

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of endoscopic axillary node retrieval for breast cancer

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2004.

Procedure names

- Endoscopic axillary lymph node retrieval.
- Axilloscopic lymph node removal.
- Endoscopic axillary lymphadenectomy

Specialty society

Specialist advice was sought from:

- British Association of Surgical Oncology.
- Association of Laparoscopic Surgeons of Great Britain and Ireland

Description

Indications

Axillary clearance is an integral part of breast cancer surgery. Biopsy of lymph node tissue helps in the staging of breast cancer, providing reliable prognostic information and identifying patients who will benefit from systemic therapy.

Current treatment and alternatives

Traditionally, surgeons removed lymph nodes for staging under direct vision through an incision in the axillary skin; however, this procedure has side effects including wound infection and lymphoedema. Two operations are standard practice. The first involves clearance to level one, two, or three of the axilla taking up to 20 lymph nodes which provides very accurate diagnostic information. The second requires sampling of a minimum of 4 lymph nodes, which causes less morbidity but provides only qualitative rather than quantitative information regarding the status of the axillary basin of lymph nodes. Endoscopic techniques, sometimes combined with liposuction have been developed to provide a minimally invasive technique (see section below).

A new procedure is sentinel node mapping, which requires the use of imaging and specific training.

What the procedure involves

In endoscopic axillary lymph node removal, very small incisions are made in the axillary skin and removes the lymph nodes using an endoscope. The patient is placed in a supine position under general anaesthesia. Liposuction is used to remove excess axillary fat. An endoscope is inserted through the incision used for liposuction, and trocars introduced through two additional small incisions. Step-by-step, fibrous tracts and small lymph and blood vessels are coagulated and cut, and lymph nodes carefully freed and removed. Following a saline rinse of the surgical field the incisions are sutured. Drains are not normally required in the axilla.

Efficacy

In one randomised controlled trial the operative time for endoscopic axillary lymph node removal was found to be significantly longer than for open surgery, the mean times being 61 and 33 minutes respectively. Another randomised controlled trial found no significant difference in operative time between axilloscopy (168 minutes) and open surgery (155 minutes) amongst 22 women undergoing quadrantectomy.

One quasi-randomised study found good shoulder-arm mobility at 7 days postoperatively with more than 90% mobility being achieved following either axilloscopy or open surgery. However, only 18% (7/40) of axilloscopy patients reported pain on the first postoperative day compared with 33% (13/40) of open surgery patients. One small randomised controlled trial found that all ten patients reported no pain at 3 days following endoscopic axillary removal.

Length of stay following axilloscopy was found to vary widely from 2.5 days to 9 days, although one study reported that most of the later cases in their series were discharged within 24 hours.

Conversion to open surgery was reported in 8% (4/53) of cases in a historically controlled study. However, in a large case series the requirement for conversion was only 2% (2/100) of cases.

Two case series reported no axillary recurrence among 100 and 103 cases followed up to 14 and 18 months respectively.

Safety

Data on procedure safety were not consistently reported across the studies identified. The incidence of seroma reported following endoscopic axillary retrieval varied widely from 90% (36/40) to 4% (4/100). Similarly, rates of haematoma formation ranged from 16% (16/100) in one case series, through 10% (1/10) and 5% (1/20) in the axilloscopy arms of two randomised controlled trials, to as little as 1% (1/103) in a second case series. This variation may be due to threshold of reporting or operator experience.

A case series of women with stage I or II primary breast cancer found port site metastases to occur in 4% (2/52) of patients at 24 months follow up, and lymphoedema in 6% (3/52) of cases at a median 72 months follow up.

Amongst other reported adverse events following endoscopic axillary lymph node removal include lymphocoele in 25% (5/20) of patients, and wound infection in 5% (2/40) of patients.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic axillary lymph node retrieval. Searches were conducted via the following databases, covering the period from their commencement to 19/01/2005: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts, the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with breast cancer.
Intervention/test	Endoscopic axillary node retrieval.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on two randomised controlled trials, one quasi-randomised study, one historically-controlled study, and three case series (see Table 1).

