116.7 (SD16.9), compared to the control group 108.1 (SD 16.4) to 107.1 (SD 21.3), (ANOVA time by group effect, $p=0.008$). The observed increase of 14 points in the intervention group was reported as a large gain in clinical terms.

During the crossover phase, the FACT-B score increased in the control group from 106.1 (SD 22.3) to 113.5 (SD 18.0) (ANOVA time by group effect, $p=0.008$). Mean scores were stable in the intervention group in the crossover phase.

The overall effect of the training at 26 weeks was significant in explaining variance in FACT-B scores (time effect, $p=0.03$), and the order of training was also significant ($p=0.015$).

For other quality of life scales, some similar, significant effects were observed, but not consistently: mean SF-36 mental health summary score improved during the intervention periods over the 26 weeks (time effect, $p=0.006$), but not the SF-36 physical summary score (time effect, $p=0.06$). Body image score improved as a result of the intervention over 13 and 26 weeks with (time effect) $p=0.001$ and $p=0.001$ respectively.

ROM in the involved shoulder increased in both groups at 13 weeks: 15 degrees (sum) in the intervention group and 8 degrees in the control group (ANOVA time effect, $p=0.03$; time by group, $p=0.58$).

At 26 weeks ROM increased in both groups: 26 degrees in the intervention group and 20 degrees in the control group (ANOVA time effect, $p=0.006$, training order effect, not significant). Greater improvements were seen in the involved shoulder than the contralateral shoulder, but not significantly so ($p=0.23$).

In all subjects, the summed arm circumference at baseline in the arm on the side of breast surgery was greater than that on the non-operated side (118.6 [SD 12.1] cm versus 116.2 [SD 9.8] cm, $p=0.004$).

There were no changes in arm circumference in either group at 13 weeks or 26 weeks for either involved arm or non-involved arm.

General comments RCT had crossover design: patients in the control group received the same intervention as those in the intervention group, but at a later stage, whereupon those in the intervention group became 'controls'. This assumes that each group was in a comparable state when receiving the intervention (or acting as control), which is likely to not be the case. However it meant that the programme (already in place and thus regarded as beneficial) could be offered to more participants.

The planned 18 dance sessions was designed to accommodate some non-

attendance (No report is made of compliance).

Analysis was by ITT and women were asked to complete all outcome measures regardless of compliance with the programme.

Shoulder ROM and arm circumference were measured by a physiotherapist, blinded to allocation.

The two groups were similar at baseline for time since surgery, type of surgery and extent of axillary surgery. 8 patients were receiving chemotherapy or radiotherapy during the programme.

The ANOVA test to assess for a training order effect due to crossover study design (for an interaction for time by group) is reported as 'exploratory' i.e. it is limited since for a full analysis, the control group should be assessed a further 13 weeks later i.e. at 39 weeks. Therefore this does not fully overcome the flaw of crossover design.

Follow-up is relatively short at 26 weeks.

Systematic reviews of combined study designs

Karki . Efficacy of physical therapy methods and exercise after a breast cancer operation: a systematic review. *Critical Reviews in Physical and Rehabilitation Medicine* 2001;13(2-3):159-90. [2-3]. 2001.

Design: Systematic review of combined study designs (therapy), evidence level: 2 -

Country: Finland/UK, setting: Secondary care/community

Inclusion criteria RCTs and observational studies written in English or Scandinavian languages that meet the following criteria:

Prospective clinical trial;

Sample of patients with breast cancer;

Design that is experimental, pre-experimental (no control group), quasi-experimental or true experimental;

Post-operative therapy, therapy used with late symptoms or therapeutic exercise training.

Exclusion criteria: Defined by inclusion criteria.

Interventions A Physical therapy for existing lymphoedema

B Early versus delayed shoulder exercise after breast cancer surgery

C Exercise therapy (provided by exercise therapists) after breast cancer surgery

D Aerobic exercise after breast cancer surgery

Outcomes A Limb volume, circumference measurement, subjective feelings, others.

B Drainage volume, complications, range of movement (ROM), functional outcome measures, pain, length of hospital stay

C ROM measures, subjective feeling

D Cardiovascular measurements, subjective feelings, weight, body mass index

Follow up Not reported collectively: follow-up period varied amongst 31 included studies but ranged from immediate postoperative period to months/years after interventions.

Results 31 studies were included:

B Early versus delayed shoulder exercise after breast cancer surgery (7 studies, 989 patients):

No study found that early shoulder exercise would benefit the later outcome of shoulder mobility.

Methodological quality score had range 31-49 (out of 70).

No meta-analysis was possible due to heterogeneity of data.

C Exercise therapy (provided by exercise therapists) after breast cancer surgery (4 studies, 354 patients):

In all three studies with a control group, patients in the intervention groups had significantly better shoulder ROM results at a follow-up time of between

1-3 months.

The control group in two studies experienced difficulty in functional movements, particularly using back-fastening zips, making a double bed and washing the upper back on the opposite side.

Methodological quality score had range 18-49 (out of 70).

No meta-analysis was possible due to heterogeneity of data.

D Aerobic exercise (e.g. walking, cycling.) after breast cancer surgery.

Programmes lasted 8 weeks-6 months (4 studies, 140 patients):

The studies evaluated exercise programmes during radiotherapy/chemotherapy. The programmes employed were notably different in intensity and duration, as were the outcomes measured by the studies and also the assessment of baseline performance.

1 study found that aerobic exercise improved functional capacity.

1 study found that the exercise group showed less fatigue and anxiety and reported higher satisfaction with their bodies than the control group.

1 study found that patients who improved in a walking test had less decline in a quality of life score but also that fatigue was provoked by both lack of exercise and high-intensity exercise.

Methodological quality score had range 40-48 (out of 70).

No meta-analysis was possible due to heterogeneity of data.

Authors conclude:

Evidence quality in the field of physical exercise therapy after breast cancer surgery is poor and follow-up generally short.

Early shoulder exercise (immediately after surgery) over delayed shoulder exercise does not appear to be justified.

Aerobic exercise appears to confer a psychological benefit in patients with breast cancer but the optimal frequency and intensity are uncertain.

General comments

Outcome group A represent advanced breast cancer guideline scope; not reported here.

Systematic review with adequate details of literature search strategy, inclusion criteria and assessment of quality of primary studies with a unique scoring scheme. Strength of evidence weakened by inclusion of observational studies and poorly conducted RCTs. The range of physical interventions studies is diverse and reporting of results is mostly in narrative with little further analysis.

Retrospective cohort studies

Petrek, Senie, Peters & Rosen . Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 92[6]. 2001.

Design: Retrospective cohort study (other), evidence level: 2-
Country: United States, setting: Community

Inclusion criteria Surviving patients within a cohort of patients consecutively treated for breast cancer at Memorial Sloan-Kettering Cancer Center between October 1976 and June 1978. Of 923 original participants, a total of 263 were alive at 20 years follow up and were eligible and willing to be studied further.

52 (20%) patients had received subsequent contralateral breast cancer treatment with axillary dissection and 211 (80%) patients received only treatment to one side.

All patients received a similar extent of axillary dissection (detail not reported)

Less than 5% of participants received radiotherapy, and none of these to the axilla.

The majority (60%) of patients were aged between 65 and 79 at the time of 20 year follow up.

Exclusion criteria Death, refusal to participate, mental/physical incapacitation, loss of contact.

Population number of patients = 263.

Interventions The study aimed to retrospectively gather data on lymphoedema and its risk factors using the following methods:
Telephone interview conducted by a Research Nurse;
Questionnaire requesting further data including that based upon patients measuring their weight and arm circumference;
Review of data from initial cohort investigations, including medical notes.

Outcomes Incidence of lymphoedema based upon patient-performed arm circumference measurements at three sites on both arms and calculated as follows:

Greatest difference of three points of measurement between both arms:

Severe Lymphoedema: difference ≥ 2 " (5.08cm);

Moderate lymphoedema: difference between 0.5" (1.27cm) and 2" (5.08cm);

Mild lymphoedema: difference < 0.5 " (1.27cm) and with subjective reporting of arm swelling by the patient;

No lymphoedema: difference < 0.5 " (1.27cm) and without subjective reporting of arm swelling by the patient.

Risk factors explored were:

Demographic (age, education);

Surgical/pathological (type of mastectomy, removal of thoracodorsal nerve

bundle and/or pectoralis muscle, total drainage volume, number of axillary lymph nodes excised, radiotherapy, primary tumour size, number of positive axillary nodes);

Subsequent events (using two scales of physical activity levels, occupation/hobbies, chronic illnesses, weight at time of treatment, change in body weight since treatment, arm infections, injuries or elective surgery).

Follow up This study was performed at the 20 year follow-up point, in survivors within the original cohort.

Results 49% (128/263) of the surviving cohort had lymphoedema and 51% (135/263) did not. Severity of lymphoedema was as follows:

Severe 13% (33/263) of surviving cohort;

Moderate 17% (45/263)

Mild 19% (50/263).

Of 211 women with unilateral axillary dissection only the results were similar:

Severe 13% (27/211)

Moderate 18% (38/211)

Mild 19% (40/211)

None 50% (106/211)

Subjectively, 40% (21/52) of the patients treated bilaterally for breast cancer reported swelling in the 'first treated' arm compared to 51% (108/211) of patients treated unilaterally.

The 21 bilaterally treated patients who reported arm swelling all reported less swelling in the 'second treated' arm than in the 'first treated' arm.

All 60% (31/52) of the patients treated bilaterally for breast cancer subjectively reporting no swelling in the 'first treated' arm also reported no swelling in the 'second treated' arm.

In all surviving patients, of all potential risk factors examined, only two were associated with the presence of lymphoedema:

History of infection/injury: 74% (41/55) of patients with one or more episodes of infection/injury had lymphoedema at 20 years compared to 42% (87/208) of patients with no episode (by Chi square for a trend, $p=0.001$);

Weight gain since treatment: 60% (50/84) of patients with a weight gain >4.54 kg since treatment had lymphoedema at 20 years compared to 51% (40/79) of patients with a weight gain of 4.54kg or less and 39% (39/100) of patients with no weight gain (by Chi square for a trend, $p=0.02$).

Considering only the 211 patients treated unilaterally for breast cancer, the results were similar except that weight at time of treatment replaced weight change since treatment as a risk factor for lymphoedema at 20 years.

Time to onset:

In the entire surviving cohort 77% (203/263) of patients reported that swelling occurred within 3 years of diagnosis. In the remaining 30 patients the rate of onset was gradual at approximately 10 patients per 5 year interval.

Only infection/injury was found to be an independent risk factor for late onset lymphoedema (no data shown).

General comments Authors report that a 2.5cm difference between arms is a common definition for lymphoedema.

No baseline arm circumference measurements were taken at original outset of the cohort study so potentially a problem arises in estimating lymphoedema in patients with bilaterally swollen arms, especially those treated for bilateral breast cancer. This would serve to underestimate incidence. However incidence and severity of lymphoedema are similar between patients treated bilaterally and patients treated unilaterally.

Definition of lymphoedema was based on a mixture of objective and subjective measurements, such that it is difficult to separate objective findings from subjective findings. Subjective reporting of lymphoedema by patients may have been influenced by their own objective measurements. The patients' objective measurements were validated in a different study population.

Authors acknowledge a possible recall bias re: reporting of infections since standard advice to patients was aimed at avoiding infection/injury. This may overestimate the importance of infection/injury as a risk factor when data is gathered retrospectively.

Prospective comparative studies

Campisi, Davini, Bellini, Taddei, Villa, Fulcheri, Zilli, Da Rin, Eretta & Boccardo . Is there a role for microsurgery in the prevention of arm lymphedema secondary to breast cancer treatment? *Microsurgery* 26[1]. 2006.

Design: Prospective comparative study (therapy), evidence level: 3
Country: Italy, setting: Tertiary care

Inclusion criteria Patients treated in 'different' centres (Genoa specified) in Italy between April 1992 and June 1994. Specified inclusion criteria were:
Invasive T1 or T2 tumours;
Treatment with axillary lymphadenectomy and radiotherapy.

Exclusion criteria None specified.

Population number of patients = 50.

Interventions Patients were allocated to two groups (allocation not reported as random):

Intervention group (n=25)

Received lymphatic scintigraphy, physical examination and volume estimation by water displacement at 1, 3 and 6 months and 1, 3 and 5 years after surgery. Patients with identified lymphoedema received a physical rehabilitation regime (manual and peristaltic-mechanical lymphatic drainage, multilayer elastic bandage and elastic stocking). Where lymphoedema persisted, microsurgery was performed, to create lymphatic-venous anastomoses.

Control group (n=25)

Received physical examination and volume estimation alone at the same frequency as above.

Outcomes Incidence of lymphoedema (based upon a volumetric difference of ≥ 150 ml)

Preventative value of early intervention

Follow up 1, 3 and 6 months and 1, 3 and 5 years after surgery.

Results In the intervention group lymphoscintigraphy indicated lymphatic impairment in 22 patients between 1 month and 3 years after treatment. All 22 patients underwent physical rehabilitation and clinically evident lymphoedema occurred in 2 patients. These 2 patients underwent microsurgery and experienced long term regression of lymphoedema (minimum 4 years post surgery at time of writing).

Lymphoedema occurred in 9 patients in the control group.

Lymphoedema incidence was higher in the control group (9/25) than in the

intervention group (2/25) (Fisher's exact test, $p=0.01$).

General comments Small, non-randomised study.

Uncertain whether the 50 patients included represent a complete series of eligible patients or a convenience sample.

Patients represented are those heavily treated in the axilla: axillary lymphadenectomy plus radiotherapy. Mean number of nodes excised 14 (range 12-26). Radiotherapy was performed in post-operative weeks 3-6.

Baseline for arm volume changes not reported.

It appears that only patients in the intervention group were treated; possibly the paper omits reporting of treatment of patients for lymphoedema in the control group. No statement is included of ethical approval.

It is difficult to determine whether the interventions were performed according to a pre-defined study protocol or whether patients were treated ad hoc.

It is possible that the authors report on two observational groups of patients treated according to individual need/choice.

Cornish, Chapman, Thomas, Ward, Bunce & Hirst . Early diagnosis of lymphedema in postsurgery breast cancer patients. Annals of the New York Academy of Sciences 904. 2000.

Design: Prospective comparative study, evidence level: 3
Country: Australia.

Inclusion criteria 102 patients treated with surgery for breast cancer at the Wesley Breast Clinic in Brisbane were selected at random for inclusion in this study.

Exclusion criteria None reported.

Population number of patients = 102.

Interventions This study aimed to assess the efficacy of _____ to predict the early onset of lymphedema in breast cancer patients following treatment.

Patients received diagnostic testing for lymphoedema using multiple frequency bioelectrical impedance analysis (MFBIA): a small AC current was passed through patient's operated and non-operated arms and volume differences between arms were estimated as a function of electrical impedance.

MFBIA measurements were recorded presurgery, at one month and three months after surgery, and then at two-month intervals for up to 24 months postsurgery.

MFBIA measurements were evaluated against clinical diagnosis by clinical diagnosis by the patients' physician(s) as an apparent 'gold standard' and also against volume estimation by limb circumferential measurement (but with no criteria stated for a positive result).

Outcomes Performance of MFBIA as an early diagnostic test compared to clinical diagnosis as a gold standard. A positive result by MFBIA was indicated by a value outside the 99.7% CI.

they were referred to their physician for clinical assessment

Follow up At the time of reporting 90/102 patients were monitored for >18 months and 52/102 for >24 months.

Results 19 patients developed clinically apparent lymphedema and, of these, 12 received treatment.

There were positive tests in 21 patients by MFBIA, including all patients with clinically diagnosed lymphoedema, and preceding clinical diagnosis by up to four months.

At the time of reporting there were no false negative results by MFBIA.

The data presented represent sensitivity 100%, specificity 97.6%, positive predictive value 90.5%, negative predictive value 100% but should be interpreted with caution: see comments.

Limb volume by arm circumference measurement as a test for lymphoedema had positive result in 1 patient.

General comments Paper represents interim report of a study before final accrual point is reached, and without the full intended analyses.

The 99.7% CI used as a threshold for a positive lymphoedema result by MFBIA was based upon testing of group of healthy control subjects (n = 50).

Although a result is cited for volume estimation by arm circumference measurement, no details are provided for criteria for a positive result for lymphoedema using this method.

Although 88% of patients were followed up for 18 months or more, further incident cases of lymphoedema would weaken the diagnostic performance of MFBIA.

Clinical diagnosis of lymphoedema is fallible as a gold standard. Inter-observer error may occur if the patients had different treating physicians. It is not reported that diagnosing clinicians were blind to MFBIA results. The 'gold standard' was not independent of the MFBIA test since only patients with positive MFBIA result were sent for clinical confirmation. It is possible that given a negative MFBIA result, a positive clinical assessment may have arisen (if referrals were thus permitted) due to the subjective nature of lymphoedema diagnosis.

The study used bi-monthly MFBIA testing to achieve the results shown, which may have accessibility and resource implications.

Gordon, Battistutta, Scuffham, Tweeddale & Newman . The impact of rehabilitation support services on health-related quality of life for women with breast cancer. Breast Cancer Research & Treatment 93[3]. 2005a.

Design: Prospective comparative study (therapy), evidence level: 3
Country: Australia, setting: Community/secondary care

Inclusion criteria

Intervention groups:

Women attending the DAART and STRETCH programmes between May 2002 and July 2003 in Queensland, Australia, who:

Were diagnosed with primary, unilateral breast cancer;

Spoke English;

Had no cognitive problems;

Were aged 25-74 years.

Control group:

Women recruited to the project titled 'Pulling through - a breast cancer recovery study'

Exclusion criteria Women who are 'too ill' or had previously attended one of the two interventions;

In the DAART group, women who were recruited in a known trial of sentinel node biopsy.

Population number of patients = 275, mean age = 56 years.

Interventions This study aimed to compare health-related quality of life (HRQOL) and upper body disability between patients receiving two community interventions and also with a non-intervention control group. Groups were as follows:

DAART group (n=36) = patients sampled from those receiving the programme of the Domiciliary Allied Health and Acute Care Rehabilitation Team (DAART): a 6 week programme commencing 4-5 days post-surgery.

STRETCH group (n=31) = patients sampled from those receiving the programme: Strength Through Recreation Exercise Togetherness Care Health (STRETCH): an 8 week programme commencing 8 weeks post-operatively.

Both the above programmes focussed on physical therapy for shoulder mobility after surgery.

Control group (n=208) = patients sourced through an existing research programme i.e. patients from the same locality identified through population-based methods.

Intervention: Patients in all three groups were sent a self-administered questionnaire at four time points: pre-intervention, post-intervention, 6 months and 12 months from date of diagnosis.

Outcomes HRQOL was assessed using four validated instruments:

Functional Assessment of Cancer Therapy including a breast cancer subscale (FACT-B);

Functional Assessment of Cancer Therapy (FACT-G, = general), which excludes the breast cancer specific subscale;

Extended Functional Assessment of Cancer Therapy with a specific arm morbidity subscale (FACT-B+4);

Disability of the Arm, Shoulder or Hand (DASH) scale, a scale based on performing daily activities.

Follow up Assessment was made at at four time points: pre-intervention, post-intervention, 6 months and 12 months from date of diagnosis (pre-intervention was post-surgery, but varied from between 3-8 weeks post-diagnosis for DAART and STRETCH groups, respectively).

Results Comparing pre/post-intervention measures, benefits were evident for functional well-being, including reductions in arm morbidity and upper-body disability (DASH) for participants completing the DAART service at one-to-two months following diagnosis.

In contrast, minimal changes were observed between pre/post-intervention measures for the STRETCH group at approximately 4-months post-diagnosis.

Overall, mean HRQoL scores (adjusted for age, chemotherapy, hormone therapy, high blood pressure and occupation type as confounding variables) improved gradually across all groups from 6- to 12-months post-diagnosis, and no prominent differences were found.

Adjusting for known confounders (see comments) there were no statistically significant differences between the three treatment groups compared for any subscale of any instrument evaluated (physical, functional, breast cancer, arm morbidity, FACT-G, FACT-B, FACT-B+4 and DASH).

However the control group had clinically important higher scores than the intervention groups for the functional, breast cancer, FACT-G and FACT-B subscales.

20-40% of women at 12 months post-diagnosis had declining HRQOL scores, despite receiving supportive care services.

General comments A study drawback is that the three study groups were independent of each other, representing different research/rehabilitation-support settings and as such, differed considerably; subjects were candidates specifically for the DAART and STRETCH interventions, and the control group is a convenience sample based upon existing, ongoing research.

In particular the DAART participants had poorer socio-demographic variables (e.g. older age, less income), STRETCH participants had more serious disease and treatment-related variables (more positive nodes, more chemotherapy) and the control group had poorer general health (e.g. cardiovascular disease, high blood pressure, asthma).

NB there were more statistically significant differences for these characteristics than there were for the outcomes of interest and several (age, chemotherapy, hormone therapy, occupation and high blood pressure were found by testing to be significant confounders).

The instruments used to measure HRQOL included meaningful levels of change that are, in validation studies in the literature, considered to represent clinical importance, irrespective of statistical significance. These, and the alpha level for the latter, were defined a priori.

Since so many scales are used, many of which have overlapping subscales, some clarity and meaning is lost in the results.

The recruitment rate was approximately 50% of eligible patients.

Study does not provide any compelling evidence: results seen may be severely influenced by unknown interactions/confounders.

Prospective case series

Berlin, Gjores, Ivarsson, Palmqvist, Thagg & Thulesius . Postmastectomy lymphoedema. Treatment and a five-year follow-up study. International Angiology 18[4]. 1999.

Design: Prospective case series (harm), evidence level: 3
Country: Sweden, setting: Secondary care/community

Inclusion criteria Patients treated with modified radical mastectomy for breast cancer between 1979 and 1983 at Central Hospital, Vaxjo, Sweden. Of 238 eligible patients, 226 were included in the study.

Exclusion criteria None reported.

Population number of patients = 226.

Interventions All patients in the series underwent arm volume measurement by water displacement

Outcomes Incidence and severity of postmastectomy arm oedema, determined as follows:

Slight: increase in arm volume of between 100ml and 400ml;

Moderate: increase in arm volume of between 400ml and 750ml;

Severe: increase in arm volume \geq 750ml

(In unilateral cases differences were based upon the untreated arm. In bilateral cases, differences were based on the pre-treatment value).

Onset of arm oedema.

Correlation of arm oedema to lymph node metastasis and post-operative radiotherapy.

Follow up 5 years in total. Assessment was performed preoperatively, 6 months post-operatively and then yearly to 5 years post-operatively.

Results 20% (46/226) of patients developed lymphoedema in the 5 year follow-up period with severity as follows:

Slight: 57% (26/46) of patients with lymphoedema;

Moderate: 30% (14/46);

Severe: 13% (6/46).

The mean volume increase was 418ml.

37% (17/46) of patients developing lymphoedema did so within 6 months of surgery and 63% (29/46) within 1 year of surgery. The risk of developing lymphoedema was highest during the first year following surgery (by Chi square, $p=0.002$).

Significantly more patients with severe or moderate lymphoedema had received radiotherapy ($p<0.01$, no further details provided).

5/6 cases of severe lymphoedema developed in patients with positive axillary nodes detected peri-operatively plus radiotherapy.

General comments

Modified radical mastectomy includes dissection of axillary lymph nodes.

During follow-up:

53 patients died

9 patients moved away

7 left the study due to non breast cancer illness

157 (70%) were followed for 5 years.

10 patients received bilateral mastectomy. Otherwise, few patient details provided.

Reported result re: axillary node involvement is confounded by subsequent radiotherapy.

Lane . The effect of a whole body exercise programme and dragon boat training on arm volume and arm circumference in women treated for breast cancer. *European Journal of Cancer Care* 14[4]. 2005.

Design: Prospective case series, evidence level: 3
Country: Canada, setting: Community

Inclusion criteria 18 women volunteered to participate in this study, of 100 women present at a novice meeting of 'Abreast in a boat' in January 2003 in Vancouver, Canada.

Eligible participants were those who had completed their treatment for Stage I-III breast cancer over 6 months ago, could satisfactorily complete a physical activity readiness questionnaire (PAR-Q) and were naive to dragon boat paddling.

2 women dropped out at the first assessment point leaving 16 women who completed the programme.

12/16 women had received axillary dissection in addition to breast surgery.
15/16 women had received radiotherapy to the axilla.
Time from diagnosis had range 6 months to 17 years.
No participant had clinical lymphoedema on entry to the study.

Exclusion criteria Defined by inclusion criteria

Population number of patients = 16, mean age = 52 years.

Interventions This study aimed to examine the effect of a dragon boat racing exercise programme on arm circumference, arm volume and upper body strength.

The exercise programme consisted of:
Aerobic exercise and resistance training 3 times a week, over the entire study period;
Dragon boat training, twice a week from week 8.
The programme was supervised and progressive in terms of frequency, duration and intensity.

Outcomes Body Mass Index;
Arm circumference determined at two points: 10cm proximal to the styloid process of the ulna (CIRC 10) and 15cm proximal to the lateral epicondyle (CIRC 15);
Arm volume determined by water displacement;
Upper body strength as measured using 1-RM bench press assessment.

Follow up Assessment of outcome was made at three points:
T1 (week 0): Prior to the start of the exercise programme;
T2 (week 8): Immediately prior to the start of the dragon boat training;
T3 (week 20): At completion of the dragon boat season

Results There was no significant change in BMI over the whole study period ($p=0.377$).

The 1-RM measure of body strength increased significantly from T1 to T3 (55.3kg and 66.2kg respectively, $p<0.0001$).

A 2 arm by 3 session MANOVA analysis indicated that there was no significant difference between the ipsilateral and contralateral arms at any of the assessment points (no further details shown).

The mean difference in CIRC 10 and CIRC 15 increased from T1 to T3: (CIRC10: difference, $d=0.49$ cm, 95% CI 0.25 to 0.73, $p<0.0001$; CIRC15: $d=1.33$ cm, 95% CI 0.78 to 1.88, $p<0.0001$).

Arm volume significantly increased from T1 to T3 ($d = 100$ ml, 95% CI 69 to 130, $p< 0.0001$).

Authors conclude that the 20 week exercise intervention was not found to cause lymphoedema.

General comments A power calculation indicated a minimum of 13 patients were required.

Time from initial breast cancer diagnosis had large range, with regard to risk of developing lymphoedema.

Authors' conclusion that the increase in arm circumference and volume is due to muscle hypertrophy and not lymphoedema should be interpreted with caution in this non randomised trial; authors report that using a threshold of a difference of 2.54cm in circumference between arms, 1 participant in this study had mild lymphoedema at the T3 assessment point. The longest assessment point was at 20 weeks i.e. end of the programme.

However the results may be promising since the majority (12/16) of the patients had received both axillary dissection and axillary radiotherapy.

Loerzel, Dow, Subramanian & Ramaswamysanthanam (2005). Secondary analysis of lymphedema incidence, prevention and management in breast cancer survivors. *Oncology Nursing Forum* 32[2]. 2005.

Design: Prospective case series (therapy), evidence level: 3
Country: United States, setting:

Inclusion criteria Study population was patients treated for breast cancer in Orlando, Florida. All 150 subjects were within the first year of diagnosis of breast cancer and were part of a larger study called the Breast Cancer Education Intervention (BCEI).

Exclusion criteria None reported.

Population number of patients = 150.

Interventions This study aimed to:

Measure the incidence of lymphoedema in a series of patients treated for breast cancer;
Discuss the use of self-care interventions to prevent and manage lymphoedema.

Outcomes Incidence of lymphoedema, self-reported by patients.
Patient application of preventive strategies.
Patient reported reasons for non-application of preventive strategies.

Follow up Incidence of lymphedema was obtained during this first year at a time point ranging from 2 to 12 months after diagnosis.

Results The lymphoedema incidence in the period studied was 33/150=22%.

119/150=79.3% of patients received lymphoedema information. Of these 48/150=40.3% used the strategies to prevent lymphoedema and 70/150=58.8% did not use the strategies at all.

Patients did not believe they were at risk for lymphoedema because:

They were unaware of the existence of lymphoedema;
Their oncology team told them they were not at risk;
They had a personal belief that they were not at risk.

General comments Information extracted from conference abstract plus contact with first author.

Neither time of onset of lymphoedema nor its severity were measured.

Prospective cross sectional studies

Yik, So, Suet & Suk . Lymphoedema care of breast cancer patients in a breast care clinic: A survey of knowledge and health practice. Supportive Care in Cancer 9[8]. 2001.

Design: Prospective cross sectional study, evidence level: 3
Country: Hong Kong, setting: Secondary care

Inclusion criteria Convenience sample of patients attending a breast cancer clinic at the Prince Of Wales Hospital, Hong Kong. Specific criteria were:

Diagnosis of breast cancer;

Either gender;

Age 18 years or above;

Ability to read Chinese;

Previous treatment with any combination of surgery, chemotherapy and radiotherapy for breast cancer.

Age of respondents ranged from under 30 years to over 60, with 41.5% aged between 40 and 49 years.

Exclusion criteria Defined by inclusion criteria.

Population number of patients = 171.

Interventions This study aimed to measure, using a patient questionnaire:

Prevalence of lymphoedema;

Patient knowledge of lymphoedema, including methods of preventing/treating lymphoedema;

Demographic/disease factors associated with lymphoedema.

Outcomes The questionnaire measured:

Section I: demographic data;

Section II: patients' knowledge of lymphoedema prevention and care;

Section III: Occurrence and management of lymphoedema;

Section IV: Practice of physiotherapy.

Follow up Single point of assessment, but not reported in terms of follow-up periods for patients or time since their diagnoses.

Results Knowledge of lymphoedema:

The mean score for knowledge of lymphoedema (of a possible range of 0-9, 9 representing most knowledge) was 4.07 (SD=2.35, mode=2) The authors cited this as 'on the low side'. 82.5% of patients reported that they knew they were at risk of lymphoedema.

There was no significant difference in the level of knowledge between patients who had developed lymphoedema and those who had not, nor between patients who had attended a health talk on lymphoedema and those who had not (Chi square, no details provided).

Nurses were the most frequently cited source of education on lymphoedema

(with frequency of 70), followed by doctors (65) and physiotherapists (61), health talk (52) and friend/relative (45).

105/171=61.4% of patients reported that they performed arm exercises on the advice of a health professional, with frequency of once daily (40.5%) to less than once weekly (36.8%). Only 11 (6.4%) patients performed manual lymphatic massage on the instruction of a health professional.

Occurrence and management of lymphoedema:
Lymphoedema was reported by 78/171=45.6% of patients.

Of 16 different treatment combinations received, the combination of mastectomy, lymph node dissection, chemotherapy and radiotherapy had a statistically higher than expected rate of lymphoedema (83/171=48.5%, Chi square=6.305, p=0.043).

The most frequent time intervals from start of treatment to onset of lymphoedema were ≤ 3 months (26.9% of cases) and between 1-3 years (29.5% of cases). Treatment modality was not found to be significantly associated with time to onset of lymphoedema.

Of 78 patients with lymphoedema, 26 (34.7%) had been referred for physiotherapy.

General comments 'Convenience sample' appears to be a case series, but no period of recruitment reported.

The questionnaire, designed by researchers, was assessed for reliability using Cronbach's alpha with values of 0.6395, 0.9984, 0.7274 and 0.9914 for sections I, II, III and IV respectively.

No ethnic data are provided but all respondents spoke Chinese.

Response rate was 171/180=95%.

Prevalence of lymphoedema result was based on patient reporting: no detail provided on the definition presented to patients in the questionnaire. Similarly, true extent of follow-up not reported.

The sources of information cited may be misleading since we do not know who provided the 'health talks' e.g. nurse etc.

Radiotherapy is not reported by anatomical site.

All outcomes are patient reported and therefore subject to recall bias or suggestion by the questionnaire.

Unruh & Elvin . In the eye of the dragon: women's experience of breast cancer and the occupation of dragon boat racing. Canadian Journal of Occupational Therapy 71[3]. 2004.

Design: Prospective cross sectional study, evidence level: 3
Country: Canada, setting: Community

Inclusion criteria 3 women treated for breast cancer were identified and contacted via a brochure about the dragon boat racing team to which they belonged.

All women were in their early 50s and were diagnosed with breast cancer 2-4 years previously. The women became interested in dragon boat racing between 6 months and 3 years following their diagnoses.

2/3 women had received surgery, 2/3 chemotherapy and 3/3 radiotherapy.

Exclusion criteria None reported.

Interventions

The aim of this small study was to investigate the impact of dragon boat racing on psychological well being of women treated for breast cancer.

Each woman underwent two semi-structured interviews designed to prompt conversation about:

1. The attraction of dragon boat racing;
2. Organisation of the dragon boat team and the woman's involvement;
3. The benefits and risks of involvement;
4. The overall meaningfulness of dragon boat racing to the participant's life.

Interview transcripts underwent content analysis and thematic analysis to create a thematic framework to present the findings.

Outcomes Themes and subthemes identified from the analysis i.e. where reported by 2 or more participants.

Follow up Single point of assessment; all women were diagnosed with breast cancer 2-4 years previously.

Results 7 themes were identified:

1. The attraction of dragon boat racing

Women were attracted to the sport for two reasons: a) Active support - the support inherent in being with other women who shared the cancer experience; b) Enthusiasm and positive energy - the energising/motivating effect of dragon boat racing.

2. Physical and emotional well-being

Women spoke more often about emotional well being but it was clear that this came from the physical achievement and of being together. Women cited

also their noted improvements in physical fitness/ability. Dragon boat racing helped the women put a positive interpretation on a negative experience, regain self-confidence and make personal changes for their well-being.

3. Competition as positive energy

Competition provided: a) An impetus for change - competition provided the emotional and physical benefits that the women experienced; b) Individual and team pride - generated amongst middle aged women who might not normally be expected to be involved in such vigorous physical activity.

4. Dragon boat racing as social support

Support given to each other was implicit and informal but it also had tangible and practical dimensions: a) support was implicit by a need to do something positive about their health without focusing on the disease itself; b) tension existed between the goals of providing support for one another and the goal of competitive racing.

5. Transcendence/connectedness/oneness

Transcendence over the cancer experience, connectedness with other women and oneness with all the women who struggled with breast cancer was a recurrent theme e.g. before racing, teams visualised together to ensure they were thinking positively.

6. Recurrence of breast cancer and death of team members: fear, identification and coping

Recurrence of breast cancer renewed fears for the individual, and the team appeared to be caught off guard when a team member died, with no prepared way of dealing with the loss.

7. Increasing public awareness and perceptions of breast cancer

The women spoke about the opportunity to promote public awareness and positive health behaviours e.g. by providing information about risk factors and screening. The positive interpretation of the negative experience of breast cancer was an important part of their public stance; the racing activities in national competitions publicly challenged the impression that women with breast cancer were ill and limited in their ability to do things.

Authors conclude that the study demonstrated that dragon boat racing holds meaning for women with breast cancer in many different ways and that future research should further explore the relationship between activity and experiences of serious illness.

General comments Study is limited by its sample size of $n=3$.

The three women sampled were already active dragon boat racing participants; therefore findings of study do not automatically apply to the whole population of patients with breast cancer.

Retrospective cross sectional studies

Coward . Lymphedema prevention and management knowledge in women treated for breast cancer. Oncology Nursing Forum 26[6]. 1999.

Design: Retrospective cross sectional study (other), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria A convenience sample of 160 women treated for breast cancer and who used the services of the Austin Breast Cancer Survivor Centre were sent questionnaires. 72 (45%) women returned questionnaires. The research was undertaken in Austin, Texas.

Most respondents stated that they had stage I (n=29) or stage II (n=31) breast cancer.

71/72 = 98.6% of women reported that they had undergone lymph node surgery.

16/72 reported that they had received radiotherapy to the axilla.

Exclusion criteria None reported.

Population number of patients = 72.

Interventions The study had two aims:

1. To measure what information patients treated for breast cancer recall being given on lymphoedema prevention/management and what activities they used;
2. To examine factors related to the occurrence of lymphoedema.

These data were gathered using a questionnaire measuring patient knowledge and disease/treatment variables.

Outcomes Score on a lymphoedema knowledge scale (LKS). Highest possible score (reflecting most knowledge) = 18, where score is based on knowledge of 18 recommendations of the US National Lymphoedema Network.

Incidence and time of onset of lymphoedema.

Disease characteristics, treatment variables, problems during treatment that may precipitate lymphoedema.

Use of lymphoedema prevention strategies.

Follow up Study has single point of measurement. The time since initial diagnosis had mean 3.9 years, median 2.6 years and range 2 months to 17 years.

Results Score on LKS had mean 8.6 (SD 4.3), median 9 and mode 8. Thus, patients typically reported being told of 8 or 9 of the 18 strategies to prevent/manage lymphoedema.

The most frequently reported items (i.e. by 50% of respondents or more) were:

Risk of lymphoedema;

That lymphoedema can occur at any time;
To not permit blood pressure measurement/venepuncture on the operated arm;
To avoid heavy lifting;
To be aware of inflammation/infection;
To avoid trauma.

For all items, surgeons reportedly provided the most information followed by reading material and other survivors. However advice on blood pressure measurement and venepuncture was most commonly reported as coming from nurses.

55/72=76% of respondents reported using at least one lymphoedema prevention/management strategy; most commonly avoiding heavy lifting (n=29) and trauma (n=16). However the mean number of strategies used was only 2.9 (SD=3.2).

27/72=37.5% of respondents reported experiencing lymphoedema.

The mean length of time from diagnosis to onset of lymphoedema was 12.6 months (range zero to 48 months) .

Women reporting lymphoedema were more likely to have received radiotherapy to the axilla (Chi square=5.486, df=1, p=0.02) and to the breast (Chi square=4.192, df=1, p=0.04).

No association was detected between lymphoedema occurrence and type and stage of breast cancer, cancer on the side of the dominant arm, any other treatment variable or reporting of problems (e.g. infection, fluid collection in the breast) after surgery.

No statistically significant difference was found in LKS score between women reporting lymphoedema and those reporting no lymphoedema (t=-0.837, df=69, p=0.40), nor in the mean number of prevention strategies reported (t=1.004, df=70, p=0.32).

Women reporting lymphoedema were statistically significantly more likely to report the use of any prevention strategy than those reporting no lymphoedema (Chi square=4.444, df=1, p=0.04).

General comments Retrospective survey susceptible to recall bias; the questionnaire apparently sought medical details from respondents such as number of lymph nodes biopsied. The patient-reported 'triggers' for lymphoedema are particularly susceptible to recall bias or 'suggestion' by the questionnaire. The 45% response rate may mean that responders were more knowledgeable than non responders.

The study population represented are women who choose to use the Austin Breast Cancer Survivor Centre; and may not represent the population of all women treated in Austin, although they were reportedly similar to other

studies reported in the literature.

The questionnaire was verified by consulting 1 expert nurse and 1 well informed breast cancer survivor and by pilot testing in 5 patients (Cronbach's alpha = 0.85). The items explored appear to be comprehensive and based upon consensus amongst experts.

The finding that women with lymphoedema were more likely to use a prevention strategy may be affected by recall (e.g. notion that patients 'did what they could' to prevent the condition). Similarly the 'prevention' strategies may have been used after onset of lymphoedema.

No detailed definition is given for patient reported lymphoedema, although likely to be subjective.

Cordero, Garrido & Langa . Need for information to prevent postmastectomy lymphedema. *Rehabilitacion* 37[3]. 2003.

Design: Retrospective cross sectional study, evidence level: 3
Country: Spain, setting: Secondary care

Inclusion criteria Patients with lymphoedema secondary to breast cancer surgery, operated on at two hospitals in Valencia between 1982 and 2001. 1.5% of participants had bilateral lymphoedema. Severity of lymphoedema was mild in 26.2% of patients, moderate in 47.7% of patients and severe in 26.2% of patients. 98.5% of patients had received axillary clearance and 75.4% radiotherapy (site of treatment not specified).

Exclusion criteria None reported.

Population number of patients = 65, age range 32 to 85 years, mean age = 57 years.

Interventions Patients were sent a questionnaire, designed to measure retrospectively, the extent of information given to patients after surgery, specifically:

Advice and lymphoedema prevention strategies;

Service;

Profession of the information provider.

Outcomes Patient reported extent of information provided.
Professionals providing information.

Follow up Not directly reported; patients included those in whom lymphoedema developed at 10 years after initial surgery.

Results Only 24.6% of patients reported receiving any information after surgery. Of these:

37.5% reported hearing the word 'lymphoedema';

3% reported a discussion of risk factors for lymphoedema;

81.3% were told to lift their arm;

87.5% were taught basic arm exercises

87.5% were told to avoid exertion;

50% were advised to avoid venepuncture or blood pressure measurement in the affected arm.

Patients reported that the following professionals provided information on lymphoedema:

Oncologists (70.8% of patients who received information);

Medical rehabilitation professionals (10.8%);

Family doctors (4.6%);

Surgeons (3.1%);

Others (10.8%).

General comments Article written in Spanish.

Exact method to sample patients not reported; likely to have been based upon

clinical diagnosis of lymphoedema in medical notes, or where patients had ongoing contact with care setting.
Study could be heavily affected by recall bias.
Very limited applicability to the UK.

Karki, Simonen, Malkia & Selfe . Postoperative education concerning the use of the upper limb, and exercise and treatment of the upper limb: cross-sectional survey of 105 breast cancer patients. *Supportive Care in Cancer* 12[5]. 2004.

Design: Retrospective cross sectional study, evidence level: 3
Country: Finland, setting: Secondary care

Inclusion criteria All patients who had undergone surgery for breast cancer at 3 hospitals in the Satakunta district of Finland in the year 1996-1997.

Exclusion criteria Subsequent local recurrence of breast cancer, acute psychiatric illness, serious co-morbidity (e.g. hip fracture) and hospitalisation.

Population number of patients = 105, age range 26 to 89 years, mean age = 59 years.

Interventions Questionnaire administered 6 months after surgery to collect qualitative and quantitative data on provision of information to patients concerning arm/shoulder mobilisation and prevention of lymphoedema.

Questionnaires were analysed in conjunction with review of medical notes for detailed information on treatment including physiotherapy.

Outcomes The questionnaire aimed to measure the amount and content of information given to patients prior to hospital discharge, specifically:

Recalled post-operative education;

Instructions for shoulder movement;

Instructions on prevention/treatment of lymphoedema;

Instructions on use of the upper limb;

The person providing the information.

Results are usually presented by two groups according to type of breast surgery:

MRM = modified radical mastectomy

BSO = breast saving operation

Follow up The questionnaire was administered at 6 months after surgery.

Results The mean hospital stay was 4.2 days (SD 1.58). Length of hospital stay was not found to have any effect on the education provided for shoulder mobility (Spearman rho $r=-0.13$, $p>0.05$), oedema prevention/treatment ($r=-0.10$, $p>0.05$), strength training ($r=-0.20$, $p>0.05$) and use of the upper limb ($r=-0.03$, $p>0.05$). Age had some effect: older patients reported that they received less instruction for oedema prevention/treatment than younger patients ($r=-0.229$, $p=0.021$).

Shoulder movement

67% of MRM patients and 55% of BSO patients reported receiving sufficient information on shoulder movement. Qualitatively patients reported that they were instructed to carry out daily shoulder exercises.

Strength training

33% of MRM patients and 27% of BSO patients reported that they received sufficient instruction for strength training. Qualitative data showed that conflicting information was given to different patients.

Use of the upper limb

38% of MRM patients and 27% of BSO patients reported receiving sufficient information for use of the upper limb. Qualitative data suggested that patients were instructed to avoid heavy lifting and having blood tests taken using the operated arm.

Person providing information

57.1% of all patients reported the physiotherapist or the physiotherapy assistant as the person providing the most information as set out above.

Authors conclude that there is insufficient time reserved for educating patients prior to discharge from hospital on use of their upper limb after breast cancer surgery and that the information provided was sometimes inconsistent; possibly because health professionals were not aware of information provided by others. Older patients appeared to receive less information than younger patients.

General comments The outcomes of interest were derived from a recommended framework setting out when and how to provide information on mobilising the upper limb. The framework itself was derived from a review of the literature, with no evidence that the review was systematic.

Of 110 eligible patients, 106 returned the questionnaire, of which 105 provided sufficient data for analysis.

Questionnaire not appended in paper.

The possibility exists that patients excluded due to requiring subsequent hospital care may have biased results e.g. patients requiring further hospitalisation may have yielded different results to those that did not.

In this setting the information investigated was routinely provided by physiotherapists: in the case of 85 patients (81%) a description of the physiotherapy consultation was found in the medical records.

Cheema, B., Gaul, C., Lane, K., Singh, M. (2008) Progressive resistance training in breast cancer: a systematic review of clinical trials *Breast Cancer Research and Treatment* 109;9-26

Design: Systematic Review **Evidence Level:** 1-

Country:

Aim: to systematically review studies that prescribed progressive resistance training (PRT)

following breast cancer surgery; to summarise the efficacy of PRT and to delineate areas for future investigations.

Inclusion criteria: RCTs, non-randomised controlled trials and uncontrolled trials published in peer reviewed journals.

Studies involving adults diagnosed and treated for breast cancer and prescribing PRT in isolation or combination with other exercise modalities.

Exclusion criteria: Studies prescribing PRT prior to breast cancer surgery.

Interventions: Progressive Resistance Training (PRT)

Outcomes:
Significant outcomes from each of the individual studies were presented and included measures of flexibility, quality of life, depression and strength.

Results

Only results relevant to the PICO (i.e. lymphoedema results) are presented here.

12 articles retrieved presenting results of 10 trials, 4 uncontrolled trials, one non-randomised controlled trial and 5 randomised controlled trials.

Unilateral, upper extremity lymphoedema was an entry criterion in one RCT and cases of lymphoedema were reported in other studies and did not preclude participation in these trials. One trial prescribed the use of compression sleeves during exercise in each enrolled participant while the use of compression sleeves was a decision made in conjunction with a lymphoedema specialist in other trials.

Lymphoedema incidence, secondary to exercise was tracked as an adverse effect in three RCT's and in three uncontrolled trials. No incidence or exacerbation of lymphoedema, either quantified or self-reported was attributed to the training regime.

No improvements in lymphoedema were reported.

General comments

No detailed information or results for lymphoedema were presented in this review as it was not the primary outcome of interest.

De Rezende, L., Franco, R., de Rezende, M., Beletti, P., Morais, S., Gurgel, M. (2006) Two exercise schemes in postoperative breast cancer: comparison of effects on shoulder movement and lymphatic disturbance *Tumori* 92;55-61

Design: Prospective Randomised Controlled Trial

Evidence Level:

Country: Brazil

Aim: To compare two schemes of exercise, directed or free, following modified radical mastectomy or quadrantectomy with axillary dissection, evaluating postoperative complications such as shoulder dysfunction and lymphatic disturbance.

De Rezende et al. (2006) conducted a small RCT to compare two schemes of exercise, directed or free, following modified radical mastectomy or quadrantectomy with axillary

dissection, evaluating postoperative complications such as shoulder dysfunction and lymphatic disturbance. There was no difference between the directed and free groups in the average range of motion for adduction, extension and internal rotation between preoperative and 42nd day postoperative when analysing the groups individually. There was a statistically significant difference in the average range of motion for abduction, flexion and external rotation when analysed individually. There was significant differences between the directed and free groups in the average range of motion for abduction ($p=0.0077$), flexion ($p=0.0087$), extension ($p=0.0447$) and external rotation ($p=0.0403$) between preoperative and 42nd day postoperative when analysed in relation to the exercise groups. There was no statistically significant difference between the two groups in relation to lymphatic disturbance and no clinically significant difference in the groups in relation to arm circumference. Statistically significant increases in the arm circumference at 7.5cm above the humeroradial joint were observed in the free group.

Inclusion criteria: women undergoing their first surgery for invasive breast cancer (modified radical mastectomy or quadrantectomy with axillary dissection) and who were treated in the Oncology ward of the Center for Integral Attention to Women's Health of the University of Campinas (CAISM-Unicamp) from March 23rd 2003 to July 13 2003.

Exclusion criteria: Women who had immediate breast reconstruction or bilateral surgery. Women who showed a difference of more than 2cm in the circumferences of the arms prior to surgery. Women who showed limitation of movement in the ipsilateral limb prior to surgery. Women who were evaluated with a greater than 20-degree difference in flexion and abduction before surgery. Those who were unable to understand the proposed exercise programme.

Population: N=60

Interventions: Directed Physiotherapy (Kinesiotherapy based on spontaneous exercises including movement for flexion, extension, abduction, adduction and internal and external rotation of the shoulder, either combined or isolated) versus Free exercise.

The directed group performed physiotherapy with a regimen of 19 exercises, performed 10 times with a 60 second interval between exercises compared with the free group who performed the exercise following the biomechanical physiological movements of the shoulder, with the exercises being done to the rhythm of music and without a defined sequence or number of repetitions.

Outcomes:

Shoulder Movement (range of Motion for abduction, adduction, extension, flexion, external rotation and internal rotation)

Lymphatic Disturbance (average drainage volume, arm circumference)

Results:

There was no difference between the directed and free groups in the average range of motion for adduction, extension and internal rotation between preoperative and 42nd day postoperative when analysing the groups individually. There was a statistically significant difference in the average range of motion for abduction, flexion and external rotation when analysed individually.

There was significant differences between the directed and free groups in the average range of motion for abduction ($p=0.0077$), flexion ($p=0.0087$), extension ($p=0.0447$) and external rotation ($p=0.0403$) between preoperative and 42nd day postoperative when analysed in relation to the exercise groups.

There was no statistically significant difference between the two groups in relation to lymphatic disturbance and no clinically significant difference in the groups in relation to arm circumference. Statistically significant increases in the arm circumference at 7.5cm above the humeroradial joint were observed in the free group.

General comments

The p value provided for the statistically significant increases in arm circumference is 0.332, it is not clear whether this is a misprint and there are no figures/tables in which the correct information may have been provided.

Authors Comment: The results of the study demonstrate that directed exercises were more efficient in the rehabilitation of ROM in the movements of flexion, abduction and external rotation than free exercise.

Although the study did not permit a longer follow-up time and the study was underpowered due to small numbers, there appeared to be an impact on shoulder dysfunction without lymphatic disturbance in postoperative rehabilitation.

Health Economics Summary

A systematic review was conducted to assess the cost-effectiveness of strategies used to prevent arm lymphoedema. The initial search identified 159 hits, from which 153 papers were excluded on the bases of the tittle and the abstract. Six papers were obtained for appraisal: 4 of them were excluded because they were not relevant for the study question or were not economic evaluations (Forchuk et al 2004; Morgan et al 2005; Norman et al 2001; Orr et al 1999), one of them was not written in English, and one study was rejected because, although it compared the effectiveness and costs of Australian rehabilitation programs for breast cancer patients, lymphoma was not assessed in the study (Gordon et al 2005b). Therefore, no economic evaluations were identified from the systematic review. The GDG considered there to be insufficient clinical information available to enable robust economic modelling.

8.2 What strategies are effective in reducing arm and shoulder mobility problems after breast cancer surgery?

Short Summary

There is a considerable body of high quality evidence that evaluates strategies to reduce arm and shoulder mobility problems after breast cancer treatment.

RCT evidence suggests that physiotherapy or exercise interventions can improve arm and shoulder function in patients who have received surgery for breast cancer. However the RCTs do not consistently show such improvements for all outcome measures. There is no evidence from RCTs of higher rates of long term complications following physiotherapy or exercise interventions (Bendz and Fagevik 2002; Dawson *et al.* 1989; Gordon *et al.* 2005a; Johannsson 2005; Kilbreath *et al.* 2006; Lauridsen *et al.* 2005; Le Vu *et al.* 1997; Sandel *et al.* 2005; Wingate *et al.* 1989). One poor quality RCT suggests that commencing exercise on the 1st postoperative day may increase short term complications (Dawson *et al.* 1989)

Data from two RCTs suggest that the addition of stretching exercise to physiotherapy has no benefit in terms of arm/shoulder function, quality of life, muscular strength or rate of adverse effects. However in one RCT data were reported unclearly and the other RCT studied only 22 patients (Kilbreath *et al.* 2006; Lee *et al.* 2007). Data from two RCTs suggest that massage can bring benefit in terms of arm function in the short term. However the trials did not consistently find massage to be advantageous for all outcome measures (Forchuk *et al.* 2004; Le Vu *et al.* 1997).

RCT evidence suggests that the timing of physiotherapy within the first two postoperative weeks does not affect outcomes that are assessed one month or later from the date of surgery. RCT evidence suggests that physiotherapy given in the first postoperative week to patients with surgical drains in situ is associated with a larger drainage volume, compared to delayed physiotherapy, or compared to other interventions (for example, massage). (Bendz and Fagevik 2002; Chen and Chen 1999; Jansen *et al.* 1990; Johannsson *et al.* 2001; Le Vu *et al.* 1997; Van der Horst *et al.* 1985). RCT evidence suggests that for exercise interventions that commence between 6 weeks and 26 weeks from the time of surgery, the precise timing of the exercises does not influence outcomes; Sandel *et al.* 2005)

RCT evidence suggests that instructed physiotherapy or instructed exercise interventions are associated with improved patient compliance, a better range of arm movement and lower rates of lymphoedema compared to control arms in which patients receive booklets or other education for unsupervised exercise (Beurskens *et al.* 2007; Box *et al.* 2002a; Cinar *et al.* 2008; Gerber *et al.* 1992; Lauridsen *et al.* 2005; Na *et al.* 1999; Wang *et al.* 2005). Data from one RCT suggest that patients treated with zaltoprofen have improved range of shoulder movement during physiotherapy compared to patients in a control group (Hase *et al.* 2006).

PICO

Population	Intervention	Comparison	Outcome
Patients who undergo surgery due to breast cancer – axillary clearance Axillary RT Both	<ul style="list-style-type: none">• Physiotherapy• Exercise, rehabilitation classes for patients with breast cancer• Education for post-surgical arm/shoulder exercise• Timing of exercises	Versus each other or none	<ul style="list-style-type: none">• Patient Acceptability• Patient Compliance• Cost-effectiveness• Muscle Strength• Pain

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There are several RCTs specifically targeting arm and shoulder mobility treatment after breast cancer treatment. Although there were several high evidence level studies, most sample sizes were very small making it unlikely that statistically significant effects could be demonstrated, the method to generate the sequence of randomisation, the allocation concealment procedure, blinding, ITT analysis and withdrawals were rarely mentioned making it difficult to assess the validity of the trials.

Several trials are directly relevant to the question, however patients with pre-existing shoulder problems were often excluded from the trials and these may be the patients who are most at risk of complications so the best strategy for treating those patients would be especially important to know.

Physiotherapy is beneficial for arm and shoulder function and does not appear to cause more adverse events than non-treatment.

There is conflicting evidence for regimes offered directly after surgery, especially when the drains are still in place and for outcomes assessed close to surgery including drainage volume.

Instructed physiotherapy shows better results regarding function compared to exercise instruction booklets or other self-exercise programmes.

Stretching exercise in addition to physiotherapy has no clear additional beneficial effect on function, quality of life, strength or adverse effects.

Exercises

Physiotherapy and 'exercises'

Physiotherapy is beneficial for arm and shoulder function. (evidence level 1+)

- Lauridsen *et al.* (2005) showed in a good quality RCT that patients receiving team instructed physiotherapy had significantly better shoulder function and

strength results after treatment and 6 months post-operatively than untreated patients.

- Bendz and Fagevik (2002) showed statistically significant differences in flexion, abduction, external and internal rotation between two groups randomised to early shoulder / arm exercises or no treatment in the first two weeks post-operational measured directly after treatment (after both groups received the programme most differences disappeared).
- Kilbreath *et al.* (2006) reported better functional results for a group randomised to resistance and stretching shoulder exercises compared to controls, e.g. 1° versus 7° difference between arms regarding forward flexion; given the sample size (N=22) it is unsurprising that the differences were not statistically significant.
- Dawson *et al.* (1989) showed less limitation regarding anteflexion and abduction in a group randomised to exercises starting on the first day post-operatively compared to immobilised patients but the effects were not statistically significant (N=100).
- Le Vu *et al.* (1997) showed better functional results at seven days post-operatively for patients randomised to receive mobilisation exercises compared to no treatment.
- Wingate *et al.* (1989) showed better shoulder abduction and flexion and less difficulties with tasks of the daily living for a group of modified radical mastectomy patients that had received physical therapy than untreated patients at five days and between one and three months post-operative.
- Johansson (2005) states in an editorial that active arm exercises are important in order to prevent reduced shoulder mobility. A non-systematic review (Anon. 2000) stated that exercise has the advantage of promoting recovery of arm strength and mobility and of capacity to pursue normal daily activities.

In this context, Gosselink can be cited who conclude from their case series tracing the recovery of upper limb function after axillary dissection that a continuation of physiotherapy after three months post-operatively is warranted. This provides evidence that can be held against the opinion that physiotherapy is unnecessary as recovery will come over time regardless of physiotherapy. However, Sandel *et al.* (2005) did not find an effect on shoulder range of motion for a dance and movement programme that included some upper extremity movement exercises when compared to waiting list controls, the authors only found a time effect (range of motion improving over time in both groups). Neither did Gordon *et al.* (2005a) find differences in functional measures when confounders were taken into account in a comparison of three groups (two were part of physiotherapy programmes, one received no physiotherapy).

Physiotherapy does not seem to cause more adverse events than non-treatment, especially when not offered directly after surgery (within a week) or when follow-ups of two weeks or more are chosen. (evidence level 1+)

- Lauridsen *et al.* (2005) found in a good quality RCT that patients receiving team instructed physiotherapy six weeks after surgery at the earliest had no more axially strings than untreated patients.

- Bendz and Fagevik (2002) found even no differences in adverse effects (e.g. lymphoma) between two groups (N=230) randomised to early shoulder / arm exercises or no treatment in the first two weeks post-operational.
- Kilbreath *et al.* (2006) reported in a small but relatively good quality RCT that more controls had an interlimb difference $\geq 2\text{cm}$ than the exercise treatment group ($p=0.03$) which started presumably started exercising after hospital discharge.
- Wingate *et al.* (1989) found no differences in post-operative complications, length of hospital stay or circumferential measurements for a group that had received physical therapy beginning on the first post-operative day compared to untreated patients at five days and between one and three months post-operative.
- Johansson (2005) states in an editorial that patients are sometimes advised to be careful with the affected arm to prevent lymphoedema but there is no empirical evidence to back this up.

There is conflicting evidence for regimes offered directly after surgery, especially when the drains are still in place and for outcomes assessed close to surgery including drainage volume: Dawson *et al.* (1989) report slightly more adverse effects (seroma, delayed wound healing; statistical significance unclear) for the exercised group in comparison to the immobilised group and they conclude that exercises before the 5th post-operative day should be abandoned, the studies mentioned under Timing come to different conclusions.

Stretching

Stretching exercise in addition to physiotherapy has no clear additional beneficial effect on function, quality of life, strength or adverse effects. (evidence level 1+)

- Lee *et al.* (2007) did not find differences for several outcomes (five function measures, quality of life, strength, adverse effects) between a group that received a pectoral muscle stretching programme in addition to physiotherapy in a good quality RCT, but two small, statistically significant function effects might have been present (horizontal extension, forward flexion; reporting unclear).
- The technically good RCT by Kilbreath *et al.* (2006) also reported no statistically significant differences between groups of which one received an additional resistance and stretching shoulder exercise programme apart from usual upper limb exercises, however, this appears to be due to the small sample size (N=22).

Massage

Massages in addition to standard post-operative care can initially be effective for selected outcomes and does not seem to be associated with additional health utilisation costs. (evidence level 1-)

- Forchuk *et al.* (2004) reported significantly fewer difficulties in several self-reported tasks such as placing an object on a high shelf two weeks post-surgery, better self-reported pain control on the first day post-operatively and no significant differences in health utilisation related costs in a group randomised to massage executed by their significant others in addition to

standard post-operative care [unclear what this is]; objectively measured range of motion showed no differences and the intervention group experienced more swelling at some follow-up points.

- Le Vu *et al.* (1997) showed the best functional results for a combination of massage and mobilisation exercises as compared to one or the other or no treatment on day seven post-operatively.

Dance and Movement

A dance and movement programme improves breast cancer specific quality of life. (evidence level 1-)

- Sandel *et al.* (2005) concluded after randomising patients to a dance and movement programme that this substantially improved a breast cancer specific quality of life measure (Functional Assessment of Cancer Therapy – Breast Questionnaire (FACTB, version 3)) compared to waiting list controls; there were no significant differences between groups for SF-36 scores or range of motion measures.

Immobilisation

Immobilisation after surgery does not appear to be more beneficial than free shoulder movement. (evidence level 2-)

- Christodoulakis *et al.* (2003) reported that patients with immobilisation of the arm for four days after surgery had a significant longer hospital stay than patients that were allowed free shoulder movement, no other differences in post-operative complications, or drainage volume, number of days with drain were observed; it has to be noted that historic controls were used for this comparison.

Other: The use of walking poles may improve muscular endurance. (evidence level 1-)

- Sprod *et al.* (2005) showed in a randomised controlled trial with 12 participants that those walking with walking poles improved considerably regarding bench press, shoulder press and latissimus dorsi pull down (7, 1 and 13 repetitions more than pre-exercise in the pole group, versus -0.8, -0.4 and 5 repetitions in the normal walking group); the statistical significance is unclear.

Timing

Period directly after the operation

The timing of physiotherapy does not significantly affect effectiveness or adverse events at follow-ups of 1 month or later. (evidence level 1-)

- Jansen *et al.* (1990) found a similar pattern of recovery and no differences six months post-operative between a group of randomised patients that started physiotherapy on day one after surgery compared to a group that was immobilised for seven days before starting physiotherapy.
- Bendz and Fagevik (2002) showed differences in flexion throughout the two year follow-up of two groups randomised to early shoulder / arm exercises or no treatment in the first two weeks post-operational, but group differences in abduction, external and internal rotation disappeared by one month when all participants received an exercise programme; no differences were observed

in adverse effects (e.g. lymphoma) but it should be noted that the authors summarise the data as mobility recovers earlier in the early exercise group.

- Chen and Chen (1999) found no differences between randomised groups (N=344) that received early, late or delayed (after drain removal) shoulder exercises with regard to anteflexion, abduction and exo-rotation range of motion at day 7, 30, 60 or 180 post-surgery.
- Van der Horst *et al.* (1985) found no differences at the six month follow-up in the percentage of patients reaching full range of motion or with restrictions between small groups that were randomised to what the authors call early (immediately following surgery) versus late (day 7) shoulder exercises and adverse effects (lymphoedema, necrosis, wound infections) were not more common in the early group; it should be noted that both groups did isometric contraction exercises throughout.
- Le Vu *et al.* (1997) found no differences in self-reported abnormalities of the amplitude at 3 month or 8 to 24 months post-operatively regardless of whether patients were randomised to massage, mobilisation training, a combination of the two or no treatment in the first week after surgery (later all patients received massages and mobilisation exercises).
- In contrast, Johansson *et al.* (2001) advocated that physiotherapeutic management pays special attention to early impairments after breast cancer treatment, especially to the group receiving radiotherapy to the axilla area and treatment might be introduced during radiotherapy; the conclusions are not directly based on the studied case series.

Physiotherapy during the first week post-surgery can lead to an increased drainage volume. (evidence level 1-)

- Chen and Chen (1999) reported a statistically significant difference in the amount of axilla fossa drainage volume at 14 days after surgery when the drain in the axilla were removed (559ml compared to 485 or 568ml) in randomised groups that received early, late or delayed (after drain removal) physiotherapy; the authors concluded upper arm exercise should start after drain removal.
- Van der Horst *et al.* (1985) reported a mean drainage volume of 935ml (range 210-3840) in a group randomised to what the authors call early exercises compared to 817ml (range 70-2600) in the group that started shoulder exercises on day seven with a mean drainage time of 8.3 versus 6.4 days; this result was not statistically significant in the small sample.
- Le Vu *et al.* (1997) found the most volume of drained lymph in a group randomised to receiving mobilisation exercises in comparison to a massage, no intervention or a combination of massage and mobilisation.
- In contrast, Johansson (2005) stated in an editorial that physiotherapy started six months post-operatively also improves shoulder functioning but that there is no rationale to postpone the start.

When during the year after surgery

The timing of exercises does not significantly affect effectiveness or adverse events. (evidence level 1+)

- Lauridsen *et al.* (2005) showed in a good quality RCT that patients receiving team instructed physiotherapy during the 6th to 8th post-operative week had no better results than physiotherapy after the 26th postoperative week – both

groups in this cross-over trial showed no differences once both groups had received physiotherapy.

- Sandel *et al.* (2005) found no training order effect when analysing patients randomised to a dance and movement programme or waiting list and later cross-over for range of motion measures, body image and SF-36 scores but this was evident for a breast cancer specific quality of life measure.

Physiotherapy offered early can result in higher compliance than when offered at a later date in the year post-surgery. (evidence level 1+)

- Lauridsen *et al.* (2005) showed in a good quality RCT that patients receiving team instructed physiotherapy during the 6th to 8th post-operative week had a 10% non-attendance rate, the groups receiving physiotherapy after the 26th postoperative week a 19% rate; no statistical significance test reported.
- In this context, Gosselink can be cited who conclude from their case series tracing the recovery of upper limb function after axillary dissection that a continuation of physiotherapy after three months post-operatively is warranted. This provides evidence that can be held against the opinion that physiotherapy is only effective shortly after surgery / recovery will come over time regardless of physiotherapy.

Setting and means of delivery

Instructed physiotherapy shows better results regarding function compared to exercise instruction booklets or other self-exercise programmes. (evidence level 1+)

- Box *et al.* (2002) in a good quality RCT showed better results regarding function up to two years after surgery for an exercise programme outlined in a care plan than the controls that were provided with an exercise instruction booklet.
- Wang *et al.* (2005) found that a group randomised to a directed functional rehabilitation gymnastic programme showed better results regarding anterior, posterior and lateral elevation angles as well as internal and external rotation angles compared to a self-exercise group.
- The study by Gerber *et al.* (1992) is also marginally relevant in this context who speculated that the better functional outcomes of a group with axillary dissection compared to modified radical mastectomy could be because the range of motion was supervised during the entire radiation treatment for these patients.
- Na *et al.* (1999) found in a clinical trial that patients receiving an intensive course of physical therapy showed better results for flexion, abduction, internal rotation and external rotation at either discharge or one month after discharge compared to patients who had received written material of a self-exercise programme.

Instructed physiotherapy shows better results regarding compliance compared to exercise instruction booklets. (evidence level 1+)

- Box *et al.* (2002) showed in a good quality RCT better compliance at each of the six follow-up times for an exercise programme outlined in a care plan than the controls that were provided with an exercise instruction booklet.

Directed exercises are more effective for selected functional outcomes than free exercises and do not appear to increase adverse events. (evidence level 1-)

- Ferreira de Rezende *et al.* (2006) reported significant better results regarding the recovery of extension, flexion, external rotation and abduction 42 days post-surgery for a group randomised to directed exercises following a specific sequence and number of repetitions as compared to the free execution of exercises; there were no statistically significant differences for adduction and internal rotation and the difference was not statistically different for all previous follow-ups, the compliance was equal and differences in adverse events were also not observed.
- Also relevant here is Wang *et al.* (2005) who showed that a group randomised to a directed functional rehabilitation gymnastic programme showed better functional results and fewer incidences of oedemas one and two months post-operatively compared to a self-exercise group. Similarly, the physical therapy clinical trial by Na *et al.* (1990) could be cited here that did report better functional outcomes but not more adverse events such as oedema, wound breakdown, infection, motor weakness or adhesional band use in the instructed group compare to the self-exercise group; however more of the former reported sensory changes (clinical and statistical significance unclear).
- Beurskens *et al.* (2007) reported on a small RCT that investigated the efficacy of physiotherapy treatment of shoulder function, pain and the quality of life in patients who have undergone breast cancer surgery and axillary lymph node dissection compared to control intervention (where the (the treatment group began physiotherapy two weeks after surgery in a private practice of their choice for a total number of nine treatments and the control was a leaflet with advice and exercises for arm and shoulder for the first weeks following surgery). Functional shoulder impairments and pain in the shoulder/arm were significantly reduced following physiotherapy at three months as compared to the control group. There was no significant improvement in handgrip strength or in volume of the related arm between both groups at baseline and follow-up.
- Cinar *et al.* (2008) conducted a small RCT which evaluated the effects of early onset rehabilitation program on shoulder mobility, functional capacity, lymphoedema and postoperative complications in patients who underwent modified radical mastectomy. The trial investigated the effect of clinical variables on the recovery of shoulder mobility, functional capacity and development of lymphoedema. The intervention included a treatment group (directed physiotherapy) versus home group (exercises taught by physiotherapist and patients to perform them by themselves). The improvement in measurements of flexion, abduction, and adduction movements of the shoulder joint and the functional questionnaire scores were significantly improved in the treatment group. No statistically significant difference in the development of lymphoedema and postoperative complications in both groups was observed.

Relevant but problematic data

A programme including home visits from physiotherapists may be beneficial and efficient with regards to costs compared to group sessions. (evidence level 2-)

- Gordon *et al.* (2005a) compared patients taking part in a domiciliary Allied Health and Acute CARE Rehabilitation Team programme (DAART), a Strength Through Recreation Exercise Togetherness Care Health and a further programme that did not offer exercises; when adjusting for all confounders no differences between groups were significant but the authors are convinced that DAART programme patients receiving home visits from a physiotherapist had clinically significant better quality of life outcomes and that the cost-effectiveness analysis shows promoting DAART is an excellent public health investment.
- Similar problematic data stem from Lauridsen *et al.* (2000), an RCT comparing team instructions and individual treatment by a physiotherapist, which reported that improvement for a variety of physical findings was more pronounced in the individual treatment regime but failed to clearly demonstrate all available results.

Miscellaneous, use unclear

Zaltoprofen intake improves range of shoulder motions during physiotherapy. (evidence level 1)

- Hase *et al.* (2006) showed that a group randomised to zaltoprofen intake showed larger flexion and abduction movements than controls before and after physiotherapy exercises. The authors imply that it could boost patients' confidence of succeeding in achieving elevated arm positions, e.g. as required for radiotherapy.

The size of the effect of different surgical procedures and radiotherapy administration are likely to overpower any effects of strategies to reduce arm and shoulder mobility problems. (evidence level 3)

- Rietman *et al.* (2004) present a risk factor study that mentions the factor exercise and physical therapy but none of the prediction models of impairment, disability and health related quality of life include these factors (rather radiotherapy and chemotherapy predict impaired range of motion).

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Evidence Tables

Lauridsen MC, Christiansen P & Hessev I (2005). The effect of physiotherapy on shoulder function in patients surgically treated for breast cancer: A randomized study. *Acta Oncologica*, 44(5), 449-457.

