NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Intrabeam Radiotherapy System for the adjuvant treatment of early breast cancer

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The manufacturer and the Assessment Group identified 1 relevant clinical trial, TARGIT-A. This trial included a pre-pathology and a post-pathology group, both the manufacturer and the Assessment Group suggested that only data from the pre-pathology group matched the decision problem. The Assessment Group also noted that in TARGIT-A, non-inferiority was not established for the post-pathology group. What is the Committee's view on the pre-pathology and post-pathology groups? Does the Committee consider it appropriate to focus solely on the pre-pathology group for the appraisal of Intrabeam?
- The overall median follow-up in the trial was 2 years and 5 months and only 35% of the patients reached a median follow-up of 5 years. A professional group highlighted that they would not recommend the use of Intrabeam radiotherapy

system outside the context of a clinical trial because of the lack of robustness and immaturity of its clinical evidence. What is the Committee's view on the follow-up duration in the trial?

- Analysis of the primary outcome, local recurrence in the conserved breast, including all patients in TARGIT-A showed that the difference in local recurrence between Intrabeam and EBRT did not exceed the non-inferiority margin of 2.5%. Local recurrence rates were higher with Intrabeam than with EBRT in the overall population, pre-pathology group and post-pathology group. What is the Committee's view on the local recurrence results from TARGIT-A?
- Results of overall survival showed that the 5-year mortality cumulative risk was lower in people receiving Intrabeam than in people receiving EBRT. Breast cancer mortality rates were higher in people receiving Intrabeam than in people receiving EBRT. However, non-breast cancer mortality rates were lower in the Intrabeam group than in the EBRT group. The professional groups noted that it is not possible to confirm whether there would be any difference between Intrabeam and EBRT in terms of non-breast cancer deaths and highlighted that, although the results from TARGIT-A showed statistically significant differences between treatment groups, the excess of non-breast cancer deaths with EBRT compared with Intrabeam was not explained by a radiation or treatment exposure with EBRT. The Assessment Group did not consider that there was an excess of deaths in the EBRT group but a shortfall of deaths in the Intrabeam group because of chance or the slightly younger mean age of patients in this group. Consultees considered that the Assessment Group's conclusion on a lower mortality in the Intrabeam group compared with the EBRT group because of chance or the possible younger age of people in the Intrabeam group was erroneous. They noted that mean age on both treatment groups was comparable, whole breast radiation is associated with cardiac toxicity and ionizing radiations which increase the subsequent rate of ischemic heart disease, and the inclusion of deaths because of ischemic bowel and stroke in the EBRT group would have increased the mortality rate because of cardiovascular death in this group. What is the Committee's view on the overall survival results?
- Neither the manufacturer nor the Assessment Group presented results on disease-free survival. The Assessment Group noted that the initial TARGIT-A

publication (2010) reported disease-free survival results but that this endpoint was not reported in the last trial publication (2014). However, the Assessment Group included other data from the 2010 publication in its report such as the rates of early complications. One consultee considered that it was more appropriate to use disease-free survival in the model and provided data on this outcome measure. What is the Committee's view on the omission of this outcome?

- Results from the safety analysis showed that there were more wound seroma complications in people receiving Intrabeam than in people receiving EBRT but radiotherapy-related complications, RTOG toxicity scope of grade 3 or 4, were less frequent in people receiving Intrabeam compared with people receiving EBRT. A professional group highlighted that in TARGIT-A, the quality control of the EBRT group was minimal and that variations in protocol commonly affect outcomes impacting on the differences between treatment groups (e.g. increased toxicity in the EBRT group).The Assessment Group noted further that the incidence of complications arising 6 months after randomisation was lower than the incidence of early complications in both treatment groups but highlighted that it was not clear whether these complications occurred in any of the same patients reporting early complications. What is the Committee's view on the adverse effect profile of Intrabeam compared with EBRT?
- Patient experts highlighted the benefits of Intrabeam to patients (e.g. treatment delivery at the same time of surgery, avoidance of continuous hospital visits and side-effects associated with conventional radiotherapy). What is the Committee's view on the particular benefits of Intrabeam to patients compared with EBRT?
- The professional groups noted that all radiotherapy centres in the UK have access to EBRT which has a relatively low cost and there are many clinical specialists trained in its use. The professional groups also noted that there are clinical trials in development studying the reduction of the scheduled treatment with EBRT from over 3 weeks to a 1 week treatment and other trials studying whether radiotherapy could be completely omitted in people with very low risk of recurrence. Does the Committee consider that clinical practice in the UK would change in the short term? What is the Committee's view on the extent to which this change would impact on the appraisal of Intrabeam?