Existing reviews on this procedure

No published systematic reviews or evidence-based guidelines on this procedure were found during literature searches.

Table 1 Summary of key efficacy and safety findings on endoscopic axillary node retrieval for breast cancer

Abbreviations used:																		
Study details	Key efficacy findings	Key safety findings	Comments															
Salvat J (1996)(1) Randomised controlled trial France 40 women with early invasive breast cancer < 3 cm diameter : - axilloscopic node dissection, n = 20 (mean age 63 years, range 42 -78) - open surgical node dissection, n = 20 (mean age 59 years, range 30 -79) length of follow-up not reported	Operative parameters 'Average' operative time (definition not stated) Axilloscopy: 61 minutes Surgery: 33 minutes p < 0.001 Damage to lymph nodes: More shearing, fragmentation and haemorrhage with axilloscopy than surgery (no further data provided) Hospital length of stay: Axilloscopy: 4.7 days Surgery: 5.3 days p value not provided	Operative difficulties With the axilloscopy procedure 10% (2/20) difficulties with node extraction, and 5% (1/20) cases demonstrated difficulty with haemostasis. With open surgery 5% (1/20) difficulty with exposure, and 5% (1/20) difficulty with haemostasis Postoperative complications <table><tr><td></td><td>endoscopic</td><td>open surgery</td></tr><tr><td>lymphocoele</td><td>25% (5/20)</td><td>5% (1/20)</td></tr><tr><td>fever</td><td>5% (1/20)</td><td>5% (1/20)</td></tr><tr><td>heamatoma</td><td>5% (1/20)</td><td>15% (3/20)</td></tr><tr><td>Lymphorrhoea</td><td>5% (1/20)</td><td>5% (1/20)</td></tr></table> Clinical follow-up There were two relapses following the endoscopic removal procedure, but none following open surgery (follow-up not stated)		endoscopic	open surgery	lymphocoele	25% (5/20)	5% (1/20)	fever	5% (1/20)	5% (1/20)	heamatoma	5% (1/20)	15% (3/20)	Lymphorrhoea	5% (1/20)	5% (1/20)	Randomisation 'using a list of numbers'. No major differences in baseline characteristics between groups. Outcome data collection methods only briefly described. No blinding of outcome assessment. Follow-up not described.
	endoscopic	open surgery																
lymphocoele	25% (5/20)	5% (1/20)																
fever	5% (1/20)	5% (1/20)																
heamatoma	5% (1/20)	15% (3/20)																
Lymphorrhoea	5% (1/20)	5% (1/20)																

Abbreviations used:			
Study details	Key efficacy findings	Key safety findings	Comments
Hüscher C G S (2002)(2) Randomised controlled trial Italy 22 women with early breast cancer who had quadrantectomy: Axilloscopic node dissection, n = 10 (mean age 57years , range 39-73; mean follow-up 66 months) Open surgical node dissection, n = 12 (mean age 63 years, range 38-77; mean follow-up 55 months)	Pain associated with procedure No pain at day 3 postoperatively Axilloscopy: 100% (10/10) Surgery: 75% (8/12) p = 0.1 Operative parameters Mean (range) operative time: Axilloscopy: 168 minutes (130-210 minutes) Surgery: 155 minutes (70-240 minutes) No significant difference Hospital length of stay Median hospital stay: Axilloscopy: 9 days Surgery: 10 days No significant difference	Adverse outcomes Median volume of lymphorrhoea: Axilloscopy: 225 ml (range 20-1200 ml) Surgery: 400 ml (range 70-970 ml) No significant difference Transient paraesthesia: Axilloscopy: 0% (0/10) Surgery: 17% (2/12) p = 0.48 Operative difficulties With the axilloscopy procedure there was one instance each of seroma and haematoma. With open surgery no complications were reported Clinical follow up Metastasis at follow-up: Axilloscopy: 1 person Surgery: None	Randomisation method not described. Power to detect differences low. 3/22 people lost to follow-up. Outcome data collection methods only briefly described. No blinding of outcome assessment.

