NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Intrabeam radiotherapy system for adjuvant treatment of early breast cancer

Recommendations

1.1 The Intrabeam radiotherapy system is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour.

1.2 Use of the Intrabeam radiotherapy system is recommended only using machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements.

1.3 The procedure should only be carried out by clinicians with specific training in the use of the Intrabeam radiotherapy system.

1.4 Patient selection for Intrabeam radiotherapy should be done by a multidisciplinary team experienced in the management of early invasive breast cancer which includes both breast surgeons and clinical oncologists.

1.5 Clinicians wishing to undertake Intrabeam radiotherapy should take the following actions:

- Inform the clinical governance leads in their NHS trusts.
- Ensure that patients understand the uncertainties about the procedure and inform them about alternative treatment options.
- Provide patients with NICE's written information on the evidence of the risks and benefits of the range of treatment options available as an aid to shared decision making.

2 The technology

Description of the technology	The Intrabeam radiotherapy system (Carl Zeiss UK) is a mobile irradiation system. It is designed to deliver a single dose of targeted low energy radiation (X-rays) directly to the tumour bed, while limiting the exposure of healthy tissue to radiation. Because it delivers low energy radiation, it can be used in an ordinary operating theatre at the time of surgery. The Intrabeam radiotherapy system provides a source of 50 kV energy from a spherical applicator of between 1.5 cm and 5.0 cm diameter. The applicator is sutured to the tumour bed so that breast tissue at risk of local recurrence receives the prescribed dose while skin and deeper structures are protected. Radiation is delivered over 20 to 30 minutes.
CE marking	The Intrabeam radiotherapy system was granted a CE (Conformité Européene) mark in 1999 for use in radiotherapy. Intrabeam can be used as an intraoperative radiotherapy system given as the sole treatment or as a boost treatment followed by external beam radiotherapy (EBRT). When intraoperative radiotherapy is given as a boost treatment with Intrabeam and followed by EBRT, there is no need for further external boost treatment. Six NHS centres in the UK have used Intrabeam for adjuvant treatment of early breast cancer.
Adverse reactions	Adverse reactions are mostly related to wound-related complications and radiotherapy-related complications.
Recommended dose and schedule	The surface of the tumour bed typically receives a single fraction of 20 grays, which attenuates to 5 grays to 7 grays at a depth of 1 cm.
Price	The cost of the Intrabeam radiotherapy system (including the spherical applicators) is £435,000 (excluding VAT, Carl Zeiss UK personal notification). The company estimates that device maintenance and servicing costs are about £35,000 per year. Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee (section 8) considered evidence from a number of sources. See the committee papers, for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of the Intrabeam radiotherapy system, having considered evidence on the nature of early invasive breast cancer and the value placed on the benefits of the Intrabeam radiotherapy system by people with the condition, those who represent them and clinical experts. It also took into account the effective use of NHS resources.

The management of early invasive breast cancer

4.1 The committee heard from the clinical experts that usual clinical practice in the NHS is to give adjuvant radiotherapy to people with early invasive breast cancer after successful breast-conserving surgery (that is, removal of the tumour with clear margins). This is given by external beam radiotherapy (EBRT) using a linear accelerator delivering 40 grays in 15 fractions over 3 weeks in line with NICE's clinical guideline on early and locally advanced breast cancer (CG80). The committee heard from the clinical experts that there was some variation in clinical practice, with some oncologists recommending EBRT over 5 weeks but that, in general, most oncologists would recommend EBRT in line with CG80. An additional external radiotherapy boost dose to the site of the excised tumour lasting a further 1 week to 2 weeks could be offered to people with a higher risk of local recurrence. The committee noted comments from professional groups and also heard from the clinical experts that radiotherapy is constantly evolving. It also noted that there are several ongoing trials investigating, for example, whether the course of radiotherapy could be reduced from 3 weeks to 1 week, or whether radiotherapy is needed at all for patients considered to be at low risk of recurrence. The clinical experts suggested that the results of these trials may influence future clinical practice in the UK. The committee understood that clinical practice is evolving and that the delivery and use of external radiotherapy may change in the future, moving towards a more targeted approach in which patients have treatment based on their

individual risks. The committee noted that Intrabeam could be used at the time of surgery as an alternative to postoperative treatment with EBRT. It also noted that, if adverse histological features are identified in the cancer cells at final pathology after treatment with Intrabeam, and subsequent EBRT is recommended, a further external boost dose would not be needed.