Design: RCT, **evidence level:** 1+

Country: Denmark, **setting:** Secondary care

Inclusion criteria unilateral surgery planned according to Danish guidelines

Exclusion criteria reported illnesses affecting upper extremities preoperatively, unable to give consent

Population N=139 patients undergoing breast conserving therapy including axillary lymph node dissection and radiation therapy or undergoing modified radical mastectomy including axillary dissection; mean age in subgroups ranging between 49 – 63 years

Interventions standard treatment of the ward [presumably a short course of immediate physiotherapy, both groups were encouraged to perform the exercises on a regular basis at home]

Group A (n=72): team instructed physiotherapy, 12 sessions of 60 minutes, 2 sessions a week, during 6th to 8th postoperative week

Group B (n=67): same physiotherapy but offered after the 26th postoperative week

Outcome note Constant Shoulder Score (subjective parameters and objective measurements of active motion range and shoulder strength); exams by same physician

Follow up 6, 12, 26 and 56 weeks

Results

Outcome	Result
Function and Strength	Directly after the treatment of Group A, these patients had better shoulder function and strength results (p=0.001) and 6 months postoperatively (p=0.001) compared to controls. After both groups had received the intervention, no differences were found These results were similar for the modified radical mastectomy patients but not the breast conserving therapy group (no difference between treatment and control). The results were not significantly different in patients with modified radical mastectomy regardless of radiation therapy treatment
Compliance	The median number of sessions missed was 1 or 3 in the early (A) subgroups and 2 or 3 in the later (B) subgroups, the number of patients not attending any session was 10% in Group A, 8 or 19% in the Group B subgroups
Adverse effects	The presence of axially strings was equally distributed in the treatment groups at all times and was not influenced by type of surgery or radiation therapy

Authors concluded team instructed physiotherapy improves shoulder function.

General comments computer generated randomisation sequence, allocation concealment by 3rd party, no blinding, withdrawals described; power calculation; ITT analysis

Box, Reul-Hirche, Bullock-Saxton & Furnival (2002). Shoulder movement after breast cancer surgery: results of a randomised controlled study of postoperative physiotherapy. Breast Cancer Research and Treatment 75[1], 35-50.

Design: RCT, **evidence level:** 1+

Country: Australia, **setting:** Secondary care

Inclusion criteria Women scheduled to undergo breast conserving surgery (complete local excision and axillary dissection) or modified radical mastectomy at two hospitals

Exclusion criteria Confused mental state or inability to follow the exercise guidelines, concurrent reconstructive surgery, residence beyond 50km radius and no monitoring as an outpatient, refusal of random allocation, insufficient time to obtain consent/perform preoperative assessment, absence of principal investigator at time of recruitment (n=5)

Population N = 65 patients, 49% with breast conserving surgery, no axillary radiotherapy but breast radiotherapy possible, mean age 56 years

Interventions

Intervention group: physiotherapy management care plan; exercise programme and lymphoedema awareness education which started preoperatively and continued post-operatively, postoperative reviews to monitor shoulder ROM, progress exercise programmes and individualised intervention as required, the care plan also included exercises when secondary lymphoedema was detected

Control group (n=33): exercise instruction booklet

Outcome note ROM assessed by blinded physiotherapist for some patients

Follow up 2 years, preoperative, prior to randomisation, Post-operatively at day 5, 1 month, 3 months, 6 months, 12 months and 24 months

Results

Outcome	Result
Function	Two years after surgery, 80% of all patients reported no residual shoulder stiffness or functional problems; the intervention group demonstrated greater abduction compared to the control group over time (p = 0.01), the intervention group at 3 months showed more abduction at 3 (p=0.05) and 24 months (p=0.01) but not at the other follow-ups The group allocation significantly influenced the tasks 'being able to hang out the washing', 'pulling a shirt on or off over head', and 'brushing or combing hair / fix wig or head scarf' no significant differences for flexion, internal rotation or external rotation were found between treatment groups
Compliance	The exercise compliance rates were better in the intervention group compared to controls at every follow up measurement (100% vs 94% at 1 month, 91% vs 61%, 73% vs 49%, 54% vs

	21%, 33% vs 22% at 2 years)
Adverse effects	Two years after surgery, 80% of all patients reported no residual problems with shoulder stiffness; the rate of residual problems at two years were not significantly different across groups: 14% vs 26% in controls

Authors concluded a physiotherapy management care plan provided in the early postoperative period is effective in facilitating and maintaining shoulder movement recovery over the first 2 years.

General comments Randomisation after informed consent, stratified by planned surgical procedure; participants blinded, physiotherpists not entirely; power calculation; all analyses controlled for age, number of lymph nodes excised, level of axillary dissection, history of previous shoulder problem, radiotherapy, chemotherapy and wound infection; ITT analysis: 3 controls received physiotherapy according to a rule set a priori due to poor recovery; drop-outs accounted for (59 out of 65 were fully evaluated); no significance tests for compliance data

Lee TS, Kilbreath SL, Refshauge KM et al. (2007). Pectoral stretching program for women undergoing radiotherapy for breast cancer. *Breast Cancer Res Treat*, 102, 313-321.

Design: RCT, **evidence level:** 1+

Country: Australia, **setting:** presumably secondary care

Inclusion criteria patients who underwent breast cancer surgery and received radiotherapy to the breast or chest wall in either 2 or 3 fields

Exclusion criteria radiotherapy to the axilla

Population N=64 consecutive patients; some conservative surgery, some mastectomy; some without axillary surgery, some sentinel node biopsy some axillary dissection, some with chemotherapy; some received tamoxifen or arimidex; some in both groups with shoulder pain at baseline; mean age in subgroups ranging between 55 (SD: 13) and 53 (SD: 12) years

Interventions usual care, physiotherapy course parallel to radiotherapy; pamphlet describing gentle shoulder range of motion exercises, patients seen by physiotherapist weekly; booklet to record use of medication, treatments and exercises performed during the radiotherapy course

Stretch group (n=31): pectoral muscle stretching programme on low-load, prolonged passive stretches of pectoralis major and minor while in supine lying, each stretch position held for up to 10 minutes twice per day, positions often adjusted, technique was reviewed weekly, patients encouraged to continue stretching until follow up; skin care and lymphoedema advice

Control (n=30): no exercise advice during weekly sessions with physiotherapist only skin care and lymphoedema info

Outcome note blind outcome assessor, pain measured on 11-point scale after 1st attempt of each movement

Follow up 6 weeks postoperatively, 8.5 months post-operatively (7 months after completion of radiotherapy and exercises), QoL: Quality of Life questionnaire Version 3 Breast Module BR23

Results

Outcome	Result
Function	No significant difference was found between groups for passive horizontal extension, forward flexion, external rotation or abduction and range of motion; A 6° difference was found between arms for horizontal extension and forward flexion (p<0.001) No differences were found between arms for external rotation or active abduction meaning both groups attained close to full range of motion at their affected shoulder 7 months post-radiotherapy
QoL	no differences were found between groups for QoL items
Compliance	28/31 patients complied with stretching exercise, 1 discontinued do to concurrent neck and jaw pain, 14/30 patients in the control group also exercised
Strength	There were no differences in strength between groups at all

	<p>follow-ups Patients maintained normal arm strength throughout the study, strength measurements did not differ between arms at any measurement occasion</p>
Adverse effects	<p>4 new arm swelling cases in control group at 7 months follow up, 1 new case in the stretch group, breast symptoms increased for both groups during radiotherapy</p>

Authors concluded stretching did not influence outcomes because symptoms reported were not a consequence of contracture.

General comments computer generated randomisation sequence, allocation concealment through opaque envelopes, single-blind, withdrawals described (only 50 patients finally analysed), power calculation, ITT analysis, sophisticated analyses, arm dominance differentiated, it would be more convincing had the statistical significance test been reported for strengths and QoL and pain alone was not reported at all

Kilbreath S, Reshaug K, Beith J & Lee M (2006). Resistance and stretching shoulder exercises early following axillary surgery for breast cancer. *Rehabilitation Oncology*, 24(2), 9-14.

Design: RCT, **evidence level:** 1+ / 1-
Country: Australia, **setting:** secondary care

Inclusion criteria patients undergoing surgery to the axilla for early stage breast cancer

Exclusion criteria -

Population N=22 patients, more than half with mastectomy, the others wide local excision, half with axillary node dissection, half sentinel node biopsy, most with radiotherapy, chemotherapy and tamoxifen; mean age 52 (SD=12) years

Interventions usual hospital care including breast care nurse visit, physiotherapist to review upper limb exercises possible and occupational therapist discussing lymphoedema prevention, patients discharged 2-7 days post-surgery

Treatment group (n=14): daily home programme of resistance and stretching shoulder exercises to increase shoulder ROM and strengthening shoulder muscles, supervised by physiotherapist once a week, stretches in supine included forward flexion, horizontal extension at 90° abduction and horizontal extension at 135° abduction, stretch was held passively for 5 minutes on day 1, progressing up to 15 minutes over 2 weeks time; Theraband was used for strengthening the shoulder flexors and abductors and external rotators, 2 sets of 8-12 repetitions daily, starting with low resistance grade of Theraband in week 1 up to a 'somewhat hard' on the Borg effort scale grade, strengthening exercises were progressed by either increasing resistance or number of repetitions

Controls (n=8): no extra resistance and stretching shoulder exercises

Outcome note European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Version 3 (QLQ-C30); lymphoedema = ≥ 2cm difference between arms; passive ROM and active abduction measured; inclinometer, dynamometer

Follow up immediately after intervention = 12 / 13 weeks post-surgery

Results

Outcome	Result
Function	The difference in forward flexion range of motion between the affected and unaffected arm was 1° (-1, 7.5) in the exercise group and 7° (2, 52) in the controls (n.s.)
Compliance	All women in the exercise group undertook resistance training and passively stretched for up to 15 minutes daily
Strength	difference in strength between affected and unaffected shoulder flexors was 0 (-5, 11) in the exercise group and 22 (14, 24) in the controls (n.s.)
QoL, Acceptability, Adverse	More controls had an interlimb difference ≥2cm than the treatment group (p=0.03) From questionnaire:

<p>effects, Pain</p>	<p>The exercise group had better scores regarding role, emotional, and cognitive functioning; no differences in QoL, physical or social functioning;</p> <p>The controls had less fatigue, but more pain, more appetite loss and more financial difficulties; there were no differences regarding nausea / vomiting, dyspnoea, insomnia, constipation or diarrhoea</p> <p>The exercise group had a better body image and sexual functioning; no differences regarding sexual enjoyment and future perspective</p> <p>The treatment group had fewer systemic therapy side effects, arm and breast symptoms and was less upset by hair loss than the controls (n.s.)</p>
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Authors concluded the intervention seem to lead to better outcomes than usual care.

General comments computer generated randomisation sequence, allocation concealment by opaque envelopes; drop-outs explained; the objectively measured function results were only depicted in full in a confusing figure; sample probably far too small to show effects

Sandel, Judge, Landry, Faria, Ouellette & Majczak (2005). Dance and movement program improves quality-of-life measures in breast cancer survivors. *Cancer Nursing*, 28[4], 301-309.

Design: RCT (crossover), **evidence level:** 1- / 1+

Country: USA, **setting:** Community, multi-centre

Inclusion criteria Patients treated for breast cancer, having undergone surgery at least one month previous, but within the preceding 5 years

Exclusion criteria metastatic breast cancer, inability to stand unaided for 3 minutes

Population N=35 patients who had surgery on average 11 months ago, most with mastectomy or partial mastectomy, a few with lumpectomy, most with lymph node removal, some with breast reconstruction; mean age 61 years, range 38 to 82 years

Interventions cross-over at week 13

Dance group (n=19): 12 week dance exercise program of a planned 18 sessions, at week 14 patients resumed their normal activities; warm up, core exercises (to shoulder, elbow and wrist), dance movements and stretching; Lebed Method, Focus on Healing Through Movement and Dance, certified instructor

Controls (n=16): maintained normal activity until week 14, when they undertook the dance programme as above from weeks 14-25

Outcomes note questionnaires Functional Assessment of Cancer Therapy-Breast (FACT-B): physical, social, functional and emotional QoL domains plus 9 breast cancer specific items; SF-36; Body Image Scale; shoulder ROM = sum of ROM in all 5 directions); ROM and arm circumference measured by blinded physiotherapist

Follow up 13 and 26 weeks

Results

Outcome	Result
Function	Shoulder ROM increased at 13 weeks in both groups (time effect $p=0.03$): 15° in the intervention group, 8° in controls
QoL	FACT-B improved in the intervention group at 13 weeks from 102.0 (SD: 15.8) to 116.7 (SD: 16.9), compared to controls 108.1 (SD: 16.4) to 106.1 (SD: 22.3), $p=0.008$, large clinical improvement; The SF-36 showed no differences between groups
Adverse events	In all subjects, the summed arm circumference at baseline in the involved arm was greater than that on the non-operated side (118.6 (SD: 12.1) cm vs 116.2 (SD 9.8) cm, $p=0.004$) No changes in arm circumference in either group at 13 weeks or 26 weeks for either involved arm or non-involved arm 3 patients with lymphoedema [group unclear]
Other	Body image scores showed no differences between groups Timing: The training order effect for function and the SF-36 was not statistically significant but it was for FACT-B (QoL, $p=0.015$)

Authors concluded that a dance movement programme improves breast cancer specific QoL.

General comments computer-generated random numbers, sequential sealed envelopes opened after baseline testing; multi-centre, problematic data (waiting list crossover design, unusual analysis method); there were several significant time effects but this abstract concentrated on differences between groups; withdrawals mentioned; ITT analysis (asked to complete measures regardless of compliance); short follow up

Jansen RFM, van Geel AN, de Groot HGW et al. (1990). Immediate versus delayed shoulder exercises after axillary lymph node dissection. American Journal of Surgery, 160(5), 481-484.

Design: RCT **evidence level:** 1-

Country: The Netherlands **setting:** 4 institutions, Secondary care and Cancer center

Inclusion criteria patients undergoing primary surgical treatment of breast carcinoma

Exclusion criteria grade 3 or 4 WHO Performance Status Scale, previous diseases or operations influencing ipsilateral shoulder movements, previous ipsilateral axillary operations or radiotherapy, immediate postoperative iridium implantation, simultaneous bilateral axillary lymph node dissection

Population N=168 patients; modified radical mastectomy (majority), axillary lymph node dissection with or without lumpectomy equally distributed amongst groups; mean age 59, range 28-81

Interventions physiotherapy, movements of the shoulder, performed actively once a day under supervision of physiotherapist, movements until pain barrier was reached; all spontaneous movements and use of arm during the day were allowed but no pain, supervision discontinued when shoulder function returned or at discharge; physiotherapy at home prescription depending on results

Early: physiotherapy starts at day 1

Late: 7 days of immobilisation, physiotherapy starts at day 8

Outcome note function measured by 1 or 2 physiotherapists (different ones for the institutions)

Follow up before surgery, 1st day of shoulder movements, discharge, 1 and 6 months post-operative

Results

Outcome	Result
Function	The pattern of recovery and the final outcome showed no difference between the groups (sharp decrease in shoulder function which disappeared during the first 6 months but all shoulder functions slightly reduced 6 months after operation)
Adverse effects	The group with previous immobilisation had 14% less wound drainage volume (n.s.), axillary drainage time, number and volume of seroma aspirations, percentage of patients with serious shoulder restrictions, wound complications and lymphoedema were equal
Other	The number of days of physiotherapy at home was equal in the 2 groups

Authors concluded there was no significant difference between groups in any outcome.

General comments randomisation not described; withdrawals explained; study is inspired by Van der Horst (too small) and Dawson (incomplete

statistical analysis); the study is remarkable in directly testing an open question in the literature, however, it is unfortunate that more modern statistical analyses were not available

Bendz & Fagevik (2002). Evaluation of immediate versus delayed shoulder exercises after breast cancer surgery including lymph node dissection - A randomised controlled trial. *Breast*, 11[3], 241-248.

Design: RCT, **evidence level:** 1- (1+ possible but not all reported)

Country: Sweden, **setting:** Secondary care, outpatient clinic / home

Inclusion criteria Women undergoing radical mastectomy or quadrantectomy, including axillary dissection for breast cancer

Exclusion criteria >80 years, senility, bilateral surgery or co-morbidity affecting the outcome e.g. rheumatoid arthritis, stroke

Population N = 230 consecutive patients, half with radiotherapy (none to the axilla), mean age = 58 (SD:11) years

Interventions after 14 days patients in both groups received an exercise programme to perform, difference is in earlier treatment

Intervention (n=101): shoulder/arm exercise programme instructions preoperatively to be started on 1st post-operative day, intermittent hand contractions with ball, elbow flexion / extension, hand pro- and subination in supine position with arm resting on wedge pillow, from day 3 arm elevation and abduction to 90° with bent elbow in sitting position, from day 8 arm elevation and abduction to 90° with straight elbows, internal rotation with hand on back, supervised by physiotherapist

Controls (n=104): advice to use arm as much as comfortable but to avoid lifting/carrying/forced movements for 14 post-operative days

Outcome note Lymphoedema: water displacement volume measurement: lymphoedema = 10% volume increase in comparison to other arm, corrected for preoperative differences and the dominant arm; goniometer; vigorimeter; subjective estimation of pain, heaviness and tension on visual analogue scale (mild, moderate, severe)

Follow up 2 week (crucial, after this both groups receive intervention), 1 month, 6 months and 2 year post-operatively

Results

Outcome	Result
Function	All measured movements in both groups were reduced at 2 weeks and 1 month post-operatively; at 2 weeks post-operatively arm elevation was 73% of its preoperative level in the intervention group compared to 55% in the control group ($p < 0.001$); at 2 years follow up the intervention group had better movement than controls for flexion (167° vs 164° , $p < 0.05$) and abduction (154° vs 145° , $p < 0.05$) but no differences for internal and external rotation no differences due to radiotherapy status
Strength	There were no statistically significant differences between groups for hand grip strength at any follow up point
Pain	There were no differences in pain between groups
Adverse effects	no differences in arm volume changes between groups at any follow up point up to 2 years post-operatively at 2 years no difference between groups in lymphoedema (13% vs 12%),

	overall incidence of lymphoedema 6.5% at 6 months and 13.8% at 2 years no differences due to radiotherapy status There were no statistically significant differences between groups regarding heaviness and stiffness at any follow up point, all reported symptoms mild or moderate
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Authors conclude that mobility recovered earlier in the early exercise group.

General comments randomisation not described, blinding unclear; withdrawals explained (49/230 lost), study took hand dominance into account, units of measurement not always reported: 'elevation' reported in results but not methods

Chen SC & Chen MF (1999). Timing of shoulder exercise after modified radical mastectomy: A prospective study. *Changgeng Yi Xue Za Zhi*, 22(1), 37-43.

Design: RCT, **evidence level:** 1-

Country: Taiwan, **setting:** Secondary care

Inclusion criteria patients undergoing modified radical mastectomy as primary surgical treatment for breast cancer

Exclusion criteria partial mastectomy, previous axillary operation or radiotherapy, bilateral breast cancer, persistent haematoma and serious infection of surgical wound

Population N=344 consecutive patients with axillary lymph node dissection with tissue removal in axillary veins, anterior edge of latissimus dorsi muscle, anterior serratus muscle and subscapular muscle; long thoracic nerve and thoracodorsal artery vein and nerve not removed; some with lymph node dissection, some with transected pectoralis minor; all with flat drain in axilla fossa and medial chest wall, dressing removed on 3rd day postoperative, drain removal varied; mean age 51 (SD: 13.6) or 48 (SD: 10.6 or 11.2) in the groups

Interventions 1st day after operation and on each additional day performed a hand squeezing exercise and elevation of the forearm not beyond 40° 4 times a day

Early exercises (n=116): upper arm exercises gradually increasing ROM until pain threshold starting on 3rd day; supervision by nurse, active and active-assisted exercise, pendulum exercise, wall climbing, pulley exercise (rope above), some exercised taught at home, patients instructed to continue exercises at home

Late exercises (n=115): started a 6th day postoperatively

Delayed exercises (n=113): started after drain was removed

Outcome note nurse who supervised exercises also performed measurements

Follow up 3rd day, 7th day, 1, 2, 6 months post-operative

Results

Outcome	Result
Function	The delayed group had the lowest ROM values for anteflexion and abduction throughout the follow-up but there was no statistically significant effect; exo-rotation ROM was not different between groups at all follow-ups; Most patients returned to full function at 6 months post-surgery
Adverse effects	The drainage amount over axillary fossa was lower in the delayed group compared to the other groups (p=0.032) No differences in chest wall or aspiration drainage volume, duration of drain for axilla fossa, chest wall or number of aspirations between the 3 groups

Authors concluded exercises can start after drains are removed, delay doesn't limit function.

General comments randomisation and blinding not reported, no power calculation but big sample

Lauridsen MC, Torsleff KR, Husted H & Erichsen C. (2000). Physiotherapy treatment of late symptoms following surgical treatment of breast cancer. *Breast*, 9(1), 45-51.

Design: RCT, **evidence level:** 1-

Country: Denmark, **setting:** unclear (data came from national register)

Inclusion criteria women treated by surgery for breast cancer according to the Danish guidelines, without recurrence and no other malignant disease

Exclusion criteria -

Population N=55 patients, 82% with mastectomy, 18% with lumpectomy, a few ; these came from a pool of 110 patients who reported to suffer one or more late symptom and wished to receive physiotherapy; mean age 55 years, range 36-73

Interventions physiotherapy once a week for 10 weeks

Group 1 (n=28): team instruction with training in a warm swimming bath and subsequent training on the floor by a physiotherapist, excercises are based on extension and relaxation, strength training, vein pump therapy and balance training

Group 2 (n=27): individual treatment by a physiotherapist, excercises based on extension and relaxation, strength training, vein pump therapy and balance training; also treated with stretching of the scar tissue and treatment with the object of increasing mobility of the skin above the pectoralis major muscle and in the area of the axilla

Outcome note assessor of physical examination did not perform the training, rest patient questionnaire

Follow up ?, investigation duration was 12 month

Results

Outcome	Result
Function	71% of group 1 showed an improvement in shoulder movement, 90% of group 2; 'significant'
Strength	86% of group 1 showed an improvement in strength, 83% of group 2; 'significant' 86% of group 1 showed an improvement in muscle tone, 83% of group 2
Adverse effects	50% of group 1 showed an improvement in traction, 84% of group 2; 'significant' 100% of group 1 showed an improvement in abnormal neural tension, 100% of group 2; 'significant' 67% of group 1 showed an improvement in winged scapula, 100% of group 2; 'significant' No statistical significance was observed in the frequency of lymphoedema before and after physiotherapy The improvement in late symptoms 'pain in the neck, ipsilateral arm or shoulder', 'pain in or around the operation scar' and 'a feeling of reduced strength in the ipsilateral arm' was more pronounced in group 2 but not statistically significant

Authors concluded physiotherapy can improve strength, movement and muscle tone and reduce the presence and severity of late symptoms.

General comments very unusual result presentation, highly selective; no details about the

randomisation; assessor blinding possible; withdrawals explained

Van der Horst CM, Kenter JA, de Jong MT & Keeman JN (1985). Shoulder function following early mobilization of the shoulder after mastectomy and axillary dissection. *Netherlands Journal of Surgery*, 37(4), 105-108.

Design: RCT, **evidence level:** 1-

Country: The Netherlands, **setting:** probably secondary care

Inclusion criteria patients undergoing axillary dissections for carcinoma of the breast

Exclusion criteria -

Population N=57 consecutive patients, majority with modified radical mastectomy, some Halsted radical mastectomy, some undergoing breast saving procedure; mean age 62, range 17-81 years

Interventions

Group A (n=31): Day 1-7: shoulder exercises started immediately following surgery under the guidance of a physiotherapist, intermittent isometric contractions of shoulder, arm and hand muscles, arms were bent and hands clasped together in front of the body, instructed to push hands together for 5 to 10 seconds then relax, number of isometric contractions determined by individual ability and pain elicited, various positions of anteflexion of both arms, anteflexion, abduction and rotation were allowed actively or with assistance from the other arm until pain barrier. Day 8-14: daily activities as before but not integrated in the exercised and patients were encouraged to use their involved arm as before the operation

Group B (n=28): Day 1-6: intermittent isometric contractions of shoulder, arm and hand muscles in zero position in the glenohumeral joint; external rotation was actively performed from zero position with elbow flexed to 90°. Day 7: anteflexion 45°, abduction 90°. Day 8: anteflexion 90°, abduction 110°, Day 12-13: anteflexion 110°, abduction 130°, full anteflexion and abduction allowed

Outcome note blind assessor

Follow up 6 months

Results

Outcome	Result
Function	81% with full range of motion in group A, 13% with minor restrictions, serious restriction 6%; respective values for group B: 79%, 11% and 11%; no statistically significant differences
Compliance	1 patient in group A was so depressed that she refused the rehabilitation programme
Adverse effects	2 cases of lymphoedema and 2 of necrosis of wound edges in both groups, superficial wound infection occurred 1x in group A and 6x in group B; The mean drainage volume was 935ml (range 210-3840) in group A and 817ml (range 70-2600) in group B, the mean drainage time including aspirations was 8.3 days versus 6.4 days, statistically n.s.

Authors concluded the disadvantageous effects of early mobilisation as mentioned in the literature was not found, neither was an advantageous effect of early active mobilisation.

General comments double blind, no info on randomisation; the authors summarise group A as 'early active mobilisation', B as 'shoulder exercises started on the 7th postoperative day'; Jansen et al. (1990) think this study is too small to show effects

Forchuk, Baruth, Prendergast, Holliday, Bareham, Brimner, Schulz, Chan & Yammine (2004). Postoperative arm massage: a support for women with lymph node dissection. *Cancer Nursing*, 27[1], 25-33.

Design: RCT, **evidence level:** 1-
Country: Canada, **setting:** Secondary care

Inclusion criteria 18 years or older, diagnosed with breast cancer scheduled for lymph node dissection, planning on having their significant other present (within 1 hour of leaving post anaesthesia care) after surgery, and both patient and significant other needed to consent to participate and be fluent in English

Exclusion criteria Organic brain disease; pre-existing disorder affecting arm function or the lymphatic system

Population N = 59 patients, age range 21 to 78 years, mean age 56

Interventions

Intervention group (n=30): Massage; patients' significant others were taught distal to proximal arm massage in circular pattern and encouraged to do so from the immediate post-operative period, no set parameters for frequency and duration of massage, a 10 minute duration was suggested and use as needed, a nurse checked a demonstration of the massage and patients received a handout

Controls (n=29): standard post-operative care

Outcome note questionnaires for self report including physician visits etc to estimate costs, tests, medication; diary for pain and massage, shoulder range of motion (ROM) measured by trained individuals, arm volume, estimated by circumferential measurements at 4 inch intervals

Follow up 24 hours, 10-14 days and 4 months post-operatively, pain and frequency of massage recorded daily

Results

Outcome	Result
Function	At 10-14 days post-surgery the intervention group reported less difficulty than the controls with washing their back, putting on a shirt, placing objects on a high shelf, placing objects in a back pocket (all p<0.05); There was no significant difference between groups for ROM 10-14 days and 4 months post-operative
Compliance	mean number of massages performed on day 1, 2 and 3 post-operatively was 1.72, 2.28 and 2.44 with a peak on day 4 with an average of 2.69 (range 0-10), 1 participant never received massage, after day 4 less massages
Pain	On 1 st day postoperatively intervention group reported more achieved pain control than the controls (p<0.05), on 2 nd and 3 rd day intervention group reported lower pain when pain was at its least (p<0.05), after the 3 rd day no differences in pain control
Adverse effects	The intervention group experienced more swelling at the 10-14 day post-operative follow-up point (e.g. proximal girth measurements 16.95 versus 16.20 respectively, p<0.05) and

	also the 4 month follow up point (no statistics reported); statistical significance ceased when outliers were removed
Cost	no significant differences between groups in health utilisation related costs, (e.g. nurse consultations, post-operative tests, medication)

Authors concluded arm massage decrease pain and discomfort and promotes a sense of closeness and support with significant other.

General comments no details on randomisation; power calculation; withdrawals explained; family stress and strengths not extracted due to baseline differences and incomplete results; especially pain data were selectively reported

Ferreira de Rezende L, Laier Franco R, Ferreira de Rezende M et al. (2006). Two exercise schemes in postoperative breast cancer: comparison of effects on shoulder movement and lymphatic disturbance. *Tumori*, 92(1), 55-61.

Design: RCT, **evidence level:** 1-

Country: Brazil, **setting:** physiotherapy outpatient centre

Inclusion criteria patients undergoing first surgery for invasive breast cancer, either modified radical mastectomy or quadrantectomy with axillary dissection

Exclusion criteria immediate breast reconstruction, bilateral surgery, difference of >2cm in arm circumference before surgery, limitation of movement in ipsilateral limb before surgery, >20° difference in flexion and abduction before surgery, unable to understand the proposed exercises

Population N = 60 women a few with chemotherapy, mean age 55 or 54 in the groups

Interventions 3 exercises started on 1st day after surgery, further exercises 48 hours after surgery in outpatient centre, 40 minute sessions, 3 times a week for 42 days, advice to maintain free activity with compromised limb in daily activities

Treatment group (n=30): directed exercises, kinesiotherapy based on spontaneous exercises including movements for flexion, extension, abduction, adduction and internal and external rotation of the shoulder, isolated or combined; 19 exercises performed 10 times with 60 second interval between exercises

Control group (n=30): free exercises, exercises following the biomechanical physiological movements of the shoulder including flexion, extension, abduction, adduction and internal and external rotation, either isolated or combined without a previously defined sequence or number of repetitions, executed to the rhythm of music, adapted to physiotherapy ability and experience

Outcome note adverse events from hospital records; goniometer; tape measure for circumference

Follow up 42 days postoperative

Results

Outcome	Result
Function	ROM for adduction, extension and internal rotation did not show differences between preoperative and 42 nd day postoperative Flexion, abduction and external rotational movements showed reduced function at follow up The directed exercises showed better results regarding recovery of extension at day 42 than the free exercise group (47.6 (SD: 6.6) vs 42.9 (SD: 10.1), p=0.0447), also for flexion on day 28 (143.5 (SD: 21.1) vs 132.1 (SD:19.4), p=0.0391) and day 42 (155.4 (SD: 18.7) vs 142, SD17.7, p=0.0087), for external rotation on day 42 (66.1 (SD: 25.5) vs 50.4, SD 30.5, 0.0403) and for abduction at day 28 (122.4 (SD: 25.3) vs 108.2 (SD: 23.3), p=0.0322) and day 42 (139.7 (SD: 26.3) vs 121.2, (SD: 23.4), p=0.0077) There were no differences for adduction or internal rotation between groups
Compliance	Number of sessions performed was similar in both groups (13.8 (SD: 3.06) vs 13.2 (SD: 1.9))
Adverse	Incidence of infection similar in both groups

effects	Lymphatic disturbance showed no statistically significant difference between treatment groups with regard to average drainage volume, seroma incidences, time of drain removal or differences in arm circumference
<p>Authors concluded the directed group had better effectiveness outcomes and the lymphatic disturbance occurrences were equal among the groups.</p>	
<p>General comments no description of randomisation process or blinding; power calculation; sketches of all exercises</p>	

Dawson I, Stam L Heslinga JM & Kalsbeek HL (1989). Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial. *British Journal of Surgery*, 76(3), 311-312.

Design: RCT, **evidence level:** 1-

Country: The Netherlands, **setting:** Secondary Care

Inclusion criteria women undergoing modified radical mastectomy

Exclusion criteria -

Population N = 100 women, mean age 64 (SD: 12) and 65 (SD: 14) in both groups

Interventions

Exercise group (n=51): group started to exercise on first postoperative day

Immobilized group (n=49): ipsilateral arm immobilized in sling for 5 days, then same shoulder exercises

Outcome note when suction drain was removed on 5th day, drainage volume was recorded, shoulder function assessed by same individual

Follow up 5 days postoperatively, wound inspection daily after day 5

Results

Outcome	Result
Function	The exercise group showed a 7° (SD: 9) anteflexion decrease, the immobilised group 10° (SD: 9), n.s. The exercise group showed a 10° (SD: 11) abduction decrease, the immobilised group 11° (SD: 10), n.s. Limitations of >15°antflexion occurred in 14% of patients in the exercise group and in 22% of immobilised patients, n.s. Limitations of >15°abduction occurred in 22% of patients in the exercise group and in 29% of immobilised patients, n.s.
Adverse events	Seromas developed more often in the exercise group but no significant difference in volume, duration or number of aspirations; 8% of the exercise and 2% of the immobilised group exhibited delayed wound healing, infections (6%) requiring either antibiotics or open drainage occurred only in the exercise group haemorrhage occurred in 2% of both groups The drainage volume for the exercise group was 15% more than for the immobilised group

Authors conclude shoulder exercises before the 5th postoperative day should be abandoned.

General comments randomisation not described, blinding not mentioned; statistical analysis missing for adverse events; Jansen et al. (1990) think this study presents an incomplete statistical analysis; published as a short notice

Sprod LK, Scott MS, Drum MS et al. (2005). The effects of walking poles on shoulder function in breast cancer survivors. *Integrative cancer therapies*, 4(4), 287-293.

Design: RCT, **evidence level:** 1-

Country: USA, **setting:** Cancer Rehabilitation Institute

Inclusion criteria women who had undergone primary breast cancer treatment

Exclusion criteria -

Population N = 16 women with mastectomy, some breast conservation therapy, some with axillary lymph node dissection, most with chemotherapy, half with radiation therapy, mean age 59 (SE: 4.6) and 55 (SE: 2.7) in both groups

Interventions aerobic conditioning, total body resistance training, flexibility training, bench press, shoulder press, latissimus dorsi pull down, 8 weeks

Treatment group (n=6): use of walking poles during aerobic exercises, demonstration, supervision, 20 min aerobic activity, 2 days per week, pole working usually took place outdoors, >18 months between treatment and exercise intervention

Controls (n=6): without walking poles

Outcome note muscular endurance measure: patients asked to perform as many repetitions as possible before volitional muscular fatigue

Follow up ?, probably immediately after exercise course

Results

Outcome	Result
Function	All participants began the study with normal shoulder ROM values, hence no differences over time
Compliance	13.17 workouts (SE: 1.04) vs 12.50 (SE: 1.41) in experimental and control group, n.s.
Strength	The difference from pre-exercise to post-exercise was with 6.83 repetitions significantly better in the experimental group for bench press, the difference was -0.8 for the controls The difference from pre-exercise to post-exercise was 1.17 repetitions in the experimental group for shoulder press, the differences was -0.4 for the controls (both n.s. improvement) The difference from pre-exercise to post-exercise was with 13 repetitions significantly better in the experimental group for latissimus dorsi pull down, the difference was 5.2 for the controls

Authors conclude using poles improves muscular endurance.

General comments randomisation not described, blinding not mentioned, withdrawals explained, sample extremely small, difference between treatment and control group not tested for significance, only pre-post measurements

Wang BG, Yuan XY, Wang QT et al. (2005). Functional rehabilitation gymnastics for the oedema of upper limbs and the activity of shoulder joint in postoperative patients with breast cancer. Zhongguo Linchuang Kangfu, 9(30), 16-19.

Design: RCT, **evidence level:** 1- (due to translation issue, 1+ possible)

Country: China, **setting:** Department of Mammary Surgery

Inclusion criteria women with breast cancer

Exclusion criteria -

Population N = 200 women, it is possible that the age range varied from 28-72 and 30-74 in the groups

Interventions

Rehabilitation: functional rehabilitation gymnastics assisted with music, 5 sessions, offered at week 1,2,3,4 and 1 month postoperatively, each session had 4 parts

Control: self-exercise

Outcome note -

Follow up 1, 2, 3 months after treatment

Results

Outcome	Result
Function	3 months postoperatively anterior (106°, SD:1.0° vs 48°, SD:2.0), posterior (49°, SD: 2.0 vs 46°, SD: 1.0) and lateral elevation angles (85°, SD: 1.0 vs 60°, SD: 4.0) and internal (61°, SD: 1.0 vs 58, SD: 1.0) and external rotation angles (83°, SD: 1.0 vs 49°, SD: 1.0) of upper limbs were bigger in the rehabilitation group than the control group; p<0.05*
Adverse events	The rehabilitation group had fewer incidences of oedemas at 1 month postoperatively (7% vs 32% p<0.05) and at 2 months postoperatively (2% vs 15%, p<0.05)

Authors concluded gymnastics improve muscles, promote blood circulation and lymphatic return, alleviate oedema and improve shoulder joint activity and functional impairment.

General comments Japanese publication, data taken from abstract and tables, the quality of the RCT could be higher than 1-; randomisation not described in abstract; ITT analysis, sketch for every exercise; * the significance test is a t-test so presumably all 5 differences were significant on the 0.05 level but it is not clear from the abstract

Le Vu B, Dumortier A, Guillaume M et al. (1997). Physiotherapy after surgery for breast cancer. Bulletin Cancer, 84(10), 957-961.

Design: RCT, **evidence level:** 1-

Country: France, **setting:** probably secondary care

Inclusion criteria surgically treated breast cancer patients

Exclusion criteria bilateral breast cancer, previous surgical or chemotherapy treatment, non French speaking, psychological problems, treatment allocation problems

Population N=264 patients with axillary clearance, 1/3 with mastectomy, some with tumorectomy, later breast reconstruction, mean age 55 (SD:11.3), 56 (SD:11.8), 57 (SD:12.5) or 58 (SD:12.5) years in the groups

Interventions intervention started the day after surgery for 7 days, all patients received 5 sessions of physiotherapy; after the 7th day all patients received massages and mobility training

Massage (n=65): massage in reclining position, gentle touch and firm gliding pressure, aiming to ease pain and at circulation

Mobilisation (n=65): shoulder movement, active, gradual, without resistance, symmetric, antepulsion, abduction and rotation

Combination (n=64): massage and mobilisation

No rehabilitation (n=63):

Outcome note 7 day data stem from hospital records, 3 months questionnaire, last follow up data from medical records; degree of motion was only assessed at day 7

Follow up 7 days (crucial), 3 months, 8-24 months

Results

Outcome	Result
Function	The degree of abduction differed between groups on day 7 (p=0.0005) with 144° for the combination, 129° for mobilisation and massage and the control group had a value of 126° The degree of forward lifting? (antépulsion) differed between groups on day 7 (p=0.002) with 143° for the combination, 131° for mobilisation, 130 for massage and 126° in the control group After all patients received massages and mobility training, there were no differences between groups at the 3 months and the last follow-up There were no differences between groups in self reported abnormalities of amplitude at 3 months nor where there differences at the last follow up
Adverse effects	The volume of lymph drained on day 7 was lowest in the massage group (336cm ³) and highest in the mobilisation group (436cm ³), the combination had a volume value of 366, the controls 389; (p=0.03) All other adverse effects including pain showed no differences at the 3 and the last follow up (8-24 months)

Authors concluded that an early treatment including both physiotherapy and shoulder movement seems advisable.

General comments published in French, the intervention description has to be regarded with

caution due to possible translation mistakes, the authors translated the massage intervention as physiotherapy, the mobilisation intervention as shoulder movement; the text and tables differ for the 7 day data; no details about randomisation / blinding, ITT analysis (257 finally analysed), withdrawals descibed

Hase K, Kamisako M, Fujiwara T et al. (2006). The effect of Zaltprofen on physiotherapy for limited shoulder movement in breast cancer patients: A single-blinded before-after trial. Arch Phys Med Rehabil, 87, 1618-1622.

Design: Controlled before-after trial, **evidence level:** 1-

Country: Japan **setting:** Rehabilitation department

Inclusion criteria women with limited shoulder movement after breast cancer surgery

Exclusion criteria preoperative shoulder dysfunction, taking other NSAIDs, history of intestinal ulcer

Population N = 40 patients with surgery 10 to 223 days ago, all with pain at the end of maximum ROM, some with spontaneous dull pain, mean age 51, range 37-72

Interventions physiotherapy, pasive stretching for full ROM in flexion, abduction, and external rotation, physiotherapist supporting arm with muscular relaxation, use of a wooden stick or wall, supine, seated or standing position, 20 min, instructions for exercises at home
Zaltprofen group: single 80mg tablet
Controls: no treatment

Outcome note examiner and physiotherapist blinded, steps to ensure allocation concealment; goniometer; ROM estimated by physiatrist

Follow up post-exercise

Results

Outcome	Result
Function	The zaltoprofen group showed larger flexion and abduction movements than the controls before ($p < 0.05$) and after ($p < 0.01$) the exercises
Pain	Pain scores decreased after ROM exercises in the control and the zaltoprofen group, 2 controls had increased pain after ROM exercises, group comparison n.s.

Authors concluded oral zaltoprofen before ROM exercises may enhance the effect of physiotherapy.

General comments randomisation not further described, only patients not blind; the study gist is that painkiller lets you lift your arm higher but the authors mention that the immediate effect gave some patients an expectation of succeeding in achieving the elevated-arm position required for radiotherapy

Gerber L, Lampert M, Wood C et al. (1992). Comparison of pain, motion, and edema after modified radical mastectomy vs. local excision with axillary dissection and radiation. Breast Cancer Research and Treatment, 21, 139-145.

Design: RCT (case series regarding physiotherapy), **evidence level:** 1-

Country: USA, **setting:** Department of Rehabilitation Medicine

Inclusion criteria ?

Exclusion criteria -

Population N=165 patients for whom pre- and postoperative ROM data was available, randomised to axillary dissection with radiation or modified radical mastectomy

Interventions heat, cold, massage and transcutaneous nerve stimulators for pain and to promote motion, use based on clinical judgement; day 1-2 postoperatively 40° flexion and abduction, day 3 45°, day 4-6 45-90° flexion and 45° abduction, day 7 / when drains removed flexion and abduction to tolerance, internal / external rotation throughout to tolerance of pain; home maintenance programme after achieving at least 110° flexion, 90° abduction and 55° external rotation of the shoulder, use of overhead pulley recommended; education about preventing arm oedema

Outcome note goniometer for ROM, manual muscle test, tenderness by examiner / utterance of pain palpitation

Follow up year 1, 2, 3, 4 and 5

Results

Outcome	Result
Function	The average number of days when post-operative ROM was reached was 172 (axillary dissection with radiation) and 195 (modified radical mastectomy), p=0.043 There was no significant loss in ROM over the first year in flexion, abduction or internal or external rotation, regardless of the surgery type
strength	The serratus anterior muscle was most frequently found to be weak, followed by the pectoralis major and latissimus dorsi (incidences in 4 to 12 patients), full strength returned within 1 year, regardless of the surgery groups
Pain	The number of participants with chest wall tenderness was 43, 44, 56, 58 and 46 in the first 5 years after surgery
Adverse events	79/131 patients had a circumferential measurement of <2, 35 had values 2-3.9, 13 4-5.9 and 4 had 6cm or more; Cosmetic differences were found in 22/121 patients; Skin elasticity was reduced to <3mm in 6 patients

Authors concluded that the axillary dissection group may have reached better ROM results because ROM was supervised during the entire radiation treatment.

General comments only marginally relevant, it is impossible to separate the effects of surgery and mobility strategy; randomisation and blinding not described, loss to follow up explained (165 or less of 247 finally analysed)

Wingate L, Croghan I, Natarajan N, Michalek M & Jordan J (1989). Rehabilitation of the mastectomy patient: A randomized, blind, prospective study. Arch Phys Med Rehabil, 70, 21-24.

Design: RCT combined with non-randomised data, **evidence level:** 2++
Country: USA, **setting:** physical therapy department

Inclusion criteria patients scheduled for a modified radical mastectomy

Exclusion criteria -

Population N = 115 patients, these included patients from a non-randomised pilot study, mean age 56 and 58 in both groups

Interventions

Treatment (n=61): physical therapy, 30 minutes twice a day, beginning on the first postoperative day active hand, wrist, elbow, and postural exercises were initiated, active and active-assisted shoulder exercises were started in conjunction with functional activities and proprioceptive neuromuscular facilitation patterning (PNF); after removal of the drain, treatment included progressive resistive exercise and PNF, exercises were made progressively more difficult; instructions with printed materials were provided for a home exercise program to be continued for at least 8 weeks, info about prostheses was given along with hand and arm care instructions
 Controls (n=54): no physical therapy

Outcome note assessor blind; psychological status (self-) assessed with SCL-90-R; goniometer; functional outcome probably observation

Follow up 5 days postoperatively and between 1-3 months (mean 2.5 months) postoperatively

Results

Outcome	Result
Function	Both groups lost range of motion but shoulder abduction and flexion was better for treated patients than controls (p<0.001) at 5 days; both groups showed improvement at the late follow up but the intervention group showed better improvement than controls (p<0.001); Controls had more difficulties with the tasks 'bring your arm behind you to wash your upper back on that side' (p=0.005), 'bring your arm across the front to wash your upper back on the opposite side' (p=0.001) and 'carry a bag with 10pounds groceries' (p=0.02) than the treatment group 5/6 tasks were more difficult for the control group at the late follow-up including zip up a back fastening zipper (p=0.02) and 'make a double bed' (p=0.05), the other mentioned tasks remained significantly more difficult for the control group
Adverse effects	Postoperative complications or lengths of hospital were not different across groups; No difference at 5 day follow up in circumferential measurements, three measurements different at late follow up but not greater than 0.2cm
Other	There were no differences in psychological status across groups

Authors concluded early physical therapy is significant for returning to normal function without

increasing postoperative complications or hospital stay.

General comments randomised sample and non-randomised pilot study combined therefore classified as cohort study; randomisation procedure not described; assessors blinded

Na YM, Lee JS Par JS et al. (1999). Early rehabilitation program in postmastectomy patients: A prospective clinical trial. Yonsei Medical Journal, 40(1), 1-8.

Design: Clinical trial, **evidence level:** 2-

Country: Korea, **setting:** presumably secondary care

Inclusion criteria patients scheduled for mastectomy with biopsy confirmed breast cancer

Exclusion criteria no consent

Population N = 33, majority with modified radical mastectomy, minority with partial mastectomy / axillary dissection, some with history of neck and shoulder pain; mean age 44 (SD: 2.1) and 47 (SD: 9.8) years in both groups

Interventions

Rehabilitation (n=20): 40 minutes physical therapy, 30 minutes exercise 4 times a day with protocol, beginning on 1st post-operative day postural exercise, assisted ROM exercise of the shoulder, elbow, wrist; active use of involved arm for light functional activities, physical modalities for pain relief or muscle spasm and therapeutic exercise including ROM exercise from 3rd post-operative day on, patients encouraged to elevate the arm as often as possible, using an elastic bandage, massaging the extremity from distal to proximal along the length, isometric and isotonic pumping exercises of the distal muscles; stretching exercises of neck or shoulder muscles after pain relief; after drain removal progressive-resistive exercises of the upper extremities, number of ordinary functional activities (e.g. dressing) progressively increased; encouraged to continue exercises after discharge for at least 4 weeks

Controls (n=13): printed material about self-exercise programme, proper positioning by physiatrist

Outcome note SCL-90-R (self report) for psychological assessment; goniometric measurement, functional evaluation using Wingate's system (questionnaire for activities of daily living) and upper extremity circumferential measurements by physiatrist

Follow up 3 days postoperatively, at discharge, 1 month after discharge

Results

Outcome	Result
Function	<p>ROM for flexion was not higher 3 days postoperative but at discharge (161 vs 150, p<0.05) and 1 month after discharge (179 vs 167, p<0.05) in the rehabilitation group compared to controls</p> <p>ROM for abduction was not higher 3 days postoperative but at discharge (129 vs 110, p<0.05) and 1 month after discharge (167 vs 119, p<0.01) in the rehabilitation group compared to controls</p> <p>ROM shoulder internal rotation was not higher 3 days postoperative or at discharge but higher 1 month after discharge (69 vs 65, p<0.05) in the rehabilitation group compared to controls</p> <p>ROM shoulder external rotation was not higher 3 days postoperative or 1 month after discharge but higher at discharge (84 vs 69, p<0.05) in the rehabilitation group compared to controls</p>
Adverse	45% of rehabilitation patients reported sensory changes, 39% of

effects	<p>the controls; oedema, wound breakdown, infection, motor weakness or adhesional bands did either not occur or only in 1 to 3 patients in both groups</p> <p>1 patient in the rehabilitation group showed an increment of circumference >1cm compared to preoperative</p> <p>Circumferential measurements did not differ between groups</p>
<p>Authors concluded that instructed rehabilitation is beneficial and does not increase complications.</p>	
<p>General comments very small control group, it is not entirely clear whether there were treatment elements that were shared between the groups; the results for the functional items were not extracted as figures indicated no differences or mixed results while the text stated statistically significant differences; the psychological variables were not compared between groups</p>	

Gordon, Battistutta, Scuffham, Tweeddale & Newman (2005a). The impact of rehabilitation support services on health-related quality of life for women with breast cancer. *Breast Cancer Research and Treatment*, 93[3], 217-226.

Gordon, LG, Scuffham P, Battistutta D et al. (2005). A cost-effectiveness analysis of two rehabilitation support services for women with breast cancer. *Breast Cancer Research and Treatment*, 94, 123-133.

Design: Prospective comparative study, Cost-effectiveness analysis **evidence level:** 2-
Country: Australia, **setting:** Community/secondary care

Inclusion criteria Intervention groups: women attending 2 rehabilitation programmes, diagnosed with primary, unilateral breast cancer, spoke English, had no cognitive problems, were aged 25-74 years; Control group: women from a different project

Exclusion criteria 'too ill', had attended the programmes previously; in one rehabilitation group, women who were recruited in a known trial of sentinel node biopsy

Population N = 275 women (about 50% of eligible patients), mean age 56 years

Interventions

DAART (n=36): Domiciliary Allied Health and Acute Care Rehabilitation Team, 6 week programme commencing 4-5 days post-surgery; home visits from physiotherapists aiming at 90% recovery of shoulder ROM and emotional support, education, tailored exercise prescription for self-management
STRETCH (n=31): Strength Through Recreation Exercise Togetherness Care Health; 8 week programme commencing 8 weeks post-operatively, group sessions, exercise physiologist, aiming at peer support, recovery of preoperative strength and shoulder ROM and alleviating psychosocial concerns

Controls (n=208): patients from the same locality, no exercises

Outcomes note mailed questionnaire, health related QoL and functional assessment self-report; Functional Assessment of Cancer Therapy including a breast cancer subscale (FACT-B); Functional Assessment of Cancer Therapy (FACT-G, = general), which excludes the breast cancer specific subscale; Extended Functional Assessment of Cancer Therapy with a specific arm morbidity subscale (FACT-B+4); Disability of the Arm, Shoulder or Hand (DASH) scale, a scale based on performing daily activities

Cost: the analysis took costs for the programme (personnel, overheads, capital equipment, other), clients (leisure forgone, travel, other expenses, health services expenditure) and the community (volunteers, lost productivity) into account; the incremental calculations were increments of the intervention over the non-intervention group; Monte-Carlo simulations

Follow up post-intervention (3-8 weeks post-diagnosis, timing varied in groups), 6 and 12 months post-diagnosis, compared to post-surgery data

Results

Outcome	Result
Function	The authors stated that DAART patients showed clinically significant improvements in arm function and upper body function Overall scores suggested relatively little disability Adjusting for known confounders there were no statistically significant differences between the three treatment groups compared for any subscale of any instrument

QoL	<p>DAART patients showed clinically significant improvements in functional well-being</p> <p>Adjusting for known confounders there were no statistically significant differences between the 3 treatment groups for any subscale</p> <p>20-40% of women at 12 months post-diagnosis had declining health related QoL scores</p> <p>According to the authors the control group had clinically important higher scores than the intervention groups for the functional, breast cancer, FACT-G and FACT-B subscales</p>
Cost	<p>The DAART intervention was most efficient with an incremental cost of \$1344 per QALY gained, the corresponding value for the STRETCH programme was \$14.478</p> <p>The cost-effectiveness acceptability curves did not cross (hence the probability that DAART is cost-effective is always higher compared to STRETCH at the same level of societal willingness to pay)</p>

Authors concluded that early physiotherapy after surgery has the potential for short-term functional, physical and overall health related QoL benefits.

General comments the 3 samples differed considerably, not just regarding the intervention (more statistically significant differences in sample characteristics than for the outcomes of interest, several variables were significant confounders); considerable conceptual overlap between the subscales and for most of the many scales it was unclear what exactly they assessed; the authors' belief in significant clinical improvements despite any statistically significant results is controversial; the effectiveness and the cost-effectiveness publications were extracted together

Christodoulakis M, Sanidas E, de Bree E et al. (2003). Axillary lymphadenectomy for breast cancer – the influence of shoulder mobilisation on lymphatic drainage. *EJSO*, 29, 303-305

Design: Cohort study with historic controls, **evidence level:** 2-

Country: Greece, **setting:** Department of Surgical Oncology

Inclusion criteria women undergoing wide local tumour excision and axillary lymph node dissection level I and II for cytologically or histologically proven invasive breast cancer

Exclusion criteria WHO performance status >2, history of disease or treatment affecting the axilla or shoulder

Population N = 100 consecutive women plus N = 60 historic controls; mean age 58 (31-81) and 58 (37-79) in both groups

Interventions

Intervention: drainage tube in axilla without restricting arm movement

Controls: external compression dressing, arm immobilised by bandage around chest and in an adduction position with the elbow in flexion and the underarm over the anterior chest wall for 4 days

Outcome note hospital records

Follow up at least 9 days; drainage recorded each day for 4 days

Results

Outcome	Result
Adverse effects	No difference between post-operative complications, only a trend towards higher drain obstruction rate in the free shoulder movement group There was no difference in drainage volume or the number of days with drain in both groups
Other	The non-restricted group had a shorter hospital stay than the immobilised historic controls (5.7 (SD: 2.3) vs 6.7 (SD: 2.2) days, p=0.009

Authors concluded external compression dressing with immobilisation has no impact on the drainage volume and duration but it is associated with adverse effects such as discomfort, prolonged hospital stay and shoulder stiffness.

General comments the difference in hospital stay between the current and the historic control can have many reasons; the conclusions regarding the adverse events is not documented in the result section apart from the length of stay

Johansson K, Ingvar C, Albertsson M & Ekdahl (2001). Arm Lymphoedema, shoulder mobility and muscle strength after breast cancer treatment – A prospective 2-year study. *Advances in Physiotherapy*, 3, 55-66.

Design: Case series, **evidence level:** 3

Country: Sweden **setting:** Departments of Physical Therapy and Surgery

Inclusion criteria women undergoing axillary dissection combined with mastectomy or segmental resection for breast cancer

Exclusion criteria previous contralateral breast disease, recurrent cancer, muscle or joint disorder, difficulties in participating such as dementia, personal reasons, too short notice

Population N = 61 (out of 90 eligible) patients, half with radiotherapy with some to the breast and axilla, mean age 56 (SD: 10)

Interventions daily home exercise programme and oedema-prevention programme, verbal and written, experienced physiotherapist; shoulder flexion and abduction in supine position, internal and external rotation sitting, 5 times, 3 times a day, at least for 6 months, to pain limit without stretching; oedema prevention: high arm position, hand pumping exercise; advice to avoid heavy or monotonous work and infections

Outcome note strength only evaluated +6 months; goniometer; Jamar dynamometer; test-retest reliability of measures assessed in pilot study; lymphoedema defined as 10% volume increase compared to non-operated arm

Follow up every month for 6 months postoperatively, at 1 and 2 years

Results

Outcome	Result
Function	Reduction of ROM for shoulder abduction was observed on 48% of patients at 5 months, at 6 months reduced internal rotation occurred in 61% of patients, abduction 41%, external rotation 34% and flexion 33%; at 2 years the corresponding values were 63, 43, 30 and 27% None of the patients returned to their preoperative values for internal rotation The patients who received radiotherapy to the breast and the axilla showed continuous impairment of ROM
Strength	A significant decrease in isometric muscle strength was found at 6 months, 1 and 2 years for flexors, adductors and internal rotators of the shoulder but no change in gripping force At 2 years there were no differences between radiotherapy and other groups
Adverse events	Arm oedema incidence 12% during 2 years

The authors concluded postoperative physiotherapeutic management needs to pay special attention to early impairments after breast cancer treatment, especially patients receiving radiotherapy to the axilla area; treatment might be introduced during radiotherapy.

General comments clearly reported; drop-outs explained; the conclusion is based on logical considerations as the study does not investigate the effect of physiotherapy alone

Rietman JS, Dijkstra PU, Debreczeni R et al. (2004). Impairments, disabilities and health related quality of life after treatment for breast cancer: A follow-up study 2.7 years after surgery. *Disability and Rehabilitation*, 26(2), 78-84.

Design: Case series, **evidence level:** 3

Country: The Netherlands, **setting:** unclear

Inclusion criteria patients undergoing modified radical mastectomy or segmental mastectomy with axillary lymph node dissection

Exclusion criteria mastectomy on both sides, metastases, patients with recurrences

Population N = 55 patients, mean age 57 (SD: 13.3) years

Interventions exercises, physical therapy

Outcome note this risk factor study assessed exercise compliance and the number of patients who had physical therapy

Follow up 2.7 years post-operatively

Results

Outcome	Result
Other	The prediction models of impairment, disability and health related quality of life did not include the factors exercise compliance or physical therapy

Authors concluded radiotherapy and chemotherapy predict impaired range of motion, pain predicts disability and health related QoL.

General comments withdrawals described (55 of 156 asked finally analysed); it is not certain that the relevant outcomes were included in the analyses in the first place but the data seemed to be theoretically available

Gosseling R, Rouffaer L, Vanhelden P et al. (2003). Recovery of upper limb function after axillary dissection. Journal of Surgical Oncology, 83, 204-211.

Design: Case series, **evidence level:** 3

Country: Belgium **setting** Department of Physiotherapy

Inclusion criteria patients undergoing at least a level I and II axillary dissection

Exclusion criteria -

Population N = 76 patients with modified radical mastectomy or breast-conserving procedure with axillary dissection, patients with mastectomy more likely to undergo irradiation of the axilla; mean age 56 (SD: 12)

Interventions Shoulder mobilisation under supervision of physiotherapist, started 2nd postoperative day to the 5th day after surgery; written and verbal instruction for lymphoedema prevention; subscription for further supervised shoulder mobilisation during 6 weeks

Outcome note active ROM; goniometer; tapemeasure for inward and outward rotation with patient standing; arm circumference with tape measure; pain visual analogue scale (0-10); questionnaire for activities of daily living, general questions regarding impairment

Follow up day 4, 3 weeks, 3 months post-surgery

Results

Outcome	Result
Function	At 4 days a significant impairment of shoulder flexion was measured, flexion improved 37° in breast-conserving and 18° in mastectomy patients after 3 months, the pattern for shoulder abduction was similar (50° and 20°) Inward rotation improved after 3 months (p=0.04), 72% of patients had a normal inward rotation, Outward rotation improved by 5 and 3 com in the two groups, 22% reached normal values 96% of patients noticed a difference in upper limb function during activities of daily living at 3 weeks
Compliance	At 3 months, the patients have had on average 25 sessions of physiotherapy (SD: 10)
Pain	The score for pain at 4 days and at 3 weeks was 3.3, after 3 months it improved to 2.6 (p=0.01)
Adverse events	5% of patients had lymphoedema at day 4, 2.5% at 3 months

Authors concluded that results warrant considering continuation of physiotherapy after 3 months post-operatively.

General comments hand dominance was considered; only marginally relevant, it is impossible to trace the results back to the mobility strategy

Johansson K (2005). Is physiotherapy useful to the breast cancer patient?
Acta Oncologica, 44, 423-424.

Design: Editorial, **evidence level:** 4

Country: Sweden, **setting:** -

Inclusion criteria -

Exclusion criteria -

Population whole review relevant

Interventions Physiotherapy, physical activity

Outcome note -

Follow up -

Results

Outcome	Result
Function	In order to prevent reduced shoulder mobility, active arm exercises are important; patients without physiotherapy postoperatively show significant limitation in range of motion and function in the shoulder (Wingate et al., 1989 cited), physiotherapy started 6 months postoperatively also improves shoulder functioning (Lauridsen et al., 2005 cited) but there is no rationale to postpone the start
Strength, Adverse events	To maintain the muscle strength of the ipsilateral arm it is important to continue on the same activity level as soon as possible postoperatively; patients are sometimes advised 'to be careful' with the affected arm to prevent lymphoedema but there is no empirical evidence to back this up

Author concluded "Yes, indeed!", physiotherapy is useful, it is worthwhile even if started after 6 months but there is no rationale to postpone the start.

General comments

Anon. (2000). Arm oedema following breast cancer treatment. <i>Drug & Therapeutics Bulletin</i> , 38(6), 41-43.	
Design: Non-systematic review evidence level: 4 Country: UK setting: - Inclusion criteria - Exclusion criteria - Population 1 relevant sentence Interventions exercise Outcome note - Follow up - Results	
Outcome	Result
Function, strength	Exercise has the advantage of promoting recovery of arm strength and mobility, and of capacity to pursue normal daily activities
The authors do not mention strategies to reduce arm and shoulder mobility problems in the conclusion.	
General comments no empirical study cited for the relevant sentence	

Beurskens, C., van Uden, C., Strobbe, L., Oostendorp, R., Wobbes, T. (2007) The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomised controlled study <i>BMC Cancer</i> 7;166.	
Design: Randomised Controlled Trial Evidence Level: 1+ Country: The Netherlands Aim: To investigate the efficacy of physiotherapy treatment of shoulder function, pain and the quality of life in patients who have undergone breast cancer surgery and axillary lymph node dissection. Beurskens <i>et al.</i> (2007) reported on a small RCT that investigated the efficacy of physiotherapy treatment of shoulder function, pain and the quality of life in patients who have undergone breast cancer surgery and axillary lymph node dissection. Functional shoulder impairments and pain in the shoulder/arm were significantly reduced following physiotherapy at three months as compared to the control group. There was no significant improvement in handgrip strength or in volume of the related arm between both groups at baseline and follow-up.	
Inclusion criteria: 18 years or older with an ALND following breast cancer A Visual Analogue Scale (VAS; 0-10) pain score of 1 or more Moderate shoulder disabilities in daily life	

<p>Exclusion criteria Previous contralateral breast cancer surgery Insufficient knowledge of the Dutch language to fill in the questionnaire</p>
<p>Population: N=30</p>
<p>Interventions: Specific physiotherapy treatment vs. no physiotherapy The control group (no physiotherapy) were given a leaflet with advice and exercises for arm and shoulder for the first weeks following surgery. Patients in the treatment group began physiotherapy two weeks after surgery in a private practice of their choice for a total number of nine treatments.</p>
<p>Outcomes: The primary outcomes were; Pain in the shoulder or arm, measured using the VAS score (0=no pain to 10=unbearable pain), shoulder mobility and abduction. Secondary outcomes included disabilities in daily life measured by DASH (Disabilities in Arm, Shoulder and Hand) questionnaire, edema, grip strength and quality of life.</p>
<p>Results Functional shoulder impairments and pain in the shoulder/arm were significantly reduced following physiotherapy ($p < 0.001$ at three months as compared to the control group). Pain decreased by 3.4 points on the VAS in the treatment group compared with a 0.5 point decrease in the control group. Shoulder flexion and abduction increased by 45 degrees and 70 degrees respectively in the treatment group compared with 11 and 13 degrees respectively in the control group ($p = 0.003$ and $p = 0.005$ respectively). There was no significant improvement in handgrip strength or in volume of the related arm between both groups at baseline and follow-up.</p>
<p>General comments Lymphoedema is a secondary outcome of this trial and so there is indirect applicability to the PICO. The length of follow-up for this study is not likely to have been sufficient to provide information on lymphatic edema following ALND as there is evidence to suggest that lymphoedema can commence anywhere between 1 month and 28 years following ALND.</p>

<p>Cinar, N., Seckin, U., Keskin, D., Bodur, H., Bozkurt, B., Cengiz, O. (2008) The effectiveness of Early rehabilitation in patients with modified radical mastectomy <i>Cancer Nursing</i> 31;2:2008</p>	
<p>Design: Randomised Trial</p>	<p>Evidence Level: 1-</p>
<p>Country:</p>	

Aim: To evaluate the effects of early onset rehabilitation program on shoulder mobility, functional capacity, lymphoedema and postoperative complications in patients who underwent modified radical mastectomy.
To determine the effect of clinical variables on the recovery of shoulder mobility, functional capacity and development of lymphoedema.

Cinar *et al.* (2008) conducted a small RCT which evaluated the effects of early onset rehabilitation program on shoulder mobility, functional capacity, lymphoedema and postoperative complications in patients who underwent modified radical mastectomy. The trial investigated the effect of clinical variables on the recovery of shoulder mobility, functional capacity and development of lymphoedema. The intervention included a treatment group (directed physiotherapy) versus home group (exercises taught by physiotherapist and patients to perform them by themselves). The improvement in measurements of flexion, abduction, and adduction movements of the shoulder joint and the functional questionnaire scores were significantly improved in the treatment group. No statistically significant difference in the development of lymphoedema and postoperative complications in both groups was observed.

Inclusion criteria: None Given

Exclusion criteria: None Given

Population: N=57

Interventions: Treatment Group (directed physiotherapy) versus Home Group (Exercises taught by physiotherapist and patients to perform them by themselves).

Outcomes: Range of Movement (ROM) including flexion, extension, and internal and external rotation
Circumferential measurements of both arms to assess lymphoedema
Upper extremity function (assessed via a functional questionnaire)

Results:

There was no statistically significant difference in the demographic properties of the patients between the groups.

There was no significant difference in preoperative ROM of the shoulder joint or upper extremity questionnaire between the operated and unoperated arms in both groups.

There were statistically significant time-related changes in all ROM and functional questionnaire scores in both groups. Flexion, abduction and adduction movements were significantly better in the treatment group compared with the home group ($p < 0.01$, $p < 0.001$, and $p < 0.005$ respectively).

The recovery of upper extremity functional questionnaire was significantly better in the treatment group compared with the home group ($p < 0.05$).

Clinical Variables

Treatment Group

- Previous Shoulder problems resulted in limited flexion ($p = 0.048$) and abduction

($p=0.019$) movements at six month assessment in the treatment group. Adduction was also limited throughout the whole follow-up period.

- Age was negatively correlated with shoulder flexion at 3 ($r = -0.415, p<0.05$) and 6 ($r = -0.487, p<0.001$) month assessment.
- Age was negatively correlated with abduction at 1 ($r = -0.510, p<0.001$), 3 ($r = -0.590, p<0.001$) and 6 ($r = -0.505, p<0.01$) month assessments.
- Body Mass Index was negatively correlated with flexion at month 3 ($r = -0.448, p<0.05$) and with abduction at month 3 ($r = -0.543, p<0.05$) and month 6 ($r = -0.456, p<0.05$).
- Body Mass Index was correlated with functional questionnaire scores at first month ($r = 0.387, P<0.05$).
- Education year was negatively correlated with first month functional questionnaire scores ($r = -0.382, p<0.05$).

Home Group

- Education year was negatively correlated with functional questionnaire scores at first month ($r = -0.400, p<0.05$).
- Education year was correlated with flexion at month 3 ($r = 0.013, p<0.05$) and extension at month 3 ($r = 0.044, p<0.05$) and month 6 ($r = 0.368, p<0.05$).
- The number of metastatic axillary lymph nodes was negatively correlated with abduction at month 1 ($r = -0.474, p<0.001$) and month 3 ($r = -0.396, p<0.05$); internal rotation at month 1 ($r = -0.452, p<0.05$) and adduction at 5th day ($r = -0.462, p<0.05$), month 1 ($r = -0.413, p<0.05$), month 3 ($r = -0.381, p<0.05$) and month 6 ($r = -0.383, p<0.05$).
- Patients who had radiotherapy had decreased shoulder abduction at six month assessment ($p=0.002$).

There was no significant time-related circumferential difference in the treatment group and a statistically significant circumferential increase in the home group ($p=0.015$) but no significant difference between the two groups.

Two patients in the treatment group and 2 patient in the home group had mild lymphoedema and 3 in the treatment group and 4 in the home group had moderate lymphoedema. In the treatment group the duration ($r = 0.586$) and amount ($r = 0.470$) of lymphoedema was correlated with the number of dissected lymph nodes

General comments:

This is not a controlled trial and there is a high potential for bias, particularly in relation to the functional questionnaire. The numbers in the study are small and no information is given as to the level of compliance with the treatment programs. The results of this study should be considered with caution.

Patients that received early postoperative rehabilitation obtained better shoulder mobility than the home group suggesting the efficacy of early rehabilitation following surgery. Recovery of functional capacity was better in the treatment group over the whole follow-up period and the six month functional questionnaire scores were better than at baseline.

Upper extremity lymphoedema following breast cancer surgery is a well known complication with reported incidence between 6% and 83%; this study recorded incidence of 19.2% for mild or moderate lymphoedema.

In the treatment group, negative correlation with age may indicate younger patients understand and apply the rehabilitation program more easily than older patients or may be indicative of the physiological decrease in mobility with age. Negative correlations with body mass index could be indicative of the difficulties obese patients may have with performing the exercises and negative correlations with education suggest that higher levels of education may lead to higher compliance with the exercise program.

8.3 What treatments are effective and safe for use to treat patients with menopausal symptoms and invasive breast cancer or DCIS?

Short Summary

Many different types of intervention were identified including pharmacological (for example, endocrine therapies), alternatives to endocrine therapies, (for example antidepressants and other prescribed medications), complementary therapies, (for example isoflavones and herbal remedies), psychological support and group activities, (for example relaxation and exercise). The majority of the evidence was drawn from systematic reviews some of which included studies of women without breast cancer. (Antoine *et al.* 2007; Bordeleau *et al.* 2007; Carpenter *et al.* 2007; Col *et al.* 2005; Deng *et al.* 2007; Ganz *et al.* 2000; Goodwin *et al.* 2008; Hickey *et al.* 2005; Kenemans *et al.* 2005; Kimmick *et al.* 2006; Kroiss *et al.* 2005; Loprinzi *et al.* 2007; MacLennan *et al.* 2004; Modelska *et al.* 2002; Mom *et al.* 2006; Nedrow *et al.* 2006; Nelson *et al.* 2006; Pritchard *et al.* 2002; Royal College of Obstetricians and Gynaecologists *et al.* 2006; Thompson *et al.* 2008; Tremblay *et al.* 2008; von Schoultz *et al.* 2005; Walji *et al.* 2007)

There was inconsistency in the findings of RCTs of Hormone Replacement Therapies (HRT) and progestational agents regarding breast cancer recurrence, several trials were ongoing. All RCTs of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine/noradrenaline reuptake inhibitors (SNRIs) were consistent in reporting a moderate effect in reducing hot flush frequency and severity. A reduction in menopausal symptoms was also reported from RCTs of clonidine and gabapentin, although the latter was only effective at high doses. A comparison of venlafaxine with clonidine found that daily hot flush frequency was reduced more effectively by venlafaxine than clonidine. The synthetic steroid, tibolone, produced a reduction in hot flushes comparable to HRT, improved sexual function and possibly mood. However there were longer term safety considerations since the drug increased blood lipids and clotting factors. There was no effect of red clover on menopausal symptoms however there were no studies of women with breast cancer. Soy extracts provided conflicting effects with a possible weak effect for women without breast cancer. There were no significant effects on hot flushes for black cohosh, vitamin E or magnetic therapy in women with breast cancer. There may be a risk of hepatic disorders with black cohosh and its safety remains under review by the Medicines and Healthcare products Regulatory Agency (MHRA). A comprehensive menopausal assessment programme found significant improvements in the menopausal symptom scale with reduced symptoms in the intervention group and an improvement in sexual functioning. Another systematic review found some effect of relaxation on hot flushes for women with breast cancer however the study quality was poor. There was no significant effect on hot flush frequency of acupuncture for women with breast cancer from one RCT.