Abbreviations used:												
Study details	Key efficacy findings	Key safety findings	Comments									
De Wilde R L (2003)(3) Quasi-randomised study (consecutive patients entered into alternate groups) Germany 80 women with confirmed invasive breast cancer with clinically and ultrasonically negative axillary lymph nodes (< 1 cm): - axilloscopic node dissection, n = 40 (mean age 58 years, range 35-79) - open surgical node dissection, n = 40 (mean age 65 years, range 41-92) Follow-up 3 months	Operative parameters Mean (range) operating time: Surgery: 36 minutes (19-66 minutes) Axilloscopy: 62 minutes (42-126 minutes) Lymphoedema was reported in 20% (8/40) of the cases treated by the Axilloscopy technique, and in 22% (9/40) of open surgery cases Procedure success Return of shoulder-arm mobility at 7 days (absolute figures not provided): Axilloscopy: 99% Surgery: 96% Pain on first postoperative day: Axilloscopy 18% (7/40) Surgery 33% (13/40) Paraesthesia at 3 months: Axilloscopy: 18% (7/40) Surgery: 5% (2/40)	Postoperative complications <table><tr><td></td><td>endoscopic</td><td>open surgery</td></tr><tr><td>Seroma</td><td>90% (36/40)</td><td>93% (37/40)</td></tr><tr><td>Wound infection</td><td>5% (2/40)</td><td>10% (4/40)</td></tr></table>		endoscopic	open surgery	Seroma	90% (36/40)	93% (37/40)	Wound infection	5% (2/40)	10% (4/40)	Allocation not random. No comparison of baseline differences except for stage. No major differences in stage between groups. Outcome data collection methods only briefly described. All participants followed up.
	endoscopic	open surgery										
Seroma	90% (36/40)	93% (37/40)										
Wound infection	5% (2/40)	10% (4/40)										
Kuehn T (2001)(4) Historical-controlled study Germany 450 women with breast cancer < 3 cm diameter and clinically negative nodes: - axilloscopic node dissection, n = 53, (mean age 50 years (range 24-85)) - surgical node dissection (historical controls), n=396 (mean age 55 years (range 22-86)) Follow-up at least 6 months	Operative parameters Range of operating time Axilloscopy (60-150 minutes) Surgery (30-45 minutes) Severe lymphoedema was not reported in any of the cases treated by the Axilloscopy technique, and in 9% of open surgery cases. Absolute figures not presented. Pain associated with procedure No pain at follow up Axilloscopy 29% Surgery 27% Conversion rate 8% (4/53) axilloscopic operations converted to open surgery.	Adverse events Axilloscopy: Lymphorrhoea: mean volume 372 ml Seroma: 15% (8/53) cases Abscess requiring drainage: 1 person	Non-randomised study. Important baseline differences between people having axilloscopy and historical controls. Data collection on 6 month morbidity only briefly described. Length of follow up in each group not provided. In the axilloscopy group only 66% (35/53) followed up, whereas surgery group 396/396 were followed up.									

Abbreviations used:

Study details	Key efficacy findings	Key safety findings	Comments																												
Langer I (2005) (7) Case series Switzerland n=55 Women with primary breast cancer stage I or II. Treated by endoscopic lymph node biopsy with liposuction After breast conserving surgery patients received radiation therapy with 45 Gray over 5 weeks, and a boost of 10 Gray to the tumour site. Follow up = 72 months	Operative parameters Median operation time was 135 minutes (range 90-240) this was significantly longer than a comparative group of patient undergoing open dissection one year earlier by the same surgeon (p<0.0001) A median of 13 lymph nodes were removed, and 31% (16/52) of patients had lymph node metastases. Conversion rate 5% (3/55) operations begun via endoscope were converted to open surgery Survival Eight patients died as a median of 34 months follow up, 4 from metastatic disease, two of which were node positive at time of operation. Local breast recurrence occurred in 2% (1/52) of patients Arm mobility Self evaluated outcomes on a 1 to 10 (best) scale at 24 months postoperatively <table><tr><td>Upper arm pain</td><td>9.4 (Range 4 to 10)</td></tr><tr><td>Lower arm pain</td><td>9.9 (Range 6 to 10)</td></tr><tr><td>Breast pain</td><td>9.2 (Range 6 to 10)</td></tr><tr><td>Shoulder range of motion</td><td>9.4 (Range 4 to 10)</td></tr><tr><td>Use of arm in daily life</td><td>9.5 (Range 5 to 10)</td></tr></table>	Upper arm pain	9.4 (Range 4 to 10)	Lower arm pain	9.9 (Range 6 to 10)	Breast pain	9.2 (Range 6 to 10)	Shoulder range of motion	9.4 (Range 4 to 10)	Use of arm in daily life	9.5 (Range 5 to 10)	Postoperative complications Immediate postoperative events <table><tr><td>Seroma</td><td>15% (8/52)</td></tr><tr><td>Winged scapula</td><td>2% (1/52)</td></tr><tr><td>Low grade infection</td><td>2% (1/52)</td></tr></table> Late complications 24 months <table><tr><td>Port site metastases</td><td>4% (2/52)</td></tr><tr><td>Restricted shoulder mobility</td><td>4% (2/52)</td></tr><tr><td>Pain at abduction and anteversion</td><td>23% (12/52)</td></tr><tr><td>Superficial pain in dorsomedial skin</td><td>17% (9/52)</td></tr><tr><td>Upper arm numbness</td><td>6% (3/52)</td></tr></table> Last follow up 72 months <table><tr><td>Lymphoedema</td><td>6% (3/52)</td></tr></table>	Seroma	15% (8/52)	Winged scapula	2% (1/52)	Low grade infection	2% (1/52)	Port site metastases	4% (2/52)	Restricted shoulder mobility	4% (2/52)	Pain at abduction and anteversion	23% (12/52)	Superficial pain in dorsomedial skin	17% (9/52)	Upper arm numbness	6% (3/52)	Lymphoedema	6% (3/52)	All interventions were undertaken by the same surgeon Prospective follow up every 4 months for 3 years, then every 6 months for 2 years. Some cases received adjuvant hormone therapy and or chemotherapy 3 patients in whom the operation was converted to an open procedure are included in the analysis for efficacy. However another 3 cases were lost to follow up.
Upper arm pain	9.4 (Range 4 to 10)																														
Lower arm pain	9.9 (Range 6 to 10)																														
Breast pain	9.2 (Range 6 to 10)																														
Shoulder range of motion	9.4 (Range 4 to 10)																														
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Abbreviations used:																			
Study details	Key efficacy findings	Key safety findings	Comments																
Malur S (2001)(5) Case series Germany n = 100 All women with early breast cancer < 2.5 cm diameter. Treated by breast conserving therapy and endoscopic lymph node biopsy without liposuction Median age 58 years (range 29-85) Median follow-up 14 months	Operative parameters Median operation time: 75 minutes (range 30-130) Mechanical trauma to lymph nodes: 3% Conversion rate 2% (2/100) operations begun in endoscopic manner were converted to open surgery. Reasons not given. Procedure success Restriction of arm mobility on day 5 was only found in 11% (11/100) of cases.	Postoperative complications Immediate postoperative events <table><tr><td>Seroma</td><td>4% (4/100)</td></tr><tr><td>Winged scapula</td><td>3% (3/100)</td></tr><tr><td>Haematoma</td><td>16% (16/100)</td></tr></table> 'Late' complications <table><tr><td>Impaired sensation</td><td>14% (14/100)</td></tr><tr><td>Axillary abscess</td><td>1% (1/100)</td></tr><tr><td>Lymphoedema</td><td>1% (1/100)</td></tr></table> Clinical follow up Axillary recurrence was not noted in any of the 100 cases.	Seroma	4% (4/100)	Winged scapula	3% (3/100)	Haematoma	16% (16/100)	Impaired sensation	14% (14/100)	Axillary abscess	1% (1/100)	Lymphoedema	1% (1/100)	Uncontrolled case series Data collection on complications not described				
Seroma	4% (4/100)																		
Winged scapula	3% (3/100)																		
Haematoma	16% (16/100)																		
Impaired sensation	14% (14/100)																		
Axillary abscess	1% (1/100)																		
Lymphoedema	1% (1/100)																		
Suzanne F (1998)(6) Abstract - case series France n = 103 Age = 50 years. Endoscopic retrieval following liposuction. Mean number of nodes retrieved per case 7.02 Follow-up 18 months	Operative parameters Drainage was required in 25% (26/103) of cases. With an average drainage time 2.82 days Patients undergoing axillary retrieval and lumpectomy had an average length of stay of 2.5 days. However in later cases no drainage was required and patients left hospital after 24 hours	Postoperative complications Immediate postoperative events <table><tr><td>No complication</td><td>79% (81/103)</td></tr><tr><td>Shoulder stiffness</td><td>6% (6/103)</td></tr><tr><td>Haematoma</td><td>1% (1/103)</td></tr><tr><td>Pain</td><td>9% (9/103)</td></tr></table> 'delayed' complications <table><tr><td>Arm stiffness</td><td>6% (6/103)</td></tr><tr><td>Temporary</td><td>3% (3/103)</td></tr><tr><td>Oedema with exercise</td><td></td></tr><tr><td>Residual pain</td><td>5% (5/103)</td></tr></table> Clinical follow up Local axillary recurrence was not noted in any of the 103 cases	No complication	79% (81/103)	Shoulder stiffness	6% (6/103)	Haematoma	1% (1/103)	Pain	9% (9/103)	Arm stiffness	6% (6/103)	Temporary	3% (3/103)	Oedema with exercise		Residual pain	5% (5/103)	Abstract presentation only, not necessarily peer reviewed. Technique employed, developed over the course of the series presented. 5-year follow-up may not be sufficient to make a definitive conclusion on local recurrence. Inexperienced operators may leave suspicious nodes in the axilla.
No complication	79% (81/103)																		
Shoulder stiffness	6% (6/103)																		
Haematoma	1% (1/103)																		
Pain	9% (9/103)																		
Arm stiffness	6% (6/103)																		
Temporary	3% (3/103)																		
Oedema with exercise																			
Residual pain	5% (5/103)																		