Potential benefits of Intrabeam

4.2 The committee noted that Intrabeam delivers a single dose of targeted low energy (X-ray) radiation to the tumour bed. It can be used in an operating theatre as a single treatment at the same time as the surgery to remove the primary tumour. Patients at low risk of recurrence do not receive any further radiotherapy. However the committee were aware that patients with a higher risk of recurrence (for example, histopathology showing invasive lobular carcinoma, extensive intraductal component, node involvement, and close margins) may go on to receive an additional course of EBRT. For patients having EBRT, treatment can only begin after the surgical wound has healed and takes several weeks of daily therapy to complete. Intrabeam also has the theoretical advantage of having the source of radiation directly applied to the tumour bed. However, the committee heard from the clinical experts that there are now techniques allowing clinical oncologists to more accurately target the dose with EBRT, such as using clips during surgery to mark the site of the tumour. Although there is a risk of clips moving within the cavity, EBRT has evolved and is generally considered to be accurate for targeting the tumour site. The committee noted comments from professional groups that the main aim of radiotherapy after surgical removal of the tumour is to prevent local recurrence. A clinical expert confirmed that local recurrence is not related to an increased risk of metastatic disease or mortality. If there is local recurrence after breast-conserving surgery and EBRT, this is usually treated by mastectomy. However, for some patients, brachytherapy may be a suitable breast-conserving treatment instead of mastectomy. If there is recurrence after treatment with Intrabeam, further

breast-conserving surgery and EBRT still remain a theoretical treatment option. The committee also heard from the patient expert that Intrabeam could be used when EBRT is unsuitable or not possible, for example, for those patients who are unable to raise their arm. The committee understood from the clinical experts that people for whom EBRT was not a suitable treatment would currently be offered mastectomy, and that Intrabeam might be an appropriate option for them. The committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed, and also represented an alternative treatment option for people for whom EBRT is not suitable, although for those people with a higher risk of recurrence an additional course of EBRT may still be required.

4.3 The committee heard from the patient expert that the psychological burden of breast cancer is high for patients and their families. The patient expert explained that, when a patient is diagnosed with breast cancer, the thought of many radiotherapy sessions over a number of weeks can cause emotional stress and anxiety and is highly disruptive to daily living. The patient may need to stop working and face substantial travel costs, which can have a considerable financial and emotional impact on the patient and their family. The committee also heard from the patient expert that some patients who live a long distance from a radiotherapy centre may need to stay away from their home to be able to complete the course of radiotherapy. The patient and clinical experts highlighted that the time between diagnosis and the end of treatment is much reduced with Intrabeam compared with EBRT. This is because the patient has the treatment at the same time as surgery and, for most people, no further treatment is needed. The patient expert also considered that Intrabeam does not have the adverse effects that are associated with EBRT such as local tenderness, breast pain, swelling and reduced range of movement. However, the committee also heard from clinical experts that the adverse effects of EBRT are mainly fatigue and that only a few patients have

radiosensitivity, which can cause swelling and weeping of the breast. The patient and the company expert stated that Intrabeam is associated with better cosmetic outcomes than EBRT, and that changes in breast appearance and texture can be avoided or reduced with Intrabeam. The patient expert highlighted that cosmetic outcomes have a big effect on patients' quality of life. However the committee heard differing opinions from the clinical experts as to whether the cosmetic outcome from Intrabeam is superior to modern EBRT because the cosmetic outcomes with EBRT have improved substantially in recent years. The committee heard from the clinical experts that breast fibrosis is more common with EBRT than with Intrabeam, but that both treatments are associated with a substantial increase in the occurrence of fibrosis in the breast. The committee noted comments from the company and patient groups stating that treatment with EBRT is associated with potential long-term damage to other organs including the heart, and that treatment with Intrabeam would reduce the radiation dose to adjacent tissues. However, a clinical expert stated that the radiation dose to the heart with modern EBRT is not clinically significant. The committee concluded that patients generally tolerate EBRT well, with good outcomes, but that avoiding multiple radiotherapy sessions by having a single treatment with Intrabeam at the same time as surgery would be considered a major advantage by some patients.