PICO

POPULATION	INTERVENTION	COMPARISON	OUTCOME
<p>Patients with invasive breast cancer/DCIS and menopausal symptoms:</p> <p>i) which arise from treatment for invasive breast cancer</p> <p>ii) which arise independently of (e.g. present prior to) treatment for breast cancer</p> <p>Consider subgroups with increased risk of breast cancer at an early age (see comment)</p>	<p>Any intervention to manage symptoms</p> <p>e.g.:</p> <p>Prescribed therapies (e.g. HRT, antidepressants)</p> <p>Over the counter remedies</p> <p>Psychological support</p> <p>Alternative therapies e.g. phyto-oestrogen, other natural remedies</p> <p>Group therapy</p> <p>Provision of literature/education</p> <p>Dietary factors</p> <p>Planned weight reduction.</p>	<p>No intervention</p> <p>Versus each other</p>	<p>Primary outcomes:</p> <p>Recurrence</p> <p>DFS</p> <p>Symptoms of</p> <ul style="list-style-type: none"> • Hot flushes • Night sweats • Loss of libido • Mood swings • Memory loss • Vaginal problems <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Sleep disturbance • Headaches • Palpitations

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

A large volume of literature was available for the time period searched between 1968 and 2007. Many different types of intervention were identified including pharmacological e.g. hormone therapies, alternatives to hormone therapies, e.g. antidepressants and other prescribed medications, complementary therapies, e.g. isoflavones and herbal remedies, psychological support, group activities, e.g. relaxation and exercise. Since studies of psychosocial support tended to be concerned with the experience of having breast cancer rather than the relief of symptoms these were not included in this section of the review. The majority of the evidence was drawn from systematic reviews and it was not possible to differentiate between patients with invasive breast cancer or DCIS as suggested in the PICO table. Some trials in the systematic reviews included a healthy population of women with menopausal symptoms. The RCT populations were sometimes heterogeneous, some women were recruited after breast cancer treatment whilst others were still undergoing treatment.

There was inconsistency in the findings of RCTs of Hormone Replacement Therapies (HRT) and progestational agents regarding breast cancer recurrence, several trials were ongoing. All RCTs of SSRI/SNRIs were consistent in reporting a moderate effect in reducing hot flush frequency and severity. A reduction in menopausal symptoms was also reported from RCTs of clonidine and gabapentin, although the latter was only effective at high doses. A comparison of venlafaxine with clonidine found that daily hot flash frequency was reduced more effectively by venlafaxine than clonidine. The synthetic steroid, tibolone, produced a reduction in hot flashes comparable to HRT, improved sexual function and possibly mood. However there were longer term safety considerations since the drug increased blood lipids and clotting factors. There was no effect of red clover on menopausal symptoms however there were no studies of women with breast cancer. Soy extracts provided conflicting effects with a possible weak effect for women without breast cancer. There were no significant effects on hot flushes for black cohosh, vitamin E or magnetic therapy in women with breast cancer. A comprehensive menopausal assessment programme found significant improvements in the menopausal symptom scale with reduced symptoms in the intervention group and an improvement in sexual functioning. Another systematic review found some effect of relaxation on hot flashes for women with breast cancer however study quality was poor. There was no significant effect on hot flash frequency of acupuncture for women with breast cancer.

Hormone Replacement Therapy

One good quality systematic review and meta-analysis comparing the findings of RCTs and non-randomized studies (NRS) of the use of HRT in breast cancer survivors reported that results of observational studies are discrepant to those of RCTs (Col *et al* 2005, 1++). The pooled RR of the two randomized trials was 3.41 (95% CI 1.59–7.33) for any breast cancer recurrence favouring no treatment with HRT. The largest contribution to this effect was from the Swedish HABITS trial (Holmberg & Anderson 2004) which was stopped early due to the increased incidence of new breast cancer events in the HRT arm. A third RCT (von Schoultz *et al* 2005) conducted since the meta-analysis

provided conflicting findings of no increase in risk with HRT (RR=0.82, 95% CI 0.35-1.9) and suggested that the choice of hormone regimen may modify the recurrence risk. However caution in the use of HRT is recommended whilst trials are ongoing. The Cochrane review (MacLennan *et al* 2004, 1++) provided evidence of the effectiveness of HRT vs. placebo in a non-breast cancer population, with a 75% reduction in hot flush frequency provided by the treatment.

An update search identified another systematic review (Antoine *et al* 2007, 1+) including two RCTs (Holmberg & Anderson 2004, von Schoultz *et al* 2005) which reported the conflicting findings of these two trials.

Epidemiological evidence

An update search identified one review of the use of hormone therapy in women without a diagnosis of breast cancer (Shapiro 2007) from recent analyses of the Million Women Study (MWS) and the Women's Health Initiative (WHI). The WHI data suggested that oestrogen therapy reduced the overall risk of breast cancer especially of ductal and localized breast cancers. The MWS suggested that the increased risk of breast cancer in women on HRT was greatest for lobular and tubular tumours, whilst the risk for ductal carcinoma was raised but to a lesser extent.

Progestational agents

A fair quality review of progestational agents (Mom *et al* 2006, 2+) reported the effectiveness of oral and intramuscular progestins in reducing hot flush frequency. Despite this, caution was recommended for women with breast cancer because of an additional increased risk of breast cancer in women using estrogen-progestagen combinations compared to estrogen only, suggesting an influence of progestagens on cancer growth.

An update search identified an RCT (Goodwin *et al* 2008, 1+) which reported that a 20mg dose of oral megestrol acetate significantly reduced hot flush frequency with little effect on other menopausal symptoms.

Antidepressants (SSRI and SNRI)

One good quality systematic review (Nelson *et al* 2006, 1++) and 2 recent good quality RCTs (Carpenter *et al* 2007, 1+; Kimmick *et al* 2006, 1+) compared the effectiveness of paroxetine, venlafaxine, fluoxetine or sertraline with placebo in women with breast cancer. The systematic review reported a combined estimate which indicated a reduction of approximately 1 hot flash/day for paroxetine, venlafaxine, fluoxetine and citalopram in 6 trials. This compares with a reduction of 2.5-3 /day on oestrogen. Different doses of paroxetine did not produce a differential effect, whilst higher doses of venlafaxine were more effective (from 1 trial). Fluoxetine was not statistically different from placebo. Citalopram was not used in studies of women with breast cancer.

A recent crossover RCT of high and low dose venlafaxine vs. placebo used a monitor to measure physiological hot flashes as well as self reports. Both doses

moderately reduced the frequency of hot flashes, but only the higher dose reduced hot flash interference (Carpenter *et al* 2007, 1+).

Another recent small crossover RCT (Kimmick *et al* 2006, 1+) reported no differences in hot flash frequency or score for sertraline vs. placebo. However the crossover analysis revealed a reduction in hot flashes of -0.9 and -1.7 at 6 and 12 weeks when changing from placebo to sertraline which was significant when compared with an increase in frequency when crossing from sertraline to placebo ($p = 0.03$ and 0.03). Measures of depression and quality of life were within normal ranges and did not change significantly within treatment groups.

One recent RCT (Loibl *et al* 2007, 1++) compared venlafaxine directly with clonidine. Venlafaxine was significantly more effective in reducing daily hot flash frequency (decrease of 7.6 / day) than clonidine (decrease of 4.9 / day). However patients taking venlafaxine had significantly more symptoms of nausea.

In an update search an RCT comparing sertraline with placebo in healthy peri- and post-menopausal women found that sertraline was ineffective and associated with bothersome symptoms (Grady *et al* 2007).

Clonidine

The good quality systematic review (Nelson *et al* 2006, 1++) of non-hormonal therapies for menopausal symptoms identified 2 RCTs of clonidine vs. placebo for women with breast cancer.

- Goldberg (1994) found a decrease in mean difference of hot flush frequency of -0.79 (95% CI -1.55 to -0.04) and a composite score (frequency x severity) of 56% vs. 30% ($P < 0.04$) in comparison to placebo.
- Pandya (2000) found a decrease in mean difference of hot flush frequency of -1.17 (95% CI -1.87 to -0.47) and reduced frequency of 24% vs. 14% $P = 0.09$ in comparison to placebo.

Both studies were of fair quality and show a moderate decrease in the frequency of hot flushes in comparison to placebo for women with breast cancer.

Gabapentin

The good quality systematic review (Nelson *et al* 2006, 1++) of non-hormonal therapies for menopausal symptoms identified 1 RCT of gabapentin vs. placebo for women with breast cancer (Pandya *et al* 2005). The severity and frequency of hot flushes was significantly reduced on the high dose of 900 mg, but not on the low dose of 300 mg (45% vs. 15%, $P < 0.001$).

An update search identified one RCT of women using antidepressants for menopausal symptoms which compared existing treatment plus gabapentin (900mg) with gabapentin alone (Loprinzi *et al* 2007, 1+). Eighty one percent of

participants had a history of breast cancer. There was a median reduction of 50% in hot flash frequencies and scores regardless of whether the patients continued on antidepressants.

Levetiracetam

An update search identified a pilot Phase II study (Thompson *et al* 2008; Level 3) on the use of levetiracetam to reduce hot flashes. A significant reduction in hot flash scores and frequency was reported. However further evaluation is required.

Tibolone (synthetic steroid)

A systematic review of tibolone assessed the effects over a range of outcomes including hot flush frequency, mood, sexual function and serum lipids (Modelska & Cummings 2002, 1+). Of the 8 RCTs identified most reported a significant reduction in hot flushes and sweating in women taking tibolone compared with placebo. Two trials reported improvements in mood for women taking tibolone. Three trials reported a beneficial effect of tibolone on fatigability, frequency of headaches, psychological instability, and insomnia.

Two randomized and double-blind trials assessed the effects of tibolone on sexual function compared with placebo. In the first trial by Nevinny-Stickel (1983), there was no significant improvement in libido in women taking tibolone. In contrast, the recent double blind, placebo-controlled trial by Laan (2001) has shown that treatment with tibolone significantly improved the physiological aspects of sexual function in postmenopausal women, such as vaginal blood flow and lubrication, and subjective measures, such as sexual desire and arousability.

Seven trials assessed the effects of tibolone on lipids and the clotting factors compared with those of placebo. Tibolone reduced HDL-C by approximately 34% and decreased triglycerides by approximately 25%, but had no effect on LDL-C and lipoprotein(a).

Compared with placebo, tibolone caused increases in hemoglobin, antithrombin III, plasminogen, and platelet count. Conclusions about risks for cardiovascular disease or venous thromboembolism cannot be drawn from these trials.

A recent RCT (Kroiss *et al* 2005, 1+) comparing tibolone with placebo found no change in the daily number of hot flushes with either tibolone or placebo ($P = 0.219$) after three months. There was a significant reduction in the severity of flushes with tibolone compared with placebo (-0.4 vs 0.2, $P = 0.031$). At 12 months there was a decrease of 30% in frequency of hot flushes and sweats in the tibolone group, and an increase of 30% in the placebo group. A significant decrease in triglycerides (-23% vs. 1.4%) and HDL (-12% vs. 19%) was observed after 12 months of treatment on tibolone.

Isoflavone extracts (red clover and soy)

A high quality systematic review assessed the effects of non-hormonal agents on hot flushes (Nelson *et al* 2006, 1++). The RCTs of red clover extracts did not include women with breast cancer. One poor quality RCT (Jeri 2002) found a reduction in hot flash frequency vs. placebo (48.5% reduction vs 0%, $P < 0.001$). However the other 5 did not show a significant difference of red clover vs. placebo. The overall effect on combining the trials was a small reduction that was not significant, weighted mean difference -0.44 (95% CI, -1.47 to 0.58).

Soy isoflavone extracts were compared with placebo in 11 trials (4 of women with breast cancer). Effects from individual trials were conflicting with 3 studies finding that severity scores improved for soy isoflavone users, and no difference between soy and placebo in severity scores for other studies. There was a significant effect of soy isoflavones in reducing hot flash frequency on 50-70 mg/day for 4-6 weeks, 12-16 weeks and 6 months. These trials did not include breast cancer patients. The effect at 4-6 weeks was not significant when the one trial of breast cancer patients using SERM and a higher dose of soy isoflavones was included (Quella *et al* 2000). The combined weighted mean difference in number of daily hot flashes for soy isoflavones compared with placebo was -1.15 (95% CI, -2.33 to 0.03) after 4 to 6 weeks in 5 trials; -1.48 (95% CI, -2.49 to -0.48) after 4 to 6 weeks in 4 trials when the study of women with breast cancer was removed; -0.97 (95% CI, -1.82 to -0.12) after 12 to 16 weeks use in 4 trials; and -1.22 (95% CI, -2.02 to -0.42) after 6 months in 2 trials.

An update search identified another systematic review (Bordeleau *et al* 2007, 1+) which also assessed soy isoflavones. One additional study in breast cancer patients was included in the review, however there was no significant difference between placebo (40% reduction) and soy beverage (30% reduction) groups (Van Patten *et al* 2002).

Black cohosh

Four RCTs analysed in two systematic reviews found conflicting evidence of effectiveness of black cohosh for women with breast cancer (Nelson *et al* 2006, 1++; Walji *et al* 2007, 1+).

Vitamin E

One fair quality crossover trial of women with breast cancer (Barton 1998, N=125, 4 weeks/phase) compared 800IU/day of vitamin E with placebo. There were no significant differences between groups in hot flash frequency or severity.

Psycho-educational interventions

A systematic review of psycho-educational interventions to relieve hot flashes was identified in an update search (Tremblay *et al* 2008, 1+). Three of the RCTs involved women with breast cancer, including the study by Ganz *et al* (2000) of the Comprehensive Menopausal Assessment programme described below, which was identified previously. There was some effect of relaxation on hot flash frequency in two RCTs however both studies were poor in quality.

Comprehensive Menopausal Assessment (CMA)

This was delivered by a nurse practitioner and focused on symptom assessment, education, counselling and, as appropriate, specific pharmacologic and behavioural interventions for each of the three target symptoms (hot flashes, vaginal dryness, stress urinary incontinence). Change scores for the menopausal symptom scale differed significantly between groups ($P=0.0004$) with reduced symptoms in the intervention group. There was a statistically significant improvement in sexual functioning for the intervention group on the CARES scale ($P=0.04$) (Ganz *et al* 2000, fair).

Magnetic therapy

One small crossover placebo controlled trial of 15 women with breast cancer evaluated magnetic devices placed over 6 Chinese acupressure points corresponding to hot-flash relief (Carpenter & Andrykowski 2002, poor). The device was only applied for 72 hours. Results from 11 survivors of breast cancer showed that magnetic therapy and placebo reduced hot flash frequency and bothersome hot flashes. There was significantly more effect in the placebo group ($p=0.02$). There were no differences between groups in hot flash severity, interference with daily activities, and overall quality of life.

Acupuncture

An update search identified one RCT of acupuncture to treat hot flashes for women with breast cancer (Deng *et al* 2007, 1+). There were no significant differences between groups after four weeks of treatment.

An update search identified a further systematic review of therapeutic options for hot flashes in breast cancer survivors (Bordeleau *et al* 2007, Level 1+). This included another RCT of an open-label study of venlafaxine (Barton *et al* 2002). The randomised phase found a reduction in hot flashes with no changes in toxicity over time. The review authors suggest that the optimal starting dose of venlafaxine is 37.5 mg/day with a doubling of the dose if no effect within 3 to 7 days.

The systematic review (Bordeleau *et al* 2007) also commented further on the paroxetine RCT of breast cancer patients (Stearns *et al* 2005). More patients favoured paroxetine 10 and 20 mg (71%-72%) than placebo (25%); and patients were less likely to discontinue treatment on 10 mg paroxetine than 20 mg (5% vs. 17%; $p=0.02$).

Bordeleau (2007) made some general comments about the use of SSRIs and SNRIs in breast cancer patients noting that as well as reducing hot flashes there were improvements in other associated symptoms such as sleeplessness, loss of libido, depression and anxiety. The adverse effects associated with use were nausea, decreased appetite, dry mouth, somnolence/insomnia and headache which may lead to discontinued treatment in 10-15% of women with breast cancer. In addition SSRIs may inhibit cytochrome P450 reducing the amount of active tamoxifen metabolites available in women with a particular genotype (CYP2D6 variant). This effect is

associated primarily with paroxetine, moderately with fluoxetine and sertraline, but not with venlafaxine.

One recent RCT of sertraline for women with breast cancer was identified and is included in the next table. In an update search a further RCT of sertraline compared with placebo in healthy perimenopausal and postmenopausal women was identified. Sertraline was found to be ineffective and associated with bothersome symptoms. (Grady D, Cohen B, Tice J, Krisof M, Olyaie A, Sawaya GF. Ineffectiveness of sertraline for treatment of menopausal hot flushes - A Randomized controlled trial. *Obstet Gynecol* 2007;109(4):823-30).

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Evidence table

Intervention: Hormone replacement therapy (HRT)

Meta-analysis of RCTs

Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Research* 2005;7(4):R535-R540.

Aim: To estimate the impact HRT has on recurrence risk from observational and randomised studies, and to examine the reliability of these estimates.

Design: Systematic review
analysis of RCTs only)

Level 1++ (for the meta-

Country: Multinational

Inclusion criteria Studies of women with invasive breast cancer receiving oral HRT, a defined comparison group and reporting of breast cancer recurrence.

Exclusion criteria Studies reporting overlapping or redundant data, those not describing control groups, topical hormones.

Population 2 RCTs (Holmberg & Anderson 2004, Marsden *et al* 2000)

N=445 patients

Mean age 55.5 years

Mean disease free interval (DFI) 33.2 months (Median 38 months Holmberg 2004; median 31.8 Marsden 2000)

Duration of HRT 19.9 months (Mean 24 months Holmberg 2004; mean 6 months Marsden 2000)

Node status not reported

ER/PR status not reported

Interventions

Oral HRT

Outcomes

Recurrence –defined as any second breast cancer event (local, regional or distant recurrence or invasive cancer in either breast)

Deaths

Follow up - Mean follow-up after HRT 25.2 months (Holmberg & Anderson 2004)

Follow-up not reported in (Marsden *et al* 2000)

Results

Study characteristics and results from the 2 trials are reported in the following table.

Study	N participants	Mean duration of HT	Mean follow-up	Recurrences	Deaths – all cause	Deaths – primary tumour
Holmberg & Anderson 2004	345	24 months	24	HT 26 No HT 7	HT 5 No HT 4	HT 3 No HT 4
Marsden <i>et al</i>	100	6	NR	HT 2	NR	NR

al 2000		months		No HT 1	NR	NR
Total	445			HT 28 No HT 8	9	7

Key:
HT = Hormone Therapy
NR = not reported

A total of 36 recurrences and 9 deaths occurred during the study period the largest contribution of these events occurred in the Holmberg (2004) trial with longer follow-up and greater recruitment. This trial was stopped early because of the increased breast cancer recurrences in participants taking hormonal therapy.

The pooled risk ratio (RR) for the two randomized trials was 3.41 (95% CI 1.59–7.33) $p=0.0016$ favouring no HT, significant statistical heterogeneity was present.

The RCT by Holmberg (2004) provided the best available data on the impact of HRT in breast cancer survivors. Col commented that the unblinded design and lack of a placebo group could lead to selective attrition, but the follow-up rates were comparable between arms.

A further RCT was reported since this analysis (The Stockholm Trial, von Schoultz *et al* 2005) that used cyclical hormone treatment for younger patients (<55 years) and a spaced regime for older women to minimize the use of progestogen combined with oestrogen. At a median follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with menopausal hormone therapy (RR = 0.82, 95% CI = 0.35 to 1.9). The authors concluded that doses of oestrogen and progestogen and treatment regimens for menopausal hormone therapy may be associated with the recurrence of breast cancer.

A further comment was that statistically significant heterogeneity in the rate of recurrence was observed ($P = .02$; two-sided likelihood-ratio test) between the two studies (HABITS vs. Stockholm), indicating that chance may not be the only explanation for the conflicting findings.

Author conclusions:

Observational studies of HRT use in breast cancer survivors have design limitations that cannot be controlled for using standard statistical methods and hence should be considered essentially uninformative with respect to the safety of HRT use in breast cancer survivors. Only randomized clinical trials are likely to provide reliable estimates of the effect of HRT use in this setting.

RCTs included:

Holmberg L, Anderson H, for the HABITS steering and data monitoring committees: HABITS (hormonal replacement therapy after breast cancer – is it safe?), a randomised comparison: trial stopped. *Lancet* 2004, 363:453-455.

Marsden J, Whitehead M, A'Hern R, Baum M, Sacks N: Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? *Fertil Steril* 2000, 73:292-299.

Added: von Schoultz E, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. Journal of the National Cancer Institute 2005;97(7):533-5.

General comments –The review also included observational studies (n=8) which have been omitted from this table.

An updated search identified another systematic review of hormone therapy in breast cancer patients and is included below.

Antoine C, Liebens F, Carly B, Pastijn A, Neusy S, Rozenberg S. Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007;22(2):616-22.

Design: Systematic review

Level 1+

Country: Belgium

Aim: To analyze the safety of hormone therapy (HT) in breast cancer patients.

Inclusion criteria Articles in English or French languages, safety data of HT or oestrogen therapy (ET) on breast cancer recurrence and survival in women with invasive breast cancer.

Search dates not reported.

Exclusion criteria Not reported

Population 2 RCTs (Holmberg & Anderson 2004, von Schoultz *et al* 2005)

18 non-randomized studies were also identified but not included in this table.

Holmberg & Anderson 2004: HABITS trial 434 postmenopausal patients with early stage breast cancer (1997-2003); duration HT 2.1 years (0.1-5.3), follow-up 2.1 years (0.1-5.5)

Node positive 24% (69/292)

HR positive 52% (159/305)

Tamoxifen 21% (72/345)

von Schoultz et al 2005: Stockholm trial 359 postmenopausal patients with early stage breast cancer (1997-2003), HT duration 4.1 years (0.2-7), follow-up 4.1 years (0.2-3.3)

Node positive 18% (65/355)

ER positive 60% (216/359)

Tamoxifen 53% (189/359)

Interventions

Intervention arm received HT in both RCTs.

Holmberg & Anderson 2004:

HT compared with controls on at least one other therapy of either clonidine, sotalol, psychological help, exercise or acupuncture.

von Schoultz et al 2005:

The treatment if any in the comparison arm was not reported.

Both trials unblinded.

Outcomes

Relapses (locoregional and contralateral breast cancer recurrences)

Recurrences

Contralateral breast cancer

Deaths

Distant metastases

Follow up –

Holmberg & Anderson 2004 follow-up 2.1 years (0.1-5.5)

von Schoultz *et al* 2005 4.1 years (0.2-3.3)

Results

The trials were not combined because of heterogeneity in the trial methods and population

characteristics.

Results reported in the review are shown in the following table:

Outcome	Holmberg 2004	Von Schoultz 2005
Total recurrences: HR Control		11 13
Locoregional recurrences: HR Control	11 2	5 5
Distant recurrence: HR Control	10 5	3 5
Contralateral breast recurrence: HR Control	5 1	3 3
Breast cancer deaths: HR Control	3 4	2 4
All cause (deaths): HR Control	5 4	4 9

Relative Hazard of breast cancer recurrence for women taking HT:

Holmberg & Anderson 2004: At a median of 2.1 years RH = 3.3 (95% CI 1.5-7.4) – trial stopped early

von Schoultz *et al* 2005. At a median of 4.1 years RH = 0.82 (95% CI 0.35-1.9)

The same conclusions apply as in the previous systematic review by Col.

Author conclusions: There are no data to indicate an absence of a harmful effect of HT. Further studies should analyze the safety of different regimens and there is a need for RCTs to assess the safety of these regimens.

General comments –

This systematic review was identified during an update search.

MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database of Systematic Reviews: Reviews. Cochrane Database of Systematic Reviews 2004 Issue 4. Chichester (UK): John Wiley & Sons, Ltd; 2004

Design: Cochrane systematic review

Level 1++

Country: Multi-national

Aim: To examine the effect of oral HRT compared to placebo on these vasomotor symptoms and the risk of early onset side-effects.

Inclusion criteria

Double-blind, randomised, placebo-controlled trials of oral HT for at least three months duration.

Exclusion criteria

Un-blinded or single-blinded trials, non-identical HT and placebo packaging, participants not randomised, no placebo.

Non-menopausal women, major intercurrent disease, previous HT within 1 month of commencement of study.

Population

Menopausal women recruited from any health care setting or a population based sample with either spontaneous menopause or bilateral oophorectomy (removal of both ovaries).

Peri-menopausal women were defined as women with spontaneous menopause and irregular menstruation over the last 12 months. Post-menopausal women were defined as women with surgical menopause or spontaneous menopause and amenorrhea for more than 12 months.

Interventions

All oral oestrogens with or without concomitant progestogens (administered as sequential or continuous progestogen therapy) for a minimum treatment period of three months.

Outcomes

The primary outcome was hot flushes which includes the symptoms of night sweats and was defined as any otherwise unexplained sensation of flushing/sweating experienced by the woman being studied.

Follow up -

Results

115 abstracts were identified, 24 trials met the selection criteria.

Study participants = 3,329.

Trial duration ranged from three months to three years.

There was a significant reduction in the weekly hot flush frequency for HT when compared to placebo (WMD -17.92, 95% CI -22.86 to -12.99). HT reduced hot flush frequency by 75% (95% CI 64.3 to 82.3) relative to placebo. Symptom severity was also significantly reduced compared to placebo (OR 0.13, 95% CI 0.07 to 0.23).

No adverse effects were found but the trials were only short term.

Author conclusions:

Oral HT is highly effective in alleviating hot flushes and night sweats. Therapies should

only be assessed in blinded trials against a placebo or a validated therapy because of the large placebo effect seen in well conducted RCTs, and because during menopause symptoms may fluctuate then after menopause symptoms decline.

General comments –

No breast cancer studies were included in this high quality systematic review. It is reported in this table to show the magnitude of effect achieved by HT on menopausal hot flushes.

Registered RCTs

Bliss J. Randomized Study of Hormone Replacement Therapy for Relieving Menopausal Symptoms in Postmenopausal Women With Prior Stage I or II Breast Cancer. 2004.

Cochrane Central Register of Controlled Trials.

Rageth C. Phase III randomised study of hormone replacement therapy in menopausal or perimenopausal women with prior stage 0-II breast cancer. 1999. Cochrane Central Register of Controlled Trials.

Cobleigh MA. Phase III randomized study of hormone replacement therapy for hot flashes and/or vaginal symptoms in postmenopausal women with a history of node-negative invasive carcinoma or ductal carcinoma in situ of the breast who are receiving adjuvant Tamoxifen. 2001. Cochrane Central Register of Controlled Trials.

Guidelines

Pritchard KI, Khan H, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. *Can Med Assoc J* 2002;166(8):1017-1022.

Recommendations:

Safety of HRT for women with a history of breast cancer

- Routine use of HRT (either oestrogen alone or oestrogen plus progesterone) is not recommended for women diagnosed with breast cancer because of the risk of recurrence and contralateral breast cancer. Randomized controlled trials are required to guide recommendations. The effect of HRT on recurrence and contralateral breast cancer has not been determined in methodologically sound studies. However animal and in vitro studies have shown the development and growth of breast cancer to be oestrogen dependent. Since there is an increased risk of breast cancer associated with HRT in women without a diagnosis of breast cancer, this risk could be of a similar magnitude for women with breast cancer
- Postmenopausal women with a previous diagnosis of breast cancer who request HRT should be encouraged to consider alternatives. If menopausal symptoms are troublesome and unresponsive to alternative approaches, then HRT may be used after discussion of the risks with her physician. Both the dose and duration of treatment should be minimized.

Validation: Internal validation within the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.

Although this guideline is now out-of-date the recommendations still stand in the light of the findings from more recent RCTs of women with breast cancer.

An update search identified another guideline on the role of local vaginal oestrogens for vaginal atrophy:

Hickey M, Saunders CM, Stuckey BGA. Non-hormonal treatments for menopausal symptoms. *Maturitas* 2007;57(1):85-9.

One recommendation relevant to cancer patients was that for women with a non-hormone dependent cancer, management of vaginal atrophy is similar to women with no history of cancer. For women with a history of hormone-dependent cancer then management recommendations are for each woman's preference in consultation with her oncologist.

Intervention: Progestational agents (progestins)
Systematic review

Mom CH, Buijs C, Willemse PH, Mourits MJ, de Vries EG. Hot flushes in breast cancer patients. [Review] [94 refs]. Critical Reviews in Oncology-Hematology 2006 Jan;57(1):63-77.

Aim: A literature search was conducted to gather information concerning the pathophysiologic mechanisms leading to hot flushes, their prevalence and severity in breast cancer patients, their influence on quality of life, and the best therapeutic option.

Design: Systematic review Level 2+ (includes non-randomized studies)
 Country: Multinational

Inclusion criteria Primary studies and relevant reviews including all types of intervention. Large randomized, double-blind, placebo controlled trials were preferable, but non-randomized studies were included where no randomized studies were available.

Exclusion criteria Case reports

Population Women with a history of breast cancer

Interventions

A range of interventions were assessed, progestational agents are the focus in this section.

Outcomes

Frequency of hot flushes.

Follow up -

Results

Studies identified:

Author	Design	Agent
N		
Loprinzi (1994) 163 (97 BrCa/66 men)	RCT (cross over)	Megestrol acetate vs. placebo prostate ca)
Barton (2002) 15 BrCa	Case series	Medroxyprogesterone (intra muscular)
Bertelli (2002) 71	RCT	Medroxyprogesterone (im) vs. oral

Loprinzi (1994)

After four weeks of treatment there was a reduction in hot flashes of 21 percent in the group receiving placebo first, and 85 percent in the group receiving megestrol acetate first (P < 0.001). An analysis of eligible treated patients found a 50 percent or more decrease in hot flash frequency over the first 4 weeks in 74 percent of the megestrol acetate group compared with 20 percent of the placebo group (P < 0.001). Efficacy was similar in men and women. The cessation of menstrual bleeding in women was the only side effect, usually occurring one to two weeks after discontinuation of megestrol acetate.

Barton (2002)

Treatment with megestrolprogesterone produced a 90% decrease in hot flashes (95% CI 82-97%). Daily hot flash frequency decreased from a mean of 10.9 on the first day of treatment (95% CI 8.0-13.8 hot flashes per day) to a mean of 1.1 hot flashes after 6 weeks (95% CI 0.5-1.8 hot flashes), and to a mean of 0.7 hot flashes at 12 weeks (95% CI 0.1-1.2). The reduction in hot flash frequency was maintained for some months after discontinuation of injections in many patients. Minimal side effects reported were reported.

Bertelli (2002)

At six weeks hot flashes were reduced by 86% for all patients with no significant differences between the two progestins. A response was achieved in 75 and 67% of patients receiving MPA or megestrol, respectively ($P = 0.5$). When responders were followed to assess whether the response was maintained (without further treatment), this was significantly greater in the i.m. MPA: group (89% of responders showed a benefit at week 24 compared with 45% in the megestrol group, $P = 0.03$).

References:

Barton D, Loprinzi C, Quella S, Sloan J, Pruthi S, Novotny P. Depomedroxyprogesterone acetate for hot flashes. *Journal of Pain & Symptom Management* 2002 Dec;24(6):603-7.

Bertelli G, Venturini M, Del ML, Bergaglio M, Sismondi P, Biglia N, et al. Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: a randomized study. *Ann Oncol* 2002 Jun;13(6):883-8.

Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, et al. Megestrol acetate for the prevention of hot flashes. *The New England journal of medicine* 1994;331(6):347-52.

Author conclusions

Despite the effectiveness of progestagens for the treatment of hot flushes, there is a hesitation to use hormonal agents in breast cancer patients. The Million Women Study (Beral 2003), of a million healthy women aged 50-64 years found an additional increased risk of breast cancer in women using oestrogen-progestagen combinations compared to oestrogen only, suggesting an influence of progestagens on cancer growth.

General comments –

These findings have also been confirmed in two Women's Health Initiative RCTs (Rossouw 2002, Anderson 2004).

**Randomized controlled trial
Megestrol acetate**

An update search identified another RCT of oral megestrol acetate for menopausal symptoms in breast cancer patients, this is included below:

Goodwin JW, Green SJ, Moinpour CM, Bearden JD 3rd, Giguere JK, Jiang CS, Lippman SM, Martino S, Albain KS. Phase III randomized placebo-controlled trial of two doses of megestrol acetate as treatment for menopausal symptoms in women with breast cancer: Southwest Oncology Group Study 9626. *Journal of Clinical Oncology* 2008 Apr 1;26(10):1650-6.

Design: RCT (1998-2000)

Level 1+

Country: USA, setting: Multi-centre

Aim: To test the progestin megestrol acetate (MA) at two doses versus placebo over 6 months for the treatment of hot flashes in women with breast cancer

Inclusion criteria

Patients with T1-3, N0-1, M0 infiltrating breast cancer after completion of surgery and chemotherapy and at least 4 months of tamoxifen (if prescribed). Women with at least 10 hot flashes of any severity or at least five severe episodes per week. Previous hormones and steroid treatments were discontinued but other ongoing medications for hot flashes were allowed.

Exclusion criteria

Pregnancy, lactating, history of deep vein thrombosis, vaginal bleeding if postmenopausal, previous malignancies.

Population number of patients =288 randomized, 286 eligible

Age range 38-82 years

On tamoxifen 80%

75% experienced hot flashes over 6 months

40% had over 63 hot flashes / week

Interventions

Randomized to:

Placebo (n=101)

20 mg megestrol acetate (MA20) (n=92)

40 mg megestrol acetate (MA40) (n=93)

Stratification was by:

Tamoxifen status – not taking tamoxifen vs. > 4 months

Number of hot flashes per week - 5 – 34; 35 – 63; > 63

Duration of hot flashes (<6 months vs. >6 months)

Drugs were administered for an initial period of 6 months and the response measured. Those that achieved a successful response continued in the blinded study for a further 3 months. Patients not achieving a response were placed on open label MA 20 for a further 3 months in addition to the blinded study drug.

Primary outcomes were measured at 3 months.

Outcomes

Patient Report of Menopausal Symptoms: Number and severity of hot flashes recorded daily for 1 week, from mild to very severe in 4 categories

Daily log of hot flashes (frequency only)

Symptom log

Common Toxicity Criteria (CTC) for depression (Grade 1 to 3 – representing mild to severe and interfering with daily living activities in the latter) and fatigue (Grade 1 to 3 – representing mild to severe-related to ECOG performance status)

Follow up Daily log of hot flashes evaluated after initial 6 month period. Failure defined as less than 75% reduction in hot flash episodes compared with baseline or discontinuation of treatment before 3 months. Patients were re-registered after evaluating the response. Those considered a success continued on the blinded study drug for an additional 3 months. Patients not successful received one open-label MA20 tablet in addition to blinded study drug for an additional 3 months. A final response evaluation was conducted at 6 months (initial period + 3 month extension).

Results

3 month assessment of Hot Flash Log (N=244).

241/286 (84%) of patients were re-registered at 3 months for the second part of the trial, 225 were eligible to continue.

206/286 (72%) completed 6 months of treatments and completed a Hot Flash Log

Treatment	Eligible at start (n=286)	Completed 3 months (n=225)	Completed 6 months (n=206)
Placebo	101	78	67
MA20	92	77	71
MA40	93	70	68

Primary outcomes at 3 months:

Treatment	% completing treatment	Success (≥75% reduction in hot flash frequency from baseline)	P value (reference placebo)
Placebo	83	14%	
MA20	90	65%	<0.001
MA40	83	48%	<0.001

After 6 months the % successful in reducing hot flashes (by ≥75% from baseline):

Placebo (also given MA20 if not successful after 3 months): 64%

MA20	77%
MA40	81%

The response to treatment at 3 months by age, tamoxifen use, or number and duration of hot flashes was not associated with the overall response (p values were not reported).

Physician rated toxicity at 3 months

Most reported toxicities were grade 1 and included: oedema, and weight gain in placebo arm;

fatigue for MA20 arm; depression, fatigue, nausea and weight gain for MA40 arm. No significant differences between treatment arms were found (data not reported). More patients taking MA had vaginal bleeding than the placebo arm. Toxicity scores ranged from 0.4 to 2.3 (scale 0 “not at all” to 4 “extremely bothersome”). The difference in scores from baseline was not reported. There were some small differences in scores at 6 months, differences and significance were not assessed.

Author conclusions: MA significantly reduced vasomotor symptoms with durable benefit over 6 months. MA 20 mg/d is the preferred dose. There was no significant impact on other menopausal symptoms.

General comments –

The results of this study were not presented very clearly. The change in symptom scores pre and post intervention were not reported and no statistical tests were applied to measure the significance of changes in symptoms other than hot flash frequency.

Guidelines

Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncology* 2005;6(9):687-95.

Alternatives to HRT for management of symptoms of the menopause. Royal College of Obstetricians and Gynaecologists (2006). Scientific Advisory Committee Opinion Paper 6.

Both of these guidelines note that the safety of progestagens is uncertain with potential risk to the breast.

Intervention: Antidepressants (SSRI and SNRI)
Systematic review of RCTs

Nelson HD, Vesco KK, Haney E, Fu RW, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes - Systematic review and meta-analysis. *Jama-Journal of the American Medical Association* 2006;295(17):2057-71.

Aim: To compare the efficacy and adverse effects of therapies other than those primarily composed of oestrogen, progestin or progesterone, or androgen for menopausal hot flashes from published RCTs.

Design: Systematic review (1966-2005)

Level 1++

Country: Multinational

Inclusion criteria

Published English-language, randomized, double-blind, placebo-controlled trials providing data on treatment of menopausal hot flashes using 1 or more non-hormonal therapies

Exclusion criteria

Head-to-head trials without a placebo group that compared non-hormonal therapies with oestrogen or other medications were excluded because of difficulty interpreting results without a placebo.

Trials of women with other major diseases or oestrogen use within 1 month of commencement of the study.

Population

Women experiencing menopausal hot flashes recruited from health care settings or the general population. Trials of women with breast cancer were included and additional data, such as use of tamoxifen or other selective oestrogen receptor modulators (SERMs), were obtained.

Interventions

Antidepressants including Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Norepinephrine/Noradrenaline Reuptake Inhibitors (SNRIs).

Outcomes

Frequency or severity of hot flashes. (Frequency obtained by self-report using symptom diaries).

Severity measures also self-reported using a graded scale or a composite measure (frequency x severity). Hot flash frequency and composite measures have demonstrated validity and reliability, and are highly correlated.

Outcomes were determined by the differences in hot flashes measured at baseline and the end of the trial. Treatment effects were defined as the differences in outcomes between the treatment and placebo groups at the end of the trial.

Follow up -

Results

Ten trials of antidepressant medications met the inclusion criteria:

6 trials of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) [paroxetine (2), venlafaxine (2), fluoxetine (2) and

citalopram (1)]. The citalopram study was not conducted in breast cancer patients.

Three trials of the antidopaminergic drug veralipride and 1 trial of a selective monoamine oxidase-A inhibitor moclobemide were also identified. These former 3 trials were conducted in the 1980s and were of poor quality, the more recent trial of moclobemide was also poor in quality. None were conducted in breast cancer patients. These agents have not been commented on in the evidence table.

Results of hot flash frequency in studies in breast cancer patients are shown in the following table:

Study	Duration	Antidepressant dose	Comparison	Hot flash frequency
Stearns 2003 (not br ca but good quality) N=165	6 weeks	Paroxetine 12.5 or 25 mg/day	Placebo	3.2-3.3 vs. 1.8 fewer episodes, P=0.01
Stearns 2005 (Br Ca patients on Tamoxifen) Cross over trial. Fair quality. N=151	4 weeks / phase	Paroxetine 10 or 20 mg/day	Placebo	50-51% vs. 15% P<0.001
Loprinzi 2000 (Br ca or high risk). Good quality. N=221	4 weeks	Venlafaxine 37.5, 75 or 150 mg/day	Placebo	30-58% vs. 19% P<0.001
Loprinzi 2002 (Br ca or high risk) Cross over trial. Fair quality. N=81	4 weeks / phase	Fluoxetine 20 mg/day	Placebo	No difference

Both paroxetine and venlafaxine were significantly effective in reducing hot flash frequency compared with placebo. There was no difference in effect between fluoxetine and placebo.

Results of the meta-analysis are reported in the following table. Only the findings from the breast cancer trials are reported as individual studies.

Study / quality	Participants	Antidepressant dose	Mean difference (95% CI) in number of hot flashes / day
Stearns 2005 fair	151	Paroxetine 10 or 20 mg/day	-2.43 (-4.43 to -0.42)
Loprinzi 2000 good	167	Venlafaxine 37.5, 75 mg/day (Excludes 150mg/day dose)	-1.09 (-1.99 to -0.18)
Loprinzi 2002 fair	81	Fluoxetine 20 mg/day	-0.90 (-3.78 to 1.98)
Trials with SERM	564	4 comparisons	-1.40 (-1.97 to -0.82)

use combined		(includes the 3 breast cancer trials) (paroxetine, venlafaxine, fluoxetine, citalopram)	
Trials of SERM use in women without breast cancer	180	2 comparisons (venlafaxine and citalopram)	-0.17 (-1.41 to 1.07)
All trials combined	844	7 comparisons	-1.13 (-1.70 to -0.57)

SSRI/SNRIs significantly reduced hot flash frequency by 1 hot flash / day overall trials. This compares with a reduction of 2.5-3 /day on oestrogen. The effect was slightly stronger in SERM users overall (includes the 3 trials of women with breast cancer). There was no significant effect in SERM users who did not have breast cancer. Different doses of paroxetine did not produce a differential effect, whilst higher doses of venlafaxine were more effective (from 1 trial).

Author conclusions:

The SSRIs or SNRIs trials provide evidence for efficacy based on a small number of fair to good quality studies; however, effects are less than for oestrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take oestrogen but are not optimal choices for most women.

RCTs of breast cancer patients included in the table and meta-analysis:

Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356(9247):2059-63.

Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2002;20(6):1578-83.

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes - A randomized controlled trial. *Jama-Journal of the American Medical Association* 2003;289(21):2827-34. (not breast cancer)

Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;23(28):6919-30.

General comments –

Some trials use cumulative symptoms scores (e.g. Kupperman Index and Greene Climacteric Scale) to assess hot flashes and other menopausal symptoms. Use of these scores is problematic because some have not been validated, different components are measured which cannot be compared directly, and measures of vasomotor symptoms may not be specific.

The authors report a significant level of heterogeneity in the meta-analyses the degree of heterogeneity is not reported or commented on in the findings. Other non-hormonal

interventions were assessed and these are reported in appropriate sections of the evidence table.

Randomized controlled trial Venlafaxine

One recently published RCT comparing venlafaxine with placebo, and another comparing venlafaxine with clonidine were identified:

Carpenter JS, Storniolo AM, Johns S, Monahan PO, Azzouz F, Elam JL, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. *Oncologist* 2007 Jan;12(1):124-35.

Design: 2 RCTs (2000-2004)

Level 1+

Double-blind, cross-over, placebo controlled

Country: USA, setting: Multicentre Cancer Centre clinics

Aim: To evaluate the efficacy of venlafaxine for self-reported and physiological hot flashes.

Inclusion criteria

Adult women with a history of breast cancer

No other cancer

Disease-free and functioning independently at the time of study enrollment

At least 4 weeks after completion of local therapy (chemotherapy or radiation)

Experiencing daily hot flashes (1 per day)

Desiring treatment for hot flashes but not currently using any other hot flash treatments

Postmenopausal or using a clinically acceptable method of birth control throughout the study to prevent pregnancy

Within 60 miles of study site to access the hot flash monitor

Verified as non-depressed by study psychologist through structured clinical interview.

Exclusion criteria

On tamoxifen or aromatase inhibitor for 6 weeks

On antidepressants

Receiving hot flash treatment within the past 4 weeks (e.g., soy supplements, botanicals, vitamin E, and prescription medications)

Pregnant or lactating.

Population number of patients :

N= 64 low dose arm

N=20 high dose arm

Interventions

Two randomized, double-blind, placebo-controlled crossover trials of 14-weeks duration.

Low-dose study = 6 weeks of 37.5 mg venlafaxine daily (n =64)

High-dose treatment = 1 week of 37.5 mg venlafaxine daily, then 4 weeks of 75 mg venlafaxine daily, then 1 week of 37.5 mg venlafaxine daily (n = 20).

Extended release formulations were used.

No washout periods because of the short half-life of the drug (5 hours) and the major metabolite (11 hours).

Outcomes

Hot flash frequency using diaries and monitors during one 24 hour period per week, evaluated using the validated Hot Flash-Related Daily Interference Scale

Psychological outcomes:

Negative affect index was calculated as the combination of standardized scores on four questionnaires:

Profile of Mood States Short Form total mood disturbance score (excluding fatigue)

Positive and Negative Affect Scale - the negative affect subscale only

Centre for Epidemiological Studies Depression Scale

Hamilton Rating Scale-Depression (Ham-D).

Follow up 14 weekly visits.

Weeks 1 and 2 provided baseline information (B1 and B2), and weeks 3 to 14 included 6 weeks of treatment (T1–T6) and 6 weeks of placebo (P1–P6).

In the high dose arm patients received 75 mg per day during weeks T2–T5 and 37.5 mg at T1 and T6 to taper on and off the drug.

Patients were telephoned 1, 6, and 12 months after completing the weekly visits to assess continued venlafaxine use.

Results

Low dose hot flash frequency

When compared with placebo the physiological hot flash frequency, self-reported frequency (diary and event marker), hot flash severity and bother were reduced. Findings are reported in the following table:

Low dose outcomes:

Hot flashes/24 hr	Mean (% change from baseline)			P value	Effect size (95% CI)
	Baseline	Placebo	Low dose		
Monitor frequency	7.46	7.49 (0)	5.80 (-22)	<0.001	0.16 (0.09 – 0.23)
Diary frequency	6.02	4.96 (-18)	3.50 (-42)	<0.001	0.22 (0.16 – 0.29)
Event marker frequency	7.72	6.02 (-22)	4.52 (-41)	<0.001	0.20 (0.14 – 0.26)
Diary severity	4.27	4.54 (6)	3.95 (-7)	<0.001	0.21 (0.14 – 0.27)
Diary distress	3.86	4.27 (10)	3.71 (-4)	<0.001	0.20 (0.13 – 0.28)
interference	2.33	1.52 (-35)	1.42 (-39)	0.47	0.05 (-0.09 – 0.20)

On low dose treatment physiological hot flashes decreased by 1.7/day (22%) compared with baseline.

Diary hot flashes decreased by: 1.46/day (24%) compared with placebo

2.52/day (42%) compared with baseline.

There was no significant difference overall in psychological outcomes when compared to placebo (negative affect, fatigue, sleep quality, quality of life).

The reported side effects that were significantly more severe compared with placebo were headaches, constipation and dry mouth during the venlafaxine treatment period.

High dose hot flash frequency

When compared with placebo the physiological hot flash frequency, self-reported frequency (diary and event marker), hot flash severity, bother and interference were reduced. Findings are reported in the following table:

High dose outcomes:

Hot flashes/24 hr	Mean (% change from baseline)			P value	Effect size (95% CI)
	Baseline	Placebo	High dose		
Monitor frequency	7.46	8.44 (13)	6.43 (-14)	0.013	0.22 (0.05 – 0.39)
Diary frequency	6.02	5.78 (-4)	4.53 (-25)	0.001	0.24 (0.10 – 0.38)
Event marker frequency	7.72	9.42 (22)	7.44 (-4)	<0.001	0.19 (0.10 – 0.29)
Diary severity	4.27	4.05 (-5)	3.12 (-27)	<0.001	0.39 (0.24 – 0.53)
Diary distress	3.86	4.10 (6)	3.15 (-19)	<0.001	0.39 (0.24 – 0.54)
interference	2.33	1.97 (-36)	1.23 (-47)	0.003	0.50 (0.18 – 0.82)

On high dose treatment physiological hot flashes decreased by 1.03/day (14%) compared with baseline.

Diary hot flashes decreased by: 1.49/day (25%) compared with baseline

Again there was no significant difference overall in psychological outcomes when compared to placebo (negative affect, fatigue, sleep quality, quality of life). Significantly less trouble sleeping but more severe constipation and dry mouth were reported when taking venlafaxine at the high dose.

There was no placebo effect for the physiological hot flash monitor in the low-dose study (p = 0.52). However, there was a placebo effect for self-reported hot flashes. In the high dose study there was no placebo effect for physiological hot flashes (p = 0.71), but again there was a placebo effect for self-reported hot flashes.

The trials found a modest reduction in physiological and self-reported hot flashes in patients on venlafaxine compared with placebo. Both doses of venlafaxine reduced physiological and subjective hot flash frequency, hot flash severity and bother. However, hot flash interference improved only at the higher dose of 75-mg. The effects on physiological hot flashes were greatest at 1 week of treatment on the 37.5mg daily dose, and at 5 weeks on the 75mg daily dose.

Limitations

The authors reported the main study limitations as (a) racially and ethnically homogeneous samples, (b) small sample sizes, (c) limited treatment time, and (d) lack of pharmacogenetic data. Because of the lack of sample diversity and lack of a non-cancer comparison group the findings may not be generalizable to a broader population.

Summary

The subjective hot flash measures showed placebo effects in comparison to the physiological measurements. There were modest decreases in hot flash frequency, severity and distress on venlafaxine, but only hot flash interference improved at the higher dose. The timing of the effects on hot flashes varied by dose. A subgroup of women with $\geq 50\%$ decrease in physiological hot flashes also experienced significant improvements in fatigue, sleep quality, and quality of life. Side effects were mild, but most patients discontinued venlafaxine in the long-term.

Author conclusions: Although venlafaxine resulted in modest and acute reductions in hot flashes with few side effects, it may not be tolerable to some patients long-term. At least 50% relief in physiological hot flashes may be needed for patients to demonstrate improvement in other outcomes, including decreased fatigue, improved sleep, and improved quality of life.

General comments –

The quality of life outcomes were only significantly improved in a small subgroup of patients who obtained at least a 50% reduction in monitor hot flashes, and have not been reported in the table.

Randomized clinical trial Venlafaxine vs. clonidine

Loibl S, Schwedler K, von MG, Strohmeier R, Mehta K, Kaufmann M. Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients--a double-blind, randomized study. *Ann Oncol* 2007 Apr;18(4):689-93.

Design: RCT (2002-2004)
Level 1 ++
Country: Germany, setting: Single university hospital
Aim: To compare venlafaxine to another non-hormonal agent in the treatment of hot flashes of breast cancer patients.

Inclusion criteria

Women aged over 18 years with primary breast cancer experiencing hot flashes at least 14 times per week or seeking help for hot flashes.

Hot flashes for at least 4 weeks.

A predefined menopausal status was not required.

ECOG performance status 0 to 1.

Exclusion criteria

Previous treatment with venlafaxine, clonidine, oestrogens, progestogens, or androgens for hot flashes.

Current treatment with hypertensive or antidepressant agents or other non-hormonal agents for hot flashes such as black cohosh, isoflavone, and vitamin E.

Patients with hypertension, hypotension, peripheral or cardiovascular diseases, symptomatic cardiac diseases or metastatic disease.

Population number of patients = 80 recruited, 64 evaluable

Interventions

Stratification was by:

Age (≤ 50 years versus > 50 years)

Adjuvant therapy (endocrine versus no endocrine therapy).

Randomization was double-blind to receive **twice** daily 0.075 mg clonidine (total 0.15mg) or 37.5 mg venlafaxine (total 75mg) in tablet form over 4 weeks.

In the original plan patients were to cross-over treatments after 4 weeks, but this was abandoned because of missing data.

Clonidine n=40, with 33 evaluable

Venlafaxine n=40, with 31 evaluable

Outcomes

Frequency of hot flashes (number of hot flashes/week)

Severity of hot flashes (hot flash severity score obtained by scoring mild =1 to severe =4)

Hot flash severity score = Sum of (severity score X frequency) per day

Toxicity

Symptoms

Follow up Four weeks

Results

Most patients (n = 55; 69%) had taken an endocrine treatment for breast cancer concurrently (85% treated if not intention to treat analysis):

Treatment	N =55	%
Tamoxifen	42	76
Tamoxifen and goserelin	6	11
Aromatase inhibitor (ARI)	5	9
ARI with goserelin	2	4

Data related to hot flash frequency for each drug are reported in the following

table:

Outcome	Clonidine (n=33)	Venlafaxine (n=31)
Decrease in median hot flash frequency from baseline (100%)	37% (SE 4.7)	57% (SE 7.4) P=0.025
Decrease in daily median hot flash frequency	4.85 / day	7.6 / day
Increase in hot flash frequency from baseline (>100%)	6% (n=2)	10% (n=3)
Decrease in hot flash frequency from baseline		
0-24%	12% (n=4)	29% (n=9)
25-49%	24% (n=8)	26% (n=8)
50-74%	33% (n=11)	19% (n=6)
75-100%	24% (n=8)	16% (n=5)
>100%	6% (n=2)	10% (n=3)
Decrease in hot flash score	8.9 units /day [57% SE 6.2]	11.4 units /day [39% SE 5.4] P=0.043

Most of the outcomes favoured venlafaxine which produced a larger decrease in hot flash frequency over the 4 week period and on a daily basis.

Toxicity

Toxicity was evaluated weekly. There was no difference in the frequency of symptoms before treatment between groups and the most common symptoms were dry mouth, restless sleep and tiredness.

After treatment there was no difference between groups for the following outcomes measured:

- Loss of appetite
- Sleeplessness
- Drowsiness
- Tiredness
- Sweating
- Constipation
- Restless sleep
- Nervousness
- Moodiness
- Mouth dryness

Nausea was significantly increased in the venlafaxine group (n=6; 19%) compared to the clonidine group (n=2; 6%; p=0.05). During the first week 39% of patients on venlafaxine had nausea.

Author conclusions: Venlafaxine is significantly more effective in reducing the frequency of hot flashes in breast cancer patients than clonidine

General comments -

Randomized controlled trials

Sertraline

Kimmick GG, Lovato J, McQuellon R, Robinson E, Muss HB. Randomized, double-blind, placebo-controlled, crossover study of sertraline (Zoloft) for the treatment of hot flashes in women with early stage breast cancer taking tamoxifen. *The breast journal* 2006;12(2):114-22.

Design: RCT (1996-2000)

Level 1+

Double-blind, cross-over, placebo controlled

Country: USA, setting: Oncology Clinic

Aim: To determine if sertraline is effective in decreasing the frequency and severity of hot flashes in breast cancer survivors taking adjuvant tamoxifen.

Inclusion criteria

Women aged ≥ 18 years with localized breast cancer (stages 0–IIIB) receiving adjuvant tamoxifen therapy and had at least one hot flash per day (or more than seven hot flashes per week).

Menopausal status determined by patient self-report.

Exclusion criteria

Pregnancy or breast-feeding, a history of seizure disorder, or hepatic or renal insufficiency.

Oestrogen, progestagen, corticosteroids, androgens or other antidepressant therapy.

Population number of patients = 62 women enrolled

Median age 53.9 years (36.6–77.1)

Postmenopausal = 89%

Breast cancer survivors on adjuvant tamoxifen reporting bothersome hot flashes.

Baseline hot flash frequency/ day 5.8 (SD 4.1)

Baseline hot flash score (SD 12.1)

Interventions

Randomized, double-blind, placebo-controlled, crossover study of a 50 mg dose of sertraline (each morning) for 6 weeks followed by placebo for 6 weeks or vice versa.

Stratification was by menopausal status and average number of hot flashes/day.

Outcomes

Daily hot flash diary recording hot flash frequency and severity, then hot flash scores (frequency x severity) were calculated.

Centre for Epidemiologic Studies depression scale to assess mood (at baseline, 6 weeks, and 12 weeks).

Functional Assessment of Cancer Therapy--Breast (FACT-B) (at baseline, 6 weeks, and 12 weeks) to assess quality of life.

Follow up

Baseline week n=54

First 6 weeks n=47

All 12 weeks n=39

Results

At 6 weeks there were no statistically significant differences in hot flash frequency or scores between groups. After 6 weeks a 50% reduction in the frequency of hot flashes was seen in 36% of women taking sertraline (n = 25) compared with 27% taking placebo (n = 22) (p = 0.7) which was also not significant.

At 12 weeks, patients initially on sertraline and had crossed over to placebo had a 1% change in hot flash frequency compared to the level at 6 weeks. No statistically significant differences were found in hot flash frequency or scores when compared to baseline.

However, the crossover analysis found sertraline to be significantly more effective in controlling hot flashes than placebo:

A comparison of hot flash frequency and score at 6 and 12 weeks, found women crossing from placebo to sertraline had a decrease (-0.9 [SD = 3.7] and -1.7 [SD = 8.4] respectively) whilst women crossing from sertraline to placebo had an increase (1.5 [SD = 2.6] and 3.4 [SD = 5.2], respectively) (p = 0.03 and 0.03).

The hot flash frequencies and scores reported in the paper are shown in the following table:

	Placebo then sertraline	Sertraline then placebo	P value
Baseline	n=25	n=29	
Frequency (SD)	5.5 (4.4)	6.1 (3.9)	0.6
Score (SD)	11.2 (13.6)	12.8 (16.1)	0.7
Week 6	n=22	n=25	
Frequency (SD)	4.4 (3.8)	4.9 (5.7)	0.8
Score (SD)	7.6 (7.9)	10.8 (22.7)	0.5
Change at 6 weeks vs baseline	n=22	n=25	
Frequency (SD)	-1.5 (3.9)	-1.6 (3.0)	0.9
Score (SD)	-4.6 (13.0)	-3.2 (8.1)	0.7
50% reduction in hot flash frequency at 6 weeks	27%	36%	0.7
Week 12	n=19	n=20	
Frequency (SD)	3.9 (5.3)	4.9 (2.9)	0.4
Score (SD)	6.5 (11.2)	8.6 (7.5)	0.5
Change at 6 weeks vs baseline	n=19	n=20	
Frequency (SD)	-0.9 (3.7)	1.5 (2.6)	0.03
Score (SD)	-1.7 (8.4)	3.4 (5.2)	0.03

There was no carry-over effect, period effect, week effect or treatment effect detected.

Forty-eight percent preferred the sertraline period, 11% preferred the placebo

period, and 41% had no preference ($p = 0.006$).

Side effects

During the first 6 weeks of the study the most frequent side effects reported were:

	Sertraline (n=25)	Placebo (n=22)
Total	14 (44%)	7 (25%)
Nausea	7 (28%)	2 (9%)
Fatigue/malaise	3 (12%)	0
Diarrhoea	5 (20%)	0
Anxiety/nervousness	3 (12%)	0

Quality of life

There were no significant differences between placebo and sertraline arms on the CES-D scale at baseline, 6 weeks and 12 weeks. The mean scores decreased sequentially over time on placebo. However mean scores decreased at 6 weeks then increased to more than baseline at 12 weeks in the sertraline arm. More than 30% of patients had dropped out by 12 weeks. Mean scores on the CES-D were below the recognized clinical cut-off point (≥ 17) for depression at all time points and in both treatment arms.

Similarly quality of life scores (FACT-B) did not differ significantly between the placebo and sertraline groups. The scores remained similar to the baseline level. In summary the depression and quality of life scores were within the normal range and did not change significantly within treatment groups.

Author conclusions

There was no significant change in hot flash frequency or score with sertraline versus placebo. Women who completed all 12 weeks of treatment preferred sertraline to placebo. Presently venlafaxine is the treatment of choice to alleviate hot flashes, as it has no effect on tamoxifen metabolites. Sertraline, a related SSRI/ SNRI, may also have efficacy and may be an alternative in women who do not tolerate venlafaxine.

General comments –

A small crossover study, questionable whether there was sufficient power to detect changes.

Guidelines

Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncology* 2005;6(9):687-95.

Alternatives to HRT for management of symptoms of the menopause. Royal College of Obstetricians and Gynaecologists (2006). Scientific Advisory Committee Opinion Paper 6.

Both guidelines predate the recent trial evidence. However RCOG suggest that venlafaxine is the most effective SNRI for vasomotor symptoms.

Intervention: Other prescribed medications

Clonidine (α -adrenergic agonist antihypertensive)

Gabapentin (γ -aminobutyric acid analogue anticonvulsive)

Levetiracetam (a pyrrolidine with antiepileptic activity)

Tibolone (a synthetic steroid)

Systematic review of RCTs

Nelson HD, Vesco KK, Haney E, Fu RW, Nedrow A, Miller J, et al. Non-hormonal therapies for menopausal hot flashes - Systematic review and meta-analysis. *Jama-Journal of the American Medical Association* 2006;295(17):2057-71.

Aim: To compare the efficacy and adverse effects of therapies other than those primarily composed of oestrogen, progestin or progesterone, or androgen for menopausal hot flashes from published RCTs.

Design: Systematic review (1966-2005)

Level 1++

Country: Multinational

Inclusion criteria

Published English-language, randomized, double-blind, placebo-controlled trials providing data on treatment of menopausal hot flashes using 1 or more non-hormonal therapies

Exclusion criteria

Head-to-head trials without a placebo group that compared non-hormonal therapies with oestrogen or other medications were excluded because of difficulty interpreting results without a placebo.

Trials of women with other major diseases or oestrogen use within 1 month of commencement of the study.

Population

Women experiencing menopausal hot flashes recruited from health care settings or the general population. Trials of women with breast cancer were included and additional data, such as use of tamoxifen or other selective oestrogen receptor modulators (SERMs), were obtained.

Interventions

Clonidine – a centrally active α -adrenergic agonist antihypertensive.

Gabapentin – γ -aminobutyric acid analogue anticonvulsive

Outcomes

Frequency or severity of hot flashes. (Frequency obtained by self-report using symptom diaries).

Severity measures also self-reported using a graded scale or a composite measure (frequency x severity). Hot flash frequency and composite measures have demonstrated validity and reliability, and are highly correlated.

Outcomes were determined by the differences in hot flashes measured at baseline and the end of the trial. Treatment effects were defined as the

differences in outcomes between the treatment and placebo groups at the end of the trial.

Follow up -

Results

Ten RCTs of clonidine were identified, two of these included women with breast cancer and were of fair quality.

Two RCTs of gabapentin were identified, one good quality trial included women with breast cancer.

Clonidine

Placebo-controlled trials of Clonidine for women with breast cancer

Results of hot flash frequency in studies of breast cancer patients are shown in the following table.

Study	Duration	Antihypertensive dose	Comparison	Hot flash frequency
Goldberg 1994 (Br Ca patients on Tamoxifen) Cross over trial. Fair quality. N=116	4 weeks / phase	Clonidine 0.1 mg/day transdermal	Placebo	44% vs. 27% P<0.04
Pandya 2000 (Br ca patients on Tamoxifen). Fair quality. N=198	8 weeks treatment 4 week follow-up	Clonidine 0.1 mg/day	Placebo	24% vs. 14% P<0.09

Both trials reported a reduction in hot flash frequency, reduced severity and composite scores were also reported. Women in these two trials were also taking tamoxifen (SERM use). Adverse effects of clonidine were dry mouth, insomnia or drowsiness.

A meta-analysis of 6 of the 10 clonidine trials (N=672) was conducted which included both of the breast cancer studies. The mean differences of hot flash frequency / day of relevant studies are shown in the following table:

Study / quality	Participants	Clonidine dose	Mean difference (95% CI) in number of hot flashes / day
Goldberg 1994 Fair quality	116	0.1 mg/day 4 weeks	-0.79 (-1.55 to -0.04)
Pandya 2000 Fair quality	198	0.1 mg/day At 4 weeks	-1.17 (-1.87 to -0.47)

Trials with SERM use combined	314	2 comparisons (includes the 2 breast cancer trials at 4 weeks)	-1.00 (-1.51 to -0.49)
All 4 week studies combined (4 trials)	444	4 comparisons	-0.95 (-1.44 to -0.47)
Pandya 2000 Fair quality	198	0.1 mg/day At 8 weeks	-1.70 (-2.91 to -0.49)
All 8 week trials combined (2 trials)	228	2 comparisons	-1.63 (-2.76 to -0.50)

There was a significant reduction in mean difference of hot flash frequency in both breast cancer trials compared to placebo. Reduced severity and composite score was also reported by Goldberg (1994). A significant reduction was also obtained when combining all trials at 4 weeks. When the 4 week trials without SERM use were combined in the meta-analysis a weaker non-significant effect was obtained [-0.53 (-2.09 to 1.04)]. The combination of 2 trials after 8 weeks of treatment produced a stronger effect than the combination at 4 weeks.

The 10 clonidine trials reported inconsistent results, with approximately half of the trials reducing hot flash frequency and severity significantly. The estimate for the 3 fair quality trials combined was a reduction of approximately 1 hot flash/day. Clonidine may relieve hot flashes by reducing peripheral vascular activity.

Gabapentin

Placebo-controlled trials of Gabapentin

Results of hot flash frequency in two studies are shown in the following table. One good quality study involved breast cancer patients.

Study	Duration	Gabapentin dose	Comparison	Hot flash frequency
Guttuso 2003 Fair quality. N=59	12 weeks	300 mg 3 times daily	Placebo	45% vs. 29% P=0.02
Pandya 2005 (Breast cancer 71% patients on Tamoxifen). Good quality. N=420	4 weeks and 8 weeks	100 mg 3 times daily 300 mg 3 times daily	Placebo	44% vs. 15% P<0.001 900mg dose Severity 46% vs. 15% P<0.001 900mg 300mg/d no difference

Meta-analysis

2 trials	N=479	Weighted mean difference vs. placebo in number of daily hot flashes. -2.05 (-2.80 to -1.30)
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Both trials reported a reduction in hot flash frequency and severity compared to placebo. Only the 900 mg/day dose was effective in reducing hot flashes. The meta-analysis reported a combined mean difference of both trials. Mean differences of individual studies was not reported. Side effects reported were somnolence, fatigue, dizziness, rash, heart palpitations and peripheral oedema.

Author conclusions:

Same comments as for SSRIs. Clonidine and gabapentin trials were effective in reducing the frequency and severity of menopausal hot flashes based on a small number of fair to good quality trials (gabapentin) or poor to fair quality trials (clonidine); however, effects are less than for oestrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take oestrogen but are not optimal choices for most women.

RCTs of breast cancer patients included in the tables and meta-analysis:

Clonidine

Goldberg RM, Loprinzi CL, O'Fallon JR, Veeder MH, Miser AW, Mailliard JA, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 1994;12(1):155-8.

Pandya KJ, Raubertas RF, Flynn PJ, Hynes HE, Rosenbluth RJ, Kirshner JJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Annals of internal medicine* 2000;132(10):788-93.

Gabapentin

Pandya KJ, Morrow GR, Roscoe JA, Zhao H, Hickok JT, Pajon E, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366(9488):818-24.

General comments –

Some trials use cumulative symptoms scores (e.g. Kupperman Index and Greene Climacteric Scale) to assess hot flashes and other menopausal symptoms. Use of these scores is problematic because some have not been validated, different components are measured which cannot be compared directly, and measures of vasomotor symptoms may not be specific. The authors report a significant level of heterogeneity in the meta-analyses but this is not commented on in the findings.

Randomized Controlled Trials

Gabapentin

An update search identified one RCT comparing gabapentin alone with gabapentin whilst taking an antidepressant.

Loprinzi CL, Kugler JW, Barton DL, Dueck AC, Tschetter LK, Nelimark RA, et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. J Clin Oncol 2007;25(3):308-12.

Design: RCT (Nov 2004 –July 2005)

Level 1+

Country: USA, setting: Multi-centre

Aim: To address the use of gabapentin in women with inadequate control of hot flashes on an antidepressant.

Inclusion criteria

Women receiving antidepressants for hot flashes with at least 14 severe hot flashes / week.

History of breast cancer or concern about taking hormones.

No current evidence of disease.

Exclusion criteria

Women taking a monoamine oxidase inhibitor, a tricyclic antidepressant, clonidine.

Population number of patients = 113 eligible

Age = median 54 years (range 39-81)

Venlafaxine treatment 78%

Paroxetine treatment 7%

Tamoxifen treatment 37%

Aromatase inhibitor 30%

Breast cancer history 81%

Interventions

Randomization was stratified by duration of treatment (<9 vs ≥ 9 months), frequency of hot flashes/day (2-3 v 4-9 v >9), antidepressant (venlafaxine v paroxetine v other).

Week 1: continue taking antidepressant already prescribed

Following 3 weeks: gabapentin 300mg for 3 days; twice daily for 3 days; 3 times daily for 22 days.

Patients in one arm continued with the prescribed antidepressant.

Patients in the other arm were weaned off the antidepressant over 7-10 days

Outcomes

Daily hot flash diary to record frequency and severity of hot flashes (1=mild, 2=moderate, 3=severe, 4=very severe)

Weekly symptom diary – scored 0-10

Weekly quality of life (QoL) questionnaire

Follow up 4 weeks

Results

Data available for:
 Hot flash frequency n=101 (89%)
 Week 4 frequencies n=91 (81%)
 Baseline hot flash scores n= 99 (88%)
 Week 4 scores n=88 (78%)

Hot flashes

No significant differences between arms at week 4 in changes from baseline of hot flash scores (p=0.37) or hot flash frequencies (p=0.61).

Week 4 findings	Gabapentin	Gabapentin + antidepressant	P value
Median reduction hot flash score	60% (95%CI 33-73%)	56% (95%CI 26-71%)	P=0.37
Median reduction hot flash frequency	49% (95%CI 26-58%)	54% (95%CI 34-70%)	P=0.61

Toxicity

No significant differences between arms in changes from baseline at each treatment week for the 17 toxicity items (from self-reports). A trend of more dizziness was noted in patients receiving gabapentin alone in week 1, which reduced over the course of treatment. A slight increase in nervousness was also noted in the gabapentin only arm.

Quality of life

No significant differences between arms in changes from baseline to week 4 in self-assessments of QoL:

- Overall QoL (p=0.98)
- Mental well-being (p=0.27)
- Physical well-being (p=0.23)
- Emotional well-being (p=0.45)
- Social activity (p=0.82)
- Spiritual well-being (p=0.77)

Author conclusions: Gabapentin decreased hot flashes by approximately 50% in women with inadequate control taking antidepressants. There was no significant additional hot flash reduction from continuation of antidepressant.

General comments -

Levetiracetam

Phase II study

An update search identified a recent phase II study of another centrally acting agent levetiracetam which is briefly described in the next table.

Thompson S, Bardia A, Tan A, Barton DL, Kottschade L, Sloan JA, et al. Levetiracetam for the treatment of hot flashes: a phase II study. Support Care Cancer 2008 Jan;16(1):75-82.

Design: Phase II study (5/12/2005 – 23/8/2006)

Level 3

Country: USA, setting: Single Centre

Aim: To demonstrate efficacy of levetiracetam in reducing hot flashes.

Inclusion criteria Women aged over 18 years with a history of breast cancer, or women without breast cancer who wanted to avoid oestrogen therapy.