Validity and generalisability of the studies

- Most studies were carried out in continental Europe.
- The randomised controlled trials were small, so may have low power to detect differences in outcome.
- The quasi- and non-randomised controlled studies have limited validity for assessing effectiveness of endoscopic axillary lymph node retrieval compared with open surgery because there may have been baseline differences between the groups that were not evaluated.
- Outcome data collection methods were only briefly described in all the studies for which full text was available.
- Most of the studies included only women with clinically node-negative disease. Results may not be generalisable to women with known nodal involvement.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr Mark Kissin, Dr David Rosin, Professor Steve Heys, Mr David England, Mr Zen Rayter

- Theoretical adverse effects of endoscopic axillary lymph node retrieval may include bleeding, damage to nerves or the axillary artery, pneumothorax, lymphoedema, and short term arm and shoulder pain or sensory disturbance.
- All advisors stated that practitioners would require special training in endoscopic procedures.
- The majority of advisors thought that the uptake of this procedure in the NHS would be slow.
- Few comparative studies have been published so far.
- Future audit work would ideally encompass outcomes of histologically confirmed removal of axillary lymph nodes, tumour recurrence, incidence of port site metastases, seroma, lymphoedema, conversion rate to open procedure, operating time, length of stay, and return to work time.

Issues for consideration by IPAC

- Following notification it was decided that this procedure be separated from the issue of sentinel node biopsy and considered in its own right.