Clinical effectiveness

The TARGIT-A trial

4.4 The committee discussed the clinical evidence presented for Intrabeam, which came from a randomised trial comparing Intrabeam with EBRT (TARGIT-A). The committee had a number of concerns with the trial; it noted several comments received from professional and patient groups, and comments made by the assessment group, highlighting concerns about the robustness of the trial and its generalisability to NHS clinical practice. The committee noted that in TARGIT-A, EBRT was delivered in

an average of 23 fractions, longer than the 15 fractions delivered in established clinical practice in the NHS. The radiation doses administered with EBRT also ranged from 40 grays to 56 grays in TARGIT-A, whereas established clinical practice in the NHS is a dose of 40 grays. The committee also noted comments from professional groups highlighting that quality control of EBRT was not reported in some centres, and may have shown considerable variation internationally. The clinical experts stated that it is not possible to predict what effect the variation in dose may have had on the results of the trial. Only 6 of the 33 centres participating in the trial were in the UK. The committee concluded that some doubt remains about the generalisability of the trial results to NHS clinical practice.

Length of follow-up in the TARGIT-A trial

4.5 The committee noted comments received from professional and patient groups that the length of follow-up in the trial was too short to reliably demonstrate the clinical effectiveness of Intrabeam compared with EBRT for the incidence of local recurrence. Median follow-up in the trial was 2 years and 5 months and only 35% of the patients had 5-year follow-up at the time of the analysis. The committee heard from the clinical experts that longer follow-up, usually of at least 5 years, is needed for clinicians to feel confident about data on local recurrence. A clinical expert noted that this is the approach being followed for reporting the results of ongoing trials that are investigating whether the course of radiotherapy could be reduced from 3 weeks to 1 week, or whether radiotherapy is needed at all for some patients considered to have low risk of recurrence. The committee also noted comments from consultation on its preliminary recommendations that questioned the reliability of the data presented and suggested that the data are too immature to be the basis of firm recommendations. The committee heard from the TARGIT-A investigators that median follow-up in the trial is currently 4 years, and that complete follow-up and publication of final results is not yet known. The committee was aware of the large debate in the medical community about

TARGIT-A, in which opposite views have been raised about the importance of mature follow-up, trial governance and the interpretation of the results. The committee concluded that the results of TARGIT-A should be interpreted with caution because the length of follow-up is less than 5 years for the full trial population.

Subgroups in the TARGIT-A trial

4.6 The committee noted that TARGIT-A included a pre-pathology group (that is, treatment with Intrabeam was delivered at the same time as surgical removal of the tumour) and a post-pathology group (that is, treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound), and that this stratification was included as a protocol amendment. A clinical expert commented that this stratification was included because of centre preferences. Some trial centres gave Intrabeam only at a second operation after pathology results were available. The committee noted that the rate of local recurrence in the post-pathology group was higher than in the pre-pathology group, and that the company stated that non-inferiority for local recurrence had not been established in the post-pathology group. The committee also noted that, because of these results, the company suggested focusing only on the pre-pathology group and that the assessment group had also focused on this group to develop its economic model. The committee heard from a clinical expert that there were plausible reasons for worse results with Intrabeam when the treatment was delivered post pathology. At a second operation there could be scar tissue or seroma present, and targeting the exact tumour bed would be more difficult. The committee concluded that it was reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour.

The non-inferiority margin in TARGIT-A

4.7 The committee noted that TARGIT-A was a non-inferiority trial, and that the primary end point was local recurrence in the conserved breast. The committee heard from the company that there were no differences in the

rate of local recurrence in this group compared with the rest of the trial population. The committee considered the low rates of local recurrence, which had so far been demonstrated in both arms of the trial: 1.1% for EBRT and 2.1% for Intrabeam in the pre-pathology group. The committee noted that the pre-specified non-inferiority margin at 5 years for the absolute difference of local recurrence between treatment groups was 2.5%. The committee heard from the clinical experts that this was based on an estimated rate of 5-year local recurrence of 6% in the EBRT group. The committee noted that the non-inferiority margin is normally estimated based on the expected hazard ratio rather than on an estimated rate in the control group and an absolute difference in rates between groups. It considered that the pre-trial estimated 5-year rate of 6% for local recurrence, on which the non-inferiority margin was based, is higher than the current expected rate of local recurrence in people having treatment with EBRT. The committee also noted that patients in the trial had a relatively good prognosis and low risk of local recurrence and heard from the clinical experts that, since 2000, when patients were first recruited into the trial, the 5-year local recurrence rate with EBRT has decreased to much lower than 6%. The committee also noted that, when assessing non-inferiority, the point estimate alone is not sufficient. The confidence interval around the point estimate should also be considered and compared with the pre-specified non-inferiority margin. The committee noted that, in their response to the committee's request, the TARGIT-A investigators quantified the difference in the Kaplan–Meier estimates of local recurrence, and its 95% confidence interval, using 2 different methods. The committee also noted that the integrated difference method presented by the investigators: is not commonly used; provided more favourable results for Intrabeam; and was not pre-specified in the TARGIT-A protocol. It further noted that, because the non-inferiority margin was based on the absolute difference in local recurrence, the same margin could not be used for assessing non-inferiority if the integrated difference method were to be accepted. The committee considered that difference in Kaplan–Meier estimates of local recurrence