Bothersome hot flashes of sufficient severity to seek treatment (≥ 14 per week)

ECOG performance status of 0 or 1

Alternative treatments for hot flashes provided commenced > 30 days before the study period

Women receiving tamoxifen, raloxifene, aromatase inhibitors or vitamin E also included.

Exclusion criteria

Adverse reaction to levetiracetam

Pregnancy or nursing mothers

Seizure disorders

Raised creatinine

Women on evening primrose oil, ginkgo biloba, chemotherapy, androgens, oestrogens, progestational agents, or gabapentin.

Population number of patients = 28 (19 evaluable)

5 had breast cancer

3 were on tamoxifen

1 was on an aromatase inhibitor

Interventions

Week 1 (baseline) no study medication

Week 2: 1 tablet once daily at night (500 mg)

Week 3: 1 tablet in morning and 1 at night

Week 4: 2 tablets in morning and 2 at night

Outcomes

Hot flash frequency- average number of hot flashes / day each week

Hot flash score = sum of (n of mild hot flashes + 2n of moderate hot flashes + 3n of severe hot flashes + 4n of very severe hot flashes) = (frequency X severity)

Adverse effects – mean change from baseline after 4 weeks of treatment

Follow up After 4 weeks of treatment

Results

Eight (29%) patients withdrew because of side effects

Changes in scores and frequency are shown in the following table:

Variable	Baseline	Week 4	Difference	P value
Hot flash score	11.9	4.6	-7.3	0.0004
Median	13.6	5.9	-7.7	
Hot flash frequency	7.6	4.1	-3.1	<0.0001
Median	8.3	3.8	-4.5	
N of severe/very severe hot flashes	0.1 0.5	0.0 0.5	0 0	0.14
Mean				

There were significant reductions in hot flash scores and frequency. The number of very severe hot flashes was low in this group initially and the change was not significant.

The most frequent adverse events were somnolence, fatigue and dizziness of mild to moderate intensity.

15/20 (75%) of participants were satisfied with hot flash control.

8/15 (53%) would continue with levetiracetam.

Author conclusions: The results suggest that levetiracetam may be an effective therapy for the treatment of hot flashes. Further data is needed to evaluate efficacy and toxicity.

General comments –

Levetiracetam does not interfere with tamoxifen metabolism.

Hot flash score obtained from hot flash diary of number and severity.

No comparison group in this pilot study.

The recent Evidence-based systematic review of therapeutic options for women with breast cancer (Bordeleau *et al* 2007) concludes that newer antidepressants and gabapentin appear to be the most promising non-hormonal agents for the treatment of hot flashes in women with breast cancer.

Guidelines

Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncology* 2005;6(9):687-95.

Alternatives to HRT for management of symptoms of the menopause. Royal College of Obstetricians and Gynaecologists (2006). Scientific Advisory Committee Opinion Paper 6.

These guidelines were not sufficiently up to date and omitted recent trial data.

Intervention: Tibolone (synthetic steroid with oestrogenic, androgenic and progestagenic properties)

Systematic review of RCTs

Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab 2002;87:16-23.

Design: Systematic review
Level 1+

Country: Multinational

Aim: To summarize the results from the randomized, controlled, and double blind trials (RCTs) of tibolone with respect to its effects on climacteric symptoms, sexual function, endometrial and breast tissue, lipid metabolism, and bone mineral density (BMD).

Inclusion criteria

Randomized, controlled, and double blind trials (RCTs) of tibolone use for postmenopausal women. Cross-over trials also included.

Exclusion criteria

Trials involving premenopausal women, retrospective analyses, nonrandomized and open label studies, and trials in which the use of a placebo was not specifically stated.

Population

Women aged from 27 to > 65 years (younger patients in one trial had oophorectomy)

Interventions

Tibolone (2.5 mg/day) compared with either placebo (6 RCTs), or oestradiol valerate (E2V) (1 RCT) or the combination of oestradiol and norethisterone (E2/NETA) (3 RCTs) in postmenopausal women.

Outcomes

Hot flushes
Mood
Sexual function
Vaginal bleeding
Lipids

Follow up -

Results

Comprehensive search between 1981 and 2001.
Number of participants in trials ranged from 20 to 437.
Duration of trials ranged from 6 to 48 weeks.
Eight RCTs assessed the effects of tibolone on climacteric symptoms.

Hot flushes

Six RCTs (305 women) comparing tibolone with placebo reported a significant reduction in hot flushes and sweating in women taking tibolone. The magnitude of the changes was not always reported. A comparison of tibolone with hormonal replacement therapy found a similar reduction in hot flushes,

however the magnitude of the effect could not be determined.

Mood

One small trial of young women who had undergone oophorectomy and hysterectomy (N=20, Crona *et al* 1988) compared tibolone with E2 valerate. A similar reduction in hot flushes and improved mood were reported. Another small trial (N=30, Genazzani *et al* 1987) reported that tibolone increased β -endorphin concentration and suggested this may contribute to improved mood in postmenopausal women, although mood was not directly assessed in this trial.

Other postmenopausal symptoms

Three trials reported a beneficial effect of tibolone on fatigability, frequency of headaches, psychological instability, and insomnia. Another trial (Genazzani *et al* 1987) reported that relief of hot flushes from the second month of treatment was also associated with an improvement in mood and insomnia. The reported changes in postmenopausal symptoms varied among trials and may be due to the heterogeneity of study duration, multicultural samples, and differences in scoring systems.

Sexual function

Two randomized, double-blind trials compared the effects of tibolone with placebo on sexual function. In one trial (Nevinny-Stickel 1983) there was no significant improvement in libido in women taking tibolone. In contrast, a more recent trial (Laan & van Lunsen 2001) found that tibolone significantly improved the physiological aspects of sexual function in postmenopausal women in comparison to placebo including vaginal blood flow and lubrication, and subjective measures e.g., sexual desire and arousability. However there were no differences in sexual practices e.g., frequency of intercourse, non-penetrative sexual activity, initiation or rejection of sexual activity. The authors comment that the small sample size of subgroups may have reduced the power to detect statistical differences.

One RCT (Doren *et al* 2001) comparing tibolone with E2/NETA reported a doubling in free testosterone levels in the tibolone group. Another trial (Nathorst-Boos & Hammar 1997) reported significant improvements in sexual satisfaction in the tibolone arm compared with E2/NETA, however there was a large drop out rate (28%).

Effects on lipids and clotting

In postmenopausal women there is a tendency for total cholesterol and triglycerides to increase, mainly caused by increases in low density lipoprotein cholesterol (LDL-C). High density lipoprotein cholesterol (HDL-C) tends to remain unchanged. Seven trials assessed the effects of tibolone on lipids and clotting factors compared with placebo. Two trials assessed the effects of tibolone vs. E2/NETA. When compared with placebo, tibolone reduced HDL-C by approximately 34% (3 RCTs), decreased triglycerides by approximately 25%, but had no effect on LDL-C and lipoprotein(a) (4 RCTs). The reduction in HDL-C by tibolone may be due to an androgenic effect. In comparison with E2/NETA tibolone decreased HDL-C and triglycerides to a lesser extent

(17%) and had no effect on LDL-C and lipoprotein(a) (1 RCT).

Compared with placebo, tibolone increased hemoglobin, antithrombin III, plasminogen, and platelet count (3 RCTs). A further 2 trials also reported significant increases in plasminogen, one trial was a comparison of tibolone with E2/NETA.

Breast cancer

In vitro studies of breast cancer cells have shown that tibolone metabolites inhibit the formation of active oestrogens in the breast. A small RCT found that tibolone did not increase breast density when compared with placebo and HRT groups.

Author conclusions

A few RCTs have shown the oestrogenic effects of tibolone in reducing hot flushes and sweating in postmenopausal women. Tibolone also may have beneficial, androgenic effects on sexual function. Other effects of tibolone in postmenopausal women, such as its influence on lipid metabolism, hemostasis, and sexual function, are less certain. The long-term effects of tibolone, particularly in reducing fractures, breast cancer, and cardiovascular disease are still unknown.

General comments –

The studies cited in this review were not specific to breast cancer patients.

Randomized Controlled Trial Tibolone

Kroiss R, Fentiman IS, Helmond FA, Rymer J, Foidart JM, Bundred N, et al. The effect of tibolone in postmenopausal women receiving tamoxifen after surgery for breast cancer: a randomised, double-blind, placebo-controlled trial. *BJOG : an international journal of obstetrics and gynaecology* 2005;112(2):228-33

Design: RCT (1996-2000)

Level 1+

Country: Multicentre, setting: Hospital outpatients

Aim: A double-blind, placebo-controlled study was conducted to assess whether tibolone could prevent, relieve or delay the occurrence of climacteric symptoms in postmenopausal women treated with tamoxifen following breast cancer surgery.

Inclusion criteria

Postmenopausal women (hospital outpatients; age \leq 75 years)

Newly diagnosed, histologically confirmed invasive or non-invasive early stage breast cancer (\leq stage IIb)

Last natural menstrual period \geq 1 year before diagnosis of breast cancer

Serum oestradiol concentration \leq 30 pg/mL.

Exclusion criteria

Other malignancies, prior hysterectomy and/or bilateral oophorectomy, endometrial hyperplasia/adenocarcinoma, abnormal cervical smear, cardiovascular, cerebrovascular or thromboembolic disorders, uterine bleeding of unknown cause, severe liver disorders, drug or alcohol abuse in the previous 12 months, requirement for cancer therapy (exceptions were tamoxifen or radiotherapy) or medication that might affect the metabolism of tibolone, and use of steroids or tamoxifen in the 6 weeks before the study, hormonal implants at any time.

Population number of patients = 70 randomized.

Mean age 59 (SD 6) years

Tibolone group exposure was 35.1 woman years

Placebo group exposure 32.9 woman years

Interventions

Women received surgical treatment (BCS or MRM) followed by tamoxifen therapy.

Randomized to 20 mg/day oral tamoxifen plus either 2.5 mg/ day oral tibolone (Livial;NV Organon) or matching placebo.

33/35 on tibolone baseline and final visit data analysed

31/35 on placebo baseline and final visit data analysed

Outcomes

Frequency and severity of hot flushes at 3 and 12 months.

Average daily severity of hot flushes used a weighted average score [(N of mild hot flushes X1) + (N of moderate hot flushes X2) + (N of severe hot flushes X3) / Total hot flushes]

Serum lipids.

Follow up

Medication was started within three days of baseline assessment (performed within 12 weeks of breast surgery) and continued for 12 months.

Results*Baseline*

There were differences at baseline in the number of women experiencing hot flushes:

tibolone (78.6%) vs placebo (50%).

Results for hot flash frequency, sweating and intensity are reported in the following table:

Outcome	Tibolone	Placebo	P value
3 months			
Daily n of hot flushes	-0.1	0.9	0.22
Severity of flushes	-0.4	0.2	0.03
12 months (from baseline)			
Mean change n of hot flushes	-0.6	+1.1	0.02
Mean change n of sweats	-0.6	1.2	0.22
Mean change intensity of hot flushes	-0.2	+0.2	0.09
Mean change intensity of sweats	-0.2	+0.3	0.15

3 months

There was no change in the daily number of hot flushes with either tibolone or placebo at three months, however there was a significant decrease in the severity of hot flushes with tibolone compared with placebo.

12 months

At 12 months there was a decrease of 30% in frequency of hot flushes and sweats in the tibolone group, and an increase of 30% in the placebo group.

Serum lipids

At 12 months there were significant decreases of triglycerides (-23% vs. 1.4%) and HDL (-12% vs. 19%) in the tibolone group compared with placebo.

Author conclusions

This study demonstrated that tibolone prevented the increase in the occurrence, severity and intensity of hot flushes and sweats associated with tamoxifen treatment following surgical treatment for breast cancer. There was also a trend for tibolone to reduce the impact of hot flushes and sweats on normal daily life. None of the patients had a breast cancer recurrence.

At present, there are no approved effective compounds to treat postmenopausal women with a history of breast cancer and climacteric symptoms. The findings from this pilot study are promising, but only a large, long term clinical trial can provide confirmatory data regarding the effects of tibolone on recurrence in breast cancer patients.

General comments –

The effect of tibolone on breast recurrence rate in women with a history of breast cancer is currently being assessed in a large double-blind, randomised, placebo-controlled, five-year clinical trial (LIBERATE).

Limitations:

Since a higher proportion of women in the tibolone group experienced hot flushes and sweats at baseline, any reduction in effects due to tibolone may be exaggerated in comparison to the placebo group.

Guidelines

The only guideline retrieved that was specific to tibolone is reported below:

Kenemans P, Speroff L. Tibolone: Clinical recommendations and practical guidelines: A report of the International Tibolone Consensus Group. *Maturitas* 2005;51(1):21-8.

Summary

The consensus was that tibolone is a valuable treatment option for women with menopausal symptoms. Its effects include relieving vasomotor symptoms, with positive effects on sexual well-being and mood, and an improvement in vaginal atrophy and urogenital symptoms. The prevention of bone loss with tibolone is comparable to that seen with oestrogen therapy (ET) and oestrogen/progestogen therapy (EPT). Endometrial proliferation is rare and no additional progestogen is required. It is well tolerated with a low incidence of vaginal bleeding and breast pain. There is no increase in mammographic density. The absolute numbers of women at increased breast cancer risk are estimated to be low with both tibolone and ET, and the risk with tibolone should be lower than that with EPT. Tibolone may be preferable to EPT in women who have not had a hysterectomy. Based on the available evidence, the panel proposed a number of subgroups of postmenopausal women with vasomotor symptoms for whom tibolone may be useful; these included women with sexual dysfunction, mood disorders, fibroids and urogenital complaints, also those with breast tenderness or high mammographic breast density with EPT use.

Breast safety

Randomized controlled clinical trials have shown that tibolone has a different clinical effect on the breast to that of EPT. In contrast to EPT, tibolone does not increase breast tissue proliferation.

No increased breast cancer risk was observed compared with placebo from pooled data of all phase III/IV trials of tibolone (relative risk (RR) 0.50; 95% confidence interval 0.11–2.54) [Helmond 2002]. The Million Women Study (MWS) reported an increased relative risk of breast cancer with tibolone (RR = 1.45; 95% CI 1.25–1.67), although this was significantly ($p < 0.0001$) less than with EPT [MWS]. Another epidemiological study using the UK General Practice Research Database (GPRD) showed no increased risk with tibolone (RR = 1.02; 95% CI 0.78–1.33) [Allen 2002]. However, this study was published only as an abstract, not as a full paper. The best evidence currently available for the effect of tibolone on breast cancer is from the observational Million Women Study, the risks reported may be overestimated [Shapiro 2004, Whitehead 2004]. Recent prospective trial data [Anderson 2004, Chlebowski 2003] found that the absolute increase in risk for breast cancer was lower than reported in the MWS, and that the risks with tibolone and ET were probably lower than that with EPT.

- Consensus: randomised controlled trials investigating breast cancer incidence with tibolone are awaited before firm conclusions may be made regarding tibolone and breast cancer.

Level of evidence inconclusive.

Intervention: Alternative and complementary therapies

Isoflavone extracts (Red clover and soy)

Systematic review of RCTs

Nelson HD, Vesco KK, Haney E, Fu RW, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes - Systematic review and meta-analysis. *Jama-Journal of the American Medical Association* 2006;295(17):2057-71.

Aim: To compare the efficacy and adverse effects of therapies other than agents primarily composed of oestrogen, progestin or progesterone, or androgen for menopausal hot flashes from published RCTs.

Design: Systematic review (1966-2005)

Level 1++

Country: Multinational

Inclusion criteria

Published English-language, randomized, double-blind, placebo-controlled trials providing data for the treatment of menopausal hot flashes with one or more non-hormonal therapies. Trials of women with breast cancer.

Exclusion criteria

Head to head comparisons with no placebo arm. Non-menopausal women, other major diseases, previous oestrogen use within 1 month of commencement of study.

Dietary sources of isoflavones were excluded.

Population

Women experiencing menopausal hot flashes recruited from health care settings or the general population. Trials of women with breast cancer required additional data such as concomitant use of tamoxifen or other selective oestrogen receptor modulators (SERMs).

Interventions

Trials evaluating red clover isoflavones, which contained genistein, daidzein, formononetin and biochanin, and soy isoflavones containing predominantly daidzein, genistein, and their glucoconjugates.

Seventeen RCTs of isoflavone extracts met inclusion criteria.

The type of red clover isoflavone extracts used were promensil (40 mg, 80-82 mg, or 160 mg daily) and one trial also used rimostil (57 mg/d).

Outcomes

Frequency or severity of hot flashes. (Frequency obtained by self-report using symptom diaries).

Severity measures also self-reported using a graded scale or a composite measure (frequency x severity). Hot flash frequency and composite measures have demonstrated validity and reliability, and are highly correlated.

Outcomes were determined by the differences in hot flashes measured at baseline and the end of the trial. Treatment effects were defined as the differences in outcomes between the treatment and placebo groups at the end of the trial.

Follow up –

Results

Red Clover

Red clover isoflavones were compared with placebo in 6 trials. (Quality ratings were good (1 trial), fair (3 trials), and poor (2 trials). No trials included women with breast cancer.

All 6 trials used promensil, which contained a higher proportion of biochanin and genistein.

One trial also used rimostil, which contained a higher proportion of formononetin and daidzein.

Doses were 40, 80 or 160 mg/day of promensil; 57 mg/day of rimostil.

N=605 participants.

Four of the trials had ≤ 51 participants.

The remaining two trials had 205 and 252 participants.

One poor quality RCT reported an improvement in hot flash frequency with promensil compared with placebo (reduction of 48.5% vs 0% $P < 0.001$). The meta-analysis reported a significant reduction in hot flush frequency/day of -2.80 (95% CI -4.31 to -1.29) for this study.

None of the trials reported differences in severity scores on the Greene Climacteric Scale or in a symptom diary. One good quality trial reported that the reduction in hot flash frequency was significantly faster with promensil than placebo.

Meta-analysis of red clover trials

The combined weighted mean difference in number of daily hot flashes for red clover isoflavones compared with placebo was -0.44 (95% CI, -1.47 to 0.58) (not significant). The trial quality and type of red clover isoflavone did not influence the results. None of the trials were conducted in women with breast cancer using SERMs. A Forest plot of the meta-analysis was presented in the paper.

Summary of meta-analysis of red clover trials

All comparisons vs placebo

Type of red clover	N of trials	N participants*	Trial quality	No of comparisons in meta-analysis	Mean difference in no of Daily hot flashes vs. placebo	Severity or composite score
Promensil 40mg/d	4	204	Poor-fair	4	-0.40 (95% CI -2.33 to 1.53)	
Promensil 80-82 mg/d	2	199	Fair to good	2	-0.79 (95% CI -2.35 to 0.78)	
Promensil 160mg/d	1	25	Poor	1	-0.30 (95% CI -5.54 to 4.94)	
Fair-good Promensil	4	349	Fair to good	4	0.10 (95% CI -0.60 to 0.79)	

All Promensil	6	428	Poor to good	7	-0.59 (95% CI -1.84 to 0.67)	
Rimostil	1	168	Good	1	0.20 (95% CI -1.26 to 1.66)	
All fair-good	4	517	Fair to good	5	0.11 (95% CI -1.51 to 0.74)	
All combined	6	596	Poor-good	8	-0.44 (95% CI -1.47 to 0.58)	No difference

*Participant numbers from Forest Plot

Although there was a small overall reduction in hot flash frequency for women taking red clover vs. placebo this was not statistically significant.

Soy isoflavones

Soy isoflavones were compared with placebo in 11 trials. Four trials were of women with breast cancer. Three trials (two of fair quality and 1 of poor quality – none of the breast cancer trials), reported a reduction in hot flash frequency with soy isoflavones compared with placebo. The isoflavone composition and doses were genistein (54 mg/day), genistein and daidzein (70 mg/d), and genistein and daidzein (50 mg/d). No differences in hot flash frequency compared with placebo were reported in another three fair quality trials of similar composition.

Severity scores improved when compared with placebo in 3 trials of genistein, diadzein and glycitein (33 mg/day- 1 trial fair quality) or genistein and daidzein (50 mg/day – 2 trials: 1 fair, 1 poor quality). Another 5 trials, including the 4 of women with breast cancer, found no differences in severity scores when compared with placebo.

There were no differences in adverse effects between isoflavone and placebo groups. Gastrointestinal symptoms were the most common in both groups. Endometrial thickness was evaluated in 6 trials and there were no differences between isoflavone and placebo groups over the duration of the trials.

Soy isoflavone studies of women with breast cancer

Four trials evaluated soy isoflavones in women with breast cancer (MacGregor et al 2005, Nikander et al 2003, Quella et al 2000, Secreto et al 2004).

Participant numbers ranged from 62 to 262 women.

Duration 8 weeks to 6 months.

Doses ranged from 35 to 150 mg / day.

Meta analysis of soy isoflavone trials

A meta-analysis of 6 trials included one RCT of women with breast cancer (Quella et al 2000).

A Forest plot was reported in the paper. The results of the meta-analysis are shown in the following table.

Summary of meta-analysis of soy isoflavone trials

All comparisons vs placebo

Dose of isoflavones	N of trials	N participants*	Trial quality	No of comparisons in meta-analysis	Mean difference in no of Daily hot flashes vs. placebo	Severity or composite score
4 to 6 weeks 50-70 mg/d	4	353	Poor-fair	4	-1.48 (95% CI -2.49 to -0.48)	
4 to 6 weeks 150 mg/d*	1	177	Fair	1	0.71 (95% CI -1.30 to 2.72)	
4 to 6 week trials combined	5	530	Poor-fair	5	-1.15 (95% CI -2.33 to 0.03)	Improved in 3/7 trials
12-16 weeks 50-70 mg/d	4	404	Fair	4	-0.97 (95% CI -1.82 to 0.12)	
6 month trials 50-70 mg/d	2	152	Fair	2	-1.22 (95% CI -2.02 to 0.42)	

*Trial of breast cancer patients, 78% on tamoxifen (Quella 2000)

There was a significant effect of soy isoflavones in reducing hot flash frequency on 50-70 mg/day for 4-6 weeks, 12-16 weeks and 6 months. These trials did not include breast cancer patients. The effect at 4-6 weeks was not significant when the one trial of breast cancer patients using SERM and a higher dose of soy isoflavones was included (Quella 2000).

References for breast cancer studies of soy isoflavones:

MacGregor CA, Canney PA, Patterson G, McDonald R, Paul J. A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. *European journal of cancer* (Oxford, England : 1990) 2005;41(5):708-14.

Nikander E, Kilkinen A, Metsa-Heikkila M, Adlercreutz H, Pietinen P, Tiitinen A, et al. A Randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol* 2003;101(6):1213-20.

Quella SK, Loprinzi CL, Barton DL, Knost JA, Sloan JA, LaVasseur BI, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. *Journal of clinical oncology : official journal of the*

American Society of Clinical Oncology 2000;18(5):1068-74.

Secreto G, Chiechi LM, Amadori A, Miceli R, Venturelli E, Valerio T, et al. Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. *Maturitas* 2004;47(1):11-20.

Author Conclusions:

Hot flash frequency was not reduced when all trials of red clover isoflavone extracts were combined, and results for soy isoflavone extracts were contradictory even among the largest and highest quality trials. These results are consistent with other recent systematic reviews.

The authors also reviewed trials of other forms of soy isoflavones, such as flour, powder, and food items, in another study. However, the trials were difficult to compare because of the variability of components and doses. Overall, evidence does not support benefit in relieving hot flashes.

General comments –

Some trials use cumulative symptoms scores (e.g. Kupperman Index and Greene Climacteric Scale) to assess hot flashes and other menopausal symptoms. Use of these scores is problematic because some have not been validated, different components are measured which cannot be compared directly, and measures of vasomotor symptoms may not be specific.

The authors report a significant level of heterogeneity in the meta-analyses of soy and red clover isoflavones but this was not commented on in the findings. It appears from the data presented in the meta-analysis that the trial of breast cancer patients (Quella 2000) reduced the effectiveness of soy isoflavones overall in the 4-6 week studies. From the way the results are presented in the paper the authors suggest that there is an inconsistent effect of soy isoflavones, as can be seen from the Forest Plot. However the combination of trials from each individual time period (4-6 weeks, 12-16 weeks and 6 months) all favoured isoflavones when the trial of breast cancer was removed. This suggests there may be a weak effect of soy isoflavones in women not undergoing breast cancer treatment. No overall estimate of effect from all trials in the meta-analysis was reported. Only studies of preparatory extracts of soy and red clover were included.

An update search identified a further systematic review of complementary and alternative therapies for hot flashes in breast cancer survivors (Bordeleau *et al* 2007). Another RCT was identified in the review of 123 breast cancer survivors randomized to a soy beverage (90mg isoflavones/drink) or placebo. A reduction in 24 hour hot flash scores was 30% with soy beverage and 40% with placebo, these were not significantly different (Van Patten *et al* 2002).

Guidelines

Hickey M, Saunders CM, Stuckey BGA. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. *Lancet Oncology* 2005;6(9):687-95.

Alternatives to HRT for management of symptoms of the menopause. Royal College of Obstetricians and Gynaecologists (2006). Scientific Advisory Committee Opinion Paper 6.

Soy isoflavone extracts

The RCOG and Hickey guidelines acknowledge the inconsistent effects of soy isoflavones on menopausal symptoms from a technology report published by the same group as the systematic review. They also raise concerns about the potential effects on endometrial hyperplasia from a recent RCT (Unfer 2004).

Red clover extracts

The RCOG guideline suggests that red clover has a small effect in reducing the frequency of hot flushes from two small RCTs (N=30) and one larger RCT (N=169). The recent systematic review in the evidence table also includes these studies and the overall combined effect is small but not statistically significant.

Intervention: Other complementary and alternative therapies

Systematic review of RCTs

Black cohosh, DHEA, Vitamin E, Kava, Phospholipid liposomes, Mind, body and behavioural therapies

Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms - A systematic evidence review. Arch Intern Med 2006;166(14):1453-65.

Design: Systematic review of RCTs (1966-2005)

Level 1++

Country: Multinational

Aim: To assess the effectiveness of complementary and alternative therapies on the management of menopausal symptoms.

Inclusion criteria

English-language, randomized controlled trials and meta-analyses comparing a complementary or alternative therapy with placebo or control for the treatment of menopausal symptoms. Trials of women with breast cancer.

Exclusion criteria Non-randomized studies, methodologically flawed studies, trials of non-menopausal women or of animals.

Population

Interventions

Phytoestrogens- these are covered in the previous review by Nelson from the same centre.

Black cohosh

2-dehydroepiandrosterone (DHEA)

Vitamin E

Kava

Phospholipid liposome injections

Mind-Body and Behavioural Therapies

Outcomes

Outcomes included hot flash frequency and severity, sleep disturbance, vaginal dryness, vaginal bleeding, urinary frequency or incontinence, quality-of-life changes, depression, anxiety, sexual dysfunction, and cognitive function.

These are commonly measured by the Kupperman Index (self report of hot flashes and 11 other symptoms) and the Greene Climacteric Scale (21 self-reported items).

Follow up -

Results

Forty eight biological therapies, 9 mind-body therapies, 1 manipulative or body-based therapy, 2 energy therapies, and 10 whole medical systems met the inclusion criteria.

Black cohosh

Four trials of black cohosh including 2 of women with breast cancer (Jacobson *et al* 2001, Hernandez Munoz & Pluchino 2003) met the inclusion criteria. Characteristics of the two breast cancer studies are shown in the table below.

Breast cancer studies

Study	Duration	Black cohosh dose	Comparison	Hot flash frequency
Jacobson 2001 Fair quality N=85	9 weeks	1 tablet twice daily	Placebo	Improved sweating in BC group P=0.04 No difference in mean no of hot flashes, severity or other symptoms
Hernandez Munoz 2003 Poor quality N=136	9 weeks	20 mg twice daily	Usual care	Improved hot flashes in BC group 47% free of hot flashes in BC group vs. 0% free in usual care P<0.01

The largest and most recent fair quality trial of 304 women randomized to 40mg/day of black cohosh or placebo for 12 weeks reported an improvement in the treatment group for several menopausal symptoms including mood, sleep disorders, sweating and hot flashes (Osmers *et al* 2005). In contrast a smaller fair quality trial with a different botanical formula of black cohosh did not find a reduction in hot flashes (Wuttke *et al* 2003). In the two trials of breast cancer survivors, one fair quality (Jacobson *et al* 2001) found no improvement in the frequency of hot flashes although sweating was significantly improved, whilst one poor quality (Munoz & Pluchino 2003) found a significant reduction in hot flash frequency in the intervention group.

One further RCT of black cohosh in women with breast cancer was identified in our search (Pockaj *et al* 2006) this is described below:

Pockaj BA, Gallagher JG, Loprinzi CL, Stella PJ, Barton DL, Sloan JA, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *Journal of clinical oncology* :Official journal of the American Society of Clinical Oncology 2006;24(18):2836-41.

Design: double-blind, randomized, cross-over clinical trial with two 4-week periods, between 2003-2004.

Intervention: Black cohosh (1 capsule, Cimicifuga racemosa 20 mg twice

daily) vs. placebo.

A daily hot flash diary was completed during one baseline week and two 4-week crossover treatment periods. Hot flash scores were measured by a point system (1 to 4 for mild to very severe) for each hot flash, the scores were then totalled.

Results

Patients recruited N=132.

Outcome	Black cohosh	Placebo	P value
Change in hot flash score (week 4 compared to week 1)	Decrease of 20%	Decrease of 27%	0.53
Mean hot flash frequency	Decrease of 17%	Decrease of 26%	0.36
Patient preference of treatment	34%	38%	28% had no preference

Both placebo and black cohosh reduced the hot flash score and frequency when compared to baseline levels. Patient treatment preferences were measured after completion of both treatment periods. Thirty-four percent of patients preferred black cohosh treatment, 38% preferred the placebo, and 28% had no preference of either treatment. No evidence of effectiveness was found for black cohosh.

DHEA

Two studies were of fair and poor quality, neither included women with breast cancer. The fair quality trial (Barnhart *et al* 1999, N=60, 12 week course) did not show any benefit between DHEA and placebo for a range of menopausal symptoms including sleep, mood, cognition, sexual symptoms, vaginal dryness or quality of life.

Vitamin E

One fair quality crossover trial of women with breast cancer (Barton *et al* 1998, N=125, 4 weeks/phase) compared 800IU/day of vitamin E with placebo. There were no significant differences between groups in hot flash frequency or severity.

Kava

One fair quality study of kava (including calcium 1g/day) vs. calcium (1g/day) found an improved anxiety score in the treatment groups (Cagnacci *et al* 2003, N=80, 12 week course). There were no between group differences in Green Climacteric Scale and depression scores. This trial did not involve women with breast cancer.

Phospholipid liposomes

A fair quality study of intramuscular liposomes vs. placebo injection found an improved Green Climacteric Scale ($p=0.001$), and anxiety score (Hamilton Anxiety Scale, $p<0.001$) in the treatment groups when compared with placebo. This trial did not involve women with breast cancer.

Mind-Body and Behavioural Therapies

Only one trial of women with breast cancer was included of the 9 trials identified (Ganz *et al* 2000). This was rated as fair in quality.

Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *Journal of the National Cancer Institute* 2000;92(13):1054-64.

Inclusion criteria:

- 1) Disease-free, female breast cancer patients, between 8 months and 5 years after diagnosis of stage I or II disease;
- 2) Perimenopausal or postmenopausal (defined by amenorrhea of ≥ 6 months);
- 3) Chemotherapy or radiation therapy completed at least 4 months before enrollment. Tamoxifen use not excluded;
- 4) Presence of at least one target symptom (hot flashes, vaginal dryness, or stress urinary incontinence) of moderate to severe intensity;
- 5) Acceptance of behavioural or pharmacological treatment for at least one target symptom.

Exclusion criteria

- 1) History of other cancers except non-melanoma skin cancer;
- 2) Serious chronic medical conditions that may influence the assessment of health-related QOL;
- 3) Abnormal Pap smear showing dysplasia or more severe changes;
- 4) Symptoms of a major psychiatric illness (e.g., depression) that were not being treated or not controlled by medication;
- 5) Inability to read and write in English;
- 6) Active alcohol or substance abuse;
- 7) Oestrogen Replacement Therapy within the past 3 months; and
- 8) Major cognitive impairment or inability to provide informed consent.

Population

76 postmenopausal breast cancer survivors
Intervention N=33
Usual care N=39

Intervention

A Comprehensive Menopausal Assessment (CMA) intervention programme. This was delivered by a nurse practitioner and focused on symptom assessment, education, counselling and, as appropriate, specific pharmacologic and behavioural interventions for each of the three target symptoms (hot flashes, vaginal dryness, stress urinary incontinence).

The comparison group received usual care and were free to use medication or alternative therapies to relieve symptoms.

Outcomes

Psychosocial symptoms were assessed by a self-report screening instrument, and distressed women were referred for counselling if needed.

Composite menopausal symptom scale

RAND Short Form Health Survey Vitality Scale

Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Scale

Follow-up

The intervention took place over a 4-month period.

Outcomes measured were scores at baseline and at 4-month follow-up.

Results

Change scores for the menopausal symptom scale differed significantly between groups (P= 0.0004) with reduced symptoms in the intervention group.

There was no significant difference between groups in the RAND Vitality Scale (P=0.77).

There was a statistically significant improvement in sexual functioning for the intervention group on the CARES scale (p=0.04).

Outcome	CMA change score	Control change score	P value
Menopausal Symptom Score	Mean change score 0.61(95%CI 0.40-0.82)	Mean change score 0.19(95%CI 0.06-0.44)	P=0.0004
Sexual functioning scale	Adjusted mean change score 0.38 (95%CI 0.05-0.71)	Adjusted mean change score 0.015 (95%CI -0.37-0.40)	P=0.04

Author conclusions: A clinical assessment and intervention program for menopausal symptom management in breast cancer survivors is feasible and acceptable to patients, leading to reduction in symptoms and improvement in sexual functioning. Measurable improvement in a general QOL measure was not demonstrated.

Body-based therapies

One small crossover placebo controlled trial enrolling 15 women with breast cancer evaluated magnetic devices placed over 6 Chinese acupressure points corresponding to hot-flash relief (Carpenter *et al* 2002). The device was only applied for 72 hours. Complete data were available from 11 survivors of breast cancer. Results showed that magnetic therapy and placebo reduced

hot flash frequency and bothersome hot flashes. There was significantly more effect in the placebo group ($p=0.02$). There were no differences between groups in hot flash severity, interference with daily activities, and overall quality of life.

General comments -

**Systematic review
Psycho-educational interventions**

An update search identified another systematic review of psycho-educational interventions to relieve hot flashes. Trials of women with breast cancer were also included.

Tremblay A, Sheeran L, Aranda SK. Psycho-educational interventions to alleviate hot flashes: a systematic review. *Menopause-the Journal of the North American Menopause Society* 2008;15(1):193-202

Design: Systematic review (1980-2006)

Level 1+

Country: Canada

Aim: To assess the evidence of psycho-educational interventions to improve severe hot flashes in women after breast cancer treatment.

Inclusion criteria

Any experimental design

Participants had to have vasomotor symptoms

English language articles

Exclusion criteria

Case reports and descriptive studies

Population

Interventions

Psycho-educational interventions defined as any intervention that included education, counselling, cognitive-behavioural therapy, group therapy, psychological or relaxation interventions.

Outcomes

Hot flash frequency

Follow up -

Results

14 articles met the inclusion criteria

The one study of women with breast cancer that evaluated psycho-educational intervention was by Ganz *et al* 2000 which is included in the evidence table.

Relaxation studies

Two studies of breast cancer survivors were identified. Both were rated as poor in quality. The findings are reported in the following table.

Study	Design	Intervention	Results
Fenlon 1999 Poor quality	RCT N=24	Deep breathing relaxation vs. control	Hot flash frequency, night sweats and distress showed a trend in improvement. Psychological morbidity improved in relaxation group

			(p=0.005). However 75% of intervention group also used other measures.
Nedstrand 2005 Poor quality	RCT N=38	Applied relaxation vs. electro-acupuncture	Hot flash frequency and menopausal symptoms improved in both groups (p<0.0001 and p<0.001 respectively). Effects were maintained at 3 and 6 months.

All the interventions for breast cancer patients appear to have had some effect. This was significant in relieving menopausal symptoms in the trials by Ganz (2000) and Nedstrand (2005). However sample sizes were very small and the effects in the intervention group in the study by Fenlon (1999) were confounded by other measures taken to relieve symptoms. In the study by Ganz (2000) reported earlier, again other medications were allowed in both the intervention and control groups. Larger randomized studies are required.

Author conclusions: Psycho-educational interventions, including relaxation, seem to alleviate hot flashes in menopausal women and breast cancer survivors; however, the methodological quality of published research is either fair or poor. More studies are required, especially in the breast cancer population where only a few studies are available, before psycho-educational interventions are offered as a treatment option.

General comments -

**Systematic review
Black cohosh**

An update search identified another systematic review of black cohosh for treatment of hot flashes in breast cancer patients.

Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh (*Cimicifuga racemosa* [L.] Nutt.): safety and efficacy for cancer patients. [Review] [60 refs] Support Care Cancer 2007 Aug;15(8):913-21.

Design: Systematic review (1950 - 2007)

Level 1+

Country: Canada

Aim: To critically assess studies of the safety and efficacy of black cohosh for breast cancer patients.

Inclusion criteria

Primary in vitro and in vivo or studies, clinical trials of black cohosh in patients with current or a history of breast cancer.

Reviews published from 2002 – March 2007

Exclusion criteria

Abstracts, letters, editorials, commentaries, preliminary and duplicate reports

Reviews published before 2002

Non-English language articles

Population

Interventions

Studies of black cohosh in women with breast cancer.

Jadad scale used for quality assessment of studies (Scale 1 – 5, 1= poor, 5 = good)

Outcomes

Efficacy

Safety

Follow up -

Results

26 articles selected

5 clinical articles included (21 pre-clinical studies not reviewed in this table)

The results of included studies are shown below:

Study	Design	N of patients	Intervention	Duration	Outcome
Jacobson 2001 QA 5	RCT	85	1 tablet twice daily	-	Improved sweating in BC group (p=0.04)
Pockaj 2006 QA 4	RCT cross-over	132	2 x 20mg daily	8 weeks	No differences in hot flashes or QoL

Munoz 2003 QA 2	RCT open- label	136	2 x 20 mg daily	12 months	Improved hot flashes in BC group (p<0.01)
Pockaj 2004 QA 1	Pilot open- label	23	20 mg	4 weeks	Significant reduction of hot flash scores and frequency
Rebbeck 2007	NRS case- control	2473	Interview of supplement intake		Breast cancer protective effect

The results show conflicting findings of the effects of black cohosh in women with breast cancer. However the strongest study indicates that there may be a reduction in excessive sweating with black cohosh, but no changes in other menopausal symptoms. The authors add that there was a large drop-out rate in this trial (20%) and intensity scores for hot flashes were on a 3 point scale, whereas a 5 or 7 point scale may have been more sensitive.

General comments -

Randomized Controlled Trial Acupuncture

An update search identified an RCT of acupuncture for treatment of hot flashes in breast cancer patients.

Deng G, Vickers A, Yeung S, Cassileth B. Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients.[see comment]. J Clin Oncol 2007 Dec 10;25(35):5584-90.

Design: RCT (2002-2005)

Level 1+

Country: USA, setting: Single setting

Aim: To determine immediate and long-term effects of true acupuncture vs sham acupuncture on hot flash frequency in women with breast cancer.

Inclusion criteria

Undergoing treatment

Karnofsky performance score > 60

Average of 3 or more hot flashes/day

Exclusion criteria

Planned surgery

Chemotherapy, radiotherapy, immunotherapy or initiation or cessation of hormonal therapy during trial or 3 weeks before

Pharmacologic treatment of hot flashes or SSRIs- unless SSRI dose was stable for 4 weeks before the study

Skin infections

Previous acupuncture

Population number of patients = 72 randomized, 70 treated

Median age 55 years (48-59)

Tamoxifen use 40%

Aromatase inhibitors 25%

SSRIs 34%

Interventions

Randomization was stratified by:

Concurrent treatment with any of: oestrogen receptor modulator, gonadotrophin-releasing hormone analogue, aromatase inhibitor

Concurrent use of hot flash medication or SSRI

More than 7 hot flashes/day at baseline

Menopausal status at diagnosis

True acupuncture (n=40) was compared with sham acupuncture (n=30)

Treated twice weekly for 4 weeks, 19 acupuncture points were applied by licensed acupuncturists.

Outcomes were assessed at week 6.

At week 7 true acupuncture was offered to the sham group.

Outcomes assessed in both groups at 6 weeks and 6 months.

Outcomes

Hot flash frequency at 6 weeks and 6 months from hot flash diaries.

Follow up Week 6 and 6 months**Results**

Data for hot flashes are shown in the following table:

Time	Acupuncture mean hot flashes/day (SD)	Placebo mean hot flashes/day (SD)	Between group comparison 95%CI	P value
Baseline	N=42 8.7 (3.9)	N=29 10 (6.1)		
Week 4	N=38 5.8 (4.8)	N=27 7.8 (5.9)	-2.7 to 0.9	0.3
Week 6	N=39 6.2 (4.2)	N=28 7.6 (5.7)	-2.4 to 0.7	0.3
6 months	N=33 6.1 (4.9)	N=17 6.8 (5.7)		

There was no difference in hot flush frequency between groups at 6 weeks. During week 1 both groups showed a reduction in hot flash frequency (7.3 acupuncture vs. 7.9 sham) but this rate of decline was not maintained. Treatment effects were maintained at 6 months.

General comments –

P values were not provided for patient characteristic data. Fewer participants in the sham group were on tamoxifen (33% sham vs. 48% true). Tamoxifen use may influence intensity of hot flashes. One third of participants were taking SSRIs to reduce hot flashes so any reduction provided by acupuncture may have been minimal in this group leading to an underestimate of the effect size.

Chapter 9 – Follow-up

9.1 What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer and in patients with DCIS?

Short Summary

Invasive Breast Cancer

Evidence from three systematic reviews of observational studies does not confirm that routine follow-up mammography directly improves survival in patients treated for breast cancer, even though one included observational study is suggestive of improved 5 year survival for patients in whom ipsilateral recurrence is detected by mammography (McGahan and Noorani 2000; Temple *et al.* 1999; Grunfeld *et al.* 2002; Montgomery *et al.* 2007).

Evidence from one RCT suggests that in the first 18 months of follow-up, further tests prompted by mammography are more frequent in patients treated initially with breast conserving surgery plus radiotherapy compared to patients who received breast conserving surgery alone (Holli *et al.* 1998).

Estimates of the proportion of cases of recurrent breast cancer that are detected first by follow-up mammography come from observational studies, but there is wide variation. Two systematic reviews of observational studies summarise this proportion. For ipsilateral local recurrence, the proportion detected first by follow-up mammography had a range of 8%-50% (Grunfeld *et al.* 2002; McGahan and Noorani 2000) and median values of 26% (McGahan & Noorani 2000) and 27% (Grunfeld *et al.* 2002). For contralateral breast cancer, the proportion detected first by follow-up mammography had a range of 8%-80% (Grunfeld *et al.* 2002; McGahan & Noorani 2000) and median values 36% (McGahan & Noorani 2000) and 45% (Grunfeld *et al.* 2002).

Evidence from a systematic review of observational studies suggests that the sensitivity of mammography in detecting ipsilateral local recurrence has range of 38%-74% and specificity of 39%-60%. Sensitivity and specificity for the detection of contralateral breast cancer was provided for physical examination plus mammography combined, with sensitivity (range): 81%-88% and specificity (range): 96.5%-99.9% (Temple *et al.* 1999).

Evidence on the role of MRI in the follow-up of patients treated for breast cancer comes from observational studies and suggests that the sensitivity and specificity of MRI in detecting locally recurrent breast cancer are potentially high. In seven diagnostic studies of follow-up MRI, sensitivity had a range of 85.7%-100%. Specificity had a range of 82%-100% (Aichinger *et al.* 2002; Bone *et al.* 1995; Buthiau *et al.* 1995; Coulthard *et al.* 1999; Heywangkobrunner *et al.* 1993; Preda *et al.* 2006; Viehweg *et al.* 1998). Follow-up MRI can detect multifocal tumours, multicentric tumours and DCIS (Bone *et al.* 1995) and also incidental breast cancer tumours in the contralateral breast in patients treated for breast cancer but in whom the

contralateral is clinically and mammographically asymptomatic (Lieberman *et al.* 2003). There is some evidence that follow-up MRI has higher diagnostic performance when the interval from radiotherapy to MRI is longer (Heywangkobrunner *et al.* 1993; Viehweg *et al.* 1998).

Evidence on the role of ultrasound in the follow-up of patients treated for breast cancer comes from observational studies and shows the sensitivity of ultrasound in detecting locally recurrent breast cancer had a range of 70.6%-90.9% and specificity had a range of 82%-98.3%.

DCIS

A very small volume of poor quality evidence was identified on follow-up mammography in patients treated initially for DCIS, in two retrospective studies (Lieberman *et al.* 1997; Weng *et al.* 2000). These two studies suggest that follow-up mammography is able to detect locally recurrent breast cancer in some patients treated initially for DCIS.

PICO

	Population	Intervention	Comparison	Outcome
Invasive Breast Cancer	Patients with invasive breast cancer	Imaging modalities for the breast including: <ul style="list-style-type: none"> • Mammography • Ultrasound • Magnetic Resonance Imaging (MRI) • Mammoscintigraphy • PET/CT 	Versus any or none	<ul style="list-style-type: none"> • Detection rates of new or recurrent disease • Psychological morbidity • Cost Effectiveness • Diagnostic Accuracy
DCIS	Patients with DCIS	Imaging Modalities for the breast including: <ul style="list-style-type: none"> • Mammography • Ultrasound • Magnetic Resonance Imaging (MRI) 	Versus any or none	<ul style="list-style-type: none"> • Detection rates of new or recurrent disease • Psychological Morbidity • Cost Effectiveness • Diagnostic Accuracy

This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

Invasive Breast Cancer

All of the identified evidence originates from observational studies resulting in poor quality evidence. For follow-up mammography, three systematic reviews of observational studies reflect the nature of the evidence. All of the studies address the role of one or more of mammography, MRI or US in the follow-up of patients treated for primary breast cancer and are aimed at detecting 'new' disease; most commonly local recurrence in the breast, but also contralateral breast cancer. There is a high degree of heterogeneity in the studies in terms of methodology, follow-up regimens, outcome measures and patient populations. There is a high degree of inconsistency with regard to values of sensitivity and specificity; many of these values are derived from small subgroups e.g. in series of patients where recurrent disease is a rare event,

and should be interpreted cautiously. With the exception of one study from South Korea, all remaining studies originate from Western Europe or North America. Follow-up regimens are not consistently reported but are likely to differ in some studies from practice in the UK.

Evidence from three systematic reviews of observational studies does not confirm that routine follow-up mammography directly improves survival in patients treated for breast cancer, even though one included observational study is suggestive of improved 5 year survival for patients in whom ipsilateral recurrence is detected by mammography.

Evidence from one RCT suggests that in the first 18 months of follow-up, further tests prompted by mammography are more frequent in patients treated initially with breast conserving surgery plus RT compared to patients who received breast conserving surgery alone.

Evidence from observational studies suggests that the sensitivity and specificity of MRI in detecting locally recurrent breast cancer are potentially high (Table 1). In 7 diagnostic studies of follow-up MRI, sensitivity had range 85.7%-100% (discounting one outlier value of 0%, based on small numbers). Specificity had range 82%-100%

Evidence on the role of US in the follow-up of patients treated for breast cancer comes from observational studies and is summarised in Table 2. In four observational studies the sensitivity of US in detecting locally recurrent breast cancer had range 70.6%-90.9% and specificity had range 82%-98.3%.

Table 1: sensitivity and specificity of follow-up MRI in detecting locally recurrent breast cancer

Study	Size	Sensitivity	Specificity	Notes
(Aichinger <i>et al.</i> 2002)	42	100%	82%	
(Bone <i>et al.</i> 1995)	83	85.7% [95% CI 60.1%- 96.0%]	100% [95% CI 94.7%- 100%].	Initial treatment: mastectomy and implant reconstruction.
(Buthiau <i>et al.</i> 1995)	82	100% [95% CI 93.7%- 100%]	84% [95% CI 65.4%- 93.6]	Existing suspicion of recurrence on conventional imaging.
(Coulthard <i>et al.</i> 1999)	59	0% [95% CI 0%-56.1%]	92.9% [95% CI 83.0%- 97.2%]	Sensitivity value based on very small subgroup.
(Heywangkobrunner <i>et al.</i> 1993)	62	100% [95% CI 74%- 100%]	85% [95% CI 74%- 92%]	Based on MRI plus conventional examination/imaging.
(Preda <i>et al.</i> 2006)	93	sensitivity 94% [95% CI 72%-	90% [95% CI 82%- 95%]	Based on MRI plus conventional examination/imaging.

		99%]		
(Viehweg <i>et al.</i> 1998)	166	100% [95% CI 87.5%-100%]	87.8% [95% CI 82.2%-91.8%]	

Table 2: sensitivity and specificity of follow-up US in detecting locally recurrent breast cancer

Study	Size	Sensitivity	Specificity	Notes
(Aichinger <i>et al.</i> 2002)		86%	82%	Colour doppler US plus echo signal amplifier.
(Balu-Maestro <i>et al.</i> 1991)	272	90.9% [95% CI 72.2%-97.5%]	Not available	
(Ciatto <i>et al.</i> 1995)	43	76.7% [95% CI 62.3%-86.9%]	Not available	
(Shin <i>et al.</i> 2005)	1968	70.6% [95% CI 53.8%-83.2%]	98.3% [95% CI 97.6%-98.8%]	Detection of occult breast cancer i.e. recurrence in the breast, adjacent node bearing areas, mastectomy bed and contralateral breast cancer.

DCIS

There is a very small body of evidence available to address this question consisting of two retrospective case studies thus providing poor quality evidence.

Neither of the included studies were well designed to evaluate the role of follow-up mammography in patients treated for DCIS.

Results from the studies suggest that follow-up mammography is able to detect locally recurrent breast cancer in some patients treated initially for DCIS.

Further details - Invasive Breast Cancer

The role of follow-up mammography

14 studies were selected which provide evidence on the role of surveillance mammography in the follow-up of patients treated for breast cancer (Aichinger *et al.* 2002; Ashkanani *et al.* 2001; Auguste *et al.* 1994; Balu-Maestro *et al.* 1991; Churn & Kelly 2001; Ciatto *et al.* 1995; Fajardo *et al.* 1993; Grunfeld *et al.* 2002; Holli *et al.* 1998; Johnson *et al.* 2000; Kaas *et al.* 2001; McGahan & Noorani 2000; Paszat *et al.* 2007; Robinson *et al.* 2007; Temple *et al.* 1999; Yau *et al.* 2007).

One RCT investigated the role of follow-up mammography in patients with low-risk breast cancer randomised to either breast conserving surgery plus RT or breast conserving surgery alone. Falsely positive mammography findings were twice as frequent in patients who received RT compared to patients who received no RT ($p=0.04$), with positive predictive values 15% and 33.3%, respectively. In the first 18 months of follow-up, further tests prompted by mammography were more frequent in patients who received RT compared to patients who received no RT with OR = 2. Beyond 18 months of follow-up the rate of further tests prompted by mammography was equal between randomised groups with OR = 1 (Holli *et al.* 1998).

A systematic review of observational studies examined the ability of physical examination and mammography to detect ipsilateral local recurrence and contralateral breast cancer (Temple *et al.* 1999). In detecting ipsilateral local recurrence (8 studies) the sensitivity of mammography had mean 59.3%, median 60% and range 38%-74%. The specificity of mammography had mean 54.5%, median 59.5% and range 39%-60%. Physical examination had mean sensitivity 63.5%, median 68% and range 29%-75% and mean specificity 23.5, median 23.5% and range 17%-30%. Data for the detection of contralateral breast cancer was provided for physical examination plus mammography combined (based upon 2 screening programme studies) and had sensitivity (range): 81%-88% and specificity (range): 96.5%-99.9%. Mammography detected more locally recurrent ipsilateral breast tumours at the noninvasive stage than did physical examination, but this was not found to influence 5 year survival. Two included studies found that the incidence of contralateral breast cancer increased after the introduction of follow-up mammography. A third study found that the incidence of contralateral breast cancer increased when mammography was added to physical examination in follow-up. None of these three studies analysed survival (Temple *et al.* 1999).

A second systematic review was conducted of observational studies of follow-up mammography in patients treated with breast conserving surgery and RT (McGahan & Noorani 2000). The review found that routine mammography was not associated with a reduction in time to detection of recurrent breast cancer, compared to clinical examination. For ipsilateral recurrent breast cancer (local or loco-regional recurrence) the detection rate of mammography had mean 28.3%, median 26% and range 12%-50%. For contralateral breast cancer the detection rate of mammography had mean 43.6%, median 36% and range 18%-80%. No evidence was found to suggest that routine mammography directly improved overall survival. However, the review suggested that local recurrence detected by mammography may be more frequently associated with smaller tumour size, lower stage and older patient age (McGahan & Noorani 2000).

A further systematic review of observational studies was conducted to examine the effect of routine surveillance mammography in detecting ipsilateral recurrence (IR) or contralateral breast cancer in patients treated predominantly with breast conserving surgery and RT (Grunfeld *et al.* 2002). The proportion of patients in whom IR was detected by mammography alone had mean 26.5%, median 27% and range 8%-50%, based on 10 studies. In

the remaining cases, IR was detected by either physical examination or a combination of physical examination and mammography. The proportion of patients in whom CBC was detected by mammography alone had mean 45.5%, median 45% and range 8%-80%, based on 9 studies. There was no evidence for any difference in the median interval to detection of IR by mammography alone compared to other methods. Two studies reported that mammography detected cases of CBC at an earlier stage than palpation alone. Two studies found no effect of mode of detection of IR and either overall survival or disease free survival. One study demonstrated improved 5 year survival in patients in whom IR was detected by mammography. Only one study examined the relationship between the mode of detection of CBC and survival and found no effect. (Grunfeld *et al.* 2002)

A systematic review by Montgomery *et al.* (2007) was conducted to establish the proportion of potentially treatable locoregional relapses and new contralateral breast cancers detected by clinical examination, mammography and patient self-examination. All studies with information on proportion of relapses detected by clinical examination, mammography and self-examination were included. A total of 30-40% of potentially treatable relapses are detected by patient self-examination. In studies published before 2000, 15% of such relapse is mammographically detected with 46% detected by routine clinical examination. In those published after 2000, 40% are mammographically detected with 15% detected on routine clinical examination. Patients with ipsilateral breast relapse detected clinically appear to do less well than those with relapse detected by self-examination or mammography. As experience with mammography has increased, routine clinical surveillance detected fewer potentially treatable relapses in more modern cohorts. There was no evidence to suggest that clinical examination provided a survival advantage compared with other methods of detection.

A relatively large observational study conducted a nested case control study to estimate the association between receipt of surveillance mammogram and breast cancer mortality in stage I and II breast cancer patients who were at least 65 years old. The study reported that with each additional surveillance mammogram there was an associated 0.69-fold decrease in the odds of breast cancer mortality. The associations evaluated showed that a protective association was strongest among women with stage I disease, those who received mastectomy, and those in the oldest age group (Lash *et al.* 2007)

A small prospective case series study assessed the performance of mammography in detecting locally recurrent breast cancer in patients treated initially by breast conserving surgery (n=38) or mastectomy (n=4) and found that mammography had sensitivity 45% and specificity 77% (Aichinger *et al.* 2002).

A retrospective case series study investigated the rate of detection of local recurrence by annual bilateral mammography in 695 women with breast cancer treated by breast conserving surgery (Ashkanani *et al.* 2001). Local recurrence was confirmed in 21/695 = 3% of patients at a mean follow-up period of 3.5 years. Clinical examination was the first method of detection of

local recurrence in 11/21 = 52.4% of patients with confirmed local recurrence. Surveillance mammography was the first method of detection of local recurrence in 10/21 = 47.6% of patients with confirmed local recurrence, although mammography was able to predict local recurrence in 13 patients i.e. 13/20 = 65% of patients with local recurrence who received mammography. In 52 patients mammogram results were falsely positive; at a rate of 52/2181 = 2.4% of all mammographies (Ashkanani *et al.* 2001).

A retrospective case series study investigated the performance of mammography in detecting recurrent breast cancer in patients treated with breast conserving surgery and radiotherapy and found that mammography had sensitivity 64% and specificity 67% (Auguste *et al.* 1994).

A retrospective case series study examined the sensitivity of follow-up mammography in detecting local recurrence in patients treated for breast cancer (Balu-Maestro *et al.* 1991). Mammography performed every 6 months in the first 3 years from treatment and annually thereafter had sensitivity 95.5% [95% CI 78.2%-99.2%] based on 22 recurrences in a subgroup of 171 patients with complete data (Balu-Maestro *et al.* 1991).

A retrospective case series examined the value of follow-up of 505 patients who underwent breast conserving surgery for breast cancer (Churn & Kelly 2001). There were 31 cases of local recurrence. There was no set protocol for follow-up mammograms, but in 25 patients in whom local recurrence was the only detected recurrence, the method of detection was as follows: mammography: 7 (28%), routine clinic appointment: 8 (32%), interim referral: 9 (36%) and unknown: 1 (4%) (Churn & Kelly 2001).

A retrospective case series study examined follow-up mammography in 121 patients with proven locally recurrent breast cancer following initial treatment with breast conserving surgery (Ciatto *et al.* 1995). A protocol of annual mammography for the first five follow-up years and biennial mammography thereafter had sensitivity of 63.6% [95% CI 54.8%-71.7%] in detecting local recurrence (Ciatto *et al.* 1995).

A retrospective case series study assessed the efficacy of routine mammography of the postoperative site in 827 patients treated with mastectomy for breast cancer, including 32 patients who underwent bilateral mastectomy (Fajardo *et al.* 1993). In 859 breasts studied 39 tumours recurred locally (4.5%) at a mean of 3.5 years from diagnosis. The Method of first detection of ipsilateral local recurrence was: clinical examination: 35/39 = 89.7%, scintigraphy: 4/39 = 10.3%, mammography: 0/39 = 0%. In 20 patients with suspicious findings on clinical examination which prompted mammography, mammography detected locally recurrent cancer in 2 patients (10%) (Fajardo *et al.* 1993).

A retrospective case series examined the efficacy of annual clinical examination and biennial mammography to detect metachronous tumours occurring in the contralateral breast in 205 patients treated for breast cancer with mastectomy (Johnson *et al.* 2000). 17 metachronous, contralateral

tumours were detected at a median of 10 years from the initial surgery. The method of detection was as follows: patient: 8/17 = 47%, clinical examination: 4/17 = 24%, routine follow-up mammography: 5/17 = 29% (Johnson *et al.* 2000).

A retrospective case series investigated the outcome of 275 patients with confirmed contralateral, metachronous breast cancer, comparing two when frequencies of follow-up mammography: annual (defined retrospectively by mean interval between mammograms of 12 months) versus biennial (defined retrospectively by mean interval between mammograms of ≥ 15 months) (Kaas *et al.* 2001). There was no significant difference in 5-year disease specific survival after detection of contralateral breast cancer between the annual mammography group (75%) and the biennial mammography group (75%, $p=1$). Disease specific survival at 5 years was statistically significantly higher (85%) for patients in whom contralateral breast cancer was mammography detected, compared to patients in whom it was clinically detected (69%, $p=0.015$). When this analysis was stratified by pathological stage of the initial breast cancer tumour, the difference remained statistically significant ($p=0.015$). The proportion of contralateral breast cancers detected by mammography was 109/275 = 39.6% in all patients, 50/141 = 35.5% in the annual mammography group and 26.9% in the biennial mammography group ($p=0.62$) (Kaas *et al.* 2001).

A large, retrospective cancer registry analysis of 12279 women treated for primary breast cancer by breast conserving surgery with or without RT or mastectomy examined the utility of annual follow-up mammography by its relationship with subsequent breast surgery (Paszat *et al.* 2007). Breast surgery occurring within 4 months of a follow-up mammogram was assumed to be prompted by follow-up mammography. Breast surgery occurring 4 months or more after a follow-up mammogram was assumed to be prompted by clinical examination and/or symptoms. Two-thirds of breast operations occurred four months or more after the previous follow-up mammography, suggesting that follow-up mammography detected one third of recurrences/contralateral tumours in the breast (Paszat *et al.* 2007).

A retrospective case series investigated how well mammography performed in young patients to detect new contralateral primary breast cancer. Characteristics of the tumor at baseline and the contralateral tumor were recorded as well as the method of detection of the contralateral breast cancer. A subset of patients was identified based on the age at which they were diagnosed with their initial primary cancer: < 40 years (group A) and 55-59 years (group B). Older patients were significantly more likely to have their second primary tumor detected by routine follow-up mammography compared with the younger cohort. Older patients were also more likely to have estrogen receptor-positive, lower grade second primary tumors, and there was a trend toward smaller tumors. Tumors detected by mammography were more likely to be lower grade, estrogen receptor positive, and smaller. Older patients were more likely to have a contralateral breast cancer detected by conventional mammography, whereas younger patients tended to have

cancer detected by physical examinations or by self-diagnosis. (Robinson *et al.* 2007)

Yau *et al.* (2008) retrospectively reviewed effectiveness on 511 invasive and non-invasive breast cancers treated with breast conservation therapy (BCT). The median follow-up was 5.9 years. The 5-year actuarial ipsilateral breast tumour recurrence (IBTR) rate was 4.5% and contralateral breast cancer (CBC) rate was 2.0% (which represented eight times increase in risk). IBTR of 43% and 62% CBC were first detected by surveillance mammography. The IBTR detection rates per 1000 mammograms were 5.2 for patients (n=349) with one or more IBTR risk factors (age \leq 45, positive/close margins or histological grade 3) and 0.6 for patients (n=162) without. No survival difference was observed between different modes of IBTR detection (p=0.342).

The role of follow-up MRI

Eight of the selected studies of follow-up imaging in patients treated for breast cancer address follow-up MRI (Aichinger *et al.* 2002; Bone *et al.* 1995; Buthiau *et al.* 1995; Coulthard *et al.* 1999; Heywangkobrunner *et al.* 1993; Liberman *et al.* 2003; Preda *et al.* 2006; Viehweg *et al.* 1998).

A small prospective case series study assessed the performance of follow-up MRI in detecting locally recurrent breast cancer in patients treated initially by breast conserving surgery (n=38) or mastectomy (n=4) and found that MRI had sensitivity 100% and specificity 82% (Aichinger *et al.* 2002).

A prospective case series study examined the role of MRI in the follow-up of 83 patients who underwent mastectomy for breast cancer followed by reconstruction with prosthetic implants (Bone *et al.* 1995). MRI was performed on both breasts and the interpreting clinicians had also information from mammography. In detecting ipsilateral recurrent breast cancer, MRI had sensitivity 85.7% [95% CI 60.1%-96.0%] and specificity 100% [95% CI 94.7%-100%]. MRI detected 1 of 5 ipsilateral multifocal tumours and 5 of 5 ipsilateral multicentric tumours. 6 of 14 histologically proven ipsilateral recurrences were DCIS. For contralateral breast cancer, MRI correctly identified as malignant 1 of 2 contralateral invasive tumours, 1 of 1 contralateral DCIS tumour. MRI was falsely positive in 1 of 2 benign lesions (Bone *et al.* 1995).

A prospective case series study examined the effectiveness of contrast-enhanced MRI of the breast to detect local recurrence in patients treated for breast cancer with either breast conserving surgery (n=61) or mastectomy plus implant reconstruction (n=21) (Buthiau *et al.* 1995). All patients underwent contrast-enhanced MRI and diagnostic biopsy due to suspicion of local recurrence on conventional imaging. The histologically proven rate of local recurrence was 69.5%. In detecting local recurrence and based on all 82 patients, contrast-enhanced MRI had sensitivity 100% [95% CI 93.7%-100%] and specificity 84% [95% CI 65.4%-93.6%] (Buthiau *et al.* 1995).

A small, retrospective case series examined the performance of contrast-enhanced follow-up MRI in 63 women treated for breast cancer, of whom 26 had suspicion of recurrent disease based upon clinical examination or mammography (Coulthard *et al.* 1999). MRI was performed once only, of both breasts. There were 4 falsely positive results on MRI in either the ipsilateral or contralateral breast, demonstrated as scarring or benign lesion by biopsy. In detecting ipsilateral local recurrence, follow-up MRI had sensitivity 0% [95% CI 0%-56.1%] and specificity 92.9% [95% CI 83.0%-97.2%] (Coulthard *et al.* 1999). The value for sensitivity is based upon a very small subgroup, as evidenced by the wide confidence interval.

A prospective case series study examined the performance of follow-up MRI in detecting recurrent breast cancer in 62 patients treated by breast conserving surgery and RT (Heywangkobrunner *et al.* 1993). All patients underwent clinical examination, mammography and MRI. Some patients underwent US in addition. Using the information provided by all examinations including MRI, sensitivity for the detection of local recurrence was 100% [95% CI 74%-100%] and specificity 85% [95% CI 74%-92%]. Specificity of MRI was higher in the subgroup of studies performed >18 months after RT (100%) than in studies performed 10-18 months after RT (76%) and those performed 0-9 months after RT (73%). Sensitivity was 100% in all three subgroups. 4 of 11 recurrences and 10 of 18 single recurrent foci were detected by MRI alone, based on focal enhancement (Heywangkobrunner *et al.* 1993).

A retrospective case series study examined the rate of detection of contralateral breast cancer by follow-up MRI in 223 patients treated for unilateral breast cancer, in whom the contralateral breast was clinically and mammographically asymptomatic (Lieberman *et al.* 2003). Biopsy of the contralateral breast was recommended due to suspicion of malignancy in 72/223 = 32% of patients, and was performed in 61 patients. In 12/61 = 20% of patients who underwent contralateral breast biopsy, contralateral cancer was histologically confirmed, representing a PPV for MRI of 12/61 = 20%. Of the 12 patients with contralateral breast cancer, 6 had DCIS and 6 had infiltrating carcinoma. In 11 patients (92%) the contralateral cancer was diagnosed within 3 months of the index cancer (Lieberman *et al.* 2003).

A retrospective case series study investigated the performance of MRI in detecting local recurrence of breast cancer in 93 patients treated initially with breast conserving surgery and in whom local recurrence was suspected based upon mammography and/or US imaging (Preda *et al.* 2006). The interpreting clinician utilised information from MRI plus previous mammography/US. For lesions at the site of the surgical scar, MRI had sensitivity 90% [95% CI 60%-98%] and specificity 92% [95% CI 84%-96%]. In addition in 7 patients 13 incidental lesions that were not in contact with the surgical scar were identified by MRI. These lesions were true positive (6), true negative (5), false positive (2) and false negative (0). For all lesions, including those that are incidental and not in contact with the surgical scar, MRI had sensitivity 94% [95% CI 72%-99%] and specificity 90% [95% CI 82%-95%] (Preda *et al.* 2006).

A retrospective case series evaluated the role of follow-up MRI in detecting local recurrence in patients who were treated initially with breast conserving surgery plus RT (Viehweg *et al.* 1998). 207 contrast-enhanced MRI procedures were performed in 166 patients. In 40 MRI procedures performed within 12 months following RT, the additional use of contrast-enhanced MRI changed the overall diagnosis in 6 of 40 procedures (15%) and MRI had sensitivity 100% [95% CI 20.7%-100%] and specificity 74.4% [95% CI 59.0%-85.4%]. These results were based on small numbers as evidenced by the wide confidence intervals. In 167 MRI procedures performed more than 12 months following RT, the additional use of MRI changed the overall diagnosis in 49 of 167 procedures performed (29.3%) and MRI had sensitivity 100% [95% CI 87.1%-100%] and specificity 91.5% [95% CI 85.7%-95.1%]. In all 207 procedures, MRI had sensitivity 100% [95% CI 87.5%-100%] and specificity 87.8% [95% CI 82.2%-91.8%] (Viehweg *et al.* 1998).

The role of follow-up US

Four of the selected studies of follow-up imaging in patients treated for breast cancer address follow-up US; all of which are observational studies (Aichinger *et al.* 2002; Balu-Maestro *et al.* 1991; Ciatto *et al.* 1995; Shin *et al.* 2005).

A small prospective case series study assessed the performance of colour doppler US, with and without echo signal amplifier (ESA), in detecting locally recurrent breast cancer in patients treated initially by breast conserving surgery (n=38) or mastectomy (n=4) (Aichinger *et al.* 2002). Colour doppler US without ESA had sensitivity 64% and specificity 86%. Colour doppler US plus ESA had sensitivity 86% and specificity 82% (Aichinger *et al.* 2002).

A retrospective case series examined the performance of follow-up of 272 patients treated for breast cancer with breast conserving surgery and RT (Balu-Maestro *et al.* 1991). Patients received bilateral US of breast, axilla and neighbouring node bearing tissues every 6 months in the first 3 years from treatment and annually thereafter. The sensitivity of US in detecting local recurrence was 90.9% [95% CI 72.2%-97.5%] (Balu-Maestro *et al.* 1991)

A retrospective case series study examined follow-up US in 43 patients with proven locally recurrent breast cancer following initial treatment with breast conserving surgery (Ciatto *et al.* 1995). In detecting local recurrence, US had sensitivity 76.7% [95% CI 62.3%-86.9%] (Ciatto *et al.* 1995).

A large, retrospective case series study investigated the effectiveness of breast US in the follow-up of 1968 patients treated for breast cancer with either modified radical mastectomy or breast conserving surgery plus RT (Shin *et al.* 2005). Bilateral US of the breast, chest wall, axilla, parasternal and supraclavicular regions was performed at intervals of 6 months or more. Sensitivity of US with regard to occult tumour (recurrence in the breast, adjacent node bearing areas, mastectomy bed and contralateral breast cancer) was 70.6% [95% CI 53.8%-83.2%] and specificity was 98.3% [95% CI 97.6%-98.8%](Shin *et al.* 2005).

Further Details - DCIS

A small, retrospective case series study examined the mode of detection of locally recurrent breast cancer in 20 patients treated initially for DCIS with breast conserving surgery and, in some cases, RT (Lieberman *et al.* 1997). The 20 patients were selected because they experienced local recurrence of breast cancer that was histologically proven and because mammograms were available for the time of detection of the local recurrence. The protocol for follow-up mammography was not reported. The method of detection of the local recurrence was mammography in 17 patients (85%), mammography and physical examination in 2 patients (10%) and physical examination alone in 1 patient (5%). In 13 patients the recurrent lesions were pure DCIS. Of these patients 12 (92%) were detected solely by mammography (Lieberman *et al.* 1997).