References

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- (2) Huscher CGS, Barreca M, Di Paola M, Ricchiuti C, Lirici MM. Quadrantectomy and video-assisted axillary dissection for stage I breast cancer. *Minimally Invasive Therapy & Allied Technologies: Mitat* 2002; Vol. 11(1):-28.
- (3) de Wilde RL, Schmidt EH, Hesselting M, Mildner R, Frank V, Tenger M. Comparison of classic and endoscopic lymphadenectomy for staging breast cancer. *Journal of the American Association of Gynecologic Laparoscopists* 2003; 10(1):75-79.
- (4) Kuehn T, Santjohanser C, Grab D, Klauss W, Koretz K, Kreienberg R. Endoscopic axillary surgery in breast cancer. *British Journal of Surgery* 2001; 88(5):698-703.
- (5) Malur S, Bechler J, Schneider A. Endoscopic axillary lymphadenectomy without prior liposuction in 100 patients with invasive breast cancer. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* 2001; 11(1):38-41.
- (6) Suzanne F, Emering C, Wattiez A, Bournazeau JA, Bruhat MA, Jacquetin B. Endoscopic axillary lymphadenectomy (E.A.L.) in breast cancer treatment (about 103 cases). 6th World congress of Endoscopic Surgery , 595-603. 1998.
- (7) Langer I, Kocher T, Guller U, Torhorst J, Oertli D, Harder F et al. Long-term outcomes of breast cancer patients after endoscopic axillary lymph node dissection: a prospective analysis of 52 patients. *Breast Cancer Research & Treatment* 2005; 90(1):85-91.

Appendix A: Additional papers on endoscopic axillary node retrieval for breast cancer not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Kamprath S, Bechler J, Kuhne-Heid R, et al. Endoscopic axillary lymphadenectomy without prior liposuction. Development of a technique and initial experience. <i>Surgical Endoscopy</i> 1999;13: 1226-9.	n = 33 4.6 months follow-up	33 cases where bigger series, and longer follow up included in overview tables	Median procedure time 75minutes No intraoperative complications 3 patients developed a seroma that required evacuation 79% unrestricted arm movement at day 5
Cangiotti L, Poiatti R, Taglietti ., et al. A mini-invasive technique for axillary lymphadenectomy in early breast cancer: a study of 15 patients. <i>Journal of Experimental & Clinical Cancer Research</i> 1999;18: 295-8.	n = 15 10 months follow-up	10 cases where bigger series, and longer follow up included in overview tables	An average 15.5 nodes removed Mean hospitalisation 6 days (with drainage) One seroma 5% was found, no shoulder stiffness, good aesthetic results
Harder F, Zuber M, Kocher T et al., "Endoscopic surgery to the axilla--a substitute for conventional axillary clearance?", <i>Recent Results in Cancer Research</i> 1998; 152: 180-9.	n = 50 15 months follow-up	50 cases where bigger series included in overview tables	Found decreased morbidity compared to conventional approach Almost unchanged range of shoulder motion without pain Conversion to open surgery in 6% (3/55)

Appendix B: Literature search for endoscopic axillary node retrieval for breast cancer

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

- 1 endoscop\$.tw. (72535)
- 2 exp ENDOSCOPY/ (138998)
- 3 1 or 2 (168114)
- 4 lymphadenectomy.tw. (5850)
- 5 exp Lymph Node Excision/ (18250)
- 6 (lymph\$ adj2 nod\$ adj3 (dissect\$ or excis\$ or resect\$ or retriev\$ or samp\$)).tw. (8547)
- 7 or/4-6 (24663)
- 8 axill\$.tw. (15592)
- 9 under?arm\$.tw. (124)
- 10 underarm\$.tw. (80)
- 11 armpit\$.tw. (101)
- 12 exp Axilla/ (6029)
- 13 exp Lymph Nodes/su [Surgery] (1016)
- 14 or/8-13 (18421)
- 15 (breast adj3 (cancer\$ or teratoma or carcinoma or neoplasm\$ or malignant or tumo?r\$ or metastasis)).tw. (104005)
- 16 exp Breast Neoplasms/ (121426)
- 17 15 or 16 (139295)
- 18 3 and 7 and 14 and 17 (40)
- 19 limit 18 to human (39)
- 20 from 19 keep 1-39 (39)
- 21 from 20 keep 1-39 (39)