and its 95% confidence interval calculated using the conventional method were more appropriate. It noted that, using this method, the absolute difference between 5-year Kaplan–Meier estimates for local recurrence in the pre-pathology group was 1% and the 95% confidence interval was −0.68 to 2.68. On the currently available evidence, the committee concluded that there was no statistical reason for using a different method to assess whether Intrabeam is non-inferior to EBRT.

Local recurrence rates

4.8 The committee acknowledged that the rate of local recurrence in TARGIT-A was low in both treatment groups, and that longer follow-up of patients is needed to provide more long-term data and less uncertain results. The committee noted that the confidence interval around the absolute difference in local recurrence at 5 years is wide, and that the upper end of the interval is higher than the pre-specified non-inferiority margin (absolute difference 1%; 95% confidence interval −0.68 to 2.68). The committee considered that the criterion for non-inferiority was not appropriately defined. This meant that the trial was underpowered and the results could not be considered robust enough to determine whether Intrabeam is non-inferior to EBRT in terms of local recurrence. The committee therefore concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence is unproven. However, it acknowledged that the recurrence rates reported in the Intrabeam group could be considered low in absolute terms and, based on the evidence available so far, not out of line with current recurrence rates with EBRT in the NHS. The committee noted that the trial investigators stated that there have been 15 additional local recurrence events in the pre-pathology group since the analysis was done. But, because data were blinded, it is not possible to know which treatment group these events occurred in. The committee concluded that, although complete follow-up is needed to reduce the uncertainty around the results, the absolute number of local recurrences was still low. The committee expressed disappointment that the trial results remained blinded because this meant the technology

appraisal was done without access to the latest data, or a date when this would be available.

Overall survival results from TARGIT-A

4.9 The committee noted that the number of breast cancer deaths was higher in the Intrabeam group compared with the EBRT group, although the difference was not statistically significant. The committee also noted that there were fewer non-breast cancer deaths in the Intrabeam group compared with the EBRT group and that this difference was statistically significant. The committee noted the assessment group's considerations and the comments received on the assessment group's report from professional groups and the company on the difference in overall survival between the 2 treatment groups in TARGIT-A. It understood that the assessment group had reported that the difference in overall survival was based on a small number of events and that it did not consider that there was an excess of deaths in the EBRT group, but rather a shortfall of deaths in the Intrabeam group occurring by chance. The committee noted that the assessment group had compared the non-breast cancer mortality data from the EBRT group with the annual all-cause mortality probabilities obtained from the Office of National Statistics data and found that they were similar. The committee acknowledged that caution is needed when comparing international trial data (such as data from TARGIT-A) and country-specific data (such as data from the Office of National Statistics in the UK). The committee also noted comments received from professional groups and the company suggesting that the assessment group's conclusion on the difference in non-breast cancer death between treatment groups occurring by chance was erroneous and that whole breast radiation is associated with cardiac toxicity, which can increase the subsequent rate of ischaemic cardiac events. The committee heard from a clinical expert that the mean radiation dose to the heart was not provided in the TARGIT-A publication and that the mean dose to the heart delivered with EBRT in clinical practice in the NHS is minimal. Therefore it is highly unlikely that the difference in non-breast cancer deaths between

treatment groups in TARGIT-A could be explained by an increased risk of cardiovascular death related to EBRT. The committee heard from clinical experts and noted comments from professional groups suggesting that it is not possible to draw any conclusions from TARGIT-A in terms of an overall survival benefit with Intrabeam compared with EBRT. The committee agreed that, because the patient baseline characteristics in the trial did not include cardiovascular risk factors, it is not possible to confirm that there is an overall survival benefit with Intrabeam compared with EBRT.