A retrospective case series studied 88 cases of pure DCIS in 85 patients who received follow-up mammography with biannual and annual frequency (Weng *et al.* 2000). Patients were treated initially for DCIS by mastectomy or breast conserving surgery plus RT or breast conserving surgery alone. Local recurrence was confirmed by histology in 12 of 88 cases (13.6%) at a median follow-up period of 99 months. The method of detection of local recurrence included mammography in 9 cases (75%). In two cases (16.7%) the local recurrence presented clinically as a palpable mass or lymphadenopathy and in one case (8.3%) local recurrence was detected incidentally at the time of cosmetic surgery (Weng *et al.* 2000).

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Evidence tables – Invasive Breast Cancer

Randomized controlled trial

Holli, Saaristo, Isola, Hyöty & Hakama . Effect of radiotherapy on the interpretation of routine follow-up mammography after conservative breast surgery: a randomized study. British journal of cancer 78[4]. 1998.

Design

Design: Randomized controlled trial (diagnosis, screening), evidence level: 1 +

Country: Finland, setting: Secondary care

Inclusion criteria

Patients with small, invasive breast cancer tumours who were considered to be at low risk, defined as follows:

Age >40 years;

Tumour size ≤ 2 cm with no extensive intraductal component;

Node negative;

Histological grade I-II;

c-erbB negative;

DNA diploid with S phase fraction $\leq 8\%$

≥ 1 cm tumour free margin from surgery.

Exclusion criteria

Defined by inclusion criteria.

Population

number of patients = 144, mean age = 56 years.

Interventions

Aim: to determine whether follow-up mammography in patients who underwent breast conserving surgery is more difficult to interpret following RT compared to following breast conserving surgery alone.

RT group (n=78): received, after breast conserving surgery and axillary staging, 50 Gy in 2 Gy fractions.

No RT group (n=66): received breast conserving surgery and axillary staging but no further treatment.

All patients underwent follow-up mammography preoperatively and at 18 month intervals during follow-up.

Outcomes

Occurrence of positive findings on follow-up mammography;

Further testing prompted by mammography.

Follow up

Mean 2.9 years; 411 cumulative follow-up years.

Results

Occurrence of positive findings on mammography:

Mammographic findings were positive in 20/78 patients in the RT group compared to 9/66 patients in the 'no RT' group ($p=0.1$). Falsely positive mammography findings were twice as frequent in the RT group (17) compared to the 'no RT' group (6), $p=0.04$.

The positive predictive values were as follows:

RT group: $3/20 = 15\%$

'No RT' group: $3/9 = 33.3\%$

Further testing:

In the first 18 months of follow-up, further tests prompted by mammography were more frequent in the RT group compared to the 'no RT' group: OR 2.

Beyond 18 months of follow-up the rate of further tests prompted by mammography was equal between randomised groups: OR 1.

General comments

Rate of false negative mammography findings not reported; study data is of limited use with regard to performance of mammography.

Results for further testing are based on the number of tests and not the number of patients. The odds ratios appear to relate to the odds of a test being prompted by mammography (as opposed to performing the test independently of mammography).

Systematic review of diagnostic studies

McGahan & Noorani . Surveillance mammography after treatment for primary breast cancer. 2000.

Design

Design: Systematic review of diagnostic studies (diagnosis, screening),
evidence level: 2+
Country: Canada, setting: Secondary care

Inclusion criteria

Patient population: patients treated with breast conserving therapy (local excision and RT) for breast cancer; mean age at diagnosis, 41-59 years.

Studies published between 1994 and 1999 were considered which:

- i) Address surveillance mammography and its impact on disease outcomes;
- ii) address other surveillance strategies for breast tumour recurrence, or;
- iii) describe follow-up methods after treatment for breast cancer.

For inclusion studies had to provide data to populate a pre-defined data collection proforma (e.g. including rate of recurrence, time to recurrence, protocol for mammography surveillance and rate of detection of recurrence by mammography). Studies also had to report on 100 subjects or more.

9 studies met all of the inclusion criteria. Studies were non-randomised, case-series studies.

Exclusion criteria

Women with a primary diagnosis of DCIS.

Population

number of patients = 7642.

Interventions

Aim: to review evidence on routine surveillance mammography after treatment for breast cancer.

In the primary studies, patients received biennial, annual or biannual mammography during their follow-up periods.

Outcomes

Detection rate of routine mammography for ipsilateral breast cancer and contralateral breast cancer.

Follow up

Not reported.

Results

Time to recurrence:

The time to breast cancer recurrence ranged from 2.2 to 5.9 years. Routine

mammography was not associated with a reduction in time to detection.

Detection rate by mammography:

Overall, the detection rate of recurrent breast cancer by routine mammography had mean 34.7%, median 32% and range 15%-80% (9 studies).

For ipsilateral breast cancer alone (local or loco-regional recurrence) the detection rate of mammography had mean 28.3%, median 26% and range 12%-50%.

For contralateral breast cancer alone the detection rate of mammography had mean 43.6%, median 36% range 18%-80%.

Authors' conclusions:

No evidence was found to suggest that overall survival increased due to the earlier detection of locally recurrent disease. However, local recurrence detected by mammography may be more frequently associated with smaller tumour size, lower stage and older patient age. Contralateral breast cancer may be more frequently detected by mammography than are ipsilateral tumours.

General comments

Literature search rigorous: MEDLINE, HealthSTAR, Cancerlit, EMBASE, Pascal, the Cochrane Library and PDQ were searched with no language restrictions.

DARE review utilised in appraising this review (available at <http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?View=Full&ID=12000008559>).

Ipsilateral recurrence defined as follows:

Local recurrence: recurrence confined to the conserved breast only

Loco-regional recurrence: recurrence in the breast or axilla

Grunfeld, Noorani, McGahan, Paszat, Coyle, van, Joyce & Sawka .
Surveillance mammography after treatment of primary breast cancer: a
systematic review (DARE review available). Breast 11[3]. 2002.

Design

Design: Systematic review of diagnostic studies (diagnosis, screening),
evidence level: 2-
Country: Canada, setting: Secondary care

Inclusion criteria

Published between 1980-2002

>=100 subjects

Reporting study period, rate of recurrence, time to recurrence and rate of
detection by mammography.

Population represented by included studies: patients treated for primary,
invasive breast cancer. Stage of disease at initial diagnosis was variable. The
vast majority of patients received breast conserving surgery and commonly,
RT. Some patients received chemotherapy or hormone therapy.

Exclusion criteria

DCIS.

No restrictions were applied in terms of language, primary treatment, protocol
for mammography surveillance.

Population

-

Interventions

Aim: to systematically review the literature on the effect of routine surveillance
mammography in detecting ipsilateral recurrence (IR) or contralateral breast
cancer (CBC).

Outcomes

Rate of detection of IR and CBC by mammography alone.

Follow up

Not reported.

Results

15 studies met the inclusion criteria. The included studies were all
observational studies.

Detection of IR by mammography:

The proportion of patients in whom IR was detected by mammography alone
had mean 26.5%, median 27% and range 8%-50%, based on 10 studies. In

the remaining cases, IR was detected by either physical examination or a combination of physical examination and mammography.

Three studies reported no difference in the median interval to detection of IR by mammography alone compared to other methods (start point of interval not reported; presumably diagnosis of cancer).

Effect of mode of detection on survival:

Two studies found no effect of mode of detection of IR and either overall survival or disease free survival. One study demonstrated improved 5 year survival in patients in whom IR was detected by mammography.

Detection of CBC by mammography:

The proportion of patients in whom CBC was detected by mammography alone had mean 45.5%, median 45% and range 8%-80%, based on 9 studies.

Two studies reported that mammography detected cases of CBC at an earlier stage than palpation alone.

Effect of mode of detection on survival:

Only one study examined the relationship between the mode of detection of CBC and survival and found no effect.

General comments

Rigorous literature search performed. Search strategy reported.

The included studies were highly heterogeneous in their methodology, mammography regimens and patient populations.

Five studies did not report their mammography regimen. In the remainder of the studies, mammography was performed bi-annually, annually or semi-annually.

The effect in favour of mammography in terms of survival demonstrated by one study is subject to lead time bias and length bias.

Temple, Wang & Mcleod . Preventive health care, 1999 update: 3. Follow-up after breast cancer. Canadian Task Force on Preventive Health Care. CMAJ Canadian Medical Association Journal 161[8]. 1999.

Design

Design: Systematic review of combined study designs (diagnosis, screening), evidence level: 2-
Country: Canada, setting: Secondary care

Inclusion criteria

Studies of women with invasive ductal carcinoma of the breast of stage I-III and also:
>= 5 years of follow-up data;
Description of adjuvant therapy, if received.

Exclusion criteria

Evidence of distant disease at the time of diagnosis.

Population

-

Interventions

Aim: to investigate the role of follow-up in improving survival and quality of life in patients with early breast cancer.

Interventions reviewed include:

Blood tests and imaging to detect distant disease (not cited here);
Physical examination with and without mammography.

Outcomes

Detection in follow up of ipsilateral disease and contralateral disease;
Survival.

Follow up

Minimum of 5 years specified as a study inclusion criterion.

Results

Detection of ipsilateral local recurrence by mammography and physical examination (based upon 8 non-randomised studies):

Sensitivity (mean; median; range):

Mammography: 59.3%; 60%; 38%-74%

Physical examination: 63.5%; 68%; 29%-75%

Specificity (mean; median; range):

Mammography: 54.5%; 59.5%; 39%-60%

Physical examination: 23.5%; 23.5%; 17%-30%.

Detection of contralateral breast cancer by physical examination plus mammography (based upon 2 screening programme studies):

Sensitivity (range): 81%-88%

Specificity (range): 96.5%-99.9%.

Stage of ipsilateral recurrence by method of detection (based on two retrospective studies):

Mammography detected more locally recurrent ipsilateral breast tumours at the noninvasive stage than did physical examination, but this was not found to influence 5 year survival.

Detection of contralateral breast cancer (based on 3 retrospective studies):

Two studies found that the incidence of contralateral breast cancer increased after the introduction of follow-up mammography. A third study found that the incidence of contralateral breast cancer increased when mammography was added to physical examination in follow-up. None of these three studies analysed survival.

General comments

DARE review (Database of Abstracts of Reviews of Effects; Centre for Reviews & Dissemination, University of York) utilised when appraising this systematic review:

<http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=11999009768>

No inclusion criteria are stated based on study design.

Literature search: MEDLINE database; English language.

Quality of included studies: assessed using a hierarchical scale of I (RCT) - III (expert opinion).

Review is weak in terms of mixed study design, lack of reporting of assessment of validity and data extraction.

Authors report that sensitivity and specificity data for mammography and physical examination are based on small, retrospective studies of highly selected patient groups; apparently patients in whom a biopsy was performed as reference standard. It is probable that reference standard was performed only in cases with suspicious mammography/physical examination result, leading to partial verification bias.

Comparisons of mammography and physical examination

Prospective case series

Aichinger, Schulz-Wendtland, Kramer, Lell & Bautz . [Scar or recurrence--comparison of MRI and color-coded ultrasound with echo signal amplifiers]. [German]. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 174[11]. 2002.

Design

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Germany, setting: Secondary care

Inclusion criteria

42 patients who underwent imaging between September 1998 and January 2000 for suspected locally recurrent breast cancer.

38 patients underwent breast conserving surgery and 4 patients underwent mastectomy.

Exclusion criteria

Not known.

Population

Age range 36 to 81 years, median age = 59 years.

Interventions

Aim: to compare the effectiveness of MRI and colour doppler US (with and without echo signal amplifier, ESA) to differentiate locally recurrent breast cancer from scar tissue after surgical treatment.

All patients underwent clinical examination, US, MRI and mammography (n=38).

Outcomes

Diagnostic performance of colour doppler US, mammography and MRI in detecting locally recurrent breast cancer.

Follow up

Not known

Results

Diagnostic performance of colour doppler US, mammography and MRI in detecting locally recurrent breast cancer was as follows:

Mammography:
Sensitivity = 45%
Specificity = 77%

Colour doppler US (without ESA):

Sensitivity = 64%
Specificity = 86%

Colour doppler US plus ESA:
Sensitivity = 86%
Specificity = 82%

MRI:
Sensitivity = 100%
Specificity = 82%

General comments

Criteria for positive result on colour doppler US were tumour vascularisation and flow pattern.

Reference standard was either histological findings or the results of follow-up for at least 12 months.

Bone, Aspelin, Isberg, Perbeck & Veress . Contrast-enhanced MR imaging of the breast in patients with breast implants after cancer surgery. Acta Radiol. 36[2]. 1995.

Design

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Sweden, setting: Secondary care

Inclusion criteria

83 patients who underwent mastectomy for breast cancer followed by reconstruction with saline or silicone-filled implants; examined with MRI between September 1992 and September 1993.

Median interval between cancer surgery and MRI: 18 months (range 4-127 months).

No patients received RT.

Exclusion criteria

None reported.

Population

, age range 33 to 75 years, median age = 50 years.

Interventions

Aim: to assess the value of contrast-enhanced MRI in detecting locally recurrent breast cancer in patients who underwent mastectomy and breast reconstruction.

All patients underwent contrast-enhanced MRI of both breasts.

Outcomes

Diagnostic performance of MRI with regard to:

Ipsilateral local recurrence;

Multifocal tumours (defined as several foci in the same quadrant);

Multicentric tumours (defined as recurrence in different quadrants of the same breast);

Contralateral breast cancer.

Follow up

Median 10 months, range 5-18 months

Results

Staging performance of MRI in detecting ipsilateral recurrent cancer:

Sensitivity = 12/14 = 85.7% [95% CI 60.1%-96.0%]

Specificity = 69/69 = 100% [95% CI 94.7%-100%]

PPV = 12/12 = 100% [95% CI 75.8%-100%]

NPV = 69/71 = 97.2% [95% CI 90.3%-99.2%].

6/14 histologically proven recurrences were DCIS.

Multifocal tumours:

MRI detected 1/5 multifocal tumours.

Multicentric tumours:

MRI detected 5/5 multicentric tumours.

Contralateral breast cancer:

MRI detected as malignant the following contralateral breast lesions:

1/2 invasive tumours;

1/1 DCIS tumour;

1/2 benign lesions (i.e. a false positive case).

General comments

Reference standard was histopathological examination of excised lesions, suspected to be locally recurrent tumour, or clinical follow-up of patients with negative MRI results (median 10 months, range 5-18 months). Biopsy was in some cases prompted by mammography.

Diagnosing clinician also had information from mammography available.

Diagnostic outcome measures are based on small subgroups.

Buthiau, Rixe, Nizri, Piette & Khayat . [Breast cancer: role of MRI in follow-up of cases treated]. [French]. Bull.Acad Natl Med 179[3]. 1995.

Design

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: France, setting: Secondary care

Inclusion criteria

82 patients treated for breast cancer with either breast conserving surgery or mastectomy plus implant reconstruction between October 1993 and December 1994.

Exclusion criteria

Not known.

Population

number of patients = 82, age range 26 to 74 years.

Interventions

Aim: to report on the effectiveness of contrast-enhanced MRI of the breast to detect local recurrence in patients treated for breast cancer with either breast conserving surgery (n=61) or mastectomy plus implant reconstruction (n=21).

All patients underwent contrast-enhanced MRI and diagnostic biopsy.

Outcomes

Diagnostic performance of contrast-enhanced MRI.

Follow up

Not known.

Results

Rate of local recurrence = $57/82 = 69.5\%$.

Performance of contrast-enhanced MRI (all 82 patients):

Sensitivity = $57/57 = 100\%$ [95% CI 93.7%-100%]

Specificity = $21/25 = 84\%$ [95% CI 65.4%-93.6%]

PPV = $57/61 = 93.4\%$ [95% CI 84.3%-97.4%]

NPV = $21/21 = 100\%$ [95% CI 84.5%-100%].

General comments

Reference standard was histological diagnosis from biopsy, performed in all cases.

High rate of local recurrence is likely to arise since patients had suspicion of recurrence on conventional imaging.

Heywangkobrunner, Schlegel, Beck, Wendt, Kellner, Lommatzsch, Untch & Nathrath . Contrast-Enhanced Mri of the Breast After Limited Surgery and Radiation-Therapy. J Comput.Assist.Tomogr. 17[6]. 1993.

Design

Design: Prospective case series (diagnosis, screening), evidence level: 3
Country: Germany, setting:

Inclusion criteria

62 patients treated by breast conserving surgery and RT and who received either 24 months of clinical and mammographic follow-up (n=60) or histopathologic results (n=17).

A total of 77 MRI studies were performed.

Exclusion criteria

None reported.

Population

number of patients = 62.

Interventions

Aim: to examine the performance of MRI in detecting recurrent breast cancer in patients treated by breast conserving surgery and RT, and to record the changes on MRI at different times since treatment.

All patients underwent mammography and MRI. Some patients underwent US in addition.

Outcomes

Sensitivity and specificity of MRI in detecting recurrent breast cancer.

Follow up

Range 2-5 years

Results

Post MRI:

Sensitivity = 11/11 = 100% [95% CI 74%-100%]

Specificity = 56/66 = 85% [95% CI 74%-92%]

Pre-MRI (conventional imaging):

Sensitivity = 7/11 = 64% [95% CI 35%-85%]

Specificity = 51/66 = 77% [95% CI 66%-86%].

Specificity of MRI was higher in the subgroup of studies performed >18 months after RT (100%) than in studies performed 10-18 months after RT (76%) and those performed 0-9 months after RT (73%). Sensitivity was 100% in all three subgroups.

4 of 11 recurrences and 10 of 18 single recurrent foci were detected by MRI alone, based on focal enhancement.

General comments

95% CIs provided by spreadsheet available at Cardiff University; Newcombe, (2006):

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/index.htm

Sensitivity and specificity values reported for subgroups based on time since RT depend on small numbers of MRI studies.

Pre-MRI data refer to diagnoses based on clinical examination, mammography and US.

Post-MRI data incorporate use of MRI and also information from clinical examination, mammography and US. This may over-estimate the performance of MRI as a single modality but reflects likely setting.

Retrospective case series

Ashkanani, Sarkar, Needham, Coldwells, Ah-See, Gilbert, Hutcheon, Eremin & Heys . What is achieved by mammographic surveillance after breast conservation treatment for breast cancer? Am J Surg 182[3]. 2001.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

695 women with breast cancer treated by breast conserving surgery between 1990-1995 identified from a total series of 2300 patients.

Exclusion criteria

Patients who underwent mastectomy.

Population

number of patients = 695, age range 33 to 76 years, mean age = 59 years.

Interventions

Aim: to investigate the rate of detection of local recurrence by mammography and clinical examination.

All patients were followed up by clinical examination as follows:
3-4 monthly in the first two years;
6 monthly for the next 3 years;
annually thereafter.

All patients received annual bilateral mammography.

Outcomes

Rate of local recurrence;
Means of detection of local recurrence

Follow up

Mean 3.5 years (range 2-7)

A total of 2181 mammograms were performed (i.e. a mean of 3.1 per patient).

Results

Local recurrence was confirmed in 21/695 = 3% of patients at a mean follow-up period of 3.5 years. Of these 21 patients, 1 patient received no mammography at all.

Clinical examination was the first method of detection of local recurrence in 11/21 = 52.4% of patients with confirmed local recurrence. Surveillance mammography was the first method of detection of local recurrence in 10/21 =

47.6% of patients with confirmed local recurrence, although mammography was able to predict local recurrence in 13 patients i.e. $13/20 = 65\%$ of patients with local recurrence who received mammography. In 52 patients mammogram results were falsely positive; at a rate of $52/2181 = 2.4\%$ of all mammographies.

General comments

Reference standard for local recurrence was fine needle aspiration cytology or biopsy. Reference standard was only performed in cases with suspicious results by either mammography or clinical examination (so there is a likelihood of partial verification bias). Furthermore these measures reflect repeated testing by mammography during each patient's follow-up period.

Auguste, Gerold, Rothenberg, Litvak & Gentin . Detection of Recurrent Carcinoma in the Irradiated Breast. Complications in Surgery 13[4]. 1994.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

103 consecutive female patients treated with lumpectomy and breast RT for stage I-II breast cancer at a single centre during a 5-year period.

Exclusion criteria

None reported.

Population

number of patients = 103, mean age = 57 years.

Interventions

Aim: to evaluate the performance of mammography in detecting recurrent breast cancer in patients treated with breast conserving surgery and radiotherapy.

Outcomes

Sensitivity and specificity of mammography in detecting recurrent breast cancer.

Follow up

Minimum 6 months (range 6 months to 5 years).

Interval from initial treatment and histological confirmation of recurrence had mean 24.7 months (range 10-42 months).

Results

Mammography:
Sensitivity = 64%
Specificity = 67%

Clinical examination:
Sensitivity = 83%
Specificity = 17%

General comments

Frequency and timing of follow-up mammography not stated, but in discussion section, authors recommend commencement at 6 months after therapy and thereafter annually.

Reference standard was histological findings of biopsy, which was performed only in suspicious cases, either on mammography or clinical examination.

Balu-Maestro, Bruneton, Geoffray, Chauvel, Rogopoulos & Bittman .
Ultrasonographic posttreatment follow-up of breast cancer patients. J
Ultrasound Med 10[1]. 1991.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: France, setting: Secondary care

Inclusion criteria

272 patients treated by breast conserving surgery and RT.

Exclusion criteria

101 patients with incomplete data (from sensitivity values).

Population

number of patients = 171.

Interventions

Aim: to report on the effectiveness of US for the follow-up of patients with treated breast cancer.

Patients received bilateral US of breast, axilla and neighbouring node bearing tissues every 6 months in the first 3 years from treatment and annually thereafter.

Patients also received clinical examination plus mammography at the same frequency as US, and in addition, annual mammography of the contralateral breast.

Outcomes

Sensitivity of US and Mammography.

Follow up

Range: 1 month to 12 years. No median reported.

Results

Recurrence rates:

in 272 patients there were 27 locally recurrent tumours, 8 cases of contralateral breast cancer and 2 cases of residual tumour.

Sensitivity of US and mammography with regard to local recurrence was as follows:

US: 20/22 = 90.9% [95% CI 72.2%-97.5%]

Mammography: 21/22 = 95.5% [95% CI 78.2%-99.2%]

General comments

Sensitivity values reported are based on 22 recurrences in a subgroup of 171 patients with complete data.

There is no way of checking any values in this paper, or of deriving further values; specificity is not reported.

No consistent reference standard is described, but is based upon comparison of clinical follow-up, sonographic, mammographic and histological data; hence high likelihood of disease progression bias/differential verification bias.

95% CIs provided by spreadsheet available at Cardiff University; Newcombe, (2006):

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/index.htm

Churn & Kelly . Outpatient follow-up after treatment for early breast cancer: updated results after 5 years. Clin Oncol (R Coll.Radiol.) 13[3]. 2001.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

612 patients referred to a single centre in 1993 for treatment for breast cancer of stage pT1-3, N0-1 or NxM0.

30.9% of patients were of <50 years of age.

Results cited here are for 505 patients who underwent breast conserving surgery; study did not audit contralateral breast cancer in patients treated by mastectomy.

Exclusion criteria

None reported.

No data are cited here for patients who underwent mastectomy.

Population

number of patients = 505.

Interventions

Aim: to investigate the value of frequent outpatient follow-up of patients treated for breast cancer.

An audit was performed of the follow-up of a series of patients with breast cancer. The follow-up schedule was:

3-4 monthly intervals for the first 2-3 years;

6 monthly up to five years;

annually thereafter.

There was no set protocol for follow-up mammograms during the study period.

Outcomes

Rate of local recurrence (in the ipsilateral breast, chest wall or axilla)

Means of detection of local recurrence.

Follow up

Median 74 months (range 4-89 months)

Results

Local recurrence-free survival at 5 years was 94.5% (local relapse rate 5.5%).

There were 31 cases of local recurrence in 5 years:
25 as first relapse;
4 concurrent with distant metastases;
2 after presentation of systemic disease.

In 25 patients in whom local recurrence was the only detected recurrence, the method of detection was as follows:

Mammography: 7 (28%)

Routine clinic appointment: 8 (32%)

Interim referral: 9 (36%)

Unknown: 1 (4%)

General comments

A study disadvantage is that the exact frequency of mammograms is not known (nor in how many patients mammography was performed), but the authors report that mammography was performed usually less frequently than annually.

Ciatto, Ambrogetti & Muraca . [Combined diagnosis of breast cancer recurrences after conservative treatment. Critical review of 143 consecutive cases]. [Italian]. Radiol.Med (Torino) 90[4]. 1995.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria

143 patients with breast cancer treated consecutively with breast conserving surgery between 1984-1994, all of whom had intramammary recurrence.

Exclusion criteria

Patients with no local recurrence.

Population

number of patients = 143, age range 32 to 87 years, mean age = 55 years.

Interventions

All patients received regular clinical examination and mammography as follows:

Clinical examination: 4 monthly for the first two years, 6 monthly up until the 5th year and annually thereafter;

Mammography: annually for the first five years and biennially thereafter.

Outcomes

Means of detection of local recurrence; sensitivity.

Follow up

Mean 3.7 years (reported as disease-free interval)

Results

Of the total of 143 patients, 121 patients underwent mammography and 43 patients underwent US. Adherence to the follow-up protocol was 90%.

Sensitivity of imaging was as follows:

Mammography: 77/121 = 63.6% [95% CI 54.8%-71.7%]

US: 33/43 = 76.7% [95% CI 62.3%-86.9%]

General comments

Study provides no data for patients without local recurrence, hence specificity cannot be calculated.

The sensitivity values reflect repeated imaging procedures, given the mean follow-up period of 3.7 years and adherence rate of 90%.

The protocol for US is not known.

Coulthard, Beveridge & Potterton . MRI in routine breast cancer follow-up: correlation with clinical outcome. Clin Radiol. 54[7]. 1999.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

63 women with breast cancer attending a follow-up clinic between October 1993 and September 1994.

59 patients had complete clinical follow up and are reported in the analysis.

Exclusion criteria

4 patients with incomplete follow-up.

Population

number of patients = 59, age range 30 to 74 years, median age = 54 years.

Interventions

Aim: to evaluate the effectiveness of contrast-enhanced MRI in the follow-up of patients treated for breast cancer.

All patients underwent contrast-enhanced MRI of both breasts.

Patients were considered in two groups:

Patients referred for MRI due to equivocal results of follow-up (possibly suggestive of malignancy) by clinical examination or mammography (equivocal group; n=26);

Patients referred for MRI with no particular suspicion of recurrent disease, and changes on mammography or clinical examination suggestive of scarring etc. (control group; n=33).

Outcomes

Diagnostic performance of MRI.

Follow up

MRI was performed at a median of 55 months since surgery (range 15-144 months).

Median follow-up after MRI: 36 months (range 10-47 months).

Results

In the 'equivocal' group, 2/26 patients experienced distant metastasis that was

detected in follow-up.

There were 4 falsely positive results on MRI in either the ipsilateral or contralateral breast, demonstrated as scarring or benign lesion by biopsy.

In the 'control' group, 1/33 patients experienced distant (pleural) metastasis that was detected by MRI and 3/33 patients experienced ipsilateral breast recurrence that was detected in follow-up.

Therefore with regard to ipsilateral local recurrence only, the diagnostic performance of MRI was as follows:

Sensitivity = $0/3 = 0\%$ [95% CI 0%-56.1%]

Specificity = $52/56 = 92.9\%$ [95% CI 83.0%-97.2%]

PPV = $0/4 = 0\%$ [95% CI 0%-50%]

NPV = $52/55 = 94.6\%$ [95% CI 85.2%-98.1%].

General comments

Criteria for apparent malignancy on MRI are vague, but appear to be abnormal enhancement.

Reference standard was either histological findings when provided by MRI prompted biopsy, or clinical outcome demonstrated by follow-up annual clinical examination and mammography).

MRI was performed once only, at a median of 55 months since surgery (range 15-144 months). Clinical follow up after MRI was reported at a median of 36 months (range 10-47 months) since MRI, after exposure to possible several further mammographies; and therefore introduces disease progression bias.

Diagnostic outcomes for MRI are based upon small subgroups.

95% CIs provided by spreadsheet available at Cardiff University; Newcombe, (2006):

http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/index.htm

Fajardo, Roberts & Hunt . Mammographic surveillance of breast cancer patients: should the mastectomy site be imaged? AJR American Journal of Roentgenology. 161[5]. 1993.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

827 patients treated with mastectomy for breast cancer between 1985 and 1992.

795 patients had unilateral mastectomy and 32 patients had bilateral mastectomy.

80 patients underwent breast reconstruction.

Exclusion criteria

Men (4);

Patients who moved away prior to 1986 (6);

Cases of partial mastectomy (8);

Cases of mastectomy for benign breast disease (20)

Cases of prophylactic mastectomy to the contralateral breast (13).

Population

number of patients = 827, age range 31 to 94 years, mean age = 67 years.

Interventions

Aim: to evaluate the efficacy of routine mammography of the postoperative site in patients treated with mastectomy for breast cancer.

Patients underwent clinical and mammographic surveillance after their breast cancer treatment (frequency not reported).

Outcomes

Method of detection of ipsilateral local recurrence (with local recurrence defined as that occurring in the ipsilateral chest wall, soft tissues, skin flap or surgical scar).

Follow up

Mean 8 years (range 2-46 years).

Results

Rate of ipsilateral local recurrence after mastectomy:

Of 859 breasts in the study group 39 tumours recurred locally (4.5%) at a mean of 3.5 years from diagnosis (range 2-10 years).

Method of first detection of ipsilateral local recurrence:

Clinical examination: $35/39 = 89.7\%$

Scintigraphy: $4/39 = 10.3\%$

Mammography: 0/39 = 0%

In 20 patients with suspicious findings on clinical examination which prompted mammography, mammography detected locally recurrent cancer in 2 patients (10%).

General comments

Study does not report the frequency of either mammography or clinical examination, beyond that all patients with local recurrence had received both in the 3 months preceding histological proof of local recurrence.

Study does not report which (if any) of 19 cases of locally recurrent tumours first detected by clinical examination (in addition to the 20 reported) were ALSO visible on mammography.

Johnson, Banerjee & Webster . Mastectomy follow-up by biennial mammograms: is it worthwhile? Breast 9[2]. 2000.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United Kingdom, setting: Secondary care

Inclusion criteria

216 patients treated with mastectomy between 1978-1985.

205 patients were analysed after exclusions.

Patient age not reported.

Exclusion criteria

Patients who underwent previous mastectomy (5);
Patients who underwent bilateral mastectomy (6).

Population

number of patients = 205.

Interventions

Aim: to assess the efficacy of annual clinical examination and biennial mammography to detect metachronous tumours occurring in the contralateral breast in patients treated for breast cancer with mastectomy.

Outcomes

Rate of metachronous (contralateral) tumours;

Method of detection.

Cost of detecting one case of metachronous, contralateral tumour.

Follow up

Minimum of 12 years.

Results

Rate of metachronous, contralateral tumours:
 $17/205 = 8.3\%$

Method of detection:

Patient: $8/17 = 47\%$

Clinical examination: $4/17 = 24\%$

Routine follow-up mammography: $5/17 = 29\%$

There was no difference in stage of metachronous tumour by method of detection.

Of 8 patient-detected metachronous tumours, 7 were detected in the second year after the last mammogram.

Median time to detection of metachronous tumour from first operation: 10 years (range 2-16 years).

The cost of detecting one case of metachronous, contralateral tumour = £6500.

General comments

Cost estimate was based upon consideration of the cost of out-patient appointments plus mammography.

Kaas, Hart, Besnard, Peterse & Rutgers . Impact of mammographic interval on stage and survival after the diagnosis of contralateral breast cancer. Br J Surg 88[1]. 2001.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Netherlands, the, setting: Secondary care

Inclusion criteria

275 patients with contralateral (metachronous) breast cancer presenting between 1976 AND 1990; 'metachronous' defined as at least 1 year after the first tumour.

Mean age was 52 years at diagnosis of first (ipsilateral) breast cancer and 58 years at diagnosis of contralateral breast cancer.

Exclusion criteria

Patients with unilateral breast cancer;
Patients with LCIS;
Patients in whom contralateral cancer was synchronous with distant metastatic disease;
Patients treated for local recurrence within the preceding two years of detection of contralateral breast cancer.

258 patients were thus excluded from an original series of 581 patients.

48 further patients were excluded due to incomplete data.

Population

number of patients = 275, age range 27 to 95 years.

Interventions

Aim: to investigate the outcome of patients with contralateral breast cancer at different frequencies of follow-up mammography.

Clinical examination was performed as follows:

3 monthly for the first two years;
6 monthly for the subsequent 3 years;
Annually thereafter.

Frequency of mammography was variable, and two patient groups were defined using a watershed of a mean of 15 months between mammograms for each individual patient:

Group 1 (n=141): 'Annual mammograms': Women with a mean interval between mammograms of 12 months; mean total of 5.7 mammograms per patient.

Group 2 (n=134): 'Biennial mammograms': Women with a mean interval between mammograms of ≥ 15 months.; mean total of 3.4 mammograms per patient.

Outcomes

Method of first detection of contralateral breast cancer; mammography or clinical examination.

Disease specific survival.

Follow up

Median length not reported; 5 year survival reported.

Results

Survival; annual versus biennial mammography:

There was no significant difference in 5-year disease specific survival after contralateral breast cancer between group 1 (75%) and group 2 (75%, $p=1$).

Disease specific survival at 5 years: Mammography detected versus clinically detected contralateral breast cancer:

Mammography: 85%

Clinical examination: 69% ($p=0.015$)

When this analysis was stratified by pathological stage of the ipsilateral breast cancer (Cox proportional hazard model), the difference remained statistically significant ($p=0.015$).

In this series of patients (aged 27-95 years) with detected contralateral breast cancer who had available the programme of mammography, clinical examination and self examination, the tumour stage at diagnosis was comparable to that of first breast cancer tumours detected in the Dutch population (aged 50-69 years) by mammography screening programme alone (by looking at the data; no formal analysis).

Proportion of contralateral breast cancers detected by mammography:

All patients: $109/275 = 39.6\%$

Group 1: $50/141 = 35.5\%$

Group 2: $36/134 = 26.9\%$ (no significant difference between the two groups, $p=0.62$).

Detection of contralateral breast cancer by mammography and age (in 185 patients with adequate data available):

Ipsilateral breast cancer: Adjusting for the mammographic results for contralateral breast cancer, patients in whom ipsilateral breast cancer was negative on mammography were a mean of 2 years younger than those with positive result on mammography (ANOVA, $p=0.0001$).

Contralateral breast cancer: Adjusting for the mammographic results for

ipsilateral breast cancer, patients in whom contralateral breast cancer was negative on mammography were a mean of 4 years younger than those with positive result on mammography (ANOVA, $p=0.03$).

The interaction term for these two variables was not statistically significant (ANOVA, $p=0.84$).

General comments

Patients in group 1 were statistically significantly younger at the time of diagnosis of ipsilateral breast cancer (mean 51 years and 54 years respectively) and contralateral breast cancer (mean 56 years and 61 years respectively) than patients in group 2 ($p=0.006$).

Lieberman, Morris, Kim, Kaplan, Abramson, Menell, Van Zee & Dershaw . MR Imaging findings in the contralateral breast of women with recently diagnosed breast cancer. Am J Roentgenol. 180[2]. 2003.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

223 patients identified from a series of 1336 breast MRI procedures performed in the years 2000-2001.

Included patients met the following criteria:

Unilateral breast cancer diagnosed in the preceding 6 months of MRI;

Contralateral breast was asymptomatic;

Mammogram undertaken in the preceding 6 months to the MRI showed no evidence of cancer.

36 (16%) patients had pure DCIS as their index cancer.

Exclusion criteria

Defined by inclusion criteria.

Population

number of patients = 223, age range 28 to 79 years, median age = 48 years.

Interventions

Aim: to determine the frequency and positive predictive value of biopsy performed on the basis of MRI in the contralateral breast in women with recently diagnosed breast cancer.

All patients underwent MRI of the contralateral breast. Biopsy was performed in cases classified as suspicious or highly suggestive of malignancy on MRI.

Outcomes

Number of biopsies provoked by MRI;

Positive predictive value of MRI.

Follow up

The median interval between diagnosis of the index cancer and MRI was 27 days (range 0-167 days).

Results

Number of biopsies provoked:

Biopsy of the contralateral breast was recommended due to suspicion of malignancy in 72/223 = 32% of patients, and was performed in 61 patients.

Positive predictive value of MRI:

12/61 = 20% of patients who underwent contralateral breast biopsy were found to have cancer; this represented 12/223 = 5% of patients who underwent MRI. Therefore:
PPV of MRI: 12/61 = 20%.

Of the 12 patients with contralateral breast cancer, 6 had DCIS and 6 had infiltrating carcinoma.

Stage of contralateral breast cancer was known in 11 patients; stage 0 in 6 patients and stage I in 5 patients.

The interval between diagnosis of index cancer and the contralateral cancer was 38 days (range 12-253 days). In 11 patients (92%) the contralateral cancer was diagnosed within 3 months of the index cancer.

General comments

This study represents detection of contralateral breast cancer close to the time of diagnosis of the index cancer (c.f. 'synchronous?'); 92% of diagnoses were within 3 months. Therefore study may be better considered as one of staging than of true follow-up.

Reference standard to evaluate MRI was biopsy, guided either by US or MRI.

Biopsy was not performed although indicated by MRI in 11 patients due to presence of stage IV disease, patients lost to follow up, patients refusing biopsy, and loss of the lesion on attempting MRI guided biopsy.

Authors offer reasons for low PPV of MRI in this setting:

MRI technique;

Learning curve;

Low threshold for requesting a biopsy based on MRI findings.

Paszat, Grunfeld, van, Coyle, Sawka, Yun, McGahan & Noorani . A Population-based Cohort Study of Surveillance Mammography After Treatment of Primary Breast Cancer. 2007.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Canada, setting: Secondary care

Inclusion criteria

12279 women treated for primary breast cancer between July 1 1991 and December 31 1993, as follows:

Lumpectomy: 19.6%

Lumpectomy plus RT: 41.7%

Mastectomy: 38.7%

Exclusion criteria

Women who received neither mastectomy nor lumpectomy to treat their primary breast cancer (15% of all registered cases).

Population

number of patients = 12279, mean age = 61 years.

Interventions

Aims:

1. To describe the rates of use of annual surveillance mammography following the treatment of primary breast cancer in Ontario.
2. To describe the rates of use of subsequent breast surgery following annual surveillance mammography.

Ontario cancer registry data for all patients treated within the study period were linked to data from the following sources:

1. Ontario Cancer Registry
2. Canadian Institute for Health Information
3. Radiation Oncology Research Unit at Queen's University at Kingston
4. Ontario Health Insurance Plan
5. 1991 Canadian Census

Outcomes

Data were collected up to December 31, 1998 for:

1. Surveillance mammography
2. Subsequent diagnostic procedures on the breast
3. Subsequent breast surgery
4. Death from any cause.

Outcomes are commonly reported by primary treatment group:
Lumpectomy versus Lumpectomy plus RT versus Mastectomy.

Follow up

60 months from diagnosis of breast cancer.

Results

Overall survival:

Overall survival at 60 months following diagnosis of breast cancer: 82.7%.

Interval between surveillance mammographies:

Median: 14.7 months, mean 16.4 months.

Use of surveillance mammography:

Women diagnosed at age 70 or older, and women treated by lumpectomy without radiation therapy (RT) were less likely to use surveillance mammography compared to other women treated for breast cancer ($p < 0.001$).

Relationship between surveillance mammography and further surgical procedures:

Two-thirds of subsequent breast surgery performed for women previously treated for breast cancer occurred more than four months following surveillance mammography (suggesting that surveillance mammography does not detect all recurrences in the breast, or all new primary contralateral breast cancers).

General comments

Study does not analyse survival according to uptake of surveillance mammography.

In the group treated initially by mastectomy, authors assume that mastectomy/lumpectomy represent the treatment of contralateral primary breast cancer. However, among women initially treated by lumpectomy, ipsilateral lumpectomies can not be distinguished from contralateral lumpectomies and mastectomies. Therefore, no estimate may be made of the proportion of women having ipsilateral breast recurrences or contralateral primary breast cancers following initial lumpectomy.

Surgical procedures occurring within 4 months of a surveillance mammogram were assumed to be prompted by surveillance mammography. Surgical procedures occurring 4 months or more after a surveillance mammogram were assumed to be prompted by clinical examination and/or symptoms, rather than by surveillance mammography.

Preda, Villa, Rizzo, Bazzi, Origgi, Cassano & Bellomi . Magnetic resonance mammography in the evaluation of recurrence at the prior lumpectomy site after conservative surgery and radiotherapy. Breast Cancer Research 8[5]. 2006.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Italy, setting: Secondary care

Inclusion criteria

93 female patients who underwent MRI to investigate suspected local recurrence of breast cancer between April 1999 and July 2003. All patients previously underwent breast conserving surgery and a minimum of 6 months had elapsed since any radiotherapy treatment.

Exclusion criteria

-

Population

number of patients = 93, age range 40 to 72 years, mean age = 53 years.

Interventions

Aim: to investigate the role of MRI in imaging suspected local recurrence of breast cancer.

All 93 patients with suspected local recurrence of breast cancer underwent contrast enhanced MRI of the breast

Outcomes

Sensitivity, specificity, PPV, NPV of MRI with regard to:
Detection of recurrent cancer in the surgical scar;
Detection of all lesions, including those that are incidental and not in contact with the surgical scar.

Follow up

36 months (range 12-48 months).

Results

Performance of MRI (lesions at the surgical scar site):

Sensitivity = 9/10 = 90% [95% CI 60%-98%]

Specificity = 76/83 = 92% [95% CI 84%-96%]

PPV = 9/16 = 56% [95% CI 33%-77%]

NPV = 76/77 = 99% [95% CI 93%-100%]

13 incidental lesions not in contact with the surgical scar were identified by MRI, in 7 patients. These lesions were true positive (6), true negative (5), false positive (2) and false negative (0).

Performance of MRI: all lesions, including those that are incidental and not in contact with the surgical scar:

Sensitivity = $15/16 = 94\%$ [95% CI 72%-99%]

Specificity = $81/90 = 90\%$ [95% CI 82%-95%]

PPV = $15/24 = 63\%$ [95% CI 43%-79%]

NPV = $81/82 = 99\%$ [95% CI 93%-100%]

General comments

In all patients the grounds for suspicion of local recurrence was the result of either mammography and/or US imaging, therefore we could expect a high prevalence of recurrent disease.

MRI results were interpreted by a radiologist who was aware of the mammographic and US findings.

MRI findings were classified as malignant or benign based on combined morphologic and time-signal intensity criteria: a multifactorial score was derived, with a score of 0-3 classed as benign and 4-8 as malignant. This score was mapped to the American College of Radiology classification:

BI-RADS I: negative; score 0-1

BI-RADS II: benign; score 2

BI-RADS III: probably benign; score 3

BI-RADS IV: suspicious; score 4-5

BI-RADS V: malignancy highly likely; score 6-8

Reference standard: histological findings where biopsy was performed (29 patients) ; clinical course of disease over 36 months' follow-up (using mammography and/or US; 64 patients) if no biopsy was performed. Use of two reference standards is unavoidable in this setting but may introduce differential verification bias, and in the case of follow-up, disease progression bias.

Shin, Han, Choe, Nam, Park & Im . Ultrasonographic detection of occult cancer in patients after surgical therapy for breast cancer. J Ultrasound Med 24[5]. 2005.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Korea (South), setting: Secondary care

Inclusion criteria

1968 women who underwent breast US during follow-up after treatment for breast cancer. Treatment for breast cancer was either modified radical mastectomy or breast conserving surgery plus RT. Chemotherapy was given for all invasive ductal carcinomas >1cm in size.

Exclusion criteria

Some data missing for four patients who received their primary treatment at outside institutions.

Population

number of patients = 1968, age range 32 to 67 years, mean age = 49 years.

Interventions

Aim: to investigate the effectiveness of breast US in the follow-up of patients treated for breast cancer.

Patients received clinical examination every 3 months for the first 2-3 years following diagnosis, with bilateral US of the breast, chest wall, axilla, parasternal and supraclavicular regions performed at intervals of 6 months or more.

Outcomes

Local recurrence

Contralateral, metachronous (defined as detected >6 months after initial diagnosis with no evidence of distant metastasis) breast tumours.

Follow up

Not reported directly; mean post-operative duration to recurrence was 3 years (range 8-108 months).

Results

Diagnostic performance of US with regard to occult tumour (recurrence in the breast, adjacent node bearing areas, mastectomy bed and contralateral breast cancer) was as follows:

Sensitivity = $24/34 = 70.6\%$ [95% CI 53.8%-83.2%]

Specificity = $1901/1934 = 98.3\%$ [95% CI 97.6%-98.8%]

PPV = 24/57 = 42.1% [95% CI 30.2%-55.0%]
NPV = 1901/1911 = 99.5% [95% CI 99.0%-99.7%]

General comments

Criteria for malignant tumour on US were based on the American College of Radiology Breast Imaging Reporting and Data System assessment categories 4 (suspicious abnormality) and 5 (suggestive of malignancy).

Reference standard was FNAC or core biopsy, performed under US guidance, but only where initial US result scored 4 or 5 as above. In all other cases reference standard was the documented course of disease observed in follow-up and utilising information from subsequent imaging (mammography, CT, PET) and clinical examination.

A total of 3329 US procedures were performed, therefore some patients received only ipsilateral US.

95% CIs provided by spreadsheet available at Cardiff University; Newcombe, (2006):
http://www.cardiff.ac.uk/medicine/epidemiology_statistics/research/statistics/newcombe/proportions/index.htm

Viehweg, Heinig, Lampe, Buchmann & Heywang-Kobrunner . Retrospective analysis for evaluation of the value of contrast-enhanced MRI in patients treated with breast conservative therapy. MAGMA. 7[3]. 1998.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: Germany, setting: Secondary care

Inclusion criteria

207 contrast-enhanced MRI procedures performed in 166 patients treated for breast cancer in the years 1988-1995. All patients had previously undergone breast conserving surgery and RT.

80 MRI procedures followed mammogram results that were indeterminate or suspicious for local recurrence.

127 MRI procedures were performed because breast tissue was difficult to evaluate due to high density, scarring or fibrosis.

Exclusion criteria

3 patients who were either lost to follow-up or died of distant metastases;
2 patients who died of other causes than cancer.

Population

number of patients = 166, age range 30 to 77 years, mean age = 55 years.

Interventions

Aim: to evaluate the role of MRI in detecting local recurrence in patients who underwent breast conserving surgery plus RT.

Patients underwent contrast-enhanced MRI.

Outcomes

Diagnostic performance of MRI, utilising all previous imaging information and presented as follows:

For patients in whom MRI was performed ≤ 12 months from RT;

For patients in whom MRI was performed > 12 months from RT.

Follow up

Minimum 2 years.

Results

MRI procedures performed up to 12 months since RT (40 procedures):

The additional use of contrast-enhanced MRI changed the overall diagnosis in 6 of 40 procedures performed (15%).

Sensitivity = $1/1 = 100\%$ [95% CI 20.7%-100%]

Specificity = $29/39 = 74.4\%$ [95% CI 59.0%-85.4%]

PPV = 1/11 = 9.1% [95% CI 1.6%-37.7%]
NPV = 29/29 = 100% [95% CI 88.3%-100%]

MRI procedures performed >12 months since RT (167 procedures):

The additional use of contrast-enhanced MRI changed the overall diagnosis in 49 of 167 procedures performed (29.3%).

Sensitivity = 26/26 = 100% [95% CI 87.1%-100%]
Specificity = 129/141 = 91.5% [95% CI 85.7%-95.1%]
PPV = 26/38 = 68.4% [95% CI 52.5%-80.9%]
NPV = 129/129 = 100% [95% CI 97.1%-100%]

Values for all 207 procedures:

Sensitivity = 27/27 = 100% [95% CI 87.5%-100%]
Specificity = 158/180 = 87.8% [95% CI 82.2%-91.8%]
PPV = 27/49 = 55.1% [95% CI 41.3%-68.2%]
NPV = 158/158 = 100% [95% CI 97.6%-100%]

General comments

The interval from primary treatment to MRI varied from 1 month to >99 months.

29 patients were examined on two or more occasions.

Criteria for malignancy on contrast-enhanced MRI were based upon lesion distribution, shape and internal structure, using pre and post-contrast images and with access to previous conventional imaging studies; all cases where MRI provoked a confirmatory biopsy were classed as positive.

The outcome values for the 40 procedures within 12 months of radiotherapy are hampered by small numbers.

Reference standard was biopsy where prompted by findings of MRI, or else a minimum of two years' follow up. This may lead to disease progression bias (unlikely to be important in this study due to zero false negative results on MRI) and differential verification bias.

Evidence Tables – DCIS

Retrospective case series

Liberman, Van Zee, Dershaw, Morris, Abramson & Samli . Mammographic features of local recurrence in women who have undergone breast-conserving therapy for ductal carcinoma in situ. AJR American Journal of Roentgenology. 168[2]. 1997.

Design

Design: Retrospective case series (diagnosis, screening), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

20 patients treated for DCIS with breast conserving surgery between 1972 and 1990 at a single centre who:

- a) experienced histologically proven local recurrence;
- b) had mammograms available for the time of detection of the local recurrence.

Selected patients were identified from a larger series of 172 patients treated during this period.

Exclusion criteria

See inclusion criteria.

Population

Number of patients = 20, age range 20 to 89 years, median age = 60 years.

Interventions

Patients underwent breast conserving surgery to treat initial DCIS; 40% underwent RT in addition.

Authors performed retrospective review of mammographies taken at the time of breast cancer recurrence, clinical charts and histopathologic findings.

Outcomes

Method of detection of recurrent breast cancer.

Follow up

Median 75 months (range 3-210 months).

Results

In 20 women with locally recurrent breast cancer after DCIS, the method of detection of the local recurrence was as follows:

Mammography: 17 (85%)

Mammography and physical examination: 2 (10%)

Physical examination: 1 (5%).

In 13/20 women, recurrent lesions were pure DCIS. Of these 12/13 = 92% were detected solely by mammography.

General comments

The 20 patients are highly selected. In all cases recurrent breast cancer was histologically proven. The protocol for follow-up mammography was not reported. Re: reported results, retrospective selection of patients with mammograms available is not as good a study design as prospective follow-up mammography plus clinical examination. For example this study design cannot demonstrate false positive rate of mammography.

Weng, Juillard, Parker, Chang & Gornbein . Outcomes and factors impacting local recurrence of ductal carcinoma in situ.[see comment]. Cancer 88[7]. 2000.

Design

Design: Retrospective case series (therapy), evidence level: 3
Country: United States, setting: Secondary care

Inclusion criteria

88 cases of pure DCIS in 85 patients, identified retrospectively as a consecutive case series.

Exclusion criteria

Not reported.

Population

Number of patients = 85, age range 28 to 81 years, median age = 55 years.

Interventions

Aims:

1. To examine survival and recurrence rates in patients treated for DCIS by mastectomy versus breast conserving surgery plus RT versus breast conserving surgery alone.
2. To analyse risk factors for local recurrence.

Patients were followed-up as follows:

Physical examination every 3 months for 2 years, then every 6 months for 2 years, then annually thereafter.

Where RT was given: baseline mammography 6-8 weeks after treatment.

Biannual mammography on the treated side for 2 years then annually thereafter.

Annual mammography on the contralateral side.

Outcomes

Recurrence-free survival

Risk factors for local recurrence

[NB Only the method of detection of local recurrence is cited]

Follow up

Mean 95.9 months, median 99 months, range 1-160 months.

Results

Local recurrence occurred in 12 of 88 cases (13.6%).

Method of detection of local recurrence included:

Mammography: 9 cases (75%)

Palpable mass or lymphadenopathy: 2 cases (16.7%)
Incidental detection at time of cosmetic surgery: 1 case (8.3%).

General comments

Local recurrence defined as biopsy-proven tumour anywhere in the previously treated breast.

Health Economics Summary

A joint literature review was performed to assess, on one hand, the cost-effectiveness of breast imaging modalities (i.e. mammography, ultrasound (US), magnetic resonance imaging (MRI), mammoscintigraphy and PET / CT) in the follow up of patients with invasive breast cancer, and on the other hand, to assess the cost-effectiveness of mammography, US and MRI in the follow up of patients with DCIS. From 347 references initially identified through the search, 333 were excluded on the grounds of the title and abstract, and 14 references were considered further. All the retrieved papers were finally excluded: 4 studies did not include an economic analysis (Emens et al 2003; Grilli 1995; Khandekar 1996; Sakorafas et al 2000), 1 did not consider the relevant PICO question (Mould 2004), 3 did not consider the relevant PICO interventions (Coleman et al 1990; Mapelli et al 1995; Schapira et al 1991), 1 did not consider the relevant PICO comparator (Mandelblatt et al 2006) and 1 was written in a foreign language (Lamy 2005). Therefore, no evidence was found to assess the cost-effectiveness of breast imaging modalities in the follow up of invasive breast cancer patients and in patients with DCIS so no further economic modelling was undertaken.

9.2 What is the role of follow-up in patients who have been treated for breast cancer?

Short Summary

There is a reasonable volume of evidence available that is related to follow-up of patients with breast cancer. A systematic review of mixed study design (Collins *et al.* 2004) found that most patients expressed a preference for attending regular follow-up sessions, even when asymptomatic. Although patients reported that the anticipation of attending these routine sessions was provoked anxiety, reduced fear of recurrence and less physical and psychological distress was experienced after attending their routine visit. A report on follow-up of a UK breast cancer charity focus group (Breakthrough 2007) concluded that patients should be given the information and support they need if they want to consider opting out of follow-up care.

With respect to optimal frequency of follow-up, one systematic review of RCTs concluded that the available trials are unable to indicate an ideal frequency of follow-up (Montgomery *et al.* 2007). However the review cited trials that suggest that detection of recurrence is not affected by 3 monthly versus 6 monthly follow up, nor by scheduled follow-up versus that available to patients on demand.

A Cochrane review (Rojas *et al.* 2000) found no statistically significant difference in 5 year overall survival arising from routine follow-up versus intensive (increased frequency and testing) follow up regimens.

With respect to evidence about where should follow-up should take place and who should perform follow-up, one systematic reviews of RCTs concluded that traditional routine clinic visits are an inefficient method of safeguarding against recurrent disease; with no difference in either total recurrences detected in hospital, versus by the GP was reported, or in serious clinical events, or total number of deaths (Montgomery *et al.* 2007). There was also no evidence for a difference in either the total number of recurrences detected, or overall survival, when follow-up is performed by a doctor, compared to a breast care nurse specialist (Montgomery *et al.* 2007). RCT evidence indicated that patient satisfaction is higher in patients followed up by nurses than in those followed up by doctors, but that quality of life is similar.

Evidence from qualitative studies also provided insight into the topic of effective follow up care for patients who had been treated for breast cancer. These studies broadly described that checking for recurrence; offering reassurance and providing information were key elements required in follow up care (Adewuyi-Dalton *et al.* 1998; Beaver *et al.* 2005; Jiwa *et al.* 2006; Kelly *et al.* 2006; Renton *et al.* 2002; Vanhuyse *et al.* 2007).

PICO

Population	Intervention	Comparison	Outcomes
Patients treated for breast	Hospital based follow-up Primary care based	Versus each other	Detection of recurrent disease

cancer, including those with DCIS	follow-up Other settings for follow-up		Management of medical therapy Management of symptoms e.g.: <ul style="list-style-type: none"> • Lymphoedema • Menopausal symptoms • Psychological Outcomes • Functional capabilities i.e. decreased shoulder mobility Cost Effectiveness Patient Satisfaction
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This PICO table was used to generate the search strategy used to search the literature for this question, see Appendix A

Evidence Summary

There is a reasonable volume of evidence available that is related to follow-up of patients with breast cancer, including two systematic reviews of RCTs, one update to an RCT and two observational studies.

A framework was developed to select studies that provide information to answer the following broadly-defined questions:

- Should follow-up be performed?
- Is there an optimal frequency of follow-up?
- Where should follow-up take place?
- Who should perform follow-up?
- What should be the aims of follow-up?

Inconsistency exists between the comparisons made in the primary studies (Table 1). However there is generally no conflict of results; the randomised trials found no difference for most outcomes arising from different follow-up strategies. Some differences, arising in the original RCTs, are highlighted by papers, but these differences were lost when pooled or when examined with longer study follow-up.

Health economic data were excluded; randomised studies exist of health economic outcomes arising from different follow-up strategies.

A systematic review of mixed study design (Collins *et al.* 2004) found that most patients expressed a preference for attending regular follow-up sessions, even when asymptomatic.

One systematic review of RCTs concluded that the available trials are unable to indicate an ideal frequency of follow-up

Table 1: follow-up strategies evaluated

Study	Design	Comparison	Follow-up schedule
Grunfeld 1996*	RCT	Follow-up in general practice vs. hospital.	3 monthly clinical exam and history during the first year, 6 monthly for 4 years, then annual in one hospital, with three monthly first year, 4 monthly second year, 6 monthly for 5 years and then annual in the other. General practice group as per hospital of diagnosis. One to two yearly mammograms.
Gulliford 1997*	RCT	Frequent follow-up vs. annual follow-up.	3 monthly clinical exam and history during the first year, 4 monthly second year, 6 monthly for 5 years and then annual. One to two yearly mammogram, depending on whether BCT or mastectomy in the control group, annual clinical exam, history and mammogram in the trial group.
Brown 2002*	RCT	Traditional clinic follow-up vs. patient-initiated follow-up.	4-6 monthly clinical exam and history for the first 5 years then annual in control group vs. on request only in the study group. Annual mammograms in both.
Koinberg 2004*	RCT	Traditional clinic follow-up vs. on demand follow-up coordinated by a breast care nurse.	3 monthly clinical exam and history for 2 years, 6 monthly for three years then annual for 5 years and annual mammogram in the traditional follow-up group, with appointments on demand only and annual mammograms in the nurse led follow up group.
Baildam 2004*	RCT	Standard follow-up by hospital doctors vs. specially trained nurses.	Not given, but identical for both arms.
Kokko 2005*	RCT	3 monthly vs. 6 monthly follow up (and of intensive vs. as required investigations).	3 monthly vs. 6 monthly clinical examination and history.
Grunfeld 2006*	RCT	Follow-up by hospital Dr vs. follow-up by GP.	3-6 monthly for 3 years, 6 monthly for 2 years then annual, with annual mammogram.
Koinberg 2006	Prospective study	Multidisciplinary education programme vs. traditional follow-up	4 educational sessions in 4 weeks between 2-6 months following surgery, then on demand access vs. clinical exam twice a year for two years then annually until the fifth year.

Breakthrough Breast cancer 2007	Focus group report	None, specifically	None
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Note: * denotes data reproduced from Montgomery *et al.* 2007.

Should follow-up be performed?

No RCTs were identified of patients who received no follow-up of any sort.

A systematic review of mixed study design (Collins *et al.* 2004) found that most patients expressed a preference for attending regular follow-up sessions, even when asymptomatic. Although patients reported that the anticipation of attending these routine sessions was anxiety provoking, reduced fear of recurrence and less physical and psychological distress was experienced after attending their routine visit.

A report on follow-up of a UK breast cancer charity focus group (Breakthrough 2007) concluded that Patients should be given the information and support they need if they want to consider opting out of follow-up care.

Is there an optimal frequency of follow-up?

One systematic review of RCTs concluded that the available trials are unable to indicate an ideal frequency of follow-up (Montgomery *et al.* 2007). However the review cited trials that suggest that detection of recurrence is not affected by 3-monthly versus 6-monthly follow up, nor by scheduled follow-up versus that available to patients on demand. There was also no difference in patient satisfaction and quality of life arising from scheduled versus 'on demand' follow-up (Montgomery *et al.* 2007).

The earlier Cochrane review of RCTs (Rojas *et al.*) found no statistically significant difference in 5-year overall survival arising from routine follow-up versus intensive (increased frequency and testing) follow up regimens. This was based on pooled data from two RCTs^u and there was also no statistically significant difference arising from the two follow-up strategies in subgroup analyses for patient age, tumour stage and nodal status (Rojas *et al.*).

A later update to one RCT included in the Cochrane review reported no difference in estimated 10-year mortality between patient groups who received either intensive follow-up (increased frequency and testing) or standard clinical follow-up (physical examination and mammography) (Palli *et al.* 1999).

A systematic review of mixed study design found that there is little, and conflicting evidence for an ideal frequency of follow-up (Collins *et al.* 2004). Some included sources suggested that the frequency and length of the follow-up service should be tailored to meet the needs of individual patients. On the other hand, one study found evidence that patients had twice as many follow-up visits than as recommended in UK guidelines.

^u GIVIO trial, and Rosselli Del Turco trial.

Where should follow-up take place? Who should perform follow-up?

One systematic reviews of RCTs concluded that traditional routine clinic visits are an inefficient method of safeguarding against recurrent disease; with no difference in either total recurrences detected in hospital, versus by the GP, or in serious clinical events, or total number of deaths (Montgomery *et al.* 2007). There was also no evidence for a difference in either the total number of recurrences detected, or overall survival, when follow-up is performed by a doctor, compared to a breast care nurse (Montgomery *et al.* 2007). RCT evidence indicated that patient satisfaction is higher in patients followed up by nurses than in those followed up by doctors, but that quality of life is similar.

The earlier systematic review of RCTs (Rojas *et al.*) also cited a secondary paper for one trial^v, using published data only; this paper was not included by Montgomery *et al.* (2007), although a different publication for the trial was used. Rojas *et al.* report that questionnaire data from Grunfeld *et al.* (1999) indicated that patients were more satisfied with service delivery, consultation and the continuity of care provided by their GP than by a specialist.

A non-randomised prospective study (Koinberg *et al.* 2006) compared quality of life in patients who received follow up consisting of regular physician examinations, compared to patients who received a multidisciplinary education programme of 4 sessions over 4 weeks, between 2-6 months from surgery; thereafter patients could access their specialist by telephoning a nurse. The multidisciplinary educational programme was associated with similar quality of life outcomes as traditional follow-up, as measured on three scales for well-being, self-care and coping ability. The authors concluded that the programme could be an alternative to traditional follow-up.

What should be the aims of follow-up?

A systematic review of mixed study design (12 predominantly non-randomised studies studies; 5045 patients) provided a pooled (weighted) estimate of the proportion of isolated locoregional recurrences diagnosed in asymptomatic patients by routine follow-up (de Bock *et al.* 2004). This proportion was 40% (95% CI 35%-40%).

A report on follow-up of a UK breast cancer charity focus group (Breakthrough 2007) stated the aims of follow-up as:

- Surveillance of ongoing treatment;
- Access to new treatments;
- Surveillance and management of chronic/long term side effects (which can emerge after 5-10 years after initial diagnosis);
- Surveillance and management of short-term side effects of treatment;
- Psychosocial welfare;
- Reassurance;
- Feeling that patient can easily access care when needed;

^v Grunfeld *et al.* (1999) Comparison of breast cancer patient satisfaction with follow-up in primary care vs specialist care: results from a randomised controlled trial. *British Journal of Clinical Practice* 1999; 49:705-710.

- Long term, wider assessment including the needs of other family members;
- Monitoring of general health and being asked about well being;
- Access to breast reconstruction;
- Prosthesis fitting and advice;
- Fast track to an oncologist if anything is wrong.

Evidence from qualitative studies:

Beaver *et al.* (2005) examined the nature and content of interactions between patients attending hospital outpatients departments for routine follow-up following completed breast cancer treatment and health care professionals. Through qualitative methods, the study reported that follow-up visits appeared to consist of three primary components: checking for recurrence, offering reassurance and providing information. All consultations involved a clinical examination of the breast and surrounding areas and the extent of examination varied depending on who was conducting the exam. Patients did not have much concern on reducing visits from 3 to 6 months, however changing from 6 to 12 months and/or discharge was a considered a bigger step and created anxieties for some who seemed to depend on follow-up visits to detect recurrent disease. Clinic nurses were active in clarifying information despite having limited time available to meet the information needs of patients. Health care professionals indicated that the primary function of follow-up was to detect recurrent disease however were of the opinion that clinical examination at follow-up was highly unlikely to detect recurrent disease in asymptomatic women. Health care professionals did perceive that patients were reassured by the clinical examinations, despite the low rate of detection of recurrence. Health care professionals felt that the provision of information was an important part of follow-up, however admitted that they found it difficult to provide information to the patients in the time available. Doctors said that patients would have to be proactive and assertive in requesting information as they did not always encourage patients to ask questions.

Jiwa *et al.* (2006) conducted focus groups with patients attending a medical oncology follow-up and surgical follow-up clinics. The study aimed to identify the elements of a follow-up protocol for treated breast cancer patients in primary care, with reference to key stakeholders by determining the type of problem commonly documented during the follow-up of breast cancer patients and identification of the type of resources used. The study reported that the most frequent problems to arise related to anxiety and unrelated medical problems such as joint pain and menopausal symptoms. The main themes to emerge from the focus groups related to patient, disease, doctor and/or process. Results from the nominal discussion outlined the essential elements of a model of primary care follow-up as identified by the majority of the group. The discussions suggested that a formal 'handover' of patients from secondary care following a 'discharge' visit where the specialist would outline the case for withdrawing specialist involvement. The patient, if agreeable, would be discharged to the care of her GP who would receive a detailed summary of the patient's progress to date. A clear indication of when and how access to specialist care could be obtained in the event of future concerns

about a possible recurrence would be provided. The patient would have access to the breast care nurse and breast cancer support group and the breast care nurse would be able to refer patients to a surgeon or oncologist directly. The data suggest that the psychosocial needs of patients need to be taken into account when offering follow-up treatment and suggest that the needs of patients and their families, regarding the fear of recurrence, are not being met

Kelly *et al.* (2006) conducted focus groups to identify the priority issues of follow-up from the patient perspective. The primary reason given by patients for attending follow-up was for reassurance that the cancer had not returned. Participants also wanted information on new treatments and further tests. Key themes to emerge from the focus group interview were: the need for reassurance; continuity of care; privacy and dignity; information and detection of new symptoms and opportunities to discuss feelings and worries.

Renton *et al.* (2002) conducted study that used questionnaires to define patients' views on follow-up and to develop optimal breast cancer follow-up arrangements which meet the needs of women and make efficient use of available resources. The study reported that in general women appeared to be satisfied with current follow-up however they were open to changes to the current set-up. Women reported a number of factors that they felt were important to discuss during follow-up such as risk of recurrence or risk to daughters, the follow-up visits appear to be effective in alleviating the concerns and worries of the majority of women. Women appeared to have more confidence in specialist nurses compared to their own GP suggesting that a nurse-led model of follow-up may be a way forward. Continuity of care was a factor which was deemed to be important.

Vanhuyse *et al* (2007) reported the feasibility of patients transferring care back to the family physician for follow-up. This study used questionnaires and showed that it may be feasible to transfer follow-up care to the family physicians/GP's however there were many factors which remain to be addressed before this could happen including cost effectiveness, willingness and ability of family physicians/GP's to take on these patients, provision of resources, optimal timing for transfer and patient considerations.

Adewuyi-Dalton *et al.*(1998), identified views of women who took part in a randomised clinical trial comparing GP follow-up with out-patient follow-up were invited to take part if they were in the out-patient arm of the trial. The study reported that Continuity of Care; Access to Specialist Care; Quality of Consultation were main areas that women were affected by most significantly.

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Vanhuyse, M., Bedard, P., Sheiner, J., Fitzgerald, B., Clemons, M. (2007) Transfer of follow-up care to family physicians for early stage breast cancer *Clinical Oncology* 19:172-176

Evidence Tables

Systematic review of RCTs

Montgomery, Krupa & Cooke . Alternative methods of follow up in breast cancer: a systematic review of the literature. *Br.J.Cancer* 96[11], 1625-1632. 2007.

Design

Design: Systematic review of RCTs (other), evidence level: 1+
Country: Various, setting: Other

Inclusion criteria

Applied to studies as follows:

- i) included patients treated for primary operable breast cancer; free of distant metastases at the time of initial treatment;
- ii) RCT comparing routine clinical mammographic follow-up (NICE 2002 guideline cited) versus alternative; or comparing different frequencies or durations of clinical follow-up.

Blinding was not considered necessary for inclusion.

Exclusion criteria

Defined by inclusion criteria

Population

-

Interventions

Aim: to review RCT evidence for different follow-up strategies, and to examine whether RCTs are suggestive of an ideal length or schedule of follow-up.

Comparisons in primary RCTs were as follows:

- i) Follow-up in hospital clinics versus that performed by GP (2 RCTs);
- ii) Traditional follow-up versus follow-up 'on demand' i.e. by contacting a breast care nurse (2 RCTs);
- iii) Routine follow-up by doctors versus routine follow-up by breast care nurses

(1 RCT);

iv) Different follow-up frequencies within a traditional follow-up framework (2 RCTs).

Outcomes

Detection of recurrence

Adverse clinical events

Survival

Patient satisfaction

Quality of life, assessed using using validated tools as follows:

Hospital anxiety and depression scale (HADS); 5 RCTs;

EORTC QLQ-C30 and BR23 scale; 2 RCTs;

Medical outcomes short form SF-36 survey; 2 RCTs.

Economic analysis/workload concerns

Follow up

Grunfeld 1996: 18 months

Gulliford 1997: 16 months

Brown 2002: 12 months

Koinberg 2004: 5 years

Baildam 2004: not reported

Kokko 2005: 4.2 years

Grunfeld 2006: 4.5 years

Results

DETECTION OF RECURRENCE

The number of total recurrences detected did not vary by frequency of traditional follow-up: 3-monthly vs. 6 monthly (Kokko et al. 2005).

The number of total recurrences detected did not vary according to whether follow-up was performed by doctor vs. a breast care nurse (Baildam et al. 2004).

There was no statistically significant difference in the number of recurrences detected by nurses by 'on demand' follow-up vs. by routine visits (Koinberg et al. 2004). There was also no difference in time to event for locoregional recurrence, distant metastasis or death (Koinberg et al. 2004).

There was no statistically significant difference in the number of recurrences detected in hospital follow-up (13) vs. GP follow-up (6); difference 4.7% (95% CI -0.8% to 10.3%; Grunfeld et al. 1996). A latter trial conducted by the same team again found no statistically significant difference in the number of recurrences detected by hospital follow-up (13.2%) vs. GP follow-up (11.2%);

difference 2.02%, (95% CI -2.13 to 6.16%; Grunfeld et al. 2006).

ADVERSE CLINICAL EVENTS

There was no statistically significant difference in the rate of serious clinical events related to recurrence (e.g. spinal cord compression) between hospital-based and GP-performed follow-up: 3.7% vs. 3.5% respectively; difference 0.19% (95% CI -2.26% to 2.65%; Grunfeld et al. 2006).

SURVIVAL

There was no difference either in the absolute number of deaths, or in estimated overall survival in patients followed up by doctors vs. patients followed up by breast care nurses (Koinberg et al. 2004).

One RCT by Grunfeld et al. (2006) studied 968 patients and found little difference in the absolute number of deaths in patients who received hospital follow-up (30) vs. those who received GP follow up (29).

PATIENT SATISFACTION

The proportion of patients who were willing to enter 5 of the 7 RCTs reporting this outcome had mean 68.5%, median 66.5% and range 50%-93%.