The relative benefits and risks of Intrabeam

4.10 The committee considered the clinical evidence available for Intrabeam, taking into account the advantages of the technology that were highlighted by the patient expert. The committee noted that the clinical evidence for Intrabeam is immature and associated with considerable uncertainty. It acknowledged that Intrabeam has not been proven to be non-inferior to EBRT and could have a higher risk of local recurrence. The committee understood that some patients are willing to accept a higher risk of local recurrence as long as the absolute risk remains low and the treatment has other benefits that they consider important (see sections 4.2 and 4.3). The patient expert highlighted that patient choice should be based on an informed discussion between the patient and clinician, and that it is really important that patients understand all the benefits and risks associated with the technology. They noted that many patients make their decisions based on their personal circumstances and not necessarily based on the possibility of a future event in the long term. The clinical experts agreed that patient choice is important and the patient should be fully and clearly informed when making their decision. The committee heard from a clinical expert and noted comments from professional groups highlighting that patient choice needs to be based on high-quality evidence with adequate follow-up, which Intrabeam currently lacks. The committee concluded that there are benefits with Intrabeam that are very important to patients, particularly those associated with length of treatment and quality of life. It

acknowledged its previous conclusion that, although complete follow-up is needed to reduce uncertainty around the results, the absolute number of local recurrences is still low (see section 4.7).

Cost effectiveness

4.11 The committee considered the cost-effectiveness evidence presented for Intrabeam compared with EBRT. It noted that both the company and the assessment group focused on the pre-pathology group of TARGIT-A to develop their economic models. The committee noted that the results from both the company's and the assessment group's models estimated that the quality-adjusted life year (QALY) difference between Intrabeam and EBRT was very small. This was despite Intrabeam being associated with slightly more QALYs than EBRT in the company's model and being associated with fewer QALYs than EBRT in the assessment group's model. The committee also noted that the results from both the company's and the assessment group's models indicated that Intrabeam provided some cost savings compared with EBRT. However, these savings were higher in the company's model than in the assessment group's model. The committee also noted that the assumptions used by the company and the assessment group to develop their models were different, particularly for the costs associated with both technologies. When existing capital equipment is decommissioned or freed up for other use the best way to incorporate this into the economic modelling is not clear. The committee noted that section 5.5.8 of the NICE guide to the methods of technology appraisal 2013 states that, if introduction of the technology needs changes in infrastructure, costs and savings should be included in the analysis. Section 5.12.6 of the guide states that, if savings are anticipated, the extent to which these finances can actually be realised should be specified. The committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model (that is, including the capital costs of equipment for both technologies), or whether only the tariff cost associated with each technology should be included. The committee considered that, if the

capital cost of EBRT were included in the economic model, the cost savings associated with Intrabeam compared with EBRT would be greater. The committee agreed that both the company and the assessment group estimated the costs of Intrabeam treatment as lower than EBRT, but it concluded that the size of the cost savings was uncertain.

Uncertainty in the cost-effectiveness analyses

4.12 The committee agreed with its previous conclusion that the clinical effectiveness of Intrabeam compared with EBRT remains considerably uncertain (see sections 4.8 and 4.9). The committee noted the results from the assessment group's probabilistic sensitivity analysis, which also showed extreme uncertainty in the model results. It noted that the point estimate of the incremental cost-effectiveness ratio (ICER) for Intrabeam is associated with lower costs and fewer QALYs compared with EBRT. The committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it was not possible to state the most plausible ICER for Intrabeam compared with EBRT. It concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT.

Conclusions

4.13 The committee discussed whether, based on the evidence available, it was reasonable to recommend Intrabeam for routine commissioning in the NHS in England. It considered that the clinical- and cost-effectiveness evidence for Intrabeam remained uncertain. The committee noted its previous conclusions that, even if the length of follow-up of patients in TARGIT-A had been longer, the quality of the trial and particularly its generalisability to NHS clinical practice would still not have provided conclusive evidence to establish the relative clinical and cost effectiveness of Intrabeam compared with EBRT as delivered in the NHS. The committee also noted that the rate of local recurrence with Intrabeam may be higher than with EBRT. However, it took into account that