Two RCTs found no difference in patient satisfaction associated with traditional follow-up versus follow-up 'on demand' i.e. by contacting a breast care nurse. Both trials reported high levels of patient satisfaction in both randomised groups (Brown et al. 2002; Koinberg et al. 2004). In the RCT by Brown et al. (2002) more women in the routine follow up group described the routine visits as reassuring ($p < 0.0001$) whereas more women in the on-demand follow-up group reported this method as convenient ($p < 0.0001$).

1 RCT found that follow-up frequency may be reduced from standard frequency without loss of patient satisfaction. In the same trial equal numbers of patients in the higher and lower frequency follow-up groups expressed a desire for less-frequent or more frequent visits, respectively (Gulliford et al. 1997).

1 RCT found that patient satisfaction, when measured using the Fallowfield Satisfaction with Consultation Questionnaire, was statistically significantly higher in patients followed up by nurses than in those followed up by doctors, with $p < 0.001$ (Baildam et al. 2004).

QUALITY OF LIFE

5 RCTs examined quality of life. No trial found any difference in quality of life arising from randomised comparisons as follows:

Routine follow-up by doctors versus routine follow-up by breast care nurses;
Traditional follow-up versus follow-up 'on demand' i.e. by contacting a breast care nurse;

Follow-up in hospital clinics versus that performed by GP.

AUTHORS' CONCLUSIONS

No RCT was identified with sufficient power to recommend an ideal frequency or duration of follow-up; No RCT to date can confirm the safety of alternative follow-up methods.

Traditional routine clinic visits are an inefficient method of safeguarding against recurrent disease; there is doubt as to whether they are the ideal setting in which to provide patients with psychological support.

General comments

In this systematic review, conducted in the UK, 'traditional follow' up is applicable to the UK; based upon NICE (2002) guidelines, and consisting of mammography, history taking and clinical examination.

Methods are well-described. Literature search performed on MEDLINE, EMBASE, EBM reviews, Cancerlit and Web of Science databases. Three literature search strategies included.

Literature reviewed to May 2006.

Study selection, data extraction and quality assessment performed independently by two reviewers, with subsequent resolution.

Assessment of study quality well-reported: 13 point checklist completed for each study which considered reporting of patient population; primary therapy; power calculation and sample size; differences between participants and non-participants; duration of follow-up (>5 years considered as important); loss to follow-up; description of interventions (follow-up schedule); use of objective, validated outcome measures; prospective assessment of outcome; publication in a peer-reviewed journal.

Cited information/data are as reported in the review; numbers, statistics, confidence intervals and p values were not always cited in the review.

METHODOLOGICAL QUALITY OF THE RCTs

Methodological quality of the 7 RCTs was generally high. Of a possible highest score of 13 on the quality checklist the mean score was 8.7. Excluding one study presented in abstract only (Baildam et al. 2004) the mean quality score was 10.7. The main drawback with the RCTs was inadequate size and follow-up duration. For this reason this well-conducted systematic review is graded as 1+.

Rojas, Telaro, Russo, Moschetti, Coe, Fossati, Palli, Roselli del & Liberati .
Follow-up strategies for women treated for early breast cancer. Cochrane
Database of Systematic Reviews: Reviews. 2000.;(4): [4], .

Design

Design: Systematic review of RCTs (other), evidence level: 1+
Country: Cochrane Review, setting: Other

Inclusion criteria

All randomised controlled trials comparing different approaches to follow-up after completion of primary treatment. Additional information was extracted and reviewed from prospective non-randomised studies but was not used for quantitative pooling.

Primary study participants: women who have had primary surgical treatment for breast cancer (clinical stage I, II or III), with no evidence of recurrence.

Four studies met the inclusion criteria. All of them are multicentre randomised controlled trials comparing different types of follow-up in breast cancer patients. Overall, these studies included 3055 women (the number of patients ranged from 196-1320).

Exclusion criteria

Defined by inclusion criteria.

Population

number of patients = 3055.

Interventions

Aim: to assess the effectiveness of different policies of routine follow-up testing on morbidity, mortality and quality of life in breast cancer patients after primary treatment.

Three comparisons were specified:

1. Follow-up based on routine clinical visits plus yearly mammogram compared to a more intensive surveillance including radiological and laboratory tests.
2. Centralised versus decentralised follow-up (i.e. surveillance offered by a specialist at a multidisciplinary breast clinic compared to that delivered by a general practitioner).
3. Regular follow-up compared to surveillance on demand.

Outcomes

Disease free survival (expression of the time to detect a recurrence). It is used in this context to compare the power of different follow-up strategies to detect recurrence earlier, possibly in

an asymptomatic stage;

Overall survival;

Occurrence of metastases detected in an asymptomatic state;

Health related quality of life.

Follow up

Median follow-up varied across trials with range 16-120 months.

Results

1. Follow-up based on routine clinical visits plus yearly mammogram intensive group) compared to a more intensive surveillance including radiological and laboratory tests.

Pooled data from 2 RCTs:

There was no statistically significant advantage for 5-year overall survival arising from intensive surveillance: HR intensive group: control group 0.96 [95% CI 0.80-1.15].

There was no statistically significant advantage for 5-year disease-free survival arising from intensive surveillance: HR intensive group: control group 0.84 [95% CI 0.71-1.00]. This pooled result did not confirm a statistically significant result of the Roselli Del Turco trial in favour of intensive follow-up strategy.

There were no statistically significant differences in overall survival between the follow-up strategies in the subgroup analyses for age, tumour size and nodal status:

Overall survival; HR (intensive: control):

Age ≤ 40 years HR 1.08 [95% CI 0.65-1.80]

Age > 40 years HR 0.95 [95% CI 0.78-1.16]

T1 tumour HR 0.8 [95% CI 0.55-1.17]

T2 tumour HR 0.92 [95% CI 0.73-1.17]

T3 tumour HR 1.44 [95% CI 0.91-2.30]

N0 nodes HR 1.35 [95% CI 0.94-1.94]

N1+ nodes HR 0.84 [95% CI 0.68-1.04]

There were no statistically significant differences in disease-free survival between the follow-up strategies in the subgroup analyses for age, tumour size and nodal status:

Disease-free survival; HR (intensive: control):

Age ≤ 40 years HR 0.94 [95% CI 0.59-1.47]

Age > 40 years HR 0.84 [95% CI 0.70-1.01]

T1 tumour HR 0.72 [95% CI 0.52-1.00]

T2 tumour HR 0.83 [95% CI 0.67-1.04]

T3 tumour HR 1.35 [95% CI 0.82-2.21]

N0 nodes HR 0.84 [95% CI 0.62-1.14]
N1+ nodes HR 0.83 [95% CI 0.68-1.02]

Asymptomatic detection of metastases:

GIVIO trial only: 31% of cases of metastases in the intensive group and 21% in the clinical group were detected in an asymptomatic phase. This is consistent with results of several prospective non-randomised studies (Hannisdal 1993, Logarar 1990, Rutgers 1989, Vestergaard 1989, Mahoney 1986, Hietanen 1986, Wick-erhan 1986, Pandya 1983).

Quality of life:

GIVIO trial only: Questionnaires were administered 4 times between 6 and 60 months with an average response rate of 73.5%; overall no significant difference was found between the two follow-up strategies.

2. Centralised versus decentralised follow-up (i.e. surveillance offered by a specialist at a multidisciplinary breast clinic compared to that delivered by a general practitioner).

Time to detection of recurrence

The Grunfeld trial, comparing follow-up offered by a hospital based specialist with follow-up offered by a general practitioner, shows no differences in time to detection of recurrence between the groups. In the hospital group, the median time from first symptoms suggesting recurrence to confirmation by a hospital

specialist was 21 days, in the general practice group it was 22 days. The median difference was 1.5 days.

The number of recurrences was different in the two groups (10/148 general practice group, 16/148 hospital group, $p=NS$) probably because of the short time of follow-up for the trial.

Quality of life

Quality of life shows an expected small deterioration for both groups during the trial. The hospital group has a statistically significant increase in symptom scores for fatigue, dyspnoea and appetite loss. There is no difference in overall health, social and emotional functioning and levels of anxiety and depression. This study also collected data on the patients who were asked about the trial but did not participate (149/445, 33.5%). These women were older than participants and had a lower education level but there were no important differences in clinical characteristics or in baseline quality of life scores.

The Grunfeld data were used in a new publication that analysed patient satisfaction with care by general practitioners versus hospital specialists over an 18-month period (see Grunfeld secondary reference). Questionnaires completed by 93% of patients indicated that they were more satisfied with service delivery, consultation and the continuity of care provided by their general practitioner than by a specialist.

3. Regular follow-up compared to surveillance on demand.

The Gulliford trial comparing conventionally scheduled follow-up and less frequent follow-up (restricted to the time of mammography) shows that 7% of eligible patients refused to enter the study. The characteristics of these patients may suggest that younger women with more aggressive primary disease are not willing to reduce the frequency of follow-up visits. Unfortunately, no assessment is available of these patients in relation to their quality of life.

No significant differences have been found between the groups in regard to the use of telephone and visits to general practitioners during the trial.

Approximately one-third of the patients in both groups expressed a preference for a less frequent schedule of follow-up visits, but only 56 women answered this question on the questionnaire.

Authors conclusions

In light of the evidence presented here, less intensive follow-up strategies based on periodical clinical exam and annual mammography seem as effective as more intense surveillance schemes. Further laboratory and radiological examinations may add useful information where women are symptomatic or the clinical visit suggests the need for further investigations. A general practitioner's participation in the delivery of follow-up care appears feasible and appropriate as long as the care is organised in such a way that access to hospital care is easy when required.

General comments

Four RCTs were included:

1. GIVIO trial
2. Rosselli Del Turco trial
3. Grunfeld trial
4. Gulliford trial

The pooled data come from 2 RCTs: GIVIO trial and the Rosselli Del Turco trial).

Literature search was performed on the Cochrane Controlled Trial Register, EMBASE and MEDLINE databases; search date 14th May 2004. Two search strategies reported in full. References within included studies were reportedly checked for further sources. Each potentially eligible study was independently assessed by two reviewers for inclusion in the review and for quality. Aspects of study quality assessment are reported; blinding was not considered to be necessary.

Systematic review of combined study designs

Collins, Bekker & Dodwell . Follow-up care of patients treated for breast cancer: a structured review. [Review] [59 refs]. Cancer Treat.Rev. 30[1], 19-35. 2004.

Design

Design: Systematic review of combined study designs (other), evidence level: 2 +

Country: Various, setting: Other

Inclusion criteria

Studies providing data according to the specific research questions on follow-up of patients treated for breast cancer (see 'interventions'), and published in English between the years 1989-2001.

Exclusion criteria

Case reports;
Views/experiences of health professionals;
Studies of health technologies/prognostic factors.

Population

-

Interventions

Aim: to identify and integrate primary empirical evidence on the effectiveness of follow-up strategies for patients treated for breast cancer.

Specific research questions:

1. What is the optimal intensity of routine follow-up investigations?
2. Which type of health professional should provide follow-up care?
3. What are the optimal frequency and length of follow-up services?
4. What is the impact of routine follow-up care on patient morbidity?
5. What interventions have been found to be effective in reducing patient morbidity?
6. What level of involvement do patients have in choices about their follow-up care?

Outcomes

Authors provide narrative summary answers to their 6 research questions, based upon tabulated data for every included study.

Follow up

NA

Results

1. What is the optimal intensity of routine follow-up investigations?

Authors conclude: a minimal approach is as effective as intensive interventions for routine breast cancer follow-up in terms of survival, timeliness of recurrence detection and quality of life. In addition, the data suggest that routine follow-up may be more beneficial in terms of survival for the detection of contralateral disease than recurrent disease.

2. Which type of health professional should provide follow-up care?

Little empirical evidence is available (NB literature search cut-off date: 2001). Prior reviews suggest GP-led care is as effective as specialist care and DH guidance (1996) recommends GPs be involved in the organisation of local arrangements for patients whose follow-up is being scaled down. Few studies have employed a design and set of outcome measures that would elicit data to address satisfactorily the question of which health professional should provide follow-up care.

3. What are the optimal frequency and length of follow-up services?

Little empirical evidence is available. Available evidence is conflicting. On the one hand, guidelines and data suggest the frequency and length of the follow-up service should be tailored to meet the needs of individual patients. On the other hand, one study found evidence that patients had twice as many follow-up visits as recommended, i.e., there is a standard of follow-up care that can be exceeded.

4. What is the impact of routine follow-up on patient morbidity?

Little empirical evidence is available. In studies that assessed this outcome, most patients expressed a preference for attending regular follow-up sessions, even when asymptomatic. Although patients reported that the anticipation of attending these routine sessions was anxiety provoking, reduced fear of recurrence and less physical and psychological distress was experienced after attending their routine visit.

5. What interventions have been found to be effective in reducing patient morbidity?

No published empirical evidence was identified to suggest factors that are associated with reduced morbidity.

6. What level of involvement do patients have in choices about their follow-up care?

Within the context of follow-up care for patients treated for breast cancer, there is no published empirical evidence describing patients' preference for involvement in decision making about treatment choices or need for (further) information. However, one study investigated the effect of patient decision-making in follow-up care and found that patients who reported more involvement in decision making reported better quality of life. Within other

health contexts, the provision of good information and the making of informed decisions are associated with better outcomes.

General comments

Literature search: performed on the following databases MEDLINE, EMBASE, CINAHL, British Nursing Index, RCN Journals Database, PsycINFO, National Research Register (NRR), Health Management Information Consortium (HMIC), Cochrane Database of Systematic Reviews (CDSR) and the NHS Centre for Reviews and Dissemination databases.

From these searches, it was evident that studies before 1989 would not add to the evidence base to meet this review's aims. Therefore, this review focussed on empirical evidence published between 1989 and 2001. In-depth searches of MESH headings, references of identified articles and hand searching of the Annals of Oncology journal were carried out for the years 1989-2001.

Data extraction: A data extraction form was developed to elicit the following data systematically from each article: study details such as aim, psychological theories informing interventions and/or measures, design, methodology, sample; aspect of service assessed; description of intervention; measures of effectiveness; results and authors conclusions.

Assesment of study quality: the research quality of the study was assessed by evaluating the following: adequacy of sample size, stratified/random sample, representativeness of study population, attrition rate, definition of intervention, blinding of assessors, randomisation procedure, similarity of study/control groups at baseline, intention to treat analysis, validation of measures, timing of measures, consistency of measures with aims, consistency of conclusions with results and analysis concerns such as confounders, interpretation and generalisability.

One researcher selected the studies, although 10% of decisions were reviewed by two other researchers.

Of 4418 articles identified by the literature search, 38 were included in the final review (including 5 randomised studies that have been reported in systematic reviews by Rojas et al. 2000 and Montgomery et al. 2007.

Cited results are based upon authors' narrative summary of the studies that scored highest for quality assessment.

de Bock, Bonnema, van der, Kievit & van d . Effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences after treatment for early-stage invasive breast cancer: a meta-analysis and systematic review (DARE provisional record). J.Clin.Oncol. 22, 4010-4018. 2004.

Design

Design: Systematic review of combined study designs (other), evidence level: 2 +
Country: Various, setting: Other

Inclusion criteria

Studies in any language published between 1966 and 2002 according to three criteria:

1. patients treated for primary operable breast cancer i.e. without known distant metastases outside the breast and the axilla at the time of treatment of the first breast tumor;
2. local-regional recurrence defined as a recurrence of breast cancer in the same breast or chest wall or regional lymph node area, including supraclavicular lymph node involvement, but excluding retrosternal lymph node involvement;
3. Rate of isolated locoregional recurrences may be compared in asymptomatic patients versus symptomatic patients.

The included studies were 1 RCT (Grunfeld et al. 1996), 1 prospective study and 10 retrospective studies.

Exclusion criteria

Defined by inclusion criteria.

Population

number of patients = 5045.

Interventions

Aim: To review the effectiveness of routine visits and routine tests in detecting isolated locoregional recurrences in asymptomatic patients after treatment for early-stage invasive breast cancer.

In 4 studies primary treatment was mastectomy. In 5 studies primary treatment was breast conserving surgery. In 1 study there was a mix of these treatments and in 2 studies primary treatment was not reported.

Outcomes

Proportion of isolated locoregional recurrences diagnosed in asymptomatic patients by routine visits/tests.

Factors that are predictive of the proportion of locoregional recurrences that

were detected whilst asymptomatic by routine visits/tests. Factors examined were: treatment of first tumor (mastectomy vs. breast-conserving therapy), year of publication (before 1995 vs. 1995 and later), number of patients in the study (less than 500 vs. more), design of the study (nonrandomised, noncontrolled, retrospective, vs. other), number of planned mammograms (up to five in 5 years vs. five in 5 years), and the quality score (above the median quality score vs. at or under the median quality score).

Follow up

Variable in primary studies.

Results

In total in 12 studies there were 378 locoregional recurrences in 5045 patients:

Detected at routine visits:

Without symptoms: 152 (40% of all recurrences)

With symptoms: 69 (18%)

Detected outside of routine visits: 155 (41%)

Unknown: 2 (1%)

Pooled estimate of the proportion of isolated locoregional recurrences diagnosed in asymptomatic patients by routine visits/tests (12 studies; 5045 patients): 40% (95% CI 35%-40%)

The proportion of locoregional recurrences that were detected whilst asymptomatic by routine visits/tests was statistically significantly higher in univariate analysis for the following variables: mastectomy, study publication prior to 1995, <500 patients in the study and ≤ 5 planned mammograms in a 5 year period. There was no significant difference for RCT study design and study quality score.

In multivariate analysis mastectomy was associated with a significantly higher rate of isolated locoregional recurrences diagnosed in asymptomatic patients (OR 1.7; 95% CI 1.1-2.8) whereas larger studies whether or not more than 5 mammographies were planned per year, were associated with a smaller number of isolated locoregional recurrences diagnosed in asymptomatic patients (OR 0.4; 95% CI 0.2-0.6) as were smaller studies with with more than five planned mammograms (OR 0.4, 95% CI 0.2-0.7).

General comments

Literature search performed on MEDLINE, CancerLit, Cochrane, Web of Sciences, Embase, and Current Contents databases. MESH search terms and free text terms described.

Data were extracted independently by two investigators by means of a predefined form. Topics in this form were: number of patients, years of patient inclusion, age at time of first diagnosis of breast cancer, distribution of stage

and treatment of this primary breast cancer, adjuvant treatment, design of the study, number of planned visits and mammograms during the first 5 years of follow-up, and median or mean time of follow-up per study.

Methodological quality of studies was assessed independently by two authors according to a predefined checklist that considered patient populations; trial participation; reporting of disease-related characteristics; primary treatment; extent of follow-up (5 years considered adequate); reporting of follow-up regimen; loss to follow-up; prospective assessment of outcomes. Of a possible maximum quality score of 9, the mean score in the 12 included studies was 4.8; median 4, range 3-8. There was no association between study size and effect size.

The pooled estimate reported is based on a meta-analysis, weighted for the sample size of each contributing study.

Randomized controlled trial

Palli, Russo, Saieva, Ciatto, Del Turco, Distante & Pacini . Intensive vs clinical follow-up after treatment of primary breast cancer: 10-Year update of a randomized trial [2]. Journal of the American Medical Association. 281[17], 1586. 1999.

Design

Design: Randomized controlled trial (other), evidence level: 1+
Country: Italy, setting: Other

Inclusion criteria

Patients surgically treated for unilateral invasive breast cancer with no evidence of metastases.

Exclusion criteria

Not reported.

Population

number of patients = 1243.

Interventions

Intensive follow-up group (n=622): received physical examination 3 monthly in the first 2 years and 6 monthly thereafter; also annual mammography, biannual chest X-ray and bone scan;

Clinical follow-up group (n=621): received physical examination and mammography according to the same schedule as above, but with no other routine diagnostic tests.

Outcomes

Estimated 10-year mortality

Follow up

Outcome assessed at 10-year follow-up.

Results

Estimated 10-year mortality were not different for the clinical (31.5%) and intensive (34.8%) follow-up groups; HR 1.05; 95% CI 0.87-1.26.

Authors conclusion: even though more local recurrences were detected in the intensive follow-up group when analysed at 5 years, this did not translate to an overall survival advantage at 10 years.

General comments

Paper provides longer (10 year) follow up data to that cited in the Cochrane Review by Rojas et al. (2000). Consider result with that of the Cochrane

Review.

Paper is a brief research letter.

The main prognostic characteristics were similar between the two randomised groups.

10-year data were available for 99.2% of patients.

Prospective comparative study

Koinberg, Langius-Eklof, Holmberg & Fridlund . The usefulness of a multidisciplinary educational programme after breast cancer surgery: a prospective and comparative study. *European Journal of Oncology Nursing*.;2006.Sep.; 10(4):273.-282. 2006 Sep; 10[4], 273-282.

Design

Design: Prospective comparative study (other), evidence level: 3
Country: Sweden, setting: Secondary care

Inclusion criteria

Patients treated for breast cancer of TNM stage I or II.

Exclusion criteria

9 patients declined to participate and received traditional follow-up outside of the study.

Population

number of patients = 96, mean age = 61 years.

Interventions

Aim: to evaluate a multidisciplinary educational programme as an alternative to standard physician-based follow-up, for patients treated for low risk breast cancer.

Two groups were defined and followed-up prospectively:

Multidisciplinary educational programme group (n=50); followed up as follows: 4 sessions in 4 weeks between 2-6 months following surgery. Sessions led by a specialist nurse with physiotherapist, social worker, physician and patient advocacy worker present. Content: recovery from surgery, prevention of lymphoedema, management of menopausal side effects, body image/sexual issues. At the close of the programme women could contact the specialist nurse by telephone for advice/referral to a physician.

Traditional group (n=46); examination by a physician twice a year for 2 years and annually for up until the 5th year

Both comparison groups were followed up with mammography; at 18-24 month intervals in the intervention group and annually in the traditional follow-up group.

Outcomes

Functional Assessment of Cancer Therapy General Scale (FACT-G): 27 item scale with 4 subscales:
Physical well-being; Functional well-being; Social/family well-being; Emotional well-being.

Self-care Aspects Questionnaire (SCA): 3 subscales: Coping ability; Participation in decision making; Knowledge about breast cancer.

Sense of Coherence Scale (SOC): based on the extent to which an individual sees the world as comprehensible; manageable; meaningful.

Follow up

Assessment was made at baseline and 1 year following diagnosis.

Results

FACT-G

At baseline there were no statistically significant differences between the groups except for physical well-being; women in the multidisciplinary educational programme had worse physical well-being than those in the traditional group. The women in the multidisciplinary educational programme increased in their physical well-being and functional well-being during the 1-year follow-up. The women in the traditional group increased in functional well-being and decreased in social well-being during the 1 year follow-up.

SCA

There were no statistically significant differences either between groups or within groups with regard to coping ability, participation in decision making and knowledge, either at baseline or at the 1-year follow up.

SOC

There were no statistically significant differences between the comparison groups at baseline or at the 1-year follow-up. There was a statistically significant difference ($p < 0.001$) in SOC in the traditional group: baseline (74.4) and 1-year (67.7) i.e. a reduction by 8.4%; regarded as clinically important.

Authors conclude: the multidisciplinary educational programme was associated with similar outcomes as traditional follow-up in terms of well-being, aspects of self-care and coping ability and could be an alternative to traditional follow-up (see comment re: local recurrence).

General comments

The two groups were defined by two different treatment centres, and were mostly similar in terms of demographic and treatment-associated variables. A smaller proportion of patients in the traditional follow-up group received breast conserving surgery (52%) than in the multidisciplinary programme group (88%); $p < 0.001$, Chi square. Authors state that this may explain the lower reported physical well-being at baseline in the multidisciplinary programme group.

Mammography surveillance varied between groups.

No specific patient-education is reported in the multidisciplinary programme for detection of locoregional recurrence; in this respect the two interventions appear to have non-identical aims, and detection of local recurrence was not evaluated as an outcome measure.

Power calculation performed to justify sample size.

Qualitative Study

Breakthrough breast cancer . Follow-up care - what do breast cancer patients want? 2007.

Design

Design: Qualitative Study (other), evidence level: 3
Country: United Kingdom, setting: Community

Inclusion criteria

10 members of the charity Breakthrough Breast Cancer's Campaigns & Advocacy Network (Breakthrough CAN).

Exclusion criteria

Attendees were self selected following an invitation to all members of Breakthrough CAN. The authors report that therefore the attendees of the group are not representative of all breast cancer patients' views but provide a useful 'snapshot' of opinions on follow up care. The 10 attendees had varying experiences of follow-up: one member attended no follow-up and another did so for 27 years.

Population

number of patients = 10.

Interventions

Aim: to assess the views on follow-up held by breast cancer advocates at a focus group facilitated by Breakthrough Breast Cancer on 20 April 2007.

Specific questions discussed by the group were:

What do breast cancer patients understand by follow up care?
What are the benefits and drawbacks of current follow up care arrangements?
What should follow up care involve?
Where should follow up care take place and who should carry it out?
How long should follow up care be provided?

Outcomes

Recommendations based upon the questions discussed.

Follow up

NA

Results

The group summed up the aims of follow-up as:

Surveillance of ongoing treatment;
Access to new treatments;
Surveillance and management of chronic/long term side effects (which can emerge after 5-10 years after initial diagnosis);

Surveillance and management of short-term side effects of treatment;
Psychosocial welfare;
Reassurance;
Feeling that patient can easily access care when needed;
Long term, wider assessment including the needs of other family members;
Monitoring of general health and being asked about well being;
Access to breast reconstruction;
Prosthesis fitting and advice;
Fast track to an oncologist if anything is wrong.

The group did not come to a consensus about where follow up care should take place, who should carry it out or how long it should be provided. However, there was agreement that a 'one size fits all' approach to follow up care is unlikely to meet the needs of breast cancer patients; follow up should be tailored to individuals, with full input from patients themselves.

The group also discussed the need for patients to have the option of opting out of follow up care but with rapid access back into the follow up care system if needed. However, other members of the group were not comfortable with the idea of patients having to self refer for follow up care.

Conclusions

1. Patients view follow up care as wider than just their clinical needs. Follow up care can help to meet psychosocial and other needs which patients consider just as important.
2. Follow up care should be tailored to the individual, with the patient fully involved at every decision making stage.
3. Patients should be given information about what to expect at their follow up care appointments.
4. Patients or breast cancer advocates could play a role in educating GPs about breast cancer. If GPs play a greater role in providing follow up care this could help ensure that they are informed about breast cancer issues.
5. Follow up care is essential as more newer targeted therapies are used (e.g. aromatase inhibitors). The longer term side effects of such treatments may not be as well known as other more established treatments.
6. Whatever follow up care arrangements are put in place, signposting to other services such as lymphoedema services, complementary therapies and further support is essential.
7. When measuring the financial costs of follow up care, patients felt that factors such as the psychological benefits of follow up should be taken into account.
8. Patients should be given the information and support they need if they want to consider opting out of follow up care.

Recommendations of the focus group:

1. Follow up should be individualised for each patient, with the patient fully involved at every decision making stage.
2. All breast cancer patients should be given information about what to expect

- at their follow up care appointments. The amount and level of information should be tailored to each patient.
3. Breast cancer patients should be signposted to lymphoedema services, complementary therapy services and other support services at their follow up care appointments.
 4. All patients discharged from follow up care should be provided with high quality, patient-focused information about how to get back into the system quickly.
 5. If GPs are to play a greater role in providing follow up care, further training should be available to support them.

General comments

Small qualitative study based upon the views of 10 breast cancer advocates i.e. individuals with a role nominated by a large UK charity, to represent patients with breast cancer.

Beaver, K., Luker, K. (2005) Follow-up in breast cancer clinics: reassuring for patients rather than detecting recurrence *Psycho-Oncology* 14:94-101

Design: Mixed Methods

Evidence Level: 3

Country: UK

Aim: To explore the nature and content of interactions between patients attending hospital outpatients departments for routine follow-up following completed breast cancer treatment and health care professionals.

Beaver *et al.* (2005) examined the nature and content of interactions between patients attending hospital outpatients departments for routine follow-up following completed breast cancer treatment and health care professionals. Through qualitative methods, the study reported that follow-up visits appeared to consist of three primary components: checking for recurrence, offering reassurance and providing information. All consultations involved a clinical examination of the breast and surrounding areas and the extent of examination varied depending on who was conducting the exam. Patients did not have much concern on reducing visits from 3 to 6 months, however changing from 6 to 12 months and/or discharge was a considered a bigger step and created anxieties for some who seemed to depend on follow-up visits to detect recurrent disease. Clinic nurses were active in clarifying information despite having limited time available to meet the information needs of patients. Health care professionals indicated that the primary function of follow-up was to detect recurrent disease however were of the opinion that clinical examination at follow-up was highly unlikely to detect recurrent disease in asymptomatic women. Health care professionals did perceive that patients were reassured by the clinical examinations, despite the low rate of detection of recurrence. Health care professionals felt that the provision of information was an important part of follow-up, however admitted that they found it difficult to provide information to the patients in the time available. Doctors said that patients would have to be proactive and assertive in requesting information as they did not always encourage patients to ask questions.

Inclusion criteria:

Patients who had successfully completed active breast cancer treatment and who had no current clinical problems and were returning for routine follow-up visits.

Health care professionals who conducted patient consultations (e.g. medical staff, breast care practitioner) and who had a supporting role (e.g. clinic nurses).

Exclusion criteria:

None given

Population:

Eligible for participation = 141

16 consented but consultations were not observed due to two women available for observation at the same time.

9 women refused to participate

10 women did not attend their appointments

2 women were not considered to be routine follow-up cases.

N=104

Interventions: Qualitative methods including: observation, audio-recording consultations and interviews with health care professionals.

Outcomes:**Results:**

No recurrences were detected by clinical examination in asymptomatic women.

Mean consultation duration was 6.2 minutes, with breast care nurse practitioners taking longer over consultations than medical colleagues.

Follow-up visits appeared to consist of three primary components: checking for recurrence, offering reassurance and providing information.

All consultations involved a clinical examination of the breast and surrounding areas and the extent of examination varied depending on who was conducting the exam.

Patients did not have much concern on reducing visits from 3 to 6 months, however changing from 6 to 12 months and/or discharge was a considered a bigger step and created anxieties for some who seemed to depend on follow-up visits to detect recurrent disease.

Clinic nurses were active in clarifying information despite having limited time available to meet the information needs of patients.

Health care professionals indicated that the primary function of follow-up was to detect recurrent disease however were of the opinion that clinical examination at follow-up was highly unlikely to detect recurrent disease in asymptomatic women. Health care professionals did perceive that patients were reassured by the clinical examinations, despite the low rate of detection of recurrence. Health care professionals felt that the provision of information was an important part of follow-up, however admitted that they found it difficult to provide information to the patients in the time available. Doctors said that patients would have to be proactive and assertive in requesting information as they did not always encourage patients to ask questions.

There was an 86.8% response rate to the patient questionnaire (N=92)
60.9% of women indicated a degree of concern associated with attendance at follow-up visits, particularly related to the possibilities of recurrence.
The mean duration of consultations was perceived to be 11.5 minutes as compared to the recorded time of 6.2 minutes. 54% of patients over-estimated their consultation time, 42% were correct to within 5 minutes and 4% under estimated duration.

77.8% of patients reported that they asked questions during consultation, though this did not appear to be the case on observation.
86.1% of those that perceived they had posed questions reported to be satisfied with the response.

General comments

The results of this study appear to support the fact that recurrent disease is unlikely to be picked up during follow-up visits. HCP's did not expect to detect recurrence yet continued to check for it.

Although women reported that they asked questions during follow-up, observation of consultation did not back this up. Perhaps women were less inclined to ask questions during an observed consultation?

Women appeared reassured by follow-up visits and the powerful nature of this reassurance should not be underestimated when considering alternative options.

Routine follow-up visits could be moved from hospital outpatients to local clinics where the need for reassurance could be met with specialist nurses taking a more prominent role in providing follow-up care.

Authors Conclusion: Continuing to ask women to attend hospital outpatients for brief consultation visits may create a cycle of dependency and give an incomplete message on how recurrent disease is detected. Any new policy initiatives will need to take into consideration patient expectations on what constitutes follow-up service provision.

Jiwa, M., Thompson, J., Coleman, R., Reed, M. (2006) Breast cancer follow-up: could primary care be the right venue? *Current Medical Research and Opinions* 22;4:625-630

Design: Retrospective Data Analysis

Evidence Level: 3

Country: UK

Aim: to identify the elements of a follow-up protocol for treated breast cancer patients in primary care, with reference to key stakeholders by determining the type of problem commonly documented during the follow-up of breast cancer patients and identification of the type of resources used.

Jiwa *et al.* (2006) conducted focus groups with patients attending a medical oncology follow-up and surgical follow-up clinics. The study aimed to identify the elements of a follow-up protocol for treated breast cancer patients in primary care, with reference to key

stakeholders by determining the type of problem commonly documented during the follow-up of breast cancer patients and identification of the type of resources used. The study reported that the most frequent problems to arise related to anxiety and unrelated medical problems such as joint pain and menopausal symptoms. The main themes to emerge from the focus groups related to patient, disease, doctor and/or process. Results from the nominal discussion outlined the essential elements of a model of primary care follow-up as identified by the majority of the group. The discussions suggested that a formal 'handover' of patients from secondary care following a 'discharge' visit where the specialist would outline the case for withdrawing specialist involvement. The patient, if agreeable, would be discharged to the care of her GP who would receive a detailed summary of the patient's progress to date. A clear indication of when and how access to specialist care could be obtained in the event of future concerns about a possible recurrence would be provided. The patient would have access to the breast care nurse and breast cancer support group and the breast care nurse would be able to refer patients to a surgeon or oncologist directly. The data suggest that the psychosocial needs of patients need to be taken into account when offering follow-up treatment and suggest that the needs of patients and their families, regarding the fear of recurrence, are not being met

Inclusion criteria: None Given

Exclusion criteria: None Given

Population: N=100; 51 patients attending a medical oncology follow-up clinic (tertiary care) and 49 attending a surgical follow-up clinic (secondary care).

Interventions: Stakeholder focus groups to identify a set of themes relating to follow-up care followed by a nominal group discussion with a representative from each of the stakeholder groups to devise a model for follow up in the primary care setting.

Outcomes: Barriers to follow-up in the primary care setting.

Results:

The evaluated records described 702 patient years of follow-up and reported that the most frequent problems to arise related to anxiety and unrelated medical problems such as joint pain and menopausal symptoms.

Anxiety and depression tended to present relatively soon after treatment and could feature for a number of years. Concomitant medical problems tended to present later in the follow-up period.

The main themes to emerge from the focus groups related to patient, disease, doctor and/or process.

Results from the nominal discussion outlined the essential elements of a model of primary care follow-up as identified by the majority of the group. The discussions suggested that a formal 'handover' of patients from secondary care following a 'discharge' visit where the specialist would outline the case for withdrawing specialist involvement. The patient, if agreeable, would be discharged to the care of her GP who would receive a detailed summary of the patient's progress to date.

A clear indication of when and how access to specialist care could be obtained in the event of future concerns about a possible recurrence would be provided.

The patient would have access to the breast care nurse and breast cancer support group

and the breast care nurse would be able to refer patients to a surgeon or oncologist directly.

General comments

Policy on follow-up varies world-wide and the advent of aromatase inhibitors may increase the length of time in specialist follow-up due to the need for expert medical surveillance, however there is debate as to whether there is a need for specialist follow-up to detect secondary lesions.

The authors acknowledge the potential risk of bias in the study in relation to the medical records examined, highlighting the fact that they may have included records of patients opposed to discharge from specialist care.

The data suggest that the psychosocial needs of patients need to be taken into account when offering follow-up treatment and suggest that the needs of patients and their families, regarding the fear of recurrence, are not being met.

There are some cases where there is a need for continued specialist care and therefore a follow-up care program may need to take account of local arrangements and the needs of the individual patient.

Kelly, L., Caldwell, K., Henshaw, L. (2006) Involving users in service planning: A focus group approach

Design: Focus Groups

Country: UK

Aim: To identify the priority issues of follow-up from the patient perspective.

Kelly *et al.* (2006) conducted focus groups to identify the priority issues of follow-up from the patient perspective. The primary reason given by patients for attending follow-up was for reassurance that the cancer had not returned. Participants also wanted information on new treatments and further tests. Key themes to emerge from the focus group interview were: the need for reassurance; continuity of care; privacy and dignity; information and detection of new symptoms and opportunities to discuss feelings and worries.

Population: N = 10 women, diagnosed with breast cancer who had completed treatment and were being followed up by the study site service or other local services within the cancer network.

Interventions:

Outcomes

Results:

The primary reason given by patients for attending follow-up was for reassurance that the cancer had not returned. Participants also wanted information on new treatments and further tests.

Key themes to emerge from the focus group interview were:

- The need for reassurance
- Continuity of care
- Privacy and dignity
- Information and detection of new symptoms
- Opportunities to discuss feelings and worries

A need for reassurance was described by women and they welcomed their regular checks at hospital, demonstrating the anxiety they experience and how this is an essential element which needs to be addressed in a follow-up program.

Continuity of care was an important feature of follow-up for the women who expressed a need to see the same person at each follow-up visit in order that they could build a patient-doctor relationship.

Concerns regarding privacy and dignity were linked to breast examination technique with some women describing instances where they felt vulnerable, frustrated and angry, although some patients did describe a positive experience. The women in this study were able to recognise consistency and experience in the examination techniques and inconsistencies appeared to raise concerns amongst the patients.

Participants in this study described their reliance on follow-up visits for obtaining new and accurate information and for detecting recurrence.

There was a need for patients to be able to discuss worries and feelings during follow-up visits.

General comments

Author's Comment: Using a qualitative approach provided a platform for patients to provide valuable information about local services while using a group of women who knew each other resulted in a positive group dynamic and interaction which appeared to enhance data collection due to the participants being able to discuss many sensitive and personal issues.

Renton, J., Twelves, C., Yuille, F. (2002) Follow-up in women with breast cancer: the patients' perspective *The Breast* 11;257-261

Design: Cross Sectional Survey

Evidence Level: 3

Country: UK

Aim: To define patients' views on follow-up and to develop optimal breast cancer follow-up arrangements which meet the needs of women and make efficient use of available resources.

Renton *et al.* (2002) conducted study that used questionnaires to define patients' views on follow-up and to develop optimal breast cancer follow-up arrangements which meet the needs of women and make efficient use of available resources. The study reported that in general women appeared to be satisfied with current follow-up however they were open to changes to the current set-up. Women reported a number of factors that they felt were important to discuss during follow-up such as risk of recurrence or risk to daughters, the follow-up visits appear to be effective in alleviating the concerns and worries of the majority of women. Women appeared to have more confidence in specialist nurses compared to their own GP suggesting that a nurse-led model of follow-up may be a way forward. Continuity of care was a factor which was deemed to be important.

Inclusion criteria: Women attending the outpatient breast cancer follow-up clinic at the Victoria Infirmary in Glasgow over a five week period between March and April 2000.

Exclusion criteria

Population: N=134

Interventions

A questionnaire consisting of both open and closed questions was developed in conjunction with breast cancer patients and staff and piloted on 23 women to check feasibility before being administered to the study population.

Outcomes:

Previous experience of the clinic (where relevant)
Attitudes to the current clinic arrangements
Patients needs and perceptions

Results

Current Clinic

88% of those surveyed were satisfied with the current duration and frequency of follow-up visits.

46% reported feeling anxious, worried or frightened before a visit and 96% of those surveyed reported feeling relaxed, happy and okay following the visit.

Importance and Satisfaction

87% of women surveyed considered follow-up visits to be important and 92% of all women surveyed expressed their satisfaction with current arrangements.

70% of women considered the risk of recurrence and 61% considered the effects of treatment to be important topics to be discussed at follow-up.

65% of patients deemed it important to see the same member of staff at each follow-up visit and 58% of women felt that waiting times of more than 30 minutes was unsatisfactory.

Other factors which appeared to cause concern included the risk of breast cancer affecting their daughters, alternative treatments, mood and body image.

Specific Alternative Arrangements

Similar proportions of women preferred to talk to a consultant (39%) and a specialist nurse (44%) regarding breast cancer.

77% of women were confident in the consultant while only 33% expressed confidence in the specialist nurse. Despite this, 67% of women indicated that they would be happy for a specialist nurse to take responsibility for follow-up care.

Only 16% of women expressed confidence in their GP although 39% indicated that they would be happy with their GP being responsible for follow-up.

General comments

In general women appeared to be satisfied with current follow-up however they were open to changes to the current set-up.

Women reported a number of factors that they felt were important to discuss during follow-up such as risk of recurrence or risk to daughters, the follow-up visits appear to be effective in alleviating the concerns and worries of the majority of women.

Women appeared to have more confidence in specialist nurses compared to their own GP suggesting that a nurse-led model of follow-up may be a way forward.

Continuity of care was a factor which was deemed to be important.

Vanhuyse, M., Bedard, P., Sheiner, J., Fitzgerald, B., Clemons, M. (2007) Transfer of follow-up care to family physicians for early stage breast cancer *Clinical Oncology* 19:172-176

Design: Prospective Study

Country: Canada

Aim: To determine the number of patients for whom transfer back to the family physician for follow-up was feasible.

Vanhuyse *et al* (2007) reported the feasibility of patients transferring care back to the family physician for follow-up. This study used questionnaires and showed that it may be feasible to transfer follow-up care to the family physicians/GP's however there were many factors which remain to be addressed before this could happen including cost effectiveness, willingness and ability of family physicians/GP's to take on these patients, provision of resources, optimal timing for transfer and patient considerations.

Inclusion criteria:

Patients were deemed eligible to transfer back to the family physician if there was a pre-existing relationship with the physician; the patient agreed to the transfer; the patient was clinically free of local or distant recurrent disease; not require follow-up as specified by clinical trial inclusion and; have completed adjuvant chemo/radiotherapy or commenced adjuvant endocrine therapy.

Exclusion criteria

Population: N=193

Interventions: Assessed for suitability for transfer of follow-up back to the family physician

Outcomes: Follow-up transferred to family physician or continuing with follow-up in a cancer care centre according to usual practice.

Results:

A total of 83 patients (43%) were deemed suitable for transfer back to family physician for continued follow-up. Reasons for not transferring patients included: clinical trial enrolment (50.9%), ongoing endocrine treatment (31.8%), new symptoms (6.3%) or recurrent disease (0.9%).

One patient refused transfer to family physician.

All patients that transferred back to family physician had a pre-existing relationship with their physician whereas 8.2% of those not transferred did not have a family physician. 57.9% of transferred patients were also being followed by other oncologists compared with 65.5% of patients not transferred (p=0.05).

Significantly more patients in the non-transferred group were being considered for switching from Tamoxifen to aromatase inhibitor therapy (p=0.005).

General comments

Transfer of patients to their family physician/GP for follow-up after completion of primary treatment could free up time for oncologists to spend with other patients.

57.9% for transferred patients were being also followed up by a radiation or surgical

oncologist which suggests duplication of resources.

This study shows that it may be feasible to transfer follow-up care to the family physicians/GP's however there are many factors which remain to be addressed before this could happen including cost effectiveness, willingness and ability of family physicians/GP's to take on these patients, provision of resources, optimal timing for transfer and patient considerations.

Adewuyi-Dalton, R., Ziebland, S., Grunfeld, E., Hall, A., (1998) Patients views of routine hospital follow-up: a qualitative study of women with breast cancer in remission *Psycho-Oncology* 7:436-439

Design: Qualitative Methods

Evidence Level: 3

Country: UK

Aim: To identify views about continuity of care, access to specialist services and quality of the consultation and relate these to the length of time since treatment.

Adewuyi-Dalton *et al.* 1998, identified views of women who took part in a randomised clinical trial comparing GP follow-up with out-patient follow-up were invited to take part if they were in the out-patient arm of the trial. The study reported that Continuity of Care; Access to Specialist Care; Quality of Consultation were main areas that women were affected by most significantly.

Inclusion criteria: Women who took part in a randomised clinical trial comparing GP follow-up with out-patient follow-up were invited to take part if they were in the out-patient arm of the trial.

Exclusion criteria

Population: N=109 transcripts available for analysis

Interventions

Outcomes:

Continuity of Care

Access to Specialist Care

Quality of Consultation

Results:

Continuity of Care

The chance to build a personal relationship with the doctor was highly valued by women, yet they rarely saw the same doctor when attending for follow-up. Other reasons for a desire for continuity included uncertainty about the expertise of different staff, apparent lack of knowledge of case history or co-morbidity, difficulties asking questions and the prospect of being given bad news by a stranger.

Access to Specialist Care

The availability of cancer expertise within the clinic environment and quick access to diagnostic tests were seen as benefits of out-patient follow-up.

There was concern that GP's are overworked and could not be expected to have specialist knowledge.

Quality of the Consultation

The limited time available for consultation appeared to be a primary theme, with the lack of time with a specialist contributing to levels of dissatisfaction regarding information about treatment, diagnosis and side effects.

General comments

Continuity of care and access to specialist care are again primary themes emerging from patient questionnaires, particularly in the early stages of follow-up.

From this presented it appears that the need for unrushed consultations persists throughout the follow-up period and perhaps is even more important in the later stages of follow-up when visits are annual.

APPENDIX A – Search strategies

NATIONAL COLLABORATING CENTRE FOR CANCER	
Early Breast Cancer Clinical Guideline	
Chapter 2 – Initial Assessment, Investigation, Staging	Literature search summary

Topic 12a&b: What is the role of MRI in the preoperative staging of patients with a) invasive breast cancer or b) DCIS?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1120	199	19/09/06
<i>Premedline</i>	Sep 18, 2006 -	37	6	19/09/06
<i>AMED</i>	1985 -	3	1	19/09/06
<i>Embase</i>	1980 -	1275	223	19/09/06
<i>Cochrane Library</i>	Wiley version	57	6	19/09/06
<i>Cinahl</i>	1982 -	142	15	19/09/06
<i>BNI</i>	1985 -	2	0	19/09/06
<i>Psychinfo</i>	1806 -	4	0	19/09/06
<i>SIGLE</i>	1980 -	3	0	19/09/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	1261	116	20/09/06
<i>Biomed Central</i>	As per database	136	3	19/09/06

Total References retrieved (after de-duplication): 323

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- 21 exp Breast Diseases/
- 22 20 or 21
- 23 (magnet\$ resonance adj10 (axill\$ or breast\$ or mammary)).mp

24 ((MRI or MRI\$1) adj10 (axill\$ or breast\$ or mammary)).tw
 25 (NMR\$1 adj10 (axill\$ or breast\$ or mammary)).tw
 26 (MRS\$1 adj10 (axill\$ or breast\$ or mammary)).tw
 27 (MRT adj10 (axill\$ or breast\$ or mammary)).tw
 28 (MR imag\$ adj10 (axill\$ or breast\$ or mammary)).tw
 29 (MR scan\$ adj10 (axill\$ or breast\$ or mammary)).tw
 30 (MR spectroscop\$ adj10 (axill\$ or breast\$ or mammary)).tw
 31 (MR elastograph\$ adj10 (axill\$ or breast\$ or mammary)).tw
 32 (magnet\$ adj3 (scan\$ or imag\$) adj10 (axill\$ or breast\$ or mammary)).tw
 33 (diffus\$ adj2 (scan\$ or imag\$) adj10 (axill\$ or breast\$ or mammary)).tw
 34 (zeugmatogra\$ adj10 (axill\$ or breast\$ or mammary)).tw
 35 (MRE adj10 (axill\$ or breast\$ or mammary)).tw
 36 (SPECT\$1 adj10 (axill\$ or breast\$ or mammary)).tw
 37 (functional adj2 (scan\$ or imag\$) adj10 (axill\$ or breast\$ or mammary)).tw
 38 (planar\$ imag\$ adj10 (axill\$ or breast\$ or mammary)).tw.
 39 or/23-38
 40 22 and 39

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	24	19/09/06
<i>Premedline</i>	2	19/09/06
<i>Embase</i>	48	19/09/06
<i>Cochrane Library (except NHSEED)</i>	7	19/09/06
<i>NHSEED</i>	4	19/09/06
<i>Cinahl</i>	5	19/09/06
<i>Psycinfo</i>	1	19/09/06
<i>AMED</i>	0	19/09/06
<i>BNI</i>	0	19/09/06
<i>EconLit</i>	0	19/09/06
<i>Web of Science (SCI & SSCI)</i>	38	20/09/06
<i>SIGLE</i>	0	19/09/06

Total References retrieved (after de-duplication): 100

3. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	224	31	19/05/08
<i>Premedline (July 1, 2008)</i>	24	4	02/07/08
<i>Embase</i>	159	25	19/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	23	6	16/05/08
<i>Cinahl</i>	71	6	19/05/08
<i>BNI</i>	1	0	16/05/08
<i>Psychinfo</i>	3	1	16/05/08
<i>AMED</i>	2	0	16/05/08
<i>Web of Science (SCI & SSCI)</i>	257	23	20/05/08

Total References retrieved (after de-duplication): 53

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 54

Topic 7: What is the role of pre-treatment ultrasound (US) assessment in staging the axilla?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	360	114	25/08/06
<i>Premedline</i>	Aug 23, 2006 -	14	8	25/08/06
<i>AMED</i>	1985 -	0	0	25/08/06
<i>Embase</i>	1980 -	412	84	25/08/06
<i>Cochrane Library</i>	Wiley version	149	1	25/08/06
<i>Cinahl</i>	1982 -	10	3	25/08/06
<i>BNI</i>	1985 -	0	0	25/08/06
<i>Psychinfo</i>	1806 -	0	0	25/08/06
<i>SIGLE</i>	1980 -	0	0	25/08/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	305	76	25/08/06
<i>Biomed Central</i>	As per database	17	4	25/08/06

Total References retrieved (after de-duplication): 148

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.

16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 17 Paget's Disease, Mammary/
 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 19 or/14-18
 20 5 or 19
 21 exp Ultrasonography/
 22 (ultrasound\$ or ultrasonograph\$ or sonograph\$ or ultrasonic or ultrasound-guided or US-guided).mp.
 23 21 or 22
 24 Lymphatic Metastasis/
 25 Lymphatic Diseases/
 26 (axill\$ adj3 metast\$).mp.
 27 (lymph\$ adj5 metast\$).mp.
 28 (node\$ adj4 (malignan\$ or abnormal or suspicious\$)).mp
 29 Lymph Nodes/us [Ultrasonography]
 30 or/24-29
 31 Axilla/
 32 20 and 23 and 30
 33 23 and 30 and 31
 34 32 or 33

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	7	25/08/06
<i>Premedline</i>	1	25/08/06
<i>Embase</i>	18	25/08/06
<i>Cochrane Library (except NHSEED)</i>	19	25/08/06
<i>NHSEED</i>	4	25/08/06
<i>Cinahl</i>	1	25/08/06
<i>Psycinfo</i>	0	25/08/06
<i>AMED</i>	0	25/08/06
<i>BNI</i>	0	25/08/06
<i>EconLit</i>	0	25/08/06
<i>Web of Science (SCI & SSCI)</i>	6	25/08/06
<i>SIGLE</i>	0	25/08/06

Total References retrieved (after de-duplication): 48

This topic was chosen for HE modelling. Therefore further searches were required to support the HE researchers in developing their HE model. Further searches were identified as required:

1. Axillary Ultrasound clinical search (as above) with a prognosis filter

Database name	No of references found	Finish date of search
<i>Medline</i>	203	05/07/07
<i>Premedline (July 3rd 2007)</i>	6	05/07/07
<i>Embase</i>	159	05/07/07
<i>Cochrane Library (except NHSEED)</i>	115	05/07/07
<i>NHSEED</i>	4	05/07/07
<i>Cinahl</i>	5	05/07/07
<i>Psycinfo</i>	0	05/07/07
<i>AMED</i>	0	05/07/07
<i>BNI</i>	0	05/07/07
<i>EconLit</i>	0	05/07/07
<i>Web of Science (SCI & SSCI)</i>	103	05/07/07
<i>SIGLE</i>	0	05/07/07

Total References retrieved (after de-duplication): 413

2. Axillary Clearance: HE/QOL data

Database name	No of references found	Finish date of search
<i>Medline</i>	65	09/07/07
<i>Premedline</i>	1	09/07/07
<i>Embase</i>	215	09/07/07
<i>Cochrane Library (except NHSEED)</i>	56	09/07/07
<i>NHSEED</i>	20	09/07/07
<i>AMED</i>	0	09/07/07
<i>Cinahl</i>	29	09/07/07
<i>Psycinfo</i>	1	09/07/07
<i>BNI</i>	0	09/07/07
<i>EconLit</i>	0	09/07/07
<i>Web of Science (SCI & SSCI)</i>	62	09/07/07
<i>SIGLE</i>	0	09/07/07

Total References retrieved (after de-duplication): 339

3. Any further comments

Exclusions filter only applied to basic search for the clinical review as limited data. SIGN Health Economics & SCHARR Quality of Life filters applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	76	13	08/04/08
<i>Premedline (June 30, 2008)</i>	15	3	01/07/08
<i>Embase</i>	104	14	08/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	29	0	24/04/08
<i>Cinahl</i>	9	4	08/04/08
<i>BNI</i>	0	0	08/04/08
<i>Psychinfo</i>	0	0	08/04/08
<i>AMED</i>	0	0	08/04/08
<i>Web of Science (SCI & SSCI)</i>	94	18	08/04/08

Total References retrieved (after de-duplication): 25

Plus 3 additional references picked up from search alerts until 1st July 2008. Final Total: 28

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 3 – Operable Breast Cancer

Literature search summary

Topic 2: What is the optimal tumour-free tissue margin to achieve in patients who undergo wide local excision (WLE) (breast conserving surgery) for ductal carcinoma in situ (DCIS)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	101	38	24/07/07
<i>Premedline</i>		5	3	24/07/07
<i>Embase</i>	1980 -	72	40	25/07/07
<i>Cochrane Library</i>	Wiley version	35	7	26/07/07
<i>Cinahl</i>	1982 -	14	6	24/07/07
<i>BNI</i>	1985 -	0	0	24/07/07
<i>Psychinfo</i>	1806 -	0	0	25/07/07
<i>SIGLE</i>	1980 -	0	0	26/07/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	367	124	25/07/07
<i>Biomed Central</i>	As per database	53	0	26/07/07

Total References retrieved (after de-duplication): 183

Medline search strategy (This search strategy is adapted to each database)

1. exp Carcinoma, Intraductal, Noninfiltrating/
2. exp Carcinoma, Ductal, Breast/
3. exp Carcinoma, Ductal/
4. exp Carcinoma, in Situ/
5. exp Breast Neoplasms/
6. (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.
7. (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
8. carcinoma\$ in situ.mp.
9. intraduct\$ carcinoma.mp.
10. (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
11. (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
12. (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
13. extensive intraduct\$ component\$.mp.
14. exp Breast/
15. Breast Disease\$.tw.
16. ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
17. (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp.
18. (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
19. or/1-4
20. or/5-7
21. 14 or 15
22. 8 or 9 or 11 or 13 or 17 or 18
23. 10 or 12 or 16
24. 19 or 22
25. 20 or 21
26. 24 and 25

- 27. 23 or 26
- 28. (breast adj10 excision).mp.
- 29. wide local excision\$.tw.
- 30. WLE\$.tw.
- 31. or/28-30
- 32. exp Mastectomy, Segmental/
- 33. breast conserv\$ surg\$.tw.
- 34. exp Breast Neoplasms/su [Surgery]
- 35. or/32-34
- 36. 31 or 35
- 37. 27 and 36
- 38. (tumo?r-free\$ or tumo?r free\$).tw.
- 39. margin\$.tw.
- 40. 38 or 39
- 41. 37 and 40

2. Any further comments

Systematic reviews (2002+) and RCT filters applied to basic search for the clinical review.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007-6/2008	68	11	01/07/08
<i>Premedline</i>	2007-6/2008	12	7	01/07/08
<i>Embase</i>	2007-6/2008	50	16	01/07/08
<i>Cochrane Library</i>	2007-6/2008	11	0	01/07/08
<i>Cinahl</i>	2007-6/2008	5	0	01/07/08
<i>BNI</i>	2007-6/2008	0	0	01/07/08
<i>Psychinfo</i>	2007-6/2008	0	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007-6/2008	54	5	01/07/08
<i>Biomed Central</i>	2007-6/2008	18	0	01/07/08

Total References retrieved (after de-duplication): 29

Topic 40: What is the role of mastectomy in patients with localised Pagets disease of the nipple?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	138	80	13/10/06
<i>Premedline</i>	October 3 rd 2006	9	3	13/10/06
<i>Embase</i>	1980 -	132	52	13/10/06
<i>Cochrane Library</i>	Issue 3, 2006	10	1	13/10/06
<i>Cinahl</i>	1982 -	1	0	13/10/06
<i>BNI</i>	1985 -	0	0	13/10/06
<i>Psychinfo</i>	1806 -	0	0	13/10/06
<i>AMED</i>	1985 -	0	0	13/10/06
<i>SIGLE</i>	1980 - 2005	0	0	13/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	86	39	13/10/06
<i>Biomed Central</i>	1997 -	9	0	13/10/06

Total References retrieved (after de-duplication): 113

Medline search strategy (This search strategy is adapted to each database)

- 1 Paget's Disease, Mammary/
- 2 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 3 1 or 2
- 4 exp Mastectomy/
- 5 mastectom\$.mp.
- 6 segmentectom\$.mp.
- 7 lumpectom\$.mp.
- 8 quadrectom\$.mp.
- 9 segmentectom\$.mp.
- 10 mammoplasty.mp.
- 11 Mammoplasty/
- 12 excision.mp.
- 13 or/4-12
- 14 3 and 13

2. Any further comments

Just a general exclusions filter applied to basic search for the clinical review as limited data. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review, undertaken on 16/10/06 but no results were identified so the search was abandoned.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	7	1	02/04/08
<i>Premedline (June 30, 2008)</i>	12	0	01/07/08
<i>Embase</i>	49	2	02/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	8	0	25/04/08
<i>Cinahl</i>	1	1	02/04/08
<i>BNI</i>	0	0	02/04/08
<i>AMED</i>	0	0	02/04/08
<i>Psychinfo</i>	0	0	02/04/08
<i>Web of Science (SCI & SSCI)</i>	17	3	03/04/08

Total References retrieved (after de-duplication): 4

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 4

Topic 6a&b: When is SLNB justified as a staging procedure in patients with a) invasive breast cancer or b) DCIS?**1. Literature search details**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	680	563	10/07/06
<i>Premedline</i>	May 22, 2006 -	13	10	10/07/06
<i>AMED</i>	1985 -	1	0	10/07/06
<i>Embase</i>	1980 -	377	280	10/07/06
<i>Cochrane Library</i>	Wiley version	56	23	10/07/06
<i>Cinahl</i>	1982 -	26	13	10/07/06
<i>BNI</i>	1985 -	5	3	10/07/06
<i>Psychinfo</i>	1806 -	1 (w/out filters)	0	10/07/06
<i>SIGLE</i>	1980 -	10	1	10/07/06

<i>Web of Science (SCI & SSCI)</i>	1970 -	858	637	11/07/06
<i>Biomed Central</i>	As per database	14	5	06/07/06

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	247	10	16/08/06
<i>Premedline</i>	May 22, 2006 -	6	2	16/08/06
<i>AMED</i>	1985 -	0	0	16/08/06
<i>Embase</i>	1980 -	108	5	16/08/06
<i>Cochrane Library</i>	Wiley version	11	1	16/08/06
<i>Cinahl</i>	1982 -	7	1	16/08/06
<i>BNI</i>	1985 -	0	0	16/08/06
<i>Psychinfo</i>	1806 -	0	0	16/08/06
<i>SIGLE</i>	1980 -	10	0	16/08/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	131	40	21/08/06
<i>Biomed Central</i>	As per database	11	0	16/08/06

Total References retrieved (after de-duplication): 969 and 46 respectively
Total References retrieved (after de-duplication): 1015 (combined results)

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- 21 Sentinel Lymph Node Biopsy/
- 22 (sentinel adj2 (mapping or lymphadenectom\$ or resection)).mp.
- 23 ((sentinel lymph node or sentinel node) adj2 biops\$).mp.
- 24 (SN or SNB or SLN or SLNB or SLNP).mp.
- 25 (sentinel lymph node or sentinel node).mp.
- 26 or/21-25
- 27 Lymph Node Excision/
- 28 ((block or lymph node) adj dissection).mp.
- 29 ((axill?ary or ALN) adj3 (clear\$ or samp1\$ or excision\$ or dissect\$ or lymphadenectom\$)).mp.
- 30 (lymph\$ adj3 map\$).mp.
- 31 lymphadenectomy.mp.
- 32 or/27-31
- 33 20 and 26 and 32
- 1 exp Carcinoma, Intraductal, Noninfiltrating/
- 2 exp Carcinoma, Ductal, Breast/
- 3 exp Carcinoma, Ductal/

4 exp Carcinoma in Situ/
5 exp Breast Neoplasms/
6 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.
7 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
8 carcinoma\$ in situ.mp.
9 intraduct\$ carcinoma.mp.
10 (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
11 (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
12 (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
13 extensive intraduct\$ component\$.mp.
14 exp Breast/
15 exp Breast Diseases/
16 ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
17 (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18 (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
19 or/1-4
20 or/5-7
21 14 or 15
22 8 or 9 or 11 or 13 or 17 or 18
23 10 or 12 or 16
24 19 or 22
25 20 or 21
26 24 and 25
27 23 or 26
28 Sentinel Lymph Node Biopsy/
29 (sentinel adj2 (mapping or lymphadenectom\$ or resection)).mp.
30 ((sentinel lymph node or sentinel node) adj2 biops\$).mp.
31 (SN or SNB or SLN or SLNB or SLNP).mp.
32 (sentinel lymph node or sentinel node).mp.
33 or/28-32
34 27 and 33

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	36	10/07/06
<i>Premedline</i>	1	10/07/06
<i>Embase</i>	54	10/07/06
<i>Cochrane Library (except NHSEED)</i>	5	10/07/06
<i>NHSEED</i>	2	10/07/06
<i>Cinahl</i>	3	10/07/06
<i>Psycinfo</i>	0	10/07/06
<i>AMED</i>	0	10/07/06
<i>BNI</i>	0	10/07/06
<i>EconLit</i>	0	10/07/06
<i>Web of Science (SCI & SSCI)</i>	16	11/07/06
<i>SIGLE</i>	0	10/07/06

Total References retrieved (after de-duplication): 80

3. Any further comments

Systematic Reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the two search strings were combined with RCT & Systematic Review filters, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	128	15	03/06/08
<i>Premedline (June 30, 2008)</i>	10	3	01/07/08
<i>Embase</i>	136	19	03/06/08
<i>Cochrane Library (Issue 2, 2008)</i>	23	11	03/06/08
<i>Cinahl</i>	7	3	04/06/08
<i>BNI</i>	1	0	03/06/08
<i>Psychinfo</i>	0	0	03/06/08
<i>AMED</i>	0	0	03/06/08
<i>Web of Science (SCI & SSCI)</i>	276	43	04/06/08

Total References retrieved (after de-duplication): 87

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 88

Topic 11: What is the prognostic significance of small metastatic deposits in sentinel nodes?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1902	139	04/05/07
<i>Premedline</i>	May 02, 2007	34	5	04/05/07
<i>AMED</i>	1985 -	3	0	08/05/07
<i>Embase</i>	1980 -	1498	162	08/05/07
<i>Cochrane Library</i>	Wiley version	562	3	08/05/07
<i>Cinahl</i>	1982 -	33	7	08/05/07
<i>BNI</i>	1985 -	0	0	08/05/07
<i>Psychinfo</i>	1806 -	0	0	08/05/07
<i>SIGLE</i>	1980 -	0	0	08/05/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1492	175	09/05/07
<i>Biomed Central</i>	As per database	36	1	09/05/07

Total References retrieved (after de-duplication): 246

Medline search strategy (This search strategy is adapted to each database)

- 1 Immunohistochemistry/
- 2 IHC.mp.
- 3 (immuno?cytochem\$ or immuno?histochem\$ or immuno?chem\$).mp.
- 4 (immuno-cytochem\$ or immuno-histochem\$ or immuno-chem\$).mp.
- 5 histological techniques/ or histocytological preparation techniques/
- 6 Immunologic Techniques/
- 7 (serial\$ adj3 section\$).mp.
- 8 ((stepped or step) adj section\$).mp.
- 9 ((multi-level or multilevel) adj section\$).mp.
- 10 Lymphatic Metastasis/
- 11 (lymph\$ adj3 metast\$).mp.
- 12 Neoplasm Metastasis/
- 13 metast\$.mp.
- 14 Lymph Nodes/
- 15 (lymph\$ adj3 node\$).mp.
- 16 exp Sentinel Lymph Node Biopsy/
- 17 Lymph Node Excision/

18 ((block or lymph node) adj dissection).mp.
 19 lymphadenectom\$.mp.
 20 (SN or SNB or SLN or SLNB or SLNP).mp.
 21 (lymph\$ adj3 map\$).mp.
 22 ((ALN or LN) adj (clear\$ or sampl\$ or assess\$ or excision\$ or dissect\$)).mp.
 23 (axill?ary adj3 (clear\$ or sampl\$ or assess\$ or excision\$ or dissect\$)).mp.
 24 (sentinel adj3 (node\$ or lymph\$)).mp.
 25 (axillar\$ adj3 surgical staging).mp.
 26 (micrometast\$ or micro-metast\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 27 (macrometast\$ or macro-metast\$).mp.
 28 (isolated adj tum?or\$ adj cell\$).mp.
 29 14 or 15
 30 13 and 29
 31 or/10-12
 32 30 or 31
 33 or/1-6
 34 or/7-9
 35 or/16-25
 36 or/26-28
 37 33 or 34
 38 32 or 36
 39 exp Breast Neoplasms/
 40 Breast Neoplasms/
 41 Carcinoma, Intraductal, Noninfiltrating/
 42 Carcinoma, Lobular/
 43 Carcinoma, Medullary/
 44 or/40-43
 45 exp Breast/
 46 breast.tw.
 47 45 or 46
 48 (breast adj milk).tw.
 49 (breast adj tender\$).tw.
 50 48 or 49
 51 47 not 50
 52 exp Neoplasms/
 53 51 and 52
 54 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 55 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 56 Paget's Disease, Mammary/ 46
 57 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 58 or/53-57
 59 44 or 58
 60 39 or 59
 61 60 and 35 and 37
 62 60 and 35 and 38
 63 61 or 62
 64 sentinel.mp
 65 64 and 36 and 60
 66 63 or 65

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	36	08/05/07
<i>Premedline</i>	0	08/05/07

Embase	59	08/05/07
Cochrane Library (except NHSEED)	52	08/05/07
NHSEED	24	08/05/07
Cinahl	3	08/05/07
Psycinfo	0	08/05/07
AMED	0	08/05/07
BNI	0	08/05/07
EconLit	0	08/05/07
Web of Science (SCI & SSCI)	40	09/05/07
SIGLE	0	08/05/07

Total References retrieved (after de-duplication): 168

3. Any further comments

Prognosis and Systematic Reviews filters (2002+) applied to basic search for the clinical review, when required. SIGN Health Economics filter and SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	185	16	23/04/08
Premedline (July 1, 2008)	47	16	02/07/08
Embase	145	15	23/04/08
Cochrane Library (Issue 2, 2008)	35	0	23/04/08
Cinahl	10	2	23/04/08
BNI	0	0	23/04/08
Psychinfo	0	0	23/04/08
AMED	0	0	23/04/08
Web of Science (SCI & SSCI)	237	39	23/04/08

Total References retrieved (after de-duplication): 41

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 41

Topic 19: What are the indications for completion axillary clearance when the axilla has found by biopsy to contain metastasis?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1564	58	08/06/07
<i>Premedline</i>	June 05, 2007	12	0	06/06/07
<i>AMED</i>	1985 -	10	0	06/06/07
<i>Embase</i>	1980 -	2015	51	12/06/07
<i>Cochrane Library</i>	Wiley version	332	12	11/06/07
<i>Cinahl</i>	1982 -	72	4	06/06/07
<i>BNI</i>	1985 -	1	0	06/06/07
<i>Psychinfo</i>	1806 -	6	0	06/06/07
<i>SIGLE</i>	1980 -	0	0	06/06/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1263	58	13/06/07
<i>Biomed Central</i>	As per database	16	0	06/06/07

Total References retrieved (after de-duplication): 105

Medline search strategy (This search strategy is adapted to each database)

- 1 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj axill\$ adj (clear\$ or dissect\$)).mp.
- 2 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj lymph\$ adj (clear\$ or dissect\$)).mp.
- 3 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj nod\$ adj (clear\$ or dissect\$)).mp.
- 4 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj lymph\$ nod\$ adj (clear\$ or dissect\$)).mp.
- 5 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj axill\$ nod\$ adj (clear\$ or dissect\$)).mp.
- 6 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj axill\$ lymph\$ nod\$ adj (clear\$ or dissect\$)).mp.
- 7 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj (ALND or LND)).mp.
- 8 CALND.mp.
- 9 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj ALN adj (clear\$ or dissect\$)).mp.
- 10 ((complet\$ or full or exten\$ or total or level 3 or level III or radical) adj (dissect\$ or clear\$) adj4 (axill\$ or lymph\$ or nod\$)).mp.
- 11 or/1-10
- 12 Lymph Nodes/
- 13 Lymphatic Metastasis/
- 14 Lymph Node Excision/
- 15 or/12-14
- 16 ((axill\$ or lymph\$ or nod\$ or ALND or ALN or LND) adj3 (clear\$ or dissect\$)).mp.
- 17 15 and 16
- 18 11 or 17
- 19 (complete or completion or full or extensive or extended or total or level 3 or level III or radical).mp.
- 20 (axill\$ or lymph\$ or nod\$ or ALN or LND or ALND).mp.
- 21 (clearance or dissection).mp.
- 22 19 and 20 and 21
- 23 18 or 22
- 24 (positiv\$ adj2 (nod\$ or axill\$ sentinel or SLN or SNB or lymph\$)).mp.
- 25 node-positive.mp.
- 26 24 or 25
- 27 22 and 26
- 28 23 or 27
- 29 Axilla/
- 30 (radiotherap\$ or irradiation or radiation).mp.
- 31 21 and 29 and 30
- 32 28 or 31
- 33 exp Breast Neoplasms/
- 34 exp "Neoplasms, Ductal, Lobular, and Medullary"/

35 Carcinoma, Intraductal, Noninfiltrating/
 36 Carcinoma, Lobular/
 37 Carcinoma, Medullary/
 38 exp mammary neoplasms/
 39 or/33-38
 40 exp Breast/
 41 breast.tw.
 42 40 or 41
 43 (breast adj milk).tw.
 44 (breast adj tender\$.tw.
 45 43 or 44
 46 42 not 45
 47 exp Neoplasms/
 48 46 and 47
 49 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 50 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 51 Paget's Disease, Mammary/
 52 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 53 or/48-52
 54 39 or 53
 55 32 and 54
 56 comple\$ axill\$ dissect\$.m_titl.
 57 54 and 56
 58 55 or 57

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	65	09/07/07
<i>Premedline</i>	1	09/07/07
<i>Embase</i>	215	09/07/07
<i>Cochrane Library (except NHSEED)</i>	56	09/07/07
<i>NHSEED</i>	20	09/07/07
<i>AMED</i>	0	09/07/07
<i>Cinahl</i>	29	09/07/07
<i>Psycinfo</i>	1	09/07/07
<i>BNI</i>	0	09/07/07
<i>EconLit</i>	0	09/07/07
<i>Web of Science (SCI & SSCI)</i>	62	09/07/07
<i>SIGLE</i>	0	09/07/07

Total References retrieved (after de-duplication): 339

3. Any further comments

Systematic Reviews (2002+), RCT and observational filters applied to basic search for the clinical review. SIGN Health Economics filter and SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	56	9	03/04/08
<i>Premedline (July 1, 2008)</i>	8	2	02/07/08
<i>Embase</i>	144	7	03/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	24	3	24/04/08
<i>Cinahl</i>	19	4	02/04/08
<i>BNI</i>	0	0	01/04/08
<i>AMED</i>	0	0	01/04/08
<i>Psychinfo</i>	0	0	01/04/08
<i>Web of Science (SCI & SSCI)</i>	117	16	02/04/08

Total References retrieved (after de-duplication): 25

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 26

Topic 22: When is it appropriate (or not appropriate) to perform immediate breast reconstruction?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	492	298	11/10/06
<i>Premedline</i>	October 3 rd 2006	7	13	11/10/06
<i>AMED</i>	1985 -	6	4	11/10/06
<i>Embase</i>	1980 -	713	256	13/10/06
<i>Cochrane Library</i>	Wiley version	35	13	09/10/06
<i>Cinahl</i>	1982 -	96	22	11/10/06
<i>BNI</i>	1985 -	16	8	11/10/06
<i>Psychinfo</i>	1806 -	16	11	11/10/06
<i>SIGLE</i>	1980 -	8	0	09/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	684	243	11/10/06
<i>Biomed Central</i>	As per database	50	2	09/10/06

Total References retrieved (after de-duplication): 428

Plus 1 additional reference picked up during guideline development. Final Total: 429

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$).tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13

15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 17 Paget's Disease, Mammary/
 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 19 or/14-18
 20 5 or 19
 21 Breast Implants/
 22 Breast/su [Surgery]
 23 "Prostheses and Implants"/
 24 or/20-23
 25 ((immediate or delay\$ or late or breast\$ or post?mastectom\$ or post-mastectom\$ or postmastectom\$ or mastectom\$) adj reconstruct\$.mp.
 26 (IBR or MIBR).mp.
 27 25 or 26
 28 24 and 27
 29 limit 30 to yr="2001 - 2006"
 30 exp Breast Neoplasms/su [Surgery]
 31 exp Mastectomy/
 32 (breast adj10 excision).mp.
 33 lumpectomy.mp.
 34 or/30-33
 35 breast implant\$.mp.
 36 exp Mammoplasty/
 37 mammoplasty.mp.
 38 (breast adj10 reconstruction).mp.
 39 or/35-38
 40 34 and 39
 41 limit 40 to yr="2002 - 2006"
 42 29 or 41

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	524	25/10/06
<i>Premedline</i>	3	25/10/06
<i>Embase</i>	82	25/10/06
<i>Cochrane Library (except NHSEED)</i>	8	25/10/06
<i>NHSEED</i>	23	25/10/06
<i>Cinahl</i>	17	25/10/06
<i>Psycinfo</i>	1	25/10/06
<i>AMED</i>	3	25/10/06
<i>BNI</i>	1	25/10/06
<i>EconLit</i>	0	25/10/06
<i>Web of Science (SCI & SSCI)</i>	41	25/10/06
<i>SIGLE</i>	0	25/10/06

Total References retrieved (after de-duplication): 637

3. Any further comments

The following report was used as a basis: *Fischbacher, C. Immediate versus delayed breast reconstruction Steer 2002; 2(17)*. Used their original search (lines 30-82 of search strategy above), limited from 2002 onwards as original search executed early that year. Systematic Reviews, RCTs and Observational filters used as appropriate. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	280	62	21/04/08
<i>Premedline (July 1, 2008)</i>	71	5	02/07/08
<i>Embase</i>	380	63	21/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	10	1	24/04/08
<i>Cinahl</i>	23	2	21/04/08
<i>BNI</i>	6	0	21/04/08
<i>AMED</i>	0	0	21/04/08
<i>Psychinfo</i>	8	0	21/04/08
<i>Web of Science (SCI & SSCI)</i>	372	68	21/04/08

Total References retrieved (after de-duplication): 78

Plus 4 additional references picked up from search alerts until 1st July 2008. Final Total: 82

Updated 2018

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 4 –Adjuvant Therapy Planning

Literature search summary

Topic 9: Does progesterone receptor (PR) status add further useful information to that of oestrogen receptor (ER) status in patients with invasive breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1,732	157	29/11/06
<i>Premedline</i>		24	1	22/11/06
<i>AMED</i>	1985 -	6	0	22/11/06
<i>Embase</i>	1980 -	1,214	79	30/11/06
<i>Cochrane Library</i>	Wiley version	281	41	22/11/06
<i>Cinahl</i>	1982 -	42	1	22/11/06
<i>BNI</i>	1985 -	0	0	22/11/06
<i>Psychinfo</i>	1806 -	5	0	22/11/06
<i>SIGLE</i>	1980 -	2	0	21/11/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	2,731	97	04/12/06
<i>Biomed Central</i>	As per database	53	0	21/11/06

Total References retrieved (after de-duplication): 264

Plus 1 additional reference picked up during guideline development. Final Total: 265

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- 21 Receptors, Progesterone/
- 22 ((progesteron\$ or progestin or PgR or PR) adj3 (status or test\$ or level\$ or receptor\$ or expression)).mp.
- 23 ((PR adj2 positiv\$) or (PR adj2 negativ\$) or (PgR adj2 positiv\$) or (PgR adj2 negativ\$) or (progesteron\$ adj2 positiv\$) or (progesteron\$ adj2 negativ\$) or (progestin adj2 negativ\$) or (progestin adj2 positiv\$)).mp.
- 24 Receptors, Estrogen/
- 25 ((oestrogen\$ or estrogen or EgR or ER) adj3 (status or test\$ or level\$ or receptor\$ or expression)).mp.