Intrabeam may provide benefits that some patients would consider substantial and that there are some patients who could particularly benefit from Intrabeam, such as people for whom EBRT is not suitable. The committee recognised its role of not recommending treatments for routine use if the benefits to patients are unproven, or if the treatments are not cost effective, in line with section 6.1.2 of the guide to the methods of technology appraisal 2013. However, it understood that, to have the benefits of Intrabeam, some patients may be willing to accept a treatment that may be associated with a higher risk of local recurrence. It noted several benefits highlighted by the patient and clinical experts in terms of improving patients' quality of life, which could not be captured in the QALY calculation. It also noted that, although non-inferiority for Intrabeam compared with EBRT was unproven for local recurrence, the rates of recurrence in the Intrabeam group in the pre-pathology group were low. The committee understood the concerns raised by the clinical experts and the comments from professional groups that it is crucial to offer informed choice in clinical practice. The committee accepted that individual patient preference is important and agreed with the patient and clinical experts that patients should be fully informed of the evidence and treatment options available. The committee concluded that, given the difficulty in interpreting the evidence (particularly when specialist clinicians do not agree), patient selection for Intrabeam radiotherapy, if made available, should be done by multidisciplinary teams experienced in managing early invasive breast cancer including breast surgeons, clinical oncologists and radiotherapy physics experts in brachytherapy. The committee agreed that clinicians wishing to carry out Intrabeam radiotherapy should ensure that patients understand the uncertainties about the procedure, and inform them about alternative treatment options. It also agreed that patients should be given written information, from NICE, on the evidence of the risks and benefits of all available treatment options to help with shared decision-making.

4.14 The committee understood that, if treatment with Intrabeam became widespread, considerable investment in equipment would be needed. However, if Intrabeam results were subsequently found to be unfavourable, this would be associated with irrecoverable costs to the NHS and potentially with overall worse outcomes at a population level. However, the option of localised single treatment with Intrabeam is welcomed by patients and, if its clinical and cost effectiveness can be confirmed, it could be beneficial for both patients and the NHS. Taking these factors into account, the committee considered that it is a technology worthy of further evaluation. The committee concluded that, because of the uncertainty in the evidence available, the Intrabeam radiotherapy system cannot be recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgery to remove the tumour.

4.15 The committee heard from the clinical experts that there are 6 Intrabeam devices in the UK, which were used in TARGIT-A but are not all being used at the moment. The committee considered that, given these existing resources, including staff trained in using Intrabeam, it would be reasonable to continue to use those devices that are available until further data is collected. The committee understood that there is considerable pressure on the existing NHS infrastructure for providing radiotherapy. As demand continues to rise the NHS will have to make further investment in new radiotherapy resources, taking into account emerging evidence on optimum pathways of care. The committee considered that collecting information about all patients having treatment with Intrabeam at a national level will allow the evidence from TARGIT-A to mature while further data are collected in the NHS in a carefully controlled manner. The committee therefore concluded that it can only recommend the use of the Intrabeam radiotherapy system using only machines that are already available and only in conjunction with NHS England specified clinical governance, data collection and submission arrangements. These

providers will also be required to comply with any NHS England service specifications pertaining to the delivery of intra-operative radiotherapy.

4.16 The committee recommended that further data collection in the NHS should include, as a minimum, a national collection of data from all patients having the Intrabeam radiotherapy system for adjuvant treatment of early invasive breast cancer in the NHS and it be recorded in the national radiotherapy dataset. Clinicians should audit, review and document clinical outcomes (described in section 6) locally, and consider the relationship between outcomes and patients' characteristics.

4.17 The committee discussed the technical requirements for Intrabeam and noted comments received from professional groups. It heard from the clinical experts that, although staff training is needed for Intrabeam, this will not necessarily mean there will be an increase in the number of staff or staff time, rather a change in their responsibilities and duties. The committee agreed with the clinical experts and concluded that the Intrabeam radiotherapy system should only be used by clinicians with specific training in its use.

Equalities issues

4.18 The committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. A committee member raised the question of whether there is the potential for some patients to be disadvantaged by the recommendations, if they lack the capacity to understand the information provided by the clinician and to make an informed choice (such as people with learning disabilities or communication difficulties). The committee considered that patients would not be disadvantaged by the recommendations, providing that clinicians act in the interest of their patients, in line with their usual responsibilities, and tailor their explanation to each patient's level of understanding, and discuss the risks and benefits with the patient's carers when applicable. The committee concluded that there was no need to alter or add to its recommendations.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Intrabeam radiotherapy system for adjuvant treatment of early breast cancer	Section
Key conclusion		
The Intrabeam radiotherapy system is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour. Use of the Intrabeam radiotherapy system is recommended only using machines that are already available and in conjunction with NHS England specified clinical governance, data collection and submission arrangements. The procedure should only be carried out by clinicians with specific training in the use of the Intrabeam radiotherapy system. Patient selection for Intrabeam radiotherapy should be done by a multidisciplinary team experienced in the management of early invasive breast cancer which includes both breast surgeons and clinical oncologists. Clinicians wishing to undertake Intrabeam radiotherapy should take the following actions: • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainties about the procedure and inform them about alternative treatment options. • Provide patients with NICE's written information on the evidence of the risks and benefits of the range of treatment options available as an aid to shared decision-making.		1.1 – 1.5

Current practice		
Clinical need of patients, including the availability of alternative treatments	Intrabeam could be used when external beam radiotherapy (EBRT) is unsuitable or not possible, for example, for those patients who are unable to raise their arm. People for whom EBRT is not a suitable treatment are currently offered mastectomy, and Intrabeam might be an appropriate option for them. Patients generally tolerate EBRT well, with good outcomes, but avoiding multiple radiotherapy sessions by having a single treatment with Intrabeam at the same time as surgery would be considered a major advantage by some patients.	4.2 4.3
The technology		
Proposed benefits of the technology How innovative is the technology/are the technologies in its/their potential to make a significant and substantial impact on health-related benefits?	The committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed, and also represented an alternative treatment option for people for whom EBRT is not suitable or not possible.	4.2

What is the position of the treatment(s) in the pathway of care for the condition?	Usual clinical practice in the NHS is to give adjuvant radiotherapy to people with early breast cancer after successful breast-conserving surgery (that is, removal of the tumour with clear margins). This is given by external beam radiotherapy (EBRT). An additional external radiotherapy boost dose to the site of the excised tumour lasting a further 1 week to 2 weeks could be offered to people with a higher risk of local recurrence. Intrabeam delivers a single dose of targeted low energy (X-ray) radiation to the tumour bed and can be used in an operating theatre as a single treatment at the same time as surgery to remove the primary tumour.	4.1 4.2
Adverse reactions	Adverse reactions are mostly related to wound-related and radiotherapy-related complications.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	A randomised trial comparing Intrabeam with EBRT (TARGIT-A). It was a non-inferiority trial and the primary end point was local recurrence in the conserved breast. Length of follow-up in the trial was too short to reliably show the clinical effectiveness of	4.4, 4.7 4.5

	Intrabeam compared with EBRT for the incidence of local recurrence. The committee noted that the clinical evidence for Intrabeam was immature and associated with considerable uncertainty. It acknowledged that Intrabeam had not been proven to be non-inferior to EBRT and could be associated with a higher risk of local recurrence.	4.10
Relevance to general clinical practice in the NHS	In TARGIT-A, EBRT was delivered in an average of 23 fractions, longer than the 15 fractions delivered in established clinical practice in the NHS. The radiation doses administered with EBRT also ranged from 40 grays to 56 grays in TARGIT-A, whereas established clinical practice in the NHS is a dose of 40 grays. Comments from professional groups highlighted that quality control of EBRT was not reported in some centres, and there may have been considerable variation internationally. The committee concluded that some doubt remained about the generalisability of the trial data to NHS clinical practice.	4.4

Uncertainties generated by the evidence	The committee noted that the clinical evidence for Intrabeam was immature and associated with considerable uncertainty. It acknowledged that Intrabeam had not been proven to be non-inferior to EBRT and could be associated with a higher risk of local recurrence. It was not possible to confirm that there is an overall survival benefit with Intrabeam compared with EBRT.	4.10 4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	TARGIT-A included a pre-pathology group (that is, treatment with Intrabeam was delivered at the same time as surgical removal of the tumour) and a post-pathology group (that is, treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound). The rate of local recurrence in the post-pathology group was higher than in the pre-pathology group, and the company stated that non-inferiority for local recurrence had not been established in the post-pathology group. The committee concluded that it was reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour.	4.6