26 ((ER adj2 positiv\$) or (ER adj2 negativ\$) or (EgR adj2 positiv\$) or (EgR adj2 negativ\$) or (oestrogen\$ adj2 positiv\$) or (oestrogen\$ adj2 negativ\$) or (estrogen adj2 negativ\$) or (estrogen adj2 positiv\$)).mp.
 27 or/21-23
 28 or/24-26
 29 27 and 28
 30 20 and 29
 31 progesterone receptor.m_titl.
 32 breast cancer.m_titl.
 33 31 and 32
 34 30 or 33

2. Any further comments

Systematic Reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	426	25	06/06/08
<i>Premedline (June 30, 2008)</i>	48	2	01/07/08
<i>Embase</i>	446	20	06/06/08
<i>Cochrane Library (Issue 2, 2008)</i>	51	4	06/06/08
<i>Cinahl</i>	21	8	06/06/08
<i>BNI</i>	2	0	06/06/08
<i>Psychinfo</i>	2	0	06/06/08
<i>AMED</i>	3	0	06/06/08
<i>Web of Science (SCI & SSCI)</i>	323	15	09/06/08

Total References retrieved (after de-duplication): 38

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 38

Topic 1: What is the optimal time interval from completion of definitive surgery to commencement of adjuvant therapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	2200	213	19/06/07
<i>Premedline</i>		91	2	19/06/07
<i>Embase</i>	1980 -	2092	80	25/06/07
<i>Cochrane Library</i>	Wiley version	563	96	13/06/07
<i>Cinahl</i>	1982 -	106	7	19/06/07
<i>BNI</i>	1985 -	7	0	19/06/07
<i>Psychinfo</i>	1806 -	25	0	19/06/07
<i>SIGLE</i>	1980 -	4	0	25/06/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1006	65	25/06/07
<i>ISI proceedings</i>	1990-	180	12	25/06/07
<i>Biomed Central</i>	As per database	281	1	25/06/07

Total References retrieved (after de-duplication): 137

Plus 1 additional reference picked up during guideline development. Final Total: 138

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
21. Breast/su [Surgery]
22. ((immediate or delay\$ or late or breast\$ or post?mastectom\$ or post-mastectom\$ or postmastectom\$ or mastectom\$) adj reconstruct\$.mp.
23. exp Mastectomy/
24. mastectom\$.tw.
25. (breast adj10 excision).mp.
26. lumpectom\$.tw.
27. segmentectom\$.tw.
28. quadrectom\$.tw.
29. ((breast\$ or mammary) adj4 surg\$.mp.
30. exp Lymph Node Excision/
31. or/21-30
32. exp Antineoplastic Combined Chemotherapy Protocols/
33. Chemotherap\$.tw.
34. exp Chemotherapy, Adjuvant/
35. adjuvant chemotherap\$.tw.
36. adjuvant hormone therap\$.tw.
37. adjuvant systemic therap\$.tw.
38. Breast Neoplasms/dt
39. exp Time factor/
40. or/32-39
41. exp Radiotherapy, Adjuvant/
42. adjuvant\$ radiotherap\$.tw.
43. adjuvant radiation therap\$.tw.
44. (breast\$ adj4 (radiation or radiotherap\$)).mp.
45. Carcinoma, Ductal, Breast/rt
46. exp Time factor/
47. or/41-46
48. 20 and 31
49. 48 and 40
50. 48 and 47
51. 49 or 50

2. Any further comments

Systematic reviews (2002+) and RCT filters applied to basic search for the clinical review.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007-6/2008	612	51	01/07/08
<i>Premedline</i>	2007-6/2008	105	1	01/07/08
<i>Embase</i>	2007-6/2008	1208	23	01/07/08
<i>Cochrane Library</i>	2007-6/2008	34	0	01/07/08
<i>Cinahl</i>	2007-6/2008	131	12	01/07/08
<i>BNI</i>	2007-6/2008	2	0	01/07/08
<i>Psychinfo</i>	2007-6/2008	6	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007-6/2008	152	3	01/07/08
<i>ISI proceedings</i>	2007-6/2008	20	2	01/07/08
<i>Biomed Central</i>	2007-6/2008	64	0	01/07/08

Total References retrieved (after de-duplication): 70

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 5 – Adjuvant Systemic Therapy

Literature search summary

Topic 29d2: In premenopausal breast cancer patients, what are the benefits of adjuvant ovarian suppression/ablation in addition to other treatments?

1. Literature search details

Part 1:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	628	40	21/06/07
<i>Premedline</i>	June 20, 2007	36 (no filters)	3	21/06/07
<i>AMED</i>	1985 -	1 (no filters)	0	21/06/07
<i>Embase</i>	1980 -	834	39	22/06/07
<i>Cochrane Library</i>	Wiley version	253	53	22/06/07
<i>Cinahl</i>	1982 -	47	4	21/06/07
<i>BNI</i>	1985 -	2 (no filters)	0	21/06/07
<i>Psychinfo</i>	1806 -	17 (no filters)	0	21/06/07
<i>SIGLE</i>	1980 -	0	0	21/06/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	955	57	25/06/07
<i>Biomed Central</i>	As per database	9	0	22/06/07

Total References retrieved (after de-duplication): 94

Part 2:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 onwards	51	13	21/06/07
<i>Premedline</i>	2006 onwards	11	1	21/06/07
<i>AMED</i>	2006 onwards	0	0	21/06/07
<i>Embase</i>	2006 onwards	55	12	21/06/07
<i>Cochrane Library</i>	2006 onwards	9	4	21/06/07
<i>Cinahl</i>	2006 onwards	7	1	21/06/07
<i>BNI</i>	2006 onwards	1	0	21/06/07
<i>Psychinfo</i>	2006 onwards	1	0	21/06/07
<i>SIGLE</i>	Not searched as database finished in 2005			
<i>Web of Science (SCI & SSCI)</i>	2006 onwards	43	15	21/06/07
<i>Biomed Central</i>	2006 onwards	141	0	21/06/07

Total References retrieved (after de-duplication): 24

Total References retrieved (after de-duplication): 115 (combined results)

Medline search strategy (This search strategy is adapted to each database)

Strategy divided into 2 parts: part 1 dealt with surgical/RT induced ovarian ablation/suppression (no date limit), part 2 dealt with hormonal/endocrine therapy induced ovarian ablation/suppression (date limit 2006 onwards as update of commissioned Cochrane Review)

Part 1:

- 1 exp Ovariectomy/
- 2 (ovariectom\$ or oophorectom\$).mp.
- 3 (surgical removal adj3 ovar\$).mp.
- 4 ((radiation or irradiation or radiotherap\$) adj3 ovar\$).mp.

5 exp Ovary/
 6 exp Radiation/
 7 (ovar\$ adj3 (suppress\$ or ablat\$)).mp.
 8 or/1-4
 9 5 and 6
 10 or/7-9
 11 exp Breast Neoplasms/
 12 exp "Neoplasms, Ductal, Lobular, and Medullary"/
 13 Carcinoma, Intraductal, Noninfiltrating/
 14 Carcinoma, Lobular/
 15 Carcinoma, Medullary/
 16 exp mammary neoplasms/
 17 or/11-16
 18 exp Breast/
 19 breast.tw.
 20 18 or 19
 21 (breast adj milk).tw.
 22 (breast adj tender\$).tw.
 23 21 or 22
 24 20 not 23 15455
 25 exp Neoplasms/
 26 24 and 25
 27 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 28 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 29 Paget's Disease, Mammary/
 30 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 31 or/26-30
 32 17 or 31
 33 10 and 32
Part 2:
 1 breast cancer.ti,ab.
 2 lutein\$ hormon\$ releas\$.ti,ab.
 3 (LHRH or LH-RH or LHRH-agonist\$ or LH-RH-agonist\$).ti,ab.
 4 gonadotrop\$ releas\$ hormon\$.ti,ab.
 5 (GnRH or GnRHA or GnRH-agonist\$ or GnRH-analog\$).ti,ab.
 6 ((ovar\$ or hormon\$) adj3 (suppress\$ or ablat\$)).ti,ab.
 7 (goserelin or zoladex or busarelin or suprefact or leuproli\$ or lupron or nafarelin or synarel or triptorelin or De-Capeptyl).ti,ab.
 8 or/2-7
 9 1 and 8
 10 limit 9 to yr="2006 - 2007"

2. Any further comments

Systematic Reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review.

3. Update Search

For the update search, the two search strings were combined with RCT & Systematic Review filters, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	77	5	15/04/08
<i>Premedline (June 30, 2008)</i>	16	1	01/07/08
<i>Embase</i>	177	4	15/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	19	2	24/04/08
<i>Cinahl</i>	45	3	16/04/08
<i>BNI</i>	0	0	15/04/08
<i>AMED</i>	0	0	15/04/08
<i>Psychinfo</i>	2	0	15/04/08
<i>Web of Science (SCI & SSCI)</i>	139	9	16/04/08

Total References retrieved (after de-duplication): 9

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 9

Topic 29c: What is the best timing/sequencing of aromatase inhibitors and the duration of treatment in post menopausal women with hormone receptor positive breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2005 - 2007	139	75	11/07/07
<i>Premedline</i>		19	12	13/07/07
<i>Embase</i>	2005 - 2007	181	72	12/07/07
<i>Cochrane Library</i>	2005-2007	29	15	13/07/07
<i>Cinahl</i>	2005 - 2007	12	8	12/07/07
<i>BNI</i>	2005 - 2007	0	0	12/07/07
<i>Psychinfo</i>	2005 - 2007	0	0	12/07/07
<i>SIGLE</i>	2005	0	0	13/07/07
<i>Web of Science (SCI & SSCI)</i>	2005 - 2007	206	81	13/07/07
<i>Biomed Central</i>	As per database	313	1	13/07/07

Total References retrieved (after de-duplication): 135

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or

leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 17 Paget's Disease, Mammary/
 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 19 or/14-18
 20 5 or 19
 21. hormone receptor\$.tw.
 22. exp Postmenopause/
 23. 21 or 22
 24. 20 or 23
 25. exp Aromatase Inhibitors/
 26. Aromatase Inhibitor\$.tw.
 27. anastrozole.mp.
 28. arimidex.mp.
 29. letrozole.mp.
 30. femara.mp.
 31. exemestane.mp.
 32. aromasin.mp.
 33. or/25-32
 34. exp Time Factors/
 35. tim\$.tw.
 36. sequenc\$.tw.
 37. duration of treatment\$.tw.
 38. or/34-37
 39. 33 and 38
 40. 24 and 39
 41. limit 40 to "2005-2007"

2. Any further comments

Because NICE had recently a TA done, this served as basis for a new search with results sifted only from 2005 onwards. No filters were applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 - 6/2008	72	12	01/07/08
<i>Premedline</i>	2007 - 6/2008	47	8	01/07/08
<i>Embase</i>	2007 - 6/2008	96	9	01/07/08
<i>Cochrane Library</i>	2007 - 6/2008	27	0	01/07/08
<i>Cinahl</i>	2007 - 6/2008	17	6	01/07/08
<i>BNI</i>	2007 - 6/2008	0	0	01/07/08
<i>Psychinfo</i>	2007 - 6/2008	0	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007 - 6/2008	140	16	01/07/08
<i>Biomed Central</i>	2007 - 6/2008	17	0	01/07/08

Total References retrieved (after de-duplication): 28

Topic 29e: Which subgroups of post menopausal breast cancer patients should receive Aromatase inhibitors as adjuvant therapy?

1. Literature search details

	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2005 - 2007	199	39	16/07/07
<i>Premedline</i>		41	1	16/07/07
<i>Embase</i>	2005 - 2007	393	43	17/07/07
<i>Cochrane Library</i>	2005 - 2007	54	4	17/07/07
<i>Cinahl</i>	2005 - 2007	31	3	16/07/07
<i>BNI</i>	2005 - 2007	4	2	16/07/07
<i>Psychinfo</i>	2005 - 2007	0	0	17/07/07
<i>SIGLE</i>	2005	0	0	17/07/07
<i>Web of Science (SCI & SSCI)</i>	2005 - 2007	25	18	17/07/07
<i>Biomed Central</i>	2005 - 2007	25	1	17/07/07

Total References retrieved (after de-duplication): 89

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
21. hormone receptor\$.tw.
22. exp Postmenopause/
23. exp Patient selection/
24. 21 or 22 or 23
25. exp Aromatase Inhibitors/
26. Aromatase Inhibitor\$.tw.
27. anastrozole.mp.
28. arimidex.mp.
29. letrozole.mp.
30. femara.mp.
31. exemestane.mp.
32. aromasin.mp.
33. or/25-32
34. 24 and 33

35. 34 and 20

2. Any further comments

Because NICE had recently a TA done, this served as basis for a new search with results sifted only from 2005 onwards. No filters were applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 6/2008	101	32	01/07/08
<i>Premedline</i>	2007 – 6/2008	98	43	01/07/08
<i>Embase</i>	2007 – 6/2008	216	60	01/07/08
<i>Cochrane Library</i>	2007 – 6/2008	47	11	01/07/08
<i>Cinahl</i>	2007 – 6/2008	43	22	01/07/08
<i>BNI</i>	2007 – 6/2008	0	0	01/07/08
<i>Psychinfo</i>	2007 – 6/2008	6	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 6/2008	22	1	01/07/08
<i>Biomed Central</i>	2007 – 6/2008	20	0	01/07/08

Total References retrieved (after de-duplication): 93

Topic 5: When should patients with DCIS who have undergone complete excision (CE) or WLE be given tamoxifen?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	905	193	12/01/07
<i>Premedline</i>	Jan 12, 2007	15	5	12/01/07
<i>AMED</i>	1985 -	0	0	15/01/07
<i>Embase</i>	1980 -	343	91	15/01/07
<i>Cochrane Library</i>	Wiley version	139	43	16/01/07
<i>Cinahl</i>	1982 -	35	10	15/01/07
<i>BNI</i>	1985 -	0	0	15/01/07
<i>Psychinfo</i>	1806 -	1	0	15/01/07
<i>SIGLE</i>	1980 -	5	0	15/01/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	720	193	16/01/07
<i>Biomed Central</i>	As per database	18	2	15/01/07

Total References retrieved (after de-duplication): 307

Plus 2 additional references picked up during guideline development. Final Total: 309

Medline search strategy (This search strategy is adapted to each database)

1 exp Carcinoma, Intraductal, Noninfiltrating/

2 exp Carcinoma, Ductal, Breast/

3 exp Carcinoma, Ductal/

4 exp Carcinoma in Situ/

5 exp Breast Neoplasms/

6 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.

7 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 8 carcinoma\$ in situ.mp.
 9 intraduct\$ carcinoma.mp.
 10 (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti.ab.
 11 (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
 12 (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti.ab.
 13 extensive intraduct\$ component\$.mp.
 14 exp Breast/
 15 exp Breast Diseases/
 16 ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
 17 (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 18 (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
 19 or/1-4
 20 or/5-7
 21 14 or 15
 22 8 or 9 or 11 or 13 or 17 or 18
 23 10 or 12 or 16
 24 19 or 22
 25 20 or 21
 26 24 and 25
 27 23 or 26
 28 ((micro-invas\$ or microinvas\$) adj5 (breast\$ or mammary)).mp.
 29 27 or 28
 30 Tamoxifen/
 31 (Nolvadex or tamoxifen\$.mp.
 32 10540-29-1.rn.
 33 or/30-32
 34 exp Radiotherapy/
 35 (radiotherap\$ or radiation or irradiation).mp.
 36 34 or 35
 37 33 or 36
 38 29 and 37

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	22	15/01/07
<i>Premedline</i>	0	15/01/07
<i>Embase</i>	36	15/01/07
<i>Cochrane Library (except NHSEED)</i>	24	16/01/07
<i>NHSEED</i>	11	16/01/07
<i>Cinahl</i>	2	15/01/07
<i>Psycinfo</i>	0	15/01/07
<i>AMED</i>	0	15/01/07
<i>BNI</i>	0	15/01/07
<i>EconLit</i>	0	15/01/07
<i>Web of Science (SCI & SSCI)</i>	18	16/01/07
<i>SIGLE</i>	0	15/01/07

Total References retrieved (after de-duplication): 98

3. Any further comments

Systematic Reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. This was a combined search with Topic 4 (Chapter 5 searches). SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	89	11	07/04/08
<i>Premedline (June 30, 2008)</i>	5	2	01/07/08
<i>Embase</i>	118	12	07/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	31	2	24/04/08
<i>Cinahl</i>	20	4	07/04/08
<i>BNI</i>	0	0	07/04/08
<i>Psychinfo</i>	2	0	07/04/08
<i>AMED</i>	0	0	07/04/08
<i>Web of Science (SCI & SSCI)</i>	171 (no filter)	37	08/04/08

Total References retrieved (after de-duplication): 39

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 39

Update of TA107: What is the clinical & cost effectiveness of trastuzumab for the treatment of early breast cancer? (incl both neoadjuvant & adjuvant). Also consider: what is the most clinical & cost-effective frequency of treatment and duration of treatment?

Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1225	81	22/01/08
<i>Premedline</i>	Jan 18, 2008	87	11	21/01/08
<i>AMED</i>	1985 -	2	0	21/01/08
<i>Embase</i>	1980 -	1389	62	22/01/08
<i>Cochrane Library</i>	Issue 4, 2007	124	42	16/01/08
<i>Cinahl</i>	1982 -	166	12	22/01/08
<i>BNI</i>	1985 -	11	0	21/01/08
<i>Psychinfo</i>	1806 -	3	0	21/01/08
<i>Web of Science (SCI & SSCI)</i>	1970 -	1377	122	25/01/08

Total References retrieved (after de-duplication): 219

Plus 4 additional references picked up during guideline development. Final Total: 223

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 (breast\$ adj4 neoplasm\$).tw.
- 3 (breast\$ adj4 cancer\$).tw.
- 4 (breast\$ adj4 tumor\$).tw.
- 5 (breast\$ adj4 tumour\$).tw.
- 6 (breast\$ adj4 carcinoma\$).tw.
- 7 (breast\$ adj4 oncolog\$).tw.
- 8 (breast\$ adj4 malign\$).tw.
- 9 or/1-8

10 trastuzumab.tw.
 11 herceptin.tw.
 12 haerceptin.tw.
 13 or/10-12
 14 9 and 13

1. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	45	Jan 2008
<i>Premedline</i>	2	Jan 2008
<i>Embase</i>	110	Jan 2008
<i>Cochrane Library (except NHSEED)</i>	6	Jan 2008
<i>NHSEED</i>	12	Jan 2008

Database name	No of references found	Finish date of search
<i>Medline</i>	48 (2 new)	01/07/08
<i>Premedline (June 30, 2008)</i>	7 (6 new)	01/07/08
<i>Embase</i>	146 (35 new)	01/07/08
<i>Cochrane Library (except NHSEED)</i>	10 (0 new)	01/07/08
<i>NHSEED</i>	15 (0 new)	01/07/08

Total References retrieved (after de-duplication): 148

Total References retrieved (after de-duplication): 38

2. Any further comments

Original TA report literature search strategy used. Exclusions filter only applied to basic search for the clinical review. SIGN Health Economics filter applied to basic search for the health economics review. Both searches executed without date limit as TA107 didn't cover neoadjuvant use of trastuzumab nor the frequency/duration of treatment.

3. Update Search

For the update search, an RCT & Systematic Review filter was used, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	163	5	14/06/08
<i>Premedline (June 30, 2008)</i>	22	1	01/07/08
<i>Embase</i>	206	5	14/06/08
<i>Cochrane Library (Issue 2, 2008)</i>	25	2	14/06/08
<i>Cinahl</i>	34	3	14/06/08
<i>BNI</i>	2	0	14/06/08
<i>Psychinfo</i>	2	0	14/06/08
<i>AMED</i>	1	0	14/06/08
<i>Web of Science (SCI & SSCI)</i>	404	22	14/06/08

Total References retrieved (after de-duplication): 28

Plus 2 additional references picked up from search alerts until 1st July 2008. Final Total: 30

Update of TA108: What is the clinical & cost effectiveness of paclitaxel for adjuvant treatment of early breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2006 onwards	449	26	14/01/08
<i>Premedline</i>	Jan 14, 2008	75	7	15/01/08
<i>AMED</i>	2006 onwards	1	0	15/01/08
<i>Embase</i>	2006 onwards	726	34	16/01/08
<i>Cochrane Library</i>	2006 onwards	72	14	14/01/08
<i>Cinahl</i>	2006 onwards	59	6	15/01/08
<i>BNI</i>	2006 onwards	0	0	15/01/08
<i>Psychinfo</i>	2006 onwards	2	0	15/01/08
<i>Web of Science (SCI/SSCI)</i>	2006 onwards	601	50	16/01/08

Total References retrieved (after de-duplication): 82

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 ((breast\$ or mamma\$) adj4 neoplasm\$).tw.
- 3 ((breast\$ or mamma\$) adj4 cancer\$).tw.
- 4 ((breast\$ or mamma\$) adj4 tumor\$).tw.
- 5 ((breast\$ or mamma\$) adj4 tumour\$).tw.
- 6 ((breast\$ or mamma\$) adj4 carcinoma\$).tw.
- 7 ((breast\$ or mamma\$) adj4 oncolog\$).tw.
- 8 ((breast\$ or mamma\$) adj4 malign\$).tw.
- 9 or/1-8
- 10 Paclitaxel/
- 11 paclitaxel.tw.
- 12 taxol.tw.
- 13 anzatax.tw.
- 14 onxol.tw.
- 15 paxene.tw.
- 16 praxel.tw.
- 17 nsc-125973.tw.
- 18 nsc125973.tw.
- 19 "Abi 007".tw.
- 20 Abi007.tw.
- 21 abraxane.tw.
- 22 Bms 181339.tw
- 23 Bms181339.tw.
- 24 coroxane.tw.
- 25 genexol.tw.
- 26 hunxol.tw.
- 27 intaxel.tw.
- 28 paxceed.tw.
- 29 yewtaxan.tw.
- 30 Toxoids/
- 31 taxoid\$.tw.
- 32 taxane\$.tw.
- 33 or/10-32
- 34 9 and 33

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	10	Jan 2008

Premedline	1	Jan 2008
Embase	4	Jan 2008
Cochrane Library (except NHSEED)	0	Jan 2008
NHSEED	6	Jan 2008
NHSEED (no date limit)	31	Jan 2008

Database name	No of references found	Finish date of search
Medline	12 (1 new)	01/07/08
Premedline (June 30, 2008)	2 (1 new)	01/07/08
Embase	6 (1 new)	01/07/08
Cochrane Library (except NHSEED)	0	01/07/08
NHSEED	9 (0 new)	01/07/08

Total References retrieved (after de-duplication): 17

Total References retrieved (after de-duplication): 1

3. Any further comments

Original TA report literature search strategy used. Exclusions filter only applied to basic search for the clinical review. SIGN Health Economics filter applied to basic search for the health economics review. Both searches executed from 2006 onwards as TA108 included both clinical and cost-effectiveness issues.

4. Update Search

For the update search, an RCT & Systematic Review filter was used, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	189	4	13/06/08
Premedline (June 30, 2008)	32	3	01/07/08
Embase	376	9	13/06/08
Cochrane Library (Issue 2, 2008)	57	1	13/06/08
Cinahl	86	3	13/06/08
BNI	0	0	13/06/08
Psychinfo	1	0	13/06/08
AMED	0	0	13/06/08
Web of Science (SCI & SSCI)	662	13	13/06/08

Total References retrieved (after de-duplication): 20

Plus 1 additional references picked up from search alerts until 1st July 2008. Final Total: 21

Update of TA109: What is the clinical & cost effectiveness of docetaxel for adjuvant treatment of early breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2005 onwards	307	90	08/01/08
<i>Premedline</i>	Jan 7, 2008	34	6	09/01/08
<i>AMED</i>	2005 onwards	0	0	09/01/08
<i>Embase</i>	2005 onwards	382	78	09/01/08
<i>Cochrane Library</i>	2005 onwards	69	33	09/01/08
<i>Cinahl</i>	2005 onwards	47	13	09/01/08
<i>BNI</i>	2005 onwards	1	0	09/01/08
<i>Psychinfo</i>	2005 onwards	1	0	09/01/08
<i>Web of Science (SCI/SSCI)</i>	2005 onwards	798	83	10/01/08

Total References retrieved (after de-duplication): 129

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 ((breast\$ or mamma\$) adj4 neoplasm\$).tw.
- 3 ((breast\$ or mamma\$) adj4 cancer\$).tw.
- 4 ((breast\$ or mamma\$) adj4 tumor\$).tw.
- 5 ((breast\$ or mamma\$) adj4 tumour\$).tw.
- 6 ((breast\$ or mamma\$) adj4 carcinoma\$).tw.
- 7 ((breast\$ or mamma\$) adj4 oncolog\$).tw.
- 8 ((breast\$ or mamma\$) adj4 malign\$).tw.
- 9 or/1-8
- 10 (docetaxel\$ or taxotere\$).tw.
- 11 9 and 10

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	9	Jan 2008
<i>Premedline</i>	1	Jan 2008
<i>Embase</i>	12	Jan 2008
<i>Cochrane Library (except NHSEED)</i>	0	Jan 2008
<i>NHSEED</i>	5	Jan 2008
<i>NHSEED (no date limit)</i>	19	Jan 2008

Database name	No of references found	Finish date of search
<i>Medline</i>	12 (2 new)	01/07/08
<i>Premedline (June 30, 2008)</i>	3 (2 new)	01/07/08
<i>Embase</i>	20 (6 new)	01/07/08
<i>Cochrane Library (except NHSEED)</i>	0	01/07/08
<i>NHSEED</i>	7 (0 new)	01/07/08

Total References retrieved (after de-duplication): 20

Total References retrieved (after de-duplication): 6

3. Any further comments

Same literature search strategy used as for the original TA report, an exclusions filter only applied to basic search for the clinical review. SIGN Health Economics filter applied to basic search for the health economics review. Both searches executed from 2005 onwards as TA109 included both clinical and cost-effectiveness issues.

4. Update Search

For the update search, an RCT & Systematic Review filter was used, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	79	4	13/06/08
<i>Premedline (June 30, 2008)</i>	17	1	01/07/08
<i>Embase</i>	122	5	13/06/08
<i>Cochrane Library (Issue 2, 2008)</i>	28	2	13/06/08
<i>Cinahl</i>	38	4	13/06/08
<i>BNI</i>	0	0	13/06/08
<i>Psychinfo</i>	1	0	13/06/08
<i>AMED</i>	0	0	13/06/08
<i>Web of Science (SCI & SSCI)</i>	401	17	14/06/08

Total References retrieved (after de-duplication): 22

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 22

Topic 35: What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2003 onwards	937	37	15/06/07
<i>Premedline</i>	2003 onwards	23	3	15/06/07
<i>AMED</i>	2003 onwards	10	1	15/06/07
<i>Embase</i>	2003 onwards	922	39	18/06/07
<i>Cochrane Library</i>	2003 onwards	280	20	18/06/07
<i>Cinahl</i>	2003 onwards	80	10	15/06/07
<i>BNI</i>	2003 onwards	2	0	15/06/07
<i>Psychinfo</i>	2003 onwards	11	1	15/06/07
<i>SIGLE</i>	2003 - 2005	0	0	18/06/07
<i>Web of Science (SCI & SSCI)</i>	2003 onwards	751	78	19/06/07
<i>Biomed Central</i>	2003 onwards	67	4	18/06/07

Total References retrieved (after de-duplication): 118

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Diphosphonates/
- 2 exp Organophosphorus Compounds/
- 3 exp Phosphoric Acids/
- 4 (bisphosphonat\$ or diphosphonat\$).af.
- 5 etidron\$.af.
- 6 didron\$.af.
- 7 difosfen.af.
- 8 osteodidronel.af.
- 9 osteum.af.
- 10 "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
- 11 pamidronate.af.
- 12 APD.af.
- 13 aredia.af.
- 14 "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
- 15 clodronate.af.
- 16 bonefos.af.

17 lora.af.
 18 ascredar.af.
 19 lodronat.af.
 20 lytos.af.
 21 ostac.af.
 22 clastoban.af.
 23 clasteon.af.
 24 difosfonal.af.
 25 ossiten.af.
 26 mebonat.af.
 27 "disodium (dichloromethylene) diphosphonate tetrahydrate".af.
 28 tiludron\$.af.
 29 skelid.af.
 30 "disodium dihydrogen{[(p-chlorophenyl)thio]methylene}diphosphonate hemihydrate".af.
 31 risedron\$.af.
 32 actonel.af.
 33 "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
 34 alendron\$.af.
 35 fosamax.af.
 36 adronat.af.
 37 alendros.af.
 38 dronal.af.
 39 "aminohydroxybutylidene diphosphonic acid".af.
 40 neridron\$.af.
 41 AHDP.af.
 42 "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.
 43 zoledron\$.af.
 44 zometa.af.
 45 ibandron\$.af.
 46 bondronat.af.
 47 "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.
 48 olpadron\$.af.
 49 OPD.af.
 50 "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
 51 incadron.af.
 52 YM175.af.
 53 YM 175.af.
 54 minodron\$.af.
 55 YM529.af.
 56 YM 529.af.
 57 or/1-56
 58 exp Breast Neoplasms/
 59 Carcinoma, Intraductal, Noninfiltrating/
 60 Carcinoma, Lobular/
 61 Carcinoma, Medullary/
 62 or/58-61
 63 exp Breast/
 64 breast.tw.
 65 63 or 64
 66 (breast adj milk).tw.
 67 (breast adj tender\$.tw.
 68 66 or 67
 69 65 not 68
 70 exp Neoplasms/
 71 69 and 70
 72 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 73 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.

74 Paget's Disease, Mammary/
 75 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 76 or/71-75
 77 62 or 76
 78 57 and 77

2. Any further comments

This search constituted an update of two guideline/systematic review documents which were developed at about the same time, in 2004. They were:

1. Cancer Care Ontario Practice Guideline ***Use of Bisphosphonates in Women with Breast Cancer*** (Breast Cancer Disease Site Group) 2003. Last searched for evidence in February 2004.
2. Cochrane Review ***Bisphosphonates for breast cancer (Pavlakis et al)*** 2005. Last searched for evidence in December 2004.

Therefore, this search was undertaken from 2003 onwards. No filters were placed on the results (only a basic exclusions filter), but only trials and good quality reviews were included.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	149	13	09/04/08
<i>Premedline (June 30, 2008)</i>	16	5	01/07/08
<i>Embase</i>	128	16	09/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	59	0	25/04/08
<i>Cinahl</i>	22	2	09/04/08
<i>BNI</i>	0	0	09/04/08
<i>Psychinfo</i>	6	0	09/04/08
<i>AMED</i>	3	0	09/04/08
<i>Web of Science (SCI & SSCI)</i>	269	24	09/04/08

Total References retrieved (after de-duplication): 32

Plus 3 additional references picked up from search alerts until 1st July 2008. Final Total: 35

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 6 – Adjuvant Radiotherapy

Literature search summary

Topic 4: When should patients with DCIS who have undergone complete excision (CE) or WLE be given RT?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	905	193	12/01/07
<i>Premedline</i>	Jan 12, 2007	15	5	12/01/07
<i>AMED</i>	1985 -	0	0	15/01/07
<i>Embase</i>	1980 -	343	91	15/01/07
<i>Cochrane Library</i>	Wiley version	139	43	16/01/07
<i>Cinahl</i>	1982 -	35	10	15/01/07
<i>BNI</i>	1985 -	0	0	15/01/07
<i>Psychinfo</i>	1806 -	1	0	15/01/07
<i>SIGLE</i>	1980 -	5	0	15/01/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	720	193	16/01/07
<i>Biomed Central</i>	As per database	18	2	15/01/07

Total References retrieved (after de-duplication): 307

Plus 2 additional references picked up during guideline development. Final Total: 309

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Carcinoma, Intraductal, Noninfiltrating/
- 2 exp Carcinoma, Ductal, Breast/
- 3 exp Carcinoma, Ductal/
- 4 exp Carcinoma in Situ/
- 5 exp Breast Neoplasms/
- 6 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.
- 7 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 8 carcinoma\$ in situ.mp.
- 9 intraduct\$ carcinoma.mp.
- 10 (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
- 11 (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
- 12 (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
- 13 extensive intraduct\$ component\$.mp.
- 14 exp Breast/
- 15 exp Breast Diseases/
- 16 ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
- 17 (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 18 (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
- 19 or/1-4
- 20 or/5-7
- 21 14 or 15
- 22 8 or 9 or 11 or 13 or 17 or 18
- 23 10 or 12 or 16
- 24 19 or 22

25 20 or 21
 26 24 and 25
 27 23 or 26
 28 ((micro-invas\$ or microinvas\$) adj5 (breast\$ or mammary)).mp.
 29 27 or 28
 30 Tamoxifen/
 31 (Nolvadex or tamoxifen\$).mp.
 32 10540-29-1.rn.
 33 or/30-32
 34 exp Radiotherapy/
 35 (radiotherap\$ or radiation or irradiation).mp.
 36 34 or 35
 37 33 or 36
 38 29 and 37

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	22	15/01/07
<i>Premedline</i>	0	15/01/07
<i>Embase</i>	36	15/01/07
<i>Cochrane Library (except NHSEED)</i>	24	16/01/07
<i>NHSEED</i>	11	16/01/07
<i>Cinahl</i>	2	15/01/07
<i>Psycinfo</i>	0	15/01/07
<i>AMED</i>	0	15/01/07
<i>BNI</i>	0	15/01/07
<i>EconLit</i>	0	15/01/07
<i>Web of Science (SCI & SSCI)</i>	18	16/01/07
<i>SIGLE</i>	0	15/01/07

Total References retrieved (after de-duplication): 98

3. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	89	11	07/04/08
<i>Premedline (June 30, 2008)</i>	5	2	01/07/08
<i>Embase</i>	118	12	07/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	31	2	24/04/08
<i>Cinahl</i>	20	4	07/04/08
<i>BNI</i>	0	0	07/04/08
<i>Psychinfo</i>	2	0	07/04/08
<i>AMED</i>	0	0	07/04/08
<i>Web of Science (SCI & SSCI)</i>	171	37	08/04/08

Total References retrieved (after de-duplication): 39

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 39

Topic 41: What is the most effective RT dose fractionation regimen for patients receiving external beam RT after surgical excision of breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	610	58	29/01/08
<i>Premedline</i>	Jan 28, 2008	52	7	29/01/08
<i>AMED</i>	1985 -	3	0	29/01/08
<i>Embase</i>	1980 -	401	39	20/01/08
<i>Cochrane Library</i>	Issue 1, 2008	333	46	30/01/08
<i>Cinahl</i>	1982 -	22	4	30/01/08
<i>BNI</i>	1985 -	1	1	29/01/08
<i>Psychinfo</i>	1806 -	1	0	29/01/08
<i>SIGLE</i>	1980 - 2005	0	0	31/01/08
<i>Web of Science (SCI & SSCI)</i>	1970 -	882	60	31/01/08
<i>Biomed Central</i>	As per database	117	0	31/01/08
<i>San Antonio Symposium</i>	Dec 2007	1	1	31/01/08
<i>ASCO Annual Meeting</i>	2007	1	1	31/01/08

Total References retrieved (after de-duplication): 137

Plus 3 additional references picked up during guideline development. Final Total: 140

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- 21 exp dose fractionation/
- 22 exp Radiotherapy Dosage/
- 23 exp Radiation Dosage/
- 24 hypofraction\$.mp.
- 25 ((irradiation or radiation or radiotherap\$ or fractionation) adj3 (schedule\$ or regimen\$ or technique\$)).mp.
- 26 (breast adj fractionation).mp.
- 27 Gy.mp.
- 28 fraction\$.mp.
- 29 or/21-28
- 30 20 and 29

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	113	2	22/04/08
<i>Premedline (June 30, 2008)</i>	12	1	01/07/08
<i>Embase</i>	85	3	22/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	36	3	25/04/08
<i>Cinahl</i>	6	0	22/04/08
<i>BNI</i>	0	0	22/04/08
<i>Psychinfo</i>	1	0	22/04/08
<i>AMED</i>	0	0	22/04/08
<i>Web of Science (SCI & SSCI)</i>	92	7	22/04/08

Total References retrieved (after de-duplication): 13

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 13

Topic 23a & 24: What are the indications for RT after breast conserving surgery? Which groups of patients should receive chest wall radiotherapy after mastectomy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1999 onwards	2184	235	11/04/07
<i>Premedline</i>	1999 onwards	52	6	11/04/07
<i>AMED</i>	1999 onwards	70	3	12/04/07
<i>Embase</i>	1999 onwards	2084	107	12/04/07
<i>Cochrane Library</i>	1999 onwards	787	64	10/04/07
<i>Cinahl</i>	1999 onwards	251	28	12/04/07
<i>BNI</i>	1999 onwards	46	0	12/04/07
<i>Psychinfo</i>	1999 onwards	104	1	12/04/07
<i>SIGLE</i>	1999 onwards	9	0	12/04/07
<i>Web of Science (SCI & SSCI)</i>	1999 onwards	1815	162	16/04/07
<i>Biomed Central</i>	1999 onwards	165	5	13/04/07

Total References retrieved (after de-duplication): 403

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9
- 11 (breast adj milk).tw.

12 (breast adj tender\$.tw.
13 11 or 12
14 10 not 13
15 exp Neoplasms/
16 14 and 15
17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
19 Paget's Disease, Mammary/
20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
21 or/17-20
22 7 or 21
23 exp Mastectomy/
24 (mastectom\$ or post?mastectom\$ or post-mastectom\$).mp.
25 (segmentectom\$ or post?segmentectom\$).mp.
26 (lumpectom\$ or post?lumpectom\$).mp.
27 (quadrectom\$ or post?quadrectom\$).mp.
28 (breast conservation or breast?conserv\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
29 or/23-28
30 22 or 29
31 (radiotherap\$ or radiation or irradiation or brachytherap\$).mp.
32 30 and 31

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	285	13/04/07
<i>Premedline</i>	6	13/04/07
<i>Embase</i>	339	13/04/07
<i>Cochrane Library (except NHSEED)</i>	208	17/04/07
<i>NHSEED</i>	60	17/04/07
<i>Cinahl</i>	186	13/04/07
<i>Psycinfo</i>	11	13/04/07
<i>AMED</i>	3	13/04/07
<i>BNI</i>	2	13/04/07
<i>EconLit</i>	0	13/04/07
<i>Web of Science (SCI & SSCI)</i>	115	17/04/07
<i>SIGLE</i>	0	13/04/07

Total References retrieved (after de-duplication): 948

3. Any further comments

Systematic Reviews (2002+) and RCT filters placed on search. Search executed from 1999 onwards as based on Cochrane Review: Radiotherapy for Early Breast Cancer. Health Economics and Quality of Life filters added to the above search, no date limit set as review did not cover cost effectiveness.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	683	61	21/05/08
<i>Premedline (July 1, 2008)</i>	46	3	02/07/08
<i>Embase</i>	638	36	21/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	234	21	20/05/08
<i>Cinahl</i>	84	6	21/05/08
<i>BNI</i>	21	0	20/05/08
<i>AMED</i>	19	0	20/05/08
<i>Psychinfo</i>	48	0	20/05/08
<i>Web of Science (SCI & SSCI)</i>	832	61	22/05/08

Total References retrieved (after de-duplication): 117

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 117

Topic 23b: What are the indications for an external beam RT boost to the site of local excision after breast conserving surgery?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	455	172	14/05/07
<i>Premedline</i>		3	2	14/05/07
<i>AMED</i>	1985 -	3	0	11/05/07
<i>Embase</i>	1980 -	704	91	14/05/07
<i>Cochrane Library</i>	Wiley version	134	41	16/05/07
<i>Cinahl</i>	1982 -	15	1	14/05/07
<i>BNI</i>	1985 -	0	0	11/05/07
<i>Psychinfo</i>	1806 -	0	0	11/05/07
<i>SIGLE</i>	1980 -	0	0	14/05/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	647	159	15/05/07
<i>Biomed Central</i>	As per database	30	0	14/05/07

Total References retrieved (after de-duplication): 267

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9
- 11 (breast adj milk).tw.
- 12 (breast adj tender\$.tw.
- 13 11 or 12
- 14 10 not 13

15 exp Neoplasms/
 16 14 and 15
 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 (boost or boosts).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 24 ((supplementary or additional) adj3 (dose or fraction)).mp.
 25 (local adj (irradiation or radiation or radiotherapy)).mp.
 26 or/23-25
 27 22 and 26

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. Health Economics and Quality of Life search done as one over-riding radiotherapy search for 23a and 24.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	35	3	24/04/08
<i>Premedline (July 1, 2008)</i>	3	0	01/07/08
<i>Embase</i>	94	4	24/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	23	1	24/04/08
<i>Cinahl</i>	17	1	24/04/08
<i>BNI</i>	0	0	24/04/08
<i>AMED</i>	1	0	24/04/08
<i>Psychinfo</i>	1	0	24/04/08
<i>Web of Science (SCI & SSCI)</i>	174	17	24/04/08

Total References retrieved (after de-duplication): 20
 Plus 3 additional references picked up from search alerts until 1st July 2008. Final Total: 23

Topic 25: What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	599	60	23/07/07
<i>Premedline</i>	July 20, 2007	57	5	23/07/07
<i>AMED</i>	1985 -	11	2	24/07/07
<i>Embase</i>	1980 -	689	65	25/07/07
<i>Cochrane Library</i>	Wiley version	386	33	23/07/07
<i>Cinahl</i>	1982 -	20	2	24/07/07
<i>BNI</i>	1985 -	1	0	24/07/07
<i>Psychinfo</i>	1806 -	8	0	24/07/07
<i>SIGLE</i>	1980 -	1	0	24/07/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	716	98	31/07/07

Total References retrieved (after de-duplication): 162

Medline search strategy (*This search strategy is adapted to each database*)

1 exp Breast Neoplasms/
 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
 3 Carcinoma, Intraductal, Noninfiltrating/
 4 Carcinoma, Lobular/
 5 Carcinoma, Medullary/
 6 exp mammary neoplasms/
 7 or/1-6
 8 exp Breast/
 9 breast.tw.
 10 8 or 9
 11 (breast adj milk).tw.
 12 (breast adj tender\$.tw.
 13 11 or 12
 14 10 not 13
 15 exp Neoplasms/
 16 14 and 15
 17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/17-20
 22 7 or 21
 23 exp Mastectomy/
 24 (mastectom\$ or post?mastectom\$ or post-mastectom\$).mp.
 25 (segmentectom\$ or post?segmentectom\$).mp.
 26 (lumpectom\$ or post?lumpectom\$).mp.
 27 (quadrectom\$ or post?quadrectom\$).mp.
 28 (breast conservation or breast?conserv\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 29 or/23-28
 30 22 or 29
 31 (radiotherap\$ or radiation or irradiation or brachytherap\$).mp.
 32 30 and 31
 33 Axilla/
 34 internal mammary.mp.
 35 supraclavicular.mp.
 36 axill\$.mp.
 37 or/33-36
 38 32 and 37

2. Any further comments

Systematic reviews (2002 onwards) and RCT filters applied to basic search for the clinical review. Health Economics and Quality of Life search done as one over-riding radiotherapy search for 23a and 24.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	42	1	02/04/08
<i>Premedline (July 1, 2008)</i>	3	0	02/07/08
<i>Embase</i>	50	1	02/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	17	0	24/04/08
<i>Cinahl</i>	6	1	02/04/08
<i>BNI</i>	0	0	02/04/08
<i>AMED</i>	0	0	02/04/08
<i>Psychinfo</i>	2	0	02/04/08
<i>Web of Science (SCI & SSCI)</i>	61	9	03/04/08

Total References retrieved (after de-duplication): 10

0 additional references picked up from search alerts until 1st July 2008. Final Total: 10

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 7 – Primary Systemic Therapy

Literature search summary

Topic 26: What is the role of primary medical treatment (incl. neoadjuvant) as a means of enabling breast conservation in patients with early, invasive breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 - 2007	4174	158	05/07/07
<i>Premedline</i>	- 2007	16	1	09/07/07
<i>Embase</i>	1980 – 2007	4302	109	09/07/07
<i>Cochrane Library</i>	Wiley version	1200	29	10/07/07
<i>Cinahl</i>	1982 – 2007	189	16	09/07/07
<i>BNI</i>	1985 – 2007	2	0	09/07/07
<i>Psychinfo</i>	1806 - 2007	17	0	09/07/07
<i>SIGLE</i>	1980 - 2005	0	0	10/07/07
<i>Web of Science (SCI & SSCI)</i>	1970 - 2007	1730	128	10/07/07
<i>Biomed Central</i>	As per database	43	2	10/07/07

Total References retrieved (after de-duplication): 289

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
21. (early invasiv\$ adj breast\$).tw.
22. 20 or 21
23. exp Antineoplastic Combined Chemotherapy Protocols/
24. exp Antineoplastic Agents, Hormonal/
25. exp Antineoplastic Agents/
26. cyto\$ chemotherap\$.tw.
27. Chemotherap\$.tw.
28. polychemotherap\$.tw.

29. exp Neoadjuvant Therapy/
30. neoadjuvant chemotherapy.ti,ab,sh,kw.
31. induction\$ chemotherap\$.tw.
32. (primary\$ adj3 chemotherap\$).tw.
33. perioperative\$ chemotherap\$.tw.
34. preoperative\$ chemotherap\$.tw.
35. (hormone adj (therap\$ or treatment\$)).tw.
36. (systemic adj (therap\$ or treatment\$)).tw.
37. (endocrine adj (therap\$ or treatment\$)).tw.
38. (primary adj (therap\$ or treatment\$)).tw.
39. or/23-38
40. exp Recurrence/ or exp Neoplasm Recurrence, Local/
41. recurren\$.tw.
42. relapse\$.tw.
43. (risk\$ adj1 recurren\$).tw.
44. or/40-43
45. 22 and 39
46. 44 and 45
47. breast conserv\$ surg\$.tw.
48. exp Mastectomy, Segmental/
49. exp Lymph Node Excision/
50. exp Breast Neoplasms/su [Surgery]
51. or/47-50
52. 39 and 51
53. 46 or 52

2. Any further comments

Systematic reviews (2002+) and RCT filters applied to basic search for the clinical review.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 6/2008	444	23	01/07/08
<i>Premedline</i>	2007 – 6/2008	33	2	01/07/08
<i>Embase</i>	2007 – 6/2008	690	7	01/07/08
<i>Cochrane Library</i>	2007 – 6/2008	121	1	01/07/08
<i>Cinahl</i>	2007 – 6/2008	65	10	01/07/08
<i>BNI</i>	2007 – 6/2008	1	0	01/07/08
<i>Psychinfo</i>	2007 – 6/2008	2	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 6/2008	245	14	01/07/08
<i>Biomed Central</i>	2007 – 6/2008	22	0	01/07/08

Total References retrieved (after de-duplication): 41

Topic 28: For patients with inflammatory or locally advanced breast cancer who are treated with primary cytotoxic chemotherapy, what is the role of surgery and/or radiotherapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	2065	171	15/05/07
<i>Premedline</i>		89	8	16/05/07
<i>Embase</i>	1980 -	2866	161	16/05/07
<i>Cochrane Library</i>	Issue 2, 2007	108	15	17/05/07
<i>Cinahl</i>	1982 -	79	9	16/05/07
<i>BNI</i>	1985 -	16	0	16/05/07
<i>Psychinfo</i>	1806 -	36	0	16/05/07
<i>SIGLE</i>	1980 - 2005	12	0	17/05/07
<i>Web of Science (SCI & SSCI)</i>	1997 -	2470	181	17/05/07
<i>Biomed Central</i>	1997 -	965	4	18/05/07

Total References retrieved (after de-duplication): 269

Medline search strategy (*This search strategy is adapted to each database*)

- 1 exp Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
21. (inflammatory breast cancer\$ or IBC\$).tw.
22. local\$ advance\$ breast\$ cancer\$.tw.
23. or/21-22
24. 20 or 23
25. exp Antineoplastic Combined Chemotherapy Protocols/
26. exp Antineoplastic Agents, Hormonal/
27. exp Antineoplastic Agents/
28. cytotoxic\$ chemotherap\$.tw.
29. Chemotherap\$.tw.
30. polychemotherap\$.tw.
31. exp Chemotherapy, Adjuvant/
32. exp Neoadjuvant Therapy/
33. adjuvant chemotherap\$.tw.
34. neoadjuvant chemotherap\$.tw.
35. exp Anthracyclines/

36. Anthracycline\$.tw.
 37. exp Taxoids/
 38. taxan\$.tw.
 39. taxoid\$.tw.
 40. induction\$ chemotherap\$.tw.
 41. (primary\$ adj3 chemotherap\$).tw.
 42. perioperative\$ chemotherap\$.tw.
 43. preoperative\$ chemotherap\$.tw.
 44. or/25-43
 45. 24 and 44
 46. exp Radiotherapy, Adjuvant/
 47. adjuvant\$ radiotherap\$.tw.
 48. radiation therap\$.tw.
 49. (breast\$ adj4 (radiation or radiotherap\$)).mp.
 50. exp Brachytherapy/
 51. brachytherap\$.tw.
 52. or/46-51
 53. exp Mastectomy/
 54. mastectom\$.tw.
 55. (breast adj10 excision).mp.
 56. lumpectom\$.tw.
 57. segmentectom\$.tw.
 58. quadrectom\$.tw.
 59. ((breast\$ or mammary) adj4 surg\$).mp.
 60. exp Lymph Node Excision/
 61. or/53-60
 62. 45 and 52
 63. 45 and 61
 64. 62 or 63

2. Any further comments

No filters applied.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 6/2008	536	40	01/07/08
<i>Premedline</i>	2007 – 6/2008	102	10	01/07/08
<i>Embase</i>	2007 – 6/2008	326	9	01/07/08
<i>Cochrane Library</i>	2007 – 6/2008	5	0	01/07/08
<i>Cinahl</i>	2007 – 6/2008	136	8	01/07/08
<i>BNI</i>	2007 – 6/2008	4	0	01/07/08
<i>Psychinfo</i>	2007 – 6/2008	9	0	01/07/08
<i>Web of Science (SCI & SSCI)</i>	2007 – 6/2008	488	26	01/07/08
<i>Biomed Central</i>	2007 – 6/2008	287	0	01/07/08

Total References retrieved (after de-duplication): 62

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 8 – Complications of Local Treatment etc.

Literature search summary

Topic 8: Which strategies are effective in preventing arm lymphoedema in breast cancer patients?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	408	24	24/05/06
<i>Premedline</i>	May 22, 2006 -	7	1	24/05/06
<i>AMED</i>	1985 -	69	11	24/05/06
<i>Embase</i>	1980 -	312	25	24/05/06
<i>Cochrane Library</i>	Wiley version	161	12	24/05/06
<i>Cinahl</i>	1982 -	63	16	24/05/06
<i>BNI</i>	1985 -	44	8	24/05/06
<i>Psychinfo</i>	1806 -	18	4	24/05/06
<i>SIGLE</i>	1980 -	10	0	24/05/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	343	23	24/05/06
<i>Biomed Central</i>	As per database	37	0	24/05/06

Total References retrieved (after de-duplication): 89

Plus 8 additional references picked up during guideline development. Final Total: 97

Medline search strategy (This search strategy is adapted to each database)

- 1 Breast Neoplasms/
- 2 Carcinoma, Intraductal, Noninfiltrating/
- 3 Carcinoma, Lobular/
- 4 Carcinoma, Medullary/
- 5 or/1-4
- 6 exp Breast/
- 7 breast.tw.
- 8 6 or 7
- 9 (breast adj milk).tw.
- 10 (breast adj tender\$.tw.
- 11 9 or 10
- 12 8 not 11
- 13 exp Neoplasms/
- 14 12 and 13
- 15 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 16 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 17 Paget's Disease, Mammary/
- 18 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
- 19 or/14-18
- 20 5 or 19
- 21 exp Mastectomy/
- 22 (mastectom\$ or post?mastectom\$ or post-mastectom\$.mp.
- 23 (segmentectom\$ or post?segmentectom\$.mp.
- 24 (lumpectom\$ or post?lumpectom\$.mp.
- 25 (quadrectom\$ or post?quadrectom\$.mp.
- 26 ((breast\$ or mammary) adj4 surg\$.mp.
- 27 (breast\$ adj4 (radiation or radiotherap\$)).mp.
- 28 or/21-27

29 20 or 28
 30 exp Lymphedema/
 31 lymph?ed\$.mp.
 32 elephantiasis.mp.
 33 (arm\$ adj4 (morbid\$ or swell\$ or swollen or pain\$ or oedema or edema)).mp.
 34 (upper limb\$ adj4 (morbid\$ or swell\$ or swollen or pain\$ or oedema or edema)).mp.
 35 (lymph\$ adj4 (oedema or edema)).mp.
 36 Edema/
 37 (upper limb\$ or arm\$).mp.
 38 36 and 37
 39 or/30-35
 40 38 or 39
 41 29 and 40

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	18	07/06/06
<i>Premedline</i>	3	07/06/06
<i>Embase</i>	53	07/06/06
<i>Cochrane Library (except NHSEED)</i>	30	07/06/06
<i>NHSEED</i>	3	07/06/06
<i>Cinahl</i>	37	07/06/06
<i>Psycinfo</i>	4	07/06/06
<i>AMED</i>	11	07/06/06
<i>BNI</i>	0	07/06/06
<i>EconLit</i>	0	07/06/06
<i>Web of Science (SCI & SSCI)</i>	41	07/06/06
<i>SIGLE</i>	0	07/06/06

Total References retrieved (after de-duplication): 159

3. Any further comments

Systematic reviews (2002+), RCT and Observational filters applied to basic search for the clinical review. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only. Search was executed for both Early and Advanced BC guidelines together.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	56	23	10/04/08
<i>Premedline (June 27, 2008)</i>	3	1	30/06/08
<i>Embase</i>	115	17	10/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	38	14	24/04/08
<i>Cinahl</i>	20	6	10/04/08
<i>BNI</i>	0	0	10/04/08
<i>Psychinfo</i>	10	0	10/04/08
<i>AMED</i>	3	0	10/04/08
<i>Web of Science (SCI & SSCI)</i>	218	35	10/04/08

Total References retrieved (after de-duplication): 50

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 51

Topic 39: What strategies are effective in reducing arm and shoulder mobility problems after

breast cancer surgery?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2005 - 2007	1260	38	08/05/07
Premedline		54	9	09/05/07
Embase	2005 - 2007	758	37	09/05/07
Cochrane Library	Wiley version 2005-2007	492	21	09/05/07
Cinahl	2005 - 2007	61	13	09/05/07
BNI	2005 - 2007	9	3	09/05/07
Psychinfo	2005 - 2007	27	3	09/05/07
SIGLE	2005	0	0	09/05/07
Web of Science	2005 - 2007	252	63	09/05/07
Biomed Central	As per database	526	1	09/05/07

Total References retrieved (after de-duplication): 127

Medline search strategy (*This search strategy is adapted to each database*)

1. Breast Neoplasms/
2. Carcinoma, Intraductal, Noninfiltrating/
3. Carcinoma, Lobular/
4. Carcinoma, Medullary/
5. or/1-4
6. exp Breast/
7. breast.tw.
8. 6 or 7
9. (breast adj milk).tw.
10. (breast adj tender\$.tw.
11. 9 or 10
12. 8 not 11
13. exp Neoplasms/
14. 12 and 13
15. (breast adj3 (neoplas\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
16. (mammary adj3 (neoplas\$ or cancer\$ or tumor?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
17. Paget's Disease, Mammary/
18. (paget\$ and (breast\$ or mammary or nipple\$)).tw.
19. or/14-18
20. 5 or 19
21. exp Breast/su [Surgery]
22. exp Breast Neoplasms/su [Surgery]
23. exp Mastectomy/
24. (post?mastectom\$ or post-mastectom\$ or postmastectom\$ or mastectom\$).tw.
25. (breast adj10 excision).mp.
26. lumpectom\$.tw.
27. (segmentectom\$ or post?segmentectom\$).mp.
28. (lumpectom\$ or post?lumpectom\$).mp.
29. (quadrectom\$ or post?quadrectom\$).mp.
30. ((breast\$ or mammary) adj4 surg\$).mp.
31. (breast\$ adj4 (radiation or radiotherap\$)).mp.
32. exp Lymph Node Excision/
33. axillary clearance\$.tw.
34. axillary radiotherap\$.tw.
35. or/21-34
36. 20 and 35

37. exp Arm/
38. exp Shoulder/
39. arm\$ mobilitt\$.tw.
40. shoulder\$ mobilitt\$.tw.
41. exp "Activities of Daily Living"/
42. exp Axilla/
43. exp "Range of Motion, Articular"/
44. exp Movement/
45. exp Postoperative Complications/
46. (post?operative\$ or postoperative\$ or post-operative\$).tw.
47. (post?surgical\$ or postsurgical\$ or post-surgical\$).tw.
48. exp Exercise/
49. exercise\$.tw.
50. exp Rehabilitation/
51. rehab\$.tw.
52. exp Exercise Therapy/ or exp Physical Therapy Modalities/
53. physiotherap\$.tw.
54. or/37-53
55. 36 and 54

2. Any further comments

Systematic reviews (2002+) and RCT filters applied to basic search for the clinical review.

3. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit 2007-2008 and English language research chosen only.

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	2007 – 6/2008	153	3	01/07/08
<i>Premedline</i>	2007 – 6/2008	71	3	01/07/08
<i>Embase</i>	2007 – 6/2008	102	5	01/07/08
<i>Cochrane Library</i>	2007 – 6/2008	43	1	01/07/08
<i>Cinahl</i>	2007 – 6/2008	24	1	01/07/08
<i>BNI</i>	2007 – 6/2008	4	0	01/07/08
<i>Psychinfo</i>	2007 – 6/2008	5	0	01/07/08
<i>Web of Science</i>	2007 – 6/2008	39	6	01/07/08
<i>Biomed Central</i>	2007 – 6/2008	201	1	01/07/08

Total References retrieved (after de-duplication): 16

Topic 14: In patients with breast cancer suffering menopausal symptoms, what interventions can be used to provide relief for hot flushes?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	204	62	05/03/07
<i>Premedline</i>	March 2, 2007 -	5	4	05/03/07
<i>AMED</i>	1985 -	20	10	05/03/07
<i>Embase</i>	1980 -	432	56	05/03/07
<i>Cochrane Library</i>	Wiley version	217	63	05/03/07
<i>Cinahl</i>	1982 -	29	16	05/03/07
<i>BNI</i>	1985 -	10	7	05/03/07
<i>Psychinfo</i>	1806 -	22	8	05/03/07
<i>SIGLE</i>	1980 -	0	0	05/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	817	116	06/03/07
<i>Biomed Central</i>	As per database	36	1	05/03/07

Total References retrieved (after de-duplication): 182
Plus 1 additional reference picked up during guideline development. Final Total: 183

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Carcinoma, Intraductal, Noninfiltrating/
- 2 exp Carcinoma, Ductal, Breast/
- 3 exp Carcinoma, Ductal/
- 4 exp Carcinoma in Situ/
- 5 exp Breast Neoplasms/
- 6 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.
- 7 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
- 8 carcinoma\$ in situ.mp.
- 9 intraduct\$ carcinoma.mp.
- 10 (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
- 11 (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
- 12 (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
- 13 extensive intraduct\$ component\$.mp.
- 14 exp Breast/
- 15 exp Breast Diseases/
- 16 ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
- 17 (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
- 18 (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
- 19 or/1-4
- 20 or/5-7
- 21 14 or 15
- 22 8 or 9 or 11 or 13 or 17 or 18
- 23 10 or 12 or 16
- 24 19 or 22
- 25 20 or 21
- 26 24 and 25
- 27 23 or 26
- 28 ((micro-invas\$ or microinvas\$) adj5 (breast\$ or mammary)).mp.
- 29 27 or 28
- 30 Breast Neoplasms/

31 Carcinoma, Intraductal, Noninfiltrating/
32 Carcinoma, Lobular/
33 Carcinoma, Medullary/
34 or/30-33
35 exp Breast/
36 breast.tw.
37 35 or 36
38 (breast adj milk).tw.
39 (breast adj tender\$.tw.
40 38 or 39
41 37 not 40
42 exp Neoplasms/
43 41 and 42
44 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
45 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
46 Paget's Disease, Mammary/
47 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
48 or/43-47
49 34 or 48
50 29 or 49
51 Hot Flashes/
52 (hot adj2 (flash\$ or flush\$)).mp.
53 (vasomotor adj4 (symptom\$ or response\$)).mp.
54 (sweat\$ or nightsweat\$ or perspir\$).ti,ab.
55 or/21-24
56 50 and 55

2. Any further comments

Used RCT filter, when required, as on first pre-search it seemed there were a number of strong RCTs on this area. For the update search, the same search criteria/filters were applied as initial search, date limit 2006-2008 and English language research chosen only. See next search as searches were combined.

Topic 14: What treatments are effective and safe for use to treat patients with menopausal symptoms and a) invasive breast cancer or b) DCIS?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	7,806	218	27/03/07
<i>Premedline</i>	March 13, 2007	127	11	14/03/07
<i>AMED</i>	1985 -	167	22	14/03/07
<i>Embase</i>	1980 -	11,137	99	29/03/07
<i>Cochrane Library</i>	Wiley version	1,336	45	20/04/07
<i>Cinahl</i>	1982 -	1,048	89	26/03/07
<i>BNI</i>	1985 -	182	30	14/03/07
<i>Psychinfo</i>	1806 -	833	59	23/03/07
<i>SIGLE</i>	1980 -	3	0	14/03/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	4,153	93	10/04/07
<i>Biomed Central</i>	As per database	215	1	14/03/07

Total References retrieved (after de-duplication): 404

Medline search strategy (This search strategy is adapted to each database)

1 exp Carcinoma, Intraductal, Noninfiltrating/

2 exp Carcinoma, Ductal, Breast/
 3 exp Carcinoma, Ductal/
 4 exp Carcinoma in Situ/
 5 exp Breast Neoplasms/
 6 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 7 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 8 carcinoma\$ in situ.mp.
 9 intraduct\$ carcinoma.mp.
 10 (duct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
 11 (duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ or duct\$ carcinoma\$ in situ or DCIS).mp.
 12 (intraduct\$ carcinoma\$ adj4 (breast\$ or mammary)).ti,ab.
 13 extensive intraduct\$ component\$.mp.
 14 exp Breast/
 15 exp Breast Diseases/
 16 ((duct\$ carcinoma\$ in situ or duct\$ carcinoma\$-in-situ or duct\$ carcinoma\$ in-situ) adj4 (breast\$ or mammary)).mp.
 17 (carcinoma\$ insitu or carcinoma\$-in-situ or carcinoma\$ in-situ or carcinoma\$ in situ).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
 18 (carcinoma\$ adj3 (insitu or in-situ or in situ)).mp.
 19 or/1-4
 20 or/5-7
 21 14 or 15
 22 8 or 9 or 11 or 13 or 17 or 18
 23 10 or 12 or 16
 24 19 or 22
 25 20 or 21
 26 24 and 25
 27 23 or 26
 28 ((micro-invas\$ or microinvas\$) adj5 (breast\$ or mammary)).mp.
 29 27 or 28
 30 Breast Neoplasms/
 31 Carcinoma, Intraductal, Noninfiltrating/
 32 Carcinoma, Lobular/
 33 Carcinoma, Medullary/
 34 or/30-33
 35 exp Breast/
 36 breast.tw.
 37 35 or 36
 38 (breast adj milk).tw.
 39 (breast adj tender\$.tw.
 40 38 or 39
 41 37 not 40
 42 exp Neoplasms/
 43 41 and 42
 44 (breast adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 45 (mammary adj3 (neoplas\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 46 Paget's Disease, Mammary/
 47 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 48 or/43-47
 49 34 or 48
 50 29 or 49
 51 exp Menopause/
 52 Climacteric/
 53 menopaus\$.mp.
 54 (pre?menopaus\$ or pre-menopaus\$ or premenopaus\$).mp.

55 (peri?menopaus\$ or peri-menopaus\$ or perimenopaus\$).mp.
 56 (post?menopaus\$ or post-menopaus\$ or postmenopaus\$).mp.
 57 climact\$.mp.
 58 or/51-57
 59 vaginosis.mp.
 60 (atroph\$ adj2 (vulvovagin\$ or vagin\$)).mp.
 61 (menopaus\$ adj2 (vulvovagin\$ or vagin\$)).mp.
 62 ((vulvovagin\$ or vagin\$) adj2 candidiasis).mp.
 63 ((vulvovagin\$ or vagin\$) adj4 (dry\$ or sore\$)).mp.
 64 or/59-63
 65 exp Depression/
 66 exp Depressive Disorder/
 67 exp Mood Disorders/
 68 exp Affect/
 69 mood\$.mp.
 70 exp Emotions/
 71 depress\$.mp.
 72 (anxi\$ or irritab\$).mp.
 73 or/65-72
 74 Libido/
 75 (decrease\$ adj4 (libido or sex drive)).mp.
 76 (low\$ adj4 (libido or sex drive)).mp.
 77 (sex\$ adj3 (dysfunct\$ or funct\$ or satisf\$ or problem\$ or symptom\$ or arouse\$ or activit\$ or disorder\$)).mp.
 78 exp Sexual Dysfunction, Physiological/
 79 exp Sexual Dysfunctions, Psychological/
 80 exp Sexual Behavior/
 81 or/74-80
 82 exp Neurobehavioral Manifestations/
 83 cognit\$.mp.
 84 exp Delirium, Dementia, Amnesic, Cognitive Disorders/
 85 exp Memory Disorders/
 86 (memory adj3 loss).mp.
 87 forgetful\$.mp.
 88 memor\$.mp.
 89 dement\$.mp.
 90 amnes\$.mp.
 91 or/82-90
 92 exp Sleep Disorders/
 93 exp Sleep/
 94 (sleep\$ or slept\$).mp.
 95 insomn\$.mp.
 96 "Sleep Initiation and Maintenance Disorders"/
 97 or/92-96
 98 exp Urination Disorders/
 99 incontinen\$.mp.
 100 (urinatt\$ adj3 (frequen\$ or pain\$ or increas\$)).mp.
 101 or/98-100
 102 exp Nutrition Therapy/ or exp Diet Therapy/
 103 diet\$.mp.
 104 (weight adj3 reduct\$).mp.
 105 Weight Loss/
 106 or/102-105
 107 50 and (58 or 64 or 73 or 81 or 91 or 97 or 101)
 108 50 and 58 and 106
 109 107 or 108

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review. Not animal or laboratory studies, only clinical studies chosen.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1025	28	03/04/08
<i>Premedline (July 1, 2008)</i>	128	4	02/07/08
<i>Embase</i>	1289	15	03/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	378	13	24/04/08
<i>Cinahl</i>	161	7	03/04/08
<i>BNI</i>	1	0	03/04/08
<i>AMED</i>	8	2	03/04/08
<i>Psychinfo</i>	397	3	03/04/08
<i>Web of Science (SCI & SSCI)</i>	982	60	03/04/08

Total References retrieved (after de-duplication): 80

Plus 2 additional references picked up from search alerts until 1st July 2008. Final Total: 82

Topic 37: What are the effective strategies to a. prevent and b. manage psychological distress in patients with early stage breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1080	190	26/06/07
<i>Premedline</i>	June 25, 2007	70	3	26/06/07
<i>AMED</i>	1985 -	104	18	27/06/07
<i>Embase</i>	1980 -	1067	125	02/07/07
<i>Cochrane Library</i>	Issue 2, 2007	369	161	27/06/07
<i>Cinahl</i>	1982 -	278	78	28/06/07
<i>BNI</i>	1985 -	56	9	26/06/07
<i>Psychinfo</i>	1806 -	411	77	28/06/07
<i>SIGLE</i>	1980 - 2005	22	3	27/06/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1044	246	04/07/07
<i>Biomed Central</i>	1997 -	29	1	27/06/07

Total References retrieved (after de-duplication): 505

Medline search strategy (This search strategy is adapted to each database)

- 1 exp Breast Neoplasms/
- 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/
- 3 Carcinoma, Intraductal, Noninfiltrating/
- 4 Carcinoma, Lobular/
- 5 Carcinoma, Medullary/
- 6 exp mammary neoplasms/
- 7 or/1-6
- 8 exp Breast/
- 9 breast.tw.
- 10 8 or 9
- 11 (breast adj milk).tw.
- 12 (breast adj tender\$.tw.
- 13 11 or 12
- 14 10 not 13
- 15 exp Neoplasms/
- 16 14 and 15

17 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 18 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumor\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or dcis or duct\$ or infiltrat\$ or intraduct\$ or lobul\$ or medullary or tubular)).mp.
 19 Paget's Disease, Mammary/
 20 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 21 or/16-20
 22 7 or 21
 23 "Anxiety"/
 24 "Anxiety Disorders"/
 25 Depression/
 26 Depressive Disorder/
 27 Affective Symptoms/
 28 Stress Disorders, Post-Traumatic/ or Stress, Psychological/
 29 Adaptation, Psychological/
 30 Psychology/
 31 Social Support/
 32 (psychological adj distress).mp.
 33 or/23-32
 34 22 and 33

2. Any further comments

Systematic reviews (2002+), RCT's and Observational filters applied to basic search for the clinical review.

3. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2007-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	100	28	14/04/08
<i>Premedline (June 30, 2008)</i>	4	0	01/07/08
<i>Embase</i>	171	16	14/04/08
<i>Cochrane Library (Issue 2, 2008)</i>	62	19	25/04/08
<i>Cinahl</i>	78	20	14/04/08
<i>BNI</i>	18	2	14/04/08
<i>Psychinfo</i>	66	7	14/04/08
<i>AMED</i>	25	2	14/04/08
<i>Web of Science (SCI & SSCI)</i>	198	29	14/04/08

Total References retrieved (after de-duplication): 53

Plus 1 additional reference picked up from search alerts until 1st July 2008. Final Total: 54

NATIONAL COLLABORATING CENTRE FOR CANCER

Early Breast Cancer Clinical Guideline

Chapter 9 – Follow-Up

Literature search summary

Topic 16a&b: What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1074	217	19/10/06
<i>Premedline</i>	Oct 18, 2006	9	1	19/10/06
<i>AMED</i>	1985 -	8	0	19/10/06
<i>Embase</i>	1980 -	530	72	19/10/06
<i>Cochrane Library</i>	Issue 4, 2006	404	23	18/10/06
<i>Cinahl</i>	1982 -	49	13	19/10/06
<i>BNI</i>	1985 -	0	0	19/10/06
<i>Psychinfo</i>	1806 -	8	2	19/10/06
<i>SIGLE</i>	1980 – 2005	1	1	19/10/06
<i>Web of Science (SCI & SSCI)</i>	1970 -	1591	172	20/10/06
<i>Biomed Central</i>	1997 -	97	5	19/10/06

Total References retrieved (after de-duplication): 346

Plus 3 additional references picked up during guideline development. Final Total: 349

Medline search strategy (This search strategy is adapted to each database)

- 1 Diagnostic Imaging/
- 2 exp Mammography/
- 3 mammograph\$.mp.
- 4 (breast adj3 radiograph\$).mp.
- 5 exp Ultrasonography/
- 6 (ultrasound\$ or ultrasonograph\$ or sonogra\$ or ultrasonic or echogra\$ or echotomogra\$).mp.
- 7 exp Radionuclide Imaging/
- 8 (radionuclide adj1 (scan\$ or imaging)).tw.
- 9 (mammoscintigraph\$ or scintigraph\$).mp.
- 10 exp Magnetic Resonance Imaging/
- 11 magnet\$ resonance.mp.
- 12 (MRI or MRI\$1 or NMR\$1).tw.
- 13 (MR adj (imag\$ or scan\$)).tw.
- 14 (magnet\$ adj (imag\$ or scan\$)).tw.
- 15 (magneti?ation adj3 imaging).tw.
- 16 exp Tomography/
- 17 exp Tomography, X-Ray Computed/
- 18 PET\$1.tw.
- 19 (PET adj (scan\$ or imag\$)).tw.
- 20 ((CT or CAT) adj (scan\$ or imaging)).tw.
- 21 (comput\$ adj1 tomogra\$).tw.
- 22 zeugmatogra\$.tw.
- 23 ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope) adj2 (scan\$ or imag\$ or tomogra\$)).tw.
- 24 or/1-23
- 25 Breast Neoplasms/
- 26 Carcinoma, Intraductal, Noninfiltrating/
- 27 Carcinoma, Lobular/
- 28 Carcinoma, Medullary/

29 or/25-28
 30 exp Breast/
 31 breast.tw.
 32 30 or 31
 33 (breast adj milk).tw.
 34 (breast adj tender\$.tw.
 35 33 or 34
 36 32 not 35
 37 exp Neoplasms/
 38 36 and 37
 39 (breast adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 40 (mammary adj3 (neoplas\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or leiomyosarcoma\$ or malignanc\$ or dcis or duct\$ or infiltrating or intraduct\$ or lobul\$ or medullary or tubular)).tw.
 41 Paget's Disease, Mammary/
 42 (paget\$ and (breast\$ or mammary or nipple\$)).tw.
 43 or/38-42
 44 29 or 43
 45 exp Breast Neoplasms/
 46 44 or 45
 47 24 and 46
 48 Aftercare/
 49 aftercare.tw.
 50 after-care.tw.
 51 followup.tw.
 52 follow-up.tw.
 53 ((post-treatment or posttreatment) adj1 surveillance).tw.
 54 ((post-treatment or posttreatment) adj1 evaluation\$.tw.
 55 ((post-treatment or posttreatment) adj1 care).tw.
 56 ((post-treatment or posttreatment) adj1 monitoring).tw.
 57 or/48-56
 58 47 and 57

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	127	19/10/06
<i>Premedline</i>	3	19/10/06
<i>Embase</i>	202	19/10/06
<i>Cochrane Library (except NHSEED)</i>	114	19/10/06
<i>NHSEED</i>	80	19/10/06
<i>Cinahl</i>	17	19/10/06
<i>Psycinfo</i>	6	19/10/06
<i>AMED</i>	1	19/10/06
<i>BNI</i>	0	19/10/06
<i>EconLit</i>	0	19/10/06
<i>Web of Science</i>	138	19/10/06
<i>SIGLE</i>	0	19/10/06

Total References retrieved (after de-duplication): 346

3. Any further comments

Systematic Review (2002+), RCT, Observational and Prognosis filters applied to basic search for the clinical review. SIGN Health Economics filter and SCHARR Quality of Life filter applied to basic search for health economics review.

4. Update Search

For the update search, only the RCT & Systematic Review filter was used in light of the evidence required for the initial evidence review for this topic, date limit 2006-2008 and English language research chosen only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	343	21	21/05/08
<i>Premedline (June 30, 2008)</i>	54	1	01/07/08
<i>Embase</i>	329	18	21/05/08
<i>Cochrane Library (Issue 2, 2008)</i>	99	3	21/05/08
<i>Cinahl</i>	53	3	21/05/08
<i>BNI</i>	5	0	21/05/08
<i>AMED</i>	2	0	21/05/08
<i>Psychinfo</i>	6	0	21/05/08
<i>Web of Science (SCI & SSCI)</i>	452	22	21/05/08

Total References retrieved (after de-duplication): 30

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 30

Topic 17: Follow-up of Breast Cancer Patients

- WHETHER to follow-up patients treated for early breast cancer i.e. Does follow-up benefit patients? Is there an optimum frequency of follow-up?
- WHERE to perform follow-up i.e. is a hospital-based model, primary-care based model or another model (e.g. integrated) of provision superior to alternatives?
- WHO should perform follow-up? Consider: different medical specialties, allied health professionals, patients.
- What should be the AIMS of follow-up? Consider: detection of recurrence, manage ongoing medication, monitor long-term side effects e.g. menopausal changes, bone loss

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	1966 -	1169	196	10/05/07
<i>Premedline</i>	May 09, 2007	19	9	10/05/07
<i>Embase</i>	1980 -	788	157	10/05/07
<i>Cochrane Library</i>	Issue 2, 2007	174	44	10/05/07
<i>Cinahl</i>	1982 -	143	34	10/05/07
<i>BNI</i>	1985 -	12	5	10/05/07
<i>Psychinfo</i>	1806 -	36	5	10/05/07
<i>AMED</i>	1985 -	18	2	10/05/07
<i>SIGLE</i>	1980 - 2005	3	2	10/05/07
<i>Web of Science (SCI & SSCI)</i>	1970 -	1304	191	11/05/07
<i>Biomed Central</i>	1997 -	10	4	10/05/07

Total References retrieved (after de-duplication): 339

Plus 5 additional references picked up during guideline development. Final Total: 344

Medline search strategy (This search strategy is adapted to each database)

- 1 *Breast Neoplasms/
- 2 exp Aftercare/
- 3 1 and 2
- 4 breast cancer.m_titl.
- 5 (aftercare or after-care or followup or follow-up or surveillance).m_titl.
- 6 ((post-treatment or posttreatment) adj1 evaluation\$.m_titl.
- 7 ((post-treatment or posttreatment) adj1 care).m_titl.
- 8 ((post-treatment or posttreatment) adj1 monitoring).m_titl.
- 9 or/5-8

10 4 and 9
 11 1 and 9
 12 10 or 11
 13 3 or 12

2. Health Economics Literature search details

Database name	No of references found	Finish date of search
<i>Medline</i>	68	10/05/07
<i>Premedline</i>	2	10/05/07
<i>Embase</i>	91	10/05/07
<i>Cochrane Library (except NHSEED)</i>	19	16/05/07
<i>NHSEED</i>	14	16/05/07
<i>Cinahl</i>	53	10/05/07
<i>BNI</i>	0	10/05/07
<i>Psychinfo</i>	1	10/05/07
<i>AMED</i>	1	10/05/07
<i>EconLit</i>	0	10/05/07
<i>Web of Science (SCI & SSCI)</i>	52	10/05/07
<i>SIGLE</i>	0	10/05/07

Total References retrieved (after de-duplication): 209

3. Any further comments

Just a general exclusions filter applied to basic search for the clinical review as such a basic focused search used. SIGN Health Economics filter & SCHARR Quality of Life filter applied to basic search for the health economics review.

4. Update Search

For the update search, the reviewer required only RCT's and so the search was re-executed using a RCT filter, date limit 2007-2008 and English language only.

Database name	No of references found	No of references retrieved	Finish date of search
<i>Medline</i>	85	15	10/04/08
<i>Premedline (June 30, 2008)</i>	27	5	01/07/08
<i>Embase</i>	78	14	11/04/08
<i>Cochrane Library</i>	12	1	24/04/08
<i>Cinahl</i>	28	6	11/04/08
<i>BNI</i>	2	1	11/04/08
<i>Psychinfo</i>	4	1	11/04/08
<i>AMED</i>	3	0	11/04/08
<i>Web of Science (SCI & SSCI)</i>	215	24	11/04/08

Total References retrieved (after de-duplication): 28

Plus 0 additional references picked up from search alerts until 1st July 2008. Final Total: 28

APPENDIX B - Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 8.1.3.1 of the Guidelines Manual (2006).

Guideline

Title of guideline: Breast cancer (early): diagnosis and treatment

Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on 3rd September 2007 by the following people ^w:

For the NCC and GDG:

NCC economist: Raquel Aguiar-Ibáñez

NCC representative(s) ^x: Andrew Champion

Victoria Titshall

Angela Bennett

GDG representative(s) ^y: Jim Smallwood (GDG Chair)

Adrian Harnett (GDG Lead Clinician)

For NICE:

CCP lead ^z: Tim Stokes

Commissioning manager: Nicole Elliott

Economic lead ^{aa}: Francis Ruiz

Costing lead: Mark Minchin

Proposals for any substantive changes will be circulated by email to this group. If revisions are agreed, they will be listed as addenda to this document (section 5 below).

^w This may be done by face-to-face meeting, teleconference, or email as convenient.

^x May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

^y May be GDG chair, clinical lead and/or other members as appropriate.

^z CCP Director or Associate Director who is taking the lead for the guideline.

^{aa} One of the CCP health economic Technical Advisors.

Proposed economic plan

Complete one row for each clinical question in the guideline:

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?</i> ^{bb}	<i>Comment and explanation</i>
<p>Topic 1:</p> <p>1 What is the optimal time interval from completion of definitive surgery to commencement of adjuvant therapy?</p>	<p>5. Low priority for a</p>	<p>The number of patients involved within this topic is large since it would affect all early breast cancer patients undergoing surgery.</p> <p>There may be some improvement in terms of longer survival and lower relapse rates for patients with earlier starting of adjuvant therapy after surgery (Colleoni et al 2000; Lorisich et al 2006; Mikeljevic t al 2004). However, evidence is not conclusive (Cold et al 2005; Froud et al 2000; Nixon et al 1994; Shannon et al 2000; Vujovic et al 2006). Moreover, there is no real consensus regarding the definition of delay.</p> <p>Costs of adjuvant therapy are not likely to change. However, if delayed treatment effectively has an impact on relapse, there may be some long-term costs of treating those patients that relapse due to delay treatment.</p>

^{bb}

- 1 'Not relevant': questions where economic analysis is not appropriate (e.g. about definitions, prognosis or information needs for patient);
- 2 'In literature': questions where high-quality, recent and relevant economic evaluations are already available;
- 3 'High priority for analysis': questions where an economic analysis is planned (important implications and analysis is thought to be feasible);
- 4 'Medium priority for analysis' questions where an economic analysis may be done (less important implications or questions over feasibility);
- 5 'Low priority for analysis': questions where economic analysis could be done, but the expected impact on outcomes and NHS resources is low.

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>Therefore, there is uncertainty for both health benefits and cost implications. If treatment delay does not cause an impact on health, the topic will not have implications in terms of health economics and therefore an economic analysis will not be required. However, if there is conclusive evidence that time of starting treatment will have an impact on health outcomes, there may be some cost implications and a further analysis may help assess the cost-effectiveness of early start of adjuvant therapy.</p>
<p>Topic 2:</p> <p>What is the optimal tumour-free tissue margin to achieve in patients who undergo wide local excision (WLE) for ductal carcinoma in situ (DCIS)?</p> <p>2</p>	<p>5. Low priority for a</p>	<p>DCIS patients represent a small proportion over the total number of patients with breast cancer (approximately 20% of all breast cancers diagnosed through mammography; Erbas et al 2006).</p> <p>If clear (tumour-free) margins in excised tissue are not obtained, even after surgical revision of the original excision, mastectomy may be required. Additionally, the risk of local recurrence increases if positive margins are found after lumpectomy and breast irradiation; this applies also to patients with DCIS (Scarath et al 2002). If margins remain positive after excision, the tumour-involved margins should be either re-excised or mastectomy should be undertaken.</p> <p>There is a lack of evidence regarding how expensive it would be to identify and achieve optimal margins of</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?</i> ^{bb}	<i>Comment and explanation</i>
		<p>excision. However, there may be a reduction in additional re-excisions and mastectomies as a consequence of correctly identifying excision margins. The cost implications are expected to be a balance of additional breast surgery (for those with “inadequate” margins) versus a reduction in risk of local recurrence. It is unlikely that the optimum margin for excision will be identified from the available evidence. Therefore, it may not be possible to conduct an economic analysis under these circumstances. The total impact on costs is not expected to be high due to the low number of patients affected.</p>
<p>3</p> <p>Topic 4: When should patients with DCIS who have undergone complete excision (CE) or WLE be given RT?</p>	<p>5. Low priority for a</p>	<p>Approximately 20% of the tumours diagnosed through mammographic screening programmes are DCIS (Erbas et al 2006). RT after breast conserving surgery may decrease recurrence and increase quality of life, although the impact on survival seems negligible (Suh et al 2005). The purpose of the question here posed is to identify if there is a group of patients that may benefit from RT after having undergone either CE or WLE.</p> <p>RT is an expensive intervention, although its costs may be compensated by the savings in salvage therapy related to the reduced risk of recurrence. In some low-risk patients, these costs may not outweigh the benefits (Silverstein 2003).</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>There is uncertainty regarding the final impact of RT since effectiveness and cost-effectiveness evidence are limited. A further economic evaluation may decrease the uncertainty related to the topic and may help assessing the cost-effectiveness implications of the topic within the guidelines. However, given the lower number of patients involved and the likelihood that problems in conducting the economic evaluation will arise due to lack of data, the topic seems to be a medium/low priority in terms of further economic analysis.</p>
<p>4</p> <p>Topic 5: Is there an indication for the use of tamoxifen after excision of pure DCIS?</p>	<p>5. Low priority for a</p>	<p>Tamoxifen may reduce local recurrence and the number of breast cancer events in patients with DCIS, although an improvement in survival has not been observed, while patients may experience relevant adverse effects (Fisher et al 1998: Fisher et al 1999).</p> <p>Tamoxifen is not expensive treatment, and the overall relevance of this topic, in terms of the number of patients affected, is low (since DCIS patients represent a relatively low percentage of breast cancer patients and, moreover, it is not clear for how many of them the treatment would be indicated, reducing therefore the overall relevance even further).</p> <p>Given the lack of conclusive evidence regarding the</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		beneficial use of tamoxifen on DCIS patients' health and the unlikely relevant impact on costs, further analysis could only be relevant if tamoxifen is found to be beneficial for DCIS patients, or for a subgroup of them. Moreover, the number of patients that would be affected for any recommendation related to this topic would be low. Therefore, the topic is considered to be a low priority for further economic analysis.
<p>Topic 6:</p> <p>6.a. In patients with invasive breast cancer when is SLNB justified as a staging procedure?</p> <p>6.b. In patients with DCIS when is SLNB justified as a staging procedure?</p> <p>5</p>	2. In literature	<p>The routine use of axillary lymph node dissection (ALND) does not benefit about 70% of patients (i.e. those with negative nodes) and it is an expensive procedure (Bombardieri et al 1998). The use of sentinel lymph node biopsy (SLNB) can reduce costs and morbidity (e.g. hospitalisations and lymphoedema) by avoiding ALND in early breast cancer patients with negative nodes, and by conducting selective ALND on those with positive nodes (Bembenek et al 2001; Borgstein et al 1998).</p> <p>Evidence regarding this topic seems to be promising but limited as to support recommendations regarding the use of SLNB alone (McCready et al 2005). However, some economic analyses considering SLNB appear to be available (Brancato et al 2004; Burak et al 2002; Fortunato et al 2004; Gemignani et al 2000; Perrier et al 2004; Roka et al 2004), which could be useful to assess the cost-effectiveness of SLNB</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>without the need to conduct further economic analyses. It should be taken into account that these analyses may not be representative of the UK clinical setting. In such a case, a further economic analysis would be required to estimate the cost-effectiveness of SLNB within the UK setting, and therefore the topic would become a high priority in terms of requiring further economic analysis.</p>
<p>6</p> <p>Topic 7:</p> <p>What is the role of pre-treatment ultrasound (US) assessment in staging the axilla?</p>	<p>3. High priority for :</p>	<p>Staging of the ipsilateral axilla is crucial to decide what local and systematic treatments are required for patients with early invasive breast cancer. Relevant information for staging can be obtained through alternative methods, such as axillary dissection, which was traditionally used although it is currently associated with increased morbidity (Damera et al 2003). There are less invasive methods for the preoperative assessment of the axilla, such as SLNB and axillary node sampling. In addition, other non-surgical techniques have been used, such as US, which may or may not be combined with Fine Needle Aspiration Cytology (FNAC) or core biopsy.</p> <p>Pre-treatment US may help offering definitive surgery for patients with lymph node metastatic disease and avoid having inappropriate surgical procedures (Brancato et al 2004), although the number of false</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
		<p>positives and false negatives with this procedure is high, and therefore further tests may be required, with the consequent implications on resource utilisation and additional costs.</p> <p>A positive recommendation regarding the use of pre-treatment US in the staging of the axila could affect all patients with early invasive breast cancer, therefore the impact in terms of the number of patients affected would be high.</p> <p>The financial consequences are considerably relevant (in terms of future savings in procedures avoided). The impact on health benefits and long-term prognosis for patients with and without US of the axila may be less relevant if the use of US does not have an impact in survival/quality of life in the long term.</p> <p>Therefore, the relevance of the topic in terms of further economic analysis seems high.</p>
<p>7 Topic 8: In patients with breast cancer which strategies are effective in preventing arm lymphoedema?</p>	<p>5. Low priority for a</p>	<p>Around 12% of women undergoing breast surgery and lymph node dissection will develop lymphodema (Forchuk, Baruth et al. 2004). In UK, one in four breast cancer patients is affected by lymphodema (Morgan, Franks et al. 2005).</p> <p>Different strategies are available that can be used with the aim of preventing lymphoedema, such as:</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?</i> ^{bb}	<i>Comment and explanation</i>
		<p>education, exercise, compression garments, skin care, simple lymph drainage massage, advice on interventions to avoid (for example, venepuncture), pharmaceuticals (e.g. diuretics), physiotherapy and psychological support.</p> <p>Literature regarding the effectiveness of interventions used to prevent lymphodema is scarce (Forchuk, Baruth et al. 2004). The systematic review of the clinical evidence for this topic found some benefit derived from preventing lymphoedema by means of generalised or aerobic exercise, although this was not consistent all across the studies, which showed high degree of heterogeneity. Additionally, no consistent evidence was found related to the benefit obtained by exercise/physiotherapy to the shoulder/arm. No economic evaluations have been found from the economic search that have considered this topic.</p> <p>The annual costs related to lymphoedema treatment are relevant. Although an estimation for the annual cost per patient treated for lymphoedema was not found for a UK setting, a study (Le et al 1993) found that the annual cost per patient in France was FF 1,655 (or approximately £1,500 as for 2006 prices). A study conducted in Spain (Gonzalez-Viejo et al 2001) found that the average annual number of sessions of manual lymphatic drainage per breast cancer patient</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>with lymphoedema following mastectomy was 28 (range: 15-50), being the health care costs associated to these sessions equal to an equivalent of £712 (range: £316, £984 for 2006 prices). Approximately between 35,000 and 37,000 new cases of breast cancer are diagnosed every year (data from 2003, www.cancerhelp.org.uk; and considering that between 80 and 85% of all breast cancer patients diagnosed are EBC; National Horizon Scanning Centre 2006). Assuming that 25% of those will experience lymphoedema (Morgan, Franks et al. 2005), i.e. between 8,800 and 9,200 patients) there is scope for improvement of the allocation of health care resources if effective treatments are available to prevent lymphoedema. However, the costs of prevention should be compared with the benefits achieved to see if lymphoedema prevention is a cost-effective intervention.</p> <p>Although there are important financial implications (in terms of the annual cost per patient treated for lymphoedema), the topic has been identified as a low priority given the relatively low number of patients affected, when compared to other topics, and the lack of consistent evidence showing that prevention of lymphoedema is an effective intervention.</p>
8 Topic 9:	5. Low priority for a	Oestrogen receptor alpha (ER) is a powerful predictor

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
<p>Does progesterone receptor (PR) status add further, useful information to that of oestrogen receptor (ER) status in patients with invasive breast cancer?</p>		<p>of tumour response to therapy. ER(+) is associated with good results using hormone therapy alone, with approximately 80% of invasive early breast cancer patients being ER(+). However, ER assessment may lack accuracy and some patients with ER(+) will not respond to hormone therapy.</p> <p>PR may add relevant information regarding prediction of tumour response to treatment when deciding the type of treatment a patient with invasive early breast cancer should receive.</p> <p>The cost per PR test is approximately between £20 and £60 (Personal Communication), although there may be potential savings by conducting the test if more accurate treatment is given as first line. Testing for ER and PR simultaneously will be cheaper and quicker than doing the tests sequentially. Since approximately 60-70% of patients are ER(+), it may be cost-effective to test all the patients (although this hypothesis should be tested).</p> <p>However, recent evidence concluded that testing for PR status added limited relevant information in any comparison and, consequently, PR should only be used as a research tool at present (Petto et al 2007, personal communication).</p> <p>There is uncertainty regarding the final impact in terms of both health benefits and costs, and recent evidence</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		highlights the difficulties of conducting an economic analysis on the topic. Therefore, at the moment, due to lack of appropriate data, this topic is a low priority in terms of further economic analysis since an economic evaluation will not be possible to be performed.
<p>Topic 11:</p> <p>What is the prognostic significance of small metastatic deposits in sentinel nodes?</p> <p>9</p>	5. Low priority for a	<p>Initially, it seems that recommendations regarding this topic will not change clinical practice considerably, although it may add more laboratory work time, additional tests (i.e. immunohistochemistry) and some additional treatment and surgery if micro-metastasis are found to be of prognostic relevance.</p> <p>There is not conclusive information about these issues and it is not clear whether the development of an economic model would solve this uncertainty since there may not be sufficient clinical data to conduct the analysis. Therefore, this topic has been considered low priority for further economic analysis.</p>
<p>Topic 12:</p> <p>a) What is the role of breast MRI in the preoperative staging of patients with biopsy proven invasive breast cancer?</p> <p>10</p> <p>b) What is the role of breast MRI in pre-operative staging of patients with DCIS?</p>	5. Low priority for a	After breast conservation, 60% of patients will require re-excision, with some of them requiring several surgeries before mastectomy (Esserman et al 1999). The use of MRI as a staging tool before surgery may reduce multiple re-excisions and anxiety for the patient. This may have a financial impact on the total costs, derived from the lower number of repeated surgeries required once an appropriate intervention has been identified and conducted.

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>Women with stage I or II breast cancer have been shown to have similar survival independently of whether mastectomy or breast conservation is undergone (Esserman 1999). However, in terms of quality of life, a reduction in the number of surgeries undergone may reduce the anxiety for the patient and therefore may influence the gain in QALYs. MRI may be specifically useful for patients with mammographically dense breasts.</p> <p>Given the potential savings that MRI may produce, it may be relevant to conduct a modelling exercise to assess the cost-effectiveness of this intervention in a UK setting. However, there is limited evidence that would make it difficult to conduct such analysis which has led to identify the topic as low priority.</p>
<p>Topic 14:</p> <p>14.a. What treatments are effective and safe for use to treat patients with menopausal symptoms and invasive breast cancer</p> <p>1</p> <p>14.b. What treatments are effective and safe for use to treat patients with menopausal symptoms and DCIS ?</p>	<p>5. Low priority for a</p>	<p>Up to 40% of women experience menopausal symptoms because of breast cancer or its treatments (http://www.plwc.org/portal/site/PLWC). Some treatments seem to improve menopausal symptoms such as hot flushes (Nelson et al 2005). However, management of menopausal symptoms does not seem to have any impact on survival.</p> <p>There are differences in costs in terms of the different hormone treatments for the management of</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>menopausal symptoms (with the monthly cost ranging from between £3.71 and £8.66 for generic estradiol to between £29.70 and £55.07 for prometrium-progesterone; 2005 UK prices, adjusted from http://www.crbestbuydrugs.org/PDFs/HormonesFINAL.pdf using OECD Purchasing Power Parities: http://www.oecd.org/dataoecd/61/56/1876133.xls).</p> <p>Therefore, it is likely that there will be cost differences when broader interventions are compared (e.g. group therapy, antidepressants or psychological support).</p> <p>No economic evidence in the form of an economic evaluation seems to be available in relation to this topic. If one or several treatments/strategies are shown to be effective for the management of menopausal symptoms, an economic analysis could help identify which is the most cost-effective intervention. However, limitations are likely to be found when conducting the economic analysis due to lack of data on clinical effectiveness. Therefore, the topic is considered to be medium/low priority in terms of the requirements for further economic analysis.</p>
<p>Topic 16:</p> <p>1 2 16.a. What is the role of breast imaging modalities in the follow-up of patients with invasive breast cancer?</p>	<p>4. Medium priority 1</p>	<p>For an imaging test to be effective and cost-effective in the follow-up of patients with either invasive breast cancer or DCIS, the detection of early recurrence and consequent therapy should lead to an improvement in survival and quality of life at a reasonable/acceptable</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
16.b. What is the role of breast imaging modalities in the follow-up of patients with DCIS?		<p>cost. Some studies have shown that most recurrences are not asymptomatic and can be detected by history and physical examination, and moreover, the impact on survival is unknown (Khandekar et al 1996). These facts would undermine the usefulness of imaging techniques to follow up breast cancer patients. For the subgroup of patients undergoing breast conserving surgery followed by RT the number of false positives with mammography are considerably high. Moreover, mammography seems to be of little use for ipsilateral local recurrence since its sensitivity and specificity are low.</p> <p>Routine long-term follow up was already recognised not to be necessary when the previous NICE Guidance on Breast Cancer Services were developed (i.e. Improving Outcomes in Breast Cancer. Manual Update 2002; http://guidance.nice.org.uk/csgbc/guidance/pdf/English); however, this is still an ongoing practice. Due to lack of evidence about the benefits for patients derived from follow-up with imaging techniques, this topic has been categorised as a medium priority for further economic evaluation. A cost analysis could be useful to highlight the savings that could be achieved by avoiding this ineffective practice.</p>
1 Topic 17:	5. Low priority for a	The purpose of following up women with breast cancer

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
<p>3 What is the best setting for clinical follow up of patients treated for breast cancer?</p>		<p>after they have received primary treatment is to identify any recurrence or contralateral new primary breast cancer as soon as possible, since it is believed that earlier identification will increase the likelihood of keeping the disease under control. However, the use of different settings/schedules for the follow-up of patients with breast cancer does not seem to have a relevant impact on the identification of recurrences or contralateral new primary breast cancer (Rojas et al 2000; Grunfeld et al 2006), while it seems to have disadvantages, such as increase in the anxiety for patients when being followed up (Grunfeld et al 1996; Grunfeld et al 1999). Furthermore, follow-up does not seem to have an impact on post-operative survival (Grogan, Rangan et al. 2002; Rojas et al 2000). However, it is believed that the health benefits could be higher than stated (as derived from GDG member's opinion).</p> <p>There are some financial implications related to the follow-up setting chosen, although the literature available is not conclusive. According to some studies, primary care-based follow-up or less intensive follow-up is less expensive than hospital-based follow-up (Grunfeld et al 1999) or more intensive follow-up (Mapelli et al 1995). However, following discussion with the GDG members, studies seem to be available showing the opposite results (i.e. primary care-based</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>follow up more expensive than hospital-based follow up).</p> <p>The topic has been identified as a low priority topic based on the fact that the setting of follow-up does not seem to have a relevant impact on the health benefits obtained by patients or on the financial implications. What has been highlighted is the importance of setting a national guideline that identify what to do, who should do it and where, and when it should be done, since at the moment, different things are done at different places.</p>
<p>Topic 19:</p> <p>What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis?</p> <p>1 4</p>	<p>4. Medium priority 1</p>	<p>Approximately 40% of breast cancer patients present with metastatic disease in the axilla (Liang, Sickle-Santanello et al. 2001). There is uncertainty regarding the status of non-sentinel nodes when a positive sentinel node is found (Chu, Turner et al. 1999) and the current clinical practice for these patients is to continue with completion axillary dissection once a positive sentinel node has been identified, even if the sentinel node is the only focus of axillary metastasis in 67% of patients (Liang, Sickle-Santanello et al. 2001).</p> <p>Patients with micrometastasis in the sentinel node and T1/T2 lesions and those with macrometastasis and T1 lesions may benefit from not undergoing completion axillary clearance in terms of avoidance of physical and</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>psychological distress (Karamlou et al 2003). The impact of this on survival has not been clearly stated.</p> <p>There may be savings by avoiding completion axillary clearance procedures in a subgroup of breast cancer patients with positive nodes. However, achieving accurate identification of node status to appropriately select those patients that should avoid completion axillary clearance may add some further costs.</p> <p>The literature regarding this topic is limited, especially in terms of identifying the (small) group who potentially do not need axillary dissection following SLN (there is some research under way but the results of the trial have not been published yet), and in terms of economic evaluations.</p> <p>This topic appears to be highly related to topic 6 (i.e. In patients with: a) invasive breast cancer; b) with DCIS, when is SLNB justified as a staging procedure?). Therefore, if both topics are finally considered to be high priority, there may be the possibility of combining them in one economic analysis.</p>
1 Topic 22: 5	4. Medium priority 1	The choice of undergoing immediate versus delayed breast reconstruction depends on many factors, such

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<p>When is it appropriate to perform immediate breast reconstructive surgery?</p>		<p>as medical, financial and emotional factors (Cheng, Lin et al. 2006).</p> <p>Immediate breast conserving surgery appears to achieve better aesthetic results after mastectomy and seems to benefit patients from a psychological viewpoint (Neyt et al 2005). However, there is not an impact in local recurrence and there is no evidence about whether survival is increased.</p> <p>Relevant savings can be realised by conducting immediate breast reconstruction in those women for whom it is possible (Khoo et al 1998; Neyt et al 2005), although the option of delayed reconstruction, which is more expensive, appeared to be required for breast cancer patients undergoing postoperative radiotherapy (Neyt et al 2005).</p> <p>Although the number of patients that would be affected by any recommendation related to this topic is high, the associated health benefits and costs of immediate versus delayed reconstructive surgery seem to be moderate. Therefore, the topic has been identified as a medium priority in terms of further economic analysis.</p> <p>There is some economic evidence available, especially in the form of cost studies, assessing the differences in costs between immediate and delayed breast</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		conserving surgery. A systematic review of the economic literature may provide relevant information to assess the cost-effectiveness of immediate breast conserving surgery and the impact of this intervention within the clinical guideline.
<p>Topic 23:</p> <p>23.a. What are the indications for RT after breast conserving surgery?</p> <p>23.b. What are the indications for an external beam RT boost to the site of local excision after breast conserving surgery?</p> <p>1 6</p>	4. Medium priority 1	<p>It is expected that about two thirds of localised breast cancer patients would be suitable for breast conservation, some of whom will opt for mastectomy rather than breast conservation (Sainsbury, Anderson et al. 2000).</p> <p>Nowadays radiation therapy (RT) after breast conserving surgery (BCS) seems to be a widely accepted standard practice, even if its impact on survival is uncertain. Post-BCS RT benefits patients by reducing the risk of local recurrence, and it may additionally improve the patient's quality of life by reducing the fear of potential recurrences and by conserving the breast (Hayman et al 2000).</p> <p>The additional use of a boost after completing RT has been suggested to reduce local recurrence for patients with positive margins after BCS, although its benefit is less evident for patients with negative margins (Hayman et al 2000). The issue of whether all patients should receive a boost after completing RT is controversial and it has important financial implications</p>

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		<p>due to the high costs of the RT boost.</p> <p>RT is routinely used for a high number of patients and it is a considerably expensive intervention, while the health benefits seem to be moderate. There could be relevant financial implications (in terms of cost savings) if RT is found to be not effective for some subgroups of BC patients. However, the costs of RT are not as high as some of the chemotherapy drugs administered to BC patients and compared, as well, to the use of aromatase inhibitors (AIs), that are prescribed for years (Personal Communication) Therefore, the topic has been identified as a medium priority.</p> <p>Some economic evidence is available that supports the use of RT following BCS (Hayman et al 1998), although it does not support the use of an electron-beam boost, in addition to post-BCS RT, for the treatment of breast cancer patients with negative margins after BCS (Hayman et al 2000).</p> <p>A systematic review of the literature may provide some insight into whether RT/ RT boost are cost-effective interventions. However, it is important to consider that the available evidence may not be applicable to the UK setting and/or to a specific subgroups of patients.</p>
1 Topic 24:	4. Medium priority	There may be a benefit, in terms of survival, for

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
<p>7</p> <p>Which groups of patients should receive chest wall radiotherapy after mastectomy?</p>		<p>postmastectomy patients receiving RT. However, the costs of RT are high, and it is necessary to show evidence that the health benefits obtained by incurring such costs are worth the money.</p> <p>There is some available cost-effectiveness evidence (Lee, Glick et al 2002; Marks, Hardenbergh et al 1999; Dunscombe, Samant et al 2000), although specific studies for a UK setting may not be available. Overall, these studies show a very low increase in the LYG and QALYs, at a higher cost than no-RT, for specific groups of patients. A greater use of postmastectomy RT, even limited to the subgroup of patients with axillary nodal involvement, would result in substantial financial costs (Hayman and Hillner 1999).</p> <p>No economic analysis seems to have been performed with the aim of identifying the type of patients that should receive postmastectomy RT, therefore there may be a need to develop a specific decision analytic model considering different types of patients that may benefit from this intervention. However, it is expected that there will be limitations if an economic analysis is to be performed.</p> <p>Although the financial implications of this topic are high, the topic has been identified as medium/low priority since the benefits derived from chest wall RT</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		after mastectomy seem to be limited to a sub-group of breast cancer patients, and because of the feasibility issues that would be expected to arise if an economic evaluation was to be developed.
<p>1 8</p> <p>Topic 25: What are the indications for RT to the supraclavicular fossa, internal mammary chain and axilla?</p>	5. Low priority for a	The evidence regarding the health benefits obtained by patients receiving RT to the supraclavicular fossa, the internal mammary chain and axilla in addition to chest wall RT after surgery is scarce and conflicting (Lievens, Kesteloot et al, 2005; Liljegren et al, 1997; Malin et al 2002). Consequently, it seems that there is not sufficient evidence to support the routine use of RT in this way. Therefore, the topic has been identified as low priority in terms of further economic analysis.
<p>1 9</p> <p>Topic 26: What is the role of primary medical (including neoadjuvant) treatment in patients with early, invasive breast cancer?</p>	5. Low priority for a	<p>By starting with adjuvant chemotherapy/neoadjuvant therapy, 90% of patients can expect a clinical response and 60% can achieve sufficient reduction as to enable lumpectomy without adversely affecting their clinical outcomes (Esserman et al 1999).</p> <p>There may be some impact on patients' health since some of them will undergo less invasive surgery. Additionally, there may be some financial implications related to the fact that breast conserving surgery is usually less expensive than mastectomy.</p> <p>Given the relatively low number of patients involved within this topic and the moderate impact on health</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		benefits and costs, the topic has been considered as medium/low priority.
<p>Topic 28:</p> <p>For patients with inflammatory or locally advanced breast cancer who are treated with primary cytotoxic chemotherapy, what is the role of surgery and/or radiotherapy?</p> <p>2 0</p>	5. Low priority for a	<p>The percentage of patients with locally advanced breast cancer (including those with inflammatory breast cancer) seems to be no higher than 25% (http://www.cancer.gov/cancertopics/factsheet/Sites-Types/IBC; Favret and Carlston 2001), and it is around 5% in UK clinical practice. Most patients have poor outcomes which may be due to micrometastatic disease (Favret and Carlson 2001).</p> <p>Primary or neoadjuvant cytotoxic chemotherapy can convert inoperable locally advanced breast cancers in operable by reducing the extent of the disease, and it can allow breast conserving surgery (BCS) rather than mastectomy in some patients by decreasing the tumour size (http://www.bcbs.com/betterknowledge/tec/vols/19/19_07.html). There is limited evidence showing that primary cytotoxic chemotherapy may avoid surgery in a small group of patients (Favret and Carlson 2001); however, surgery seems to be necessary in most of the patients. On the other hand, RT seems to increase local response in some patients (Rodger, Leonard et al. 1994). For patients undergoing BCS rather than mastectomy (after response to primary chemotherapy), there may be an increase in the risk of ipsilateral</p>

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		<p>breast tumour recurrence (Technology Evaluation Centre 2004). The impact on survival of undergoing surgery and/or RT after chemotherapy is not clear from the available evidence.</p> <p>Surgery costs may be reduced if breast conserving surgery, rather than mastectomy, is undergone by most of the patients after treatment with primary chemotherapy. Further savings could be achieved if breast surgery is shown not to be necessary for all patients with inflammatory or locally advanced breast cancer after receiving primary cytotoxic chemotherapy. On the other hand, if RT is considered to be an effective intervention, this will have relevant financial implications given the fact that RT is comparatively expensive.</p> <p>If surgery and/or RT are found to be beneficial for patients with inflammatory or locally advanced breast cancer, a further economic evaluation could help identify whether the interventions (i.e. surgery and/or RT) are cost-effective, since no economic evaluation seems to be currently available. However, given that the number of patients affected is considerably low, the topic seems to be a medium/low priority for further economic analysis.</p>
2 Topic 29c:	4. Medium priority	Adjuvant treatment with aromatase inhibitors (AIs) for

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
<p>1</p> <p>What is the best timing/ sequencing of aromatase inhibitors and the duration of treatment as adjuvant therapy in post menopausal women with hormone receptor positive breast cancer?</p>		<p>postmenopausal women with hormone-receptor-positive (HR(+)) cancer have been shown to achieve lower recurrence rates compared to tamoxifen. These patients represent a large subgroup group within the overall population of breast cancer patients.</p> <p>On the other hand, there is no available data to identify the optimal duration of treatment with an AI or the optimal sequencing of treatment (Cuzick, Sasieni et al. 2006). The health benefits derived from using different timings, sequencings and durations for AIs are not clear due to the limited information available regarding this issue.</p> <p>There may be relevant financial implications related to the different times/sequencing and durations of AIs treatment, not only for the differences in costs associated with each of the timing/sequencing treatment options, but additionally because they may lead to different levels of prevention of recurrences. The effect on drug cancer spending will be considerably high since not only are AIs more expensive than tamoxifen (NICE Technology Appraisal Guidance 112, 2006) but many patients will be treated with AIs instead; additionally, duration of treatment is being lengthened, with a consequent increase of costs.</p> <p>Economic evidence in the form of economic</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>evaluations seems to be very limited (Hillner 2004). Although the NHS is spending a considerable amount of money on AIs, lack of data on the different timings and sequencing on the use of AIs will limit the development of any further economic evaluation. Due to these feasibility issues, the topic has been identified as medium to low priority.</p>
<p>2 Topic 29d2: 2 In premenopausal breast cancer patients, what are the benefits of adjuvant ovarian suppression/ablation in addition to other treatments?</p>	<p>4. Medium priority 1</p>	<p>Ovarian ablation has been shown to reduce significantly the number of recurrences and improve survival among women under 50 if they do not receive chemotherapy, although the results were more uncertain when chemotherapy was administered (Early Breast Cancer Trialists' Collaborative Group 2000). Patients seem to benefit more in terms of recurrence-free survival and overall survival if they are oestrogen receptor positive.</p> <p>Although an improvement in survival has been observed after ovarian ablation, the topic seems to be medium to low priority since the number of patients benefiting from this intervention is limited to those that do not achieve ovarian suppression by chemotherapy. Moreover, the additional costs associated with ovarian ablation are expected to be low (e.g. the cost of one year's supply of tamoxifen has been shown to be equivalent to the overall cost of surgical oophorectomy;</p>

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		<p>Kwon, Yamada et al. 1997).</p> <p>Available economic evidence seems to be limited and not sufficient to identify if ovarian suppression/ablation is a cost-effective intervention. Further economic analysis may be required to definitely assess the cost-effectiveness of this topic and its implications within the guideline.</p>
<p>2 Topic 29e: 3 Which subgroups of post menopausal breast cancer patients should receive AIs as adjuvant therapy?</p>	<p>4. Medium priority †</p>	<p>Breast cancer patients that are postmenopausal comprise a large subgroup of early breast cancer patients (Hillner 2004). Therefore the number of patients that could be potentially affected by the decisions taken regarding topic 29e seems high.</p> <p>The use of AIs (e.g. anastrozole) seems to reduce recurrences and it possibly improves patient's quality of life (Hillner 2004), but no impact on survival has been observed. There may be some relevant adverse events that need to be taken into account when assessing the overall health benefit.</p> <p>AIs appear to be more expensive than tamoxifen, although the higher costs may be compensated in part by lower costs in the treatment of recurrences (Hillner 2004; Rocchi and Verma 2006).</p> <p>Although the financial implications of this topic are high</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>(since a considerable amount of cancer budget is spent on AIs), the topic has been identified as medium to low priority because of the limited available evidence, which will lead to feasibility problems when conducting any further economic evaluation. Some economic evaluations are already available that may help identify whether the use of AIs is cost-effective; however, they seem to be limited to the assessment of anastrozole (Hillner 2004; Rocchi and Verma 2006), which would limit cost-effectiveness comparisons across different AIs.</p>
<p>2 Topic 30: 4 What are the indications for the measurement of bone mineral density in patients with invasive breast cancer who are on adjuvant hormonal therapy?</p>	<p>3. High priority for :</p>	<p>Use of bone mineral density measurements may help detecting breast cancer patients with relevant bone loss and therefore target treatment, which may reduce the number of fractures experienced by these patients. Additionally, different levels of accuracy in detecting bone loss are achieved depending on the technique used. It is not clear if measuring bone mineral density will have an impact on survival.</p> <p>There may be differences in costs between the different techniques used to measure bone mineral density. Moreover, if measurement of bone density reduces the number of fractures, there will be a reduction in the use of health care resources which may compensate the costs incurred in using the</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
		<p>technique.</p> <p>This topic has been identified as a high priority in terms of conducting further economic analysis given that the use of AIs (which have been associated with bone loss) is likely to become routine practice for the treatment of postmenopausal patients. However, it should be considered that the available clinical evidence is limited and therefore some feasibility problems may arise when undertaking such analysis.</p>
<p>2 Topic 31: 5 Is adjuvant online a clinically effective tool to assist with clinical decisions about adjuvant therapy in patients with EBC?</p>	<p>5. Low priority for a</p>	<p>The primary purpose of this topic is to summarise and critique what is known about Adjuvant! (www.adjuvantonline.com), its validity and usefulness as a tool for supporting clinical decisions about adjuvant chemotherapy in NHS patients with early invasive breast cancer. Given the difficulties of identifying how this tool could change the behaviour of clinicians when making choices about the adjuvant chemotherapy treatment to give to the patients, and how this change in behaviours would impact patients' outcomes, the topic has been considered not relevant for further economic analysis. Adjuvant! is based exclusively on effectiveness and it does not consider the cost-effectiveness and the quality of life of the recommended treatments.</p> <p>In relation to the use of adjuvant chemotherapies in</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>UK, three technology appraisals have been recently published which assess the use of three adjuvant chemotherapies for EBC patients: trastuzumab for early-stage human epidermal growth factor receptor-2 (HER2) positive breast cancer patients (TA107), paclitaxel for early node-positive breast cancer patients (TA108) and docetaxel for early node-positive breast cancer patients (TA109). It is initially expected that the recommendations from these technology appraisals will be incorporated verbatim into the EBC clinical guideline. However, these technology appraisals may be updated in the following period and therefore, the resulting recommendations may change. In any case, the latest/most up-to-date recommendations should be the ones to be considered for this guideline.</p>
<p>2 Topic 35: 6 What are the indications (if any) for the use of bisphosphonates in patients with early breast cancer?</p>	<p>5. Low priority for a</p>	<p>Bisphosphonates do not seem to improve survival but may reduce pain and skeletal problems in women who have had bone metastases. Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to prevent skeletal related events or improve survival in women with early breast cancer.</p> <p>Even if the widespread use of bisphosphonates would have a major financial impact, the topic has been identified as low priority because this widespread use is not likely to occur given the lack of clinical evidence supporting its use.</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
		<p>Since bisphosphonates seem to have no relevant impact in terms of the health benefits achieved and, consequently, they are unlikely to be recommended for patients with early breast cancer, further economic analysis seems not to be required.</p>
<p>2 7</p> <p>Topic 37:</p> <p>37.a. What are the effective strategies to prevent psychological distress in patients with early stage breast cancer?</p> <p>37.b. What are the effective strategies to manage psychological distress in patients with early stage breast cancer?</p>	<p>5. Low priority for a</p>	<p>The first months following the diagnosis of breast cancer are critical for patients. Some interventions, such as the use of advanced practice nurses (APN), nursing support or cognitive behavioural therapy, can reduce patients' anxiety and improve their knowledge of the disease and the control of symptoms with specialised care, and improve additionally their quality of life, although improvement in survival has not been shown (Ritz, Nissen et al. 2000; Whatley et al 2000; Zabalegui et al 2005; Tatrow and Montgomery 2006).</p> <p>There are approximately 25% of patients affected by distress and no clear guidelines about what should be done, when, how often and by whom. The biggest issue seems to be related to prevention of distress, rather than treatment (since prevention would be applied to all women while only 25% of breast cancer patients would require treatment for psychological distress, or even less if preventative measures work).</p> <p>Antidepressants are currently used to treat</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?</i> ^{bb}	<i>Comment and explanation</i>
		<p>psychological distress and have been shown to benefit patients. Given that they are very expensive treatments, the financial implications associated with this topic are high.</p> <p>It is expected that lack of data in terms of the size of treatment and the number of people benefiting from some of the available treatments (Whatley 2000) will make the development of an economic evaluation difficult. Therefore, the topic has been identified as a low priority for further economic analysis.</p>
<p>2 Topic 39: 8 What strategies are effective in reducing arm and shoulder mobility problems after breast cancer surgery??</p>	<p>4. Medium priority 1</p>	<p>Arm and shoulder mobility problems are the two most frequent impairments observed among breast cancer patients. They seem to be related to axillary lymph node dissection and axillary radiation therapy (RT), especially if RT is combined with surgery (McNeely, Campbell et al. 2005). Many patients are affected by decreased shoulder range of motion (ROM) and by the impact it has on quality of life.</p> <p>Some interventions (such as physical exercise and nursing support) have been shown to be effective in improving physical functioning and quality of life of patients (Markes, Brockow et al. 2006; McNeely, Campbell et al. 2006; Knols, Aaronson et al. 2005;). However, no impact in survival has been shown (Zabalegui, Sanchez et al. 2005).</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>There is uncertainty in terms of the content, frequency, intensity and duration of the optimal strategy (Karki, Simonen et al. 2001; Shamley, Barker et al. 2005). Moreover, the economic evidence in relation to this topic is very limited (Gordon, Scuffham et al. 2005). There may be relevant differences in costs depending on the type of intervention undergone; the main economic factor is expected to be manpower since not all hospitals have physiotherapy cover.</p> <p>This topic seems to be a medium priority topic. It may be related to topic 8. Further economic analyses may help identify the most cost-effective intervention for improvement of arm and shoulder mobility at the same time as there may be a possibility of linking this topic with topic 8? However, there may be some limitations in data availability that may hinder the development of such analysis.</p>
<p>2 9 Topic 40: What is the role of mastectomy in patients with localised Paget's disease of the nipple?</p>	<p>5. Low priority for a</p>	<p>Between 0.5 and 4.3 out of every 100 women with breast cancer have Paget's disease (Sutton, Singh et al. 1999; Marcus 2004; http://www.cancerbackup.org.uk/Cancertype/Breast/Typesofbreastcancer/Pagetsdisease) and the optimal surgical management for these patients is yet to be defined, with modified radical mastectomy being the standard care (Sutton, Singh et</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?</i> ^{bb}	<i>Comment and explanation</i>
		<p>al. 1999; Kawase, Dimaio et al. 2005).</p> <p>Patients with Paget's disease of the breast that undergo mastectomy may benefit by experiencing lower recurrence rates, although a subgroup of patients (i.e. those without palpable masses or mammographic abnormalities) may benefit in the same way by undergoing wide local excision instead. Survival does not appear to be influenced by the type of surgical procedure undergone (Kawase et al 2005; Marcus et al 2004; Marshall et al 2003).</p> <p>If a subgroup of patients is identified as benefiting from wide local excision rather than mastectomy, there may be a reduction in costs derived from shorter hospital stay and lower costs for less invasive surgery.</p> <p>There is uncertainty regarding both health benefits and cost implications since the evidence is quite limited, especially regarding economic studies. An economic analysis could help shed light on the identification of the cost-effective surgical management for patients with Paget's disease of the breast. However, given the small number of patients affected and the relatively low impact of the interventions on the health benefits experienced by patients, the overall impact of this analysis on the whole clinical guideline is expected to be minor and therefore the topic has been identified as</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
3 Topic 41:	4. Medium priority 1	low priority for further economic analysis.
0 What is the most effective RT dose fractionation regimen for patients undergoing external beam RT after surgical excision of breast cancer?		<p>In 2004 there were 44,659 new cases of breast cancer diagnosed in the UK, 44,335 (99%) of them in women (http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/). Between 70 and 80% of these patients will present with early invasive ductal BC, and 10% with invasive lobular BC, while the percentage of patients with either inflammatory BC or Paget's disease are between 1 and 2% for each category. Surgery (either breast conserving surgery or mastectomy) is a usual treatment for early invasive BC patients (with some exceptions such as not being fit for the operation), while RT appears to be a widely accepted standard practice after surgery. According to a recent report, 71.7% of BC patients will require RT (http://www.cancer.nhs.uk/documents/nrag_files/Scenario%20Sub%20Group%20report%20-%20Jan%202007%20-%20fin.pdf). Therefore, the number of patients that can be potentially affected by any recommendation regarding the appropriate RT fractionation rate is high.</p> <p>Around 10-20% of BC patients with large primary tumours and extensive lymph node involvement experience local relapse despite receiving postoperative RT (Koukourakis 2003). Late side effects may be more likely for fraction sizes over 2 Gy (Rodger</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>1998). Moreover, the clinical practice regarding the use of RT in UK BC patients has been shown to vary in terms of the dose, fractionation and areas irradiated (Goy and Dobbs 1998).</p> <p>In 2003 a 1-week audit was conducted across all UK RT centres to document RT fractionation practice. In the case of post-operative management of BC, it was concluded that the uniform use of 15 fractions would reduce the overall RT workload by 4%, while the use of 25 fractions would increase it by 7% (Williams et al 2006).</p> <p>The most relevant costs to consider in relation to the administration of different fractionation regimes comprises the cost per fraction and the number of fractions administered. According to the results of a study that assessed the potential changes in the net costs of focal RT at differing doses per fraction and interfraction intervals, higher costs of treatment are related to the administration of smaller doses and to higher number of fractions administered (Jones et al. 1998). In addition, the authors of this study suggested that in the estimation of the RT costs, the additional costs related to treatment failure (i.e. administration of subsequent chemotherapy, surgery, palliative and terminal care) should be included as well. Therefore, differences in the cost per fractionation, in the number</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis? ^{bb}</i>	<i>Comment and explanation</i>
		<p>of sessions given and in the failure rates associated with each of the alternative fractionation regimes will be crucial and may derive in relevant financial implications.</p> <p>The only randomised control trial (RCT) that has been conducted considering different RT fractionation regimes among UK EBC patients aims to find alternative radiotherapy regimens using fraction sizes larger than 2 Gy that could be as effective but less costly than the standard regimen (i.e. 2 Gy in 25 fractions; Policy Research Programme, Department of Health: http://www.info.doh.gov.uk/doh/rd2policy.nsf/vwwebheadings/1D56F5060B262DA680256BB5005621F6?opendocument). Alongside the START trial an economic evaluation is being conducted. It seems that the results of this RCT will be available in the near future. What it is not so clear is that the results of the economic evaluation will be available at the same time.</p> <p>Given that this trial is UK-based, the results of the associated economic evaluation are likely to be applicable to the EBC clinical guideline. A further economic analysis may not be required if the results of the economic evaluation are available on time; in this case, the economic evaluation could be critically appraised in terms of its methodological quality and</p>

<i>Clinical Question (in PICO format if possible)</i>	<i>Requires analysis?^{bb}</i>	<i>Comment and explanation</i>
		applicability for the UK setting to determine if the recommendations for this topic can be based on these cost-effectiveness results. However, in case the cost-effectiveness results are not available on time, it may be necessary to conduct an economic evaluation based on the clinical results of the RCT.

For each question where economic analysis is proposed:

Question number(s) ^{cc}	Outline proposed method of analysis ^{dd}
Topic 7	<p><u>Aim:</u> The role of pre-treatment US in the staging of the axilla is to offer definitive surgery for patients with lymph node involvement and avoid having unnecessary second procedures. A cost-effectiveness analysis will be developed to assess the cost-effectiveness of pre-treatment US to stage the axilla in patients with early invasive breast cancer from the NHS perspective.</p> <p><u>Intervention:</u> The types of pre-treatment US ultrasound that will be considered at analysis are:</p> <ul style="list-style-type: none"> • US with concurrent FNAC • US with concurrent core biopsy <p>US alone will not be included for not being considered to be good clinical practice since the management of the axilla is largely dependent on histological findings in support of imaging and clinical examination.</p> <p><u>Comparator:</u> The comparators with which pre-treatment US will be compared do not involve pre-treatment US assessment, and will be:</p> <ul style="list-style-type: none"> • SLNB, with ANC conducted only on those patients with evidence of lymph node involvement based on SLNB results. • 4 node sampling, with ANC conducted only on those patients with evidence of lymph node involvement based on 4 node sampling results. • For completeness, the other alternative included in the economic analysis will be axillary node clearance without the initial use of either pre-treatment US, SLNB or 4 node sampling. The inclusion of this comparator is justified on the fact that it represents traditional practice and a recent survey conducted in UK has reported that 27% of surgeons still perform ANC as initial management, without previous consideration of the nodal status (Mansfield et al 2007).

^{cc} Two or more questions may be addressed by a single analysis if appropriate.

^{dd} Give a brief description of the type of analysis that is proposed, as far as is known at this stage. Consider the type of economic evaluation (CEA, CUA, CCA,...); how outcomes will be measured (QALYs, LYS,...); the type of modelling (decision tree, Markov, simulation...); proposed comparators and population subgroups to be considered; potential sources of information and assumptions; and whether analysis could be based on an existing model. Follow methods advised in the Guidelines Manual whenever possible. Note that this is not expected to be a full project protocol, and that the methods of analysis may change.

(Note that, following recommendations of the GDG contacts, palpation alone as the basis of axillary staging, will not be considered as an alternative comparator for this analysis for not being a recommended clinical practice).

Methods:

Decision analysis will be used to model the clinical pathway and to estimate the cost-effectiveness of the strategies to stage the axilla that will be included in this economic evaluation.

The clinical data used to populate the model will be mainly derived from the systematic reviews conducted to identify clinical and cost-effectiveness evidence for the topic. In addition, data related to other EBC topics may be included in this model. For example, it may be of interest to consider data from topics 6 and 19 (in terms of whether recurrences and survival differ for patients undergoing SLNB, axillary node sampling or axillary clearance). This type of data will allow to estimate a more accurate lifetime horizon for patients undergoing pre-treatment US versus the comparators. Additional searches will be conducted to identify data on the prognosis, quality of life (QoL) and health care resource utilisation of patients according to each treatment group. Unit costs will be derived, whenever possible, from national sources (e.g. NHS Reference Costs).

If sufficient data are available to populate the model, a total of 4 groups of patients will be considered, according to whether they undergo US, either with core biopsy or with FNAC, or no pre-treatment US (either SLNB, 4-node sampling or initial axillary dissection).

In general terms, patients without evidence of lymph node involvement undergo SLNB or 4 node sampling (avoiding axillary clearance, which is a more invasive procedure, with higher levels of associated morbidity) while those with evidence of lymph node involvement undergo axillary clearance (avoiding unnecessary SLNB or 4 node sampling).

For the group of patients undergoing pre-treatment US, a positive result would mean that the patient will undergo definitive axillary surgery if abnormal axillary lymph nodes are detected (avoiding additional surgical procedures, i.e. SLNB or 4 node sampling). If the results are negative, surgical staging of the axilla will be conducted by either SLNB or 4 node sampling to identify further patients with node involvement. By using pre-treatment US a more accurate, definitive surgery is supposed to be offered to patients, avoiding having additional, unnecessary axillary surgery.

For the groups of patients undergoing SLNB or 4 node sampling, axillary dissection would be conducted on the basis of their results:

no further axillary surgery would be recommended for those with negative axilla, while those with positive axilla should undergo axillary clearance.

The last strategy considered is the use of axillary clearance for all patients as the initial management procedure to stage the axilla, without any previous axillary assessment by either pre-treatment US, SLNB or 4 node sampling. This strategy is expected to derive in higher number of complications and morbidity among patients.

The NHS perspective will be adopted, which means that the health benefits and costs to be considered in the analysis will be those relevant to the NHS:

- In terms of costs, those to be included will be the costs borne by the NHS, including personal social services (PSS) if applicable.
- In terms of health benefits, the ideal outcome to consider will be the number of quality adjusted life years (QALYs) gained. However, there may be some data limitations when identifying whether recurrences, survival and QoL differ for patients having pre-treatment US compared to those patients who do not have pre-treatment US. An alternative outcome that can be estimated through the model is the number of unnecessary procedures (axillary clearances and/or SLNB or 4 node sampling) avoided by using pre-treatment US.

Following the methodological recommendations presented in the Guide to the Methods of Technology Appraisal (www.nice.org.uk; reference N0515), a lifetime horizon is to be adopted, and discounting will be conducted using a discount rate of 3.5% for both health outcomes and costs.

An incremental cost-effectiveness analysis will be conducted after ranking the alternative strategies from the most to the least cost-effective and excluding, if necessary, the dominated strategies (i.e. those strategies achieving lower effectiveness and incurring higher costs when compared to any other). The results of the incremental analysis will be reported as the incremental cost per additional unit of benefit obtained with the most effective and most expensive strategy when compared to the next most effective and most expensive one.

A Markov process will be used to include recurrences and mortality in the model. one-way and multi-way deterministic sensitivity analyses will be conducted to identify those variables contributing the more to uncertainty. In addition, whenever possible probability distributions will be assigned to different clinical and cost parameters so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the model and the

	<p>robustness of the results.</p> <p><u>Feasibility issues:</u> Lack of data may limit the time horizon of this model. The sensitivity and specificity of US may vary depending on specific subgroups of patients, such as those with non-palpable axillary nodes, or those for whom US allows to obtain biopsy material. However, it is not likely that specific prognostic data will be found for each patient subgroup depending on whether they have undertaken US as staging procedure of the axilla. In such a situation, GDG members will be consulted to identify, if possible, appropriate assumptions to allow the estimation of final outcomes (i.e. life years gained and QALYs). If this is not possible, intermediate outcomes, such as the number of unnecessary procedures avoided, may be considered for the estimation of the cost-effectiveness ratios.</p> <p>In addition, data about the accuracy of pre-treatment US conducted concurrently with core biopsy or with FNAB are scarce, which has led to the GDG contacts of this topic to suggest that both interventions should be considered in combination, although it is likely that US combined with FNAB will be considered in the base case analysis, while if data are available for that, the consideration of US with core biopsy will be done through sensitivity analyses.</p>
Topic 30	<p><u>Aim:</u> Adjuvant hormonal therapy may cause relevant bone loss in breast cancer patients. The use of BMD measurements may help detecting breast cancer patients with relevant bone loss and therefore target treatment to reduce the number of fractures and increase their quality of life. An economic evaluation may be conducted to assess the cost-effectiveness of undergoing measurements of BMD in patients with early invasive breast cancer who are receiving adjuvant hormonal therapy from an NHS perspective. However, at the moment this analysis is pending on the availability of clinical data, which will be derived either from the Osteoporosis guideline or from a systematic review of the clinical evidence carried out by the NCC-C.</p> <p><u>Intervention:</u> The intervention to be considered at analysis would be the measurement of BMD by means of Peripheral dual energy X-ray Absorptiometry (P-DEXA). Further clarification would be required from the GDG contact members to identify whether any other method to measure BMD will be considered at analysis.</p> <p><u>Comparator:</u> The comparators that would be considered are:</p> <ul style="list-style-type: none"> • Do nothing • Lifestyle advice • Bisphosphonate therapy

- Calcium and vitamin D supplements
- NTX CTX measurements
- Any other alternative to BMD measurement identified from the systematic review of the literature (?)

It will be necessary to discuss with the GDG members on what grounds these comparators (e.g. lifestyle advice, bisphosphonate therapy and calcium and vitamin D supplements) would be administered for all patients or for a selected group of patients in whom bone loss has been identified, perhaps based on post-BMD measurement.

Methods:

Decision analysis is the proposed method to model the clinical pathway and to estimate the cost-effectiveness of measuring BMD compared to the other alternative strategies considered for this economic evaluation. A decision tree could be used and it is likely that Markov processes would be embedded in the decision tree in order to estimate fractures and recurrent fractures, as well as cancer recurrence.

The clinical data used to populate the model will be mainly derived from the systematic reviews conducted to identify clinical and cost-effectiveness evidence for the topic. If data from the NICE Guidelines for Osteoporosis are available on time, they are likely to be used as well to populate the model. In addition, data related to topic 35 (i.e. indications for the use of bisphosphonates in early breast cancer patients) may be used, based on the recommendations formulated for this topic.

The number of patient groups will depend on the number of alternative interventions to that of the measurement of BMD identified by the systematic review.

The aim of measuring BMD is to identify patients with bone loss and therefore commence treatment earlier, so that the number (and severity?) of bone fractures can be reduced, and the patient's quality of life increased. The NHS perspective will be adopted, which means that the health benefits and costs to be considered in the analysis will be those relevant to the NHS:

- In terms of costs, those to be included will be the costs borne by the NHS, including personal social services (PSS) if applicable.
- In terms of health outcomes, the model will estimate the number of fractures avoided and the improvements in quality of life (i.e. QALYs gained) according to the alternative strategies.

Following the methodological recommendations presented in the Guide to the Methods of Technology Appraisal (www.nice.org.uk;

	<p>reference N0515), a lifetime horizon is to be adopted, and discounting will be conducted using a discount rate of 3.5% for both health outcomes and costs.</p> <p>An incremental cost-effectiveness analysis will be conducted after ranking the alternative strategies from the most to the least cost-effective and excluding, if necessary, the dominated strategies (i.e. those strategies achieving lower effectiveness and incurring higher costs when compared to any other). The results of the incremental analysis will be reported as the incremental cost per additional unit of benefit obtained with the most effective and most expensive strategy when compared to the next most effective and most expensive one.</p> <p>Whenever possible, probability distributions will be assigned to different clinical and cost parameters within the model so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the model and the robustness of the results. In addition, one-way and multi-way deterministic sensitivity analyses will be conducted to identify those variables contributing the more to uncertainty.</p> <p><u>Feasibility issues:</u> It is not clear at this point that the available literature is sufficient to populate this model for all the comparators previously mentioned. The available evidence seems to be limited and this may lead to relevant feasibility problems when developing and populating the model.</p>
Topic 6	<p>While developing this economic plan, some evidence in the form of economic evaluations was identified in relation to topic 6. Therefore, a systematic review of the economic literature related to this topic will be conducted. This will serve to assess the cost-effectiveness of the use of SLNB as staging procedure in patients with invasive breast cancer (Topic 6.a) and in patients with DCIS (Topic 6.b). It is expected that the economic literature available will be related exclusively to topic 6.a and, therefore, assessment of the cost-effectiveness of SLNB as staging procedure for DCIS patients may not be possible from the systematic review.</p> <p>The results of the systematic review will be presented to the GDG for further discussion of the limitations, consistency and applicability/directness of the results for the NHS.</p>

Topic 41	<p>The issue of what type of fractionation should be administered for RT seems to be a relevant one, although it was not initially considered in the guideline since the results of the only RCT assessing the issue (the START trial) were not to be available on time to meet the deadline for this guideline.</p> <p>Once the timeline was extended, it was recognised that the results of the RCT will be available on time to be included here and therefore the issue of fractionation became a relevant one and needed to be included in the guideline.</p> <p>The GDG contacts have decided that this new topic 41 has a higher priority than topic 23 for economic analysis; therefore topic 23 has been removed from the list of high priority topics within the Economic Plan. Given that a RCT is on its way for publication and may include an economic evaluation of the different fractionation regimes considered in the trial, a further economic analysis may not be required for this topic.</p> <p>The GDG has suggested that, in case the economic evaluation is not available on time, and in case time permits, a cost-minimisation analysis could be conducted under the expectation that there will not be relevant differences in terms of the effectiveness of different fractionation regimes. Before any economic analysis is conducted, we need to be able to identify the most appropriate way to go forward with this topic. For this, before conducting a cost-minimisation analysis it needs to be confirmed that effectiveness does not differ across different fractionation regimes. In case adverse events differ depending on the fractionation regimen administered, a cost-minimisation analysis would not be appropriate.</p>
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Addenda to economic plan

The following substantive revisions to the plans set out in section 3 above have been agreed.

<i>Date</i>	<i>Question number(s)</i>	<i>Agreed change to number or type of analyses</i>