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee considered the low rates of local recurrence that had so far been shown in both arms of the trial: 1.1% for EBRT and 2.1% for Intrabeam in the pre-pathology group. It noted that the pre-specified non-inferiority margin at 5 years for the absolute difference of local recurrence between treatment groups was 2.5%. The clinical experts stated that this was based on an estimated rate of a 5-year local recurrence of 6% in the EBRT group. The committee considered that the difference in Kaplan–Meier estimates of local recurrence was 1% and the 95% confidence interval was −0.68 to 2.68.	4.7, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	Both the company and the assessment group focused on the pre-pathology group of TARGIT-A to develop their economic models.	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The assumptions used by the company and the assessment group to develop their models were different, particularly for the costs associated with both technologies. When existing capital equipment is decommissioned or freed up for other use, the best way to incorporate this into the economic modelling is not clear. The committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model (that is, including the capital costs of equipment for both technologies) or whether only the tariff cost associated with each technology should be included. The committee considered that, if the capital cost of EBRT had been included in the economic model, the cost savings associated with Intrabeam compared with EBRT would have been greater.	4.11

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee concluded that there are benefits of Intrabeam that are very important to patients, particularly those associated with length of treatment and quality of life. The committee understood that, to have the benefits of Intrabeam, some patients may be willing to accept a treatment that may be associated with a higher risk of local recurrence. It noted several benefits highlighted by the patient expert and clinical experts in terms of improving patients' quality of life, which could not be captured in the quality-adjusted life year (QALY) calculation.	4.10 4.13
Are there specific groups of people for whom the technology is particularly cost effective?	Only the pre-pathology group of patients was considered.	–

What are the key drivers of cost effectiveness?	The results from both the company's and the assessment group's models estimated that the QALY difference between Intrabeam and EBRT was very small. This was despite Intrabeam being associated with slightly more QALYs than EBRT in the company's model and being associated with fewer QALYs than EBRT in the assessment group's model. The results from both the company's and the assessment group's models indicated that Intrabeam provided some cost savings compared with EBRT. However, these savings were higher in the company's model than in the assessment group's model. The assumptions used by the company and the assessment group to develop their models were different, particularly for the costs associated with both technologies. When existing capital equipment is decommissioned or freed up for other use the best way to incorporate this into the economic modelling is not clear.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The results from both the company's and the assessment group's models estimated that the QALY difference between Intrabeam and EBRT was very small. The committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it was not possible to state the most plausible incremental cost-effectiveness ratio (ICER) for Intrabeam compared with EBRT. It concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT.	4.11, 4.12
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	–
End-of-life considerations	Not applicable	–

Equalities considerations and social value judgements	A committee member raised the question of whether there is the potential for some patients to be disadvantaged if they lack the capacity to understand the information provided by the clinician and to make an informed choice (such as people with learning disabilities or communication difficulties). The committee considered that patients would not be disadvantaged by the preliminary recommendations, providing that clinicians act in the interest of their patients, in line with their usual responsibilities, and tailor their explanation to each patient's level of understanding, and discuss the risks and benefits with the patient's carers when applicable.	4.18

5 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal. The normal period of compliance is 3 months, but may be extended under Section 7(5) of the Regulations.

5.1 This technology has not been recommended for routine commissioning. The committee has recommended the use of the technology using only machines that are available and only in conjunction with NHS England specified clinical governance and data collection arrangements.

6 Recommendations for further data collection

6.1 Clinicians should enter details about all patients who choose to have the Intrabeam radiotherapy system for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour in the NHS onto a national register. They should audit, review and document clinical outcomes locally, and consider the relationship between outcomes and patients' characteristics.

6.2 The data and clinical outcomes to be collected include:

- histology of the cancer and patients' characteristics including: type, size and grade of the tumour; side of the body affected; lymph node status; oestrogen receptor status; progesterone receptor status; human epidermal growth factor receptor 2 status; and age of the patient
- local recurrence
- treatment after local recurrence
- metastatic disease
- disease-free survival
- overall survival
- adverse effects of treatment
- health-related quality of life (including EQ-5D).

7 Review of guidance

7.1 The review date for this guidance will be informed by the duration of the further data collection, which is to be confirmed.

Jane Adam
Chair, appraisal committee
August 2017

8 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Pilar Pinilla-Dominguez
Technical Lead

Joanna Richardson
Technical Adviser

Bijal Joshi/Liv Gualda
Project Manager(s)

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