Cost effectiveness

- The Assessment Group noted that the manufacturer did not conduct a systematic review of economic evaluations and that the information provided about the manufacturer's model was limited. It considered that the results of the manufacturer's model should be considered with caution because of methodological and reporting limitations and that the manufacturer should not have assumed:
  - a simplified structure of the model because it would have been more appropriate to include an additional state for progressed disease and
  - a time horizon of 20 years because it was too short to reflect the entire follow-up period of the disease.

  What is the Committee's view on the manufacturer's economic model and the critiques from the Assessment Group on it?
- The Assessment Group noted that its clinical advisers suggested that the risk of local recurrence continues relatively liner over the lifetime of the patient and applied a log-normal distribution to the 5-years data from the TARGIT-A to extrapolate these results over the time horizon of the model. Consultees noted that local recurrence data should not be extrapolated beyond 5 years because the peak of local recurrence is observed during the first 2 – 3 years after surgery and radiation. Does the Committee consider it appropriate to extrapolate local recurrence over the 40-years' time horizon?
- The manufacturer assumed in its model that:
  - the number of annual procedures with Intrabeam was 100
  - the average number of fractions with EBRT was 23
  - Intrabeam was given concurrently with initial lumpectomy
  - patients will have lumpectomy after local recurrence with Intrabeam and mastectomy after local recurrence with EBRT.

  The Assessment Group assumed that:
  - 16% of the people diagnosed of breast cancer would be eligible to receive treatment with Intrabeam and with a hospital catchment of 1,000,000, the number of annual procedures with Intrabeam was assumed to be 126

- the average number of fractions with EBRT was 15 in line with UK clinical practice
- 80% of the patients received mastectomy at local recurrence
- 31% of patients who received mastectomy would also receive breast reconstruction
- the proportion of patients receiving Intrabeam who also received EBRT was 15.2%.

Comments from consultation on the Assessment Group's report noted that:

- in clinical practice the proportion of patients who have mastectomy after local recurrence is lower
- the proportion of patients who have breast reconstruction following mastectomy is higher and
- the proportion of patients eligible to receive treatment with Intrabeam is higher.

The Assessment Group noted that varying the proportion of patients who have mastectomy after local recurrence, the proportion of patients who have breast reconstruction following mastectomy or the proportion of patients eligible to receive Intrabeam did not have a big impact on the ICER.

Which assumptions does the Committee consider best represent clinical practice in the UK?

- The Assessment Group assumed in its economic model that that only 1 local recurrence was possible and that it was only possible to die from breast cancer whilst in the 'any other recurrence' state. What is the Committee's view on these assumptions?
- The Assessment Group obtained the probability of non-breast cancer death from life tables in England and assumed that it was the same in both treatment groups. The Assessment Group confirmed that the annual probability of death in the EBRT group was similar to the one observed in the life tables in England and restated that the shortfall of death observed in the Intrabeam group in TARGIT-A could be explained by chance or a slightly younger mean age of patients in this group. Does the Committee consider it appropriate to assume the same probability of non-breast cancer death for Intrabeam and EBRT?

- The Assessment Group applied, in its base-case analysis, the same utility value to the first year after local recurrence and to the second and following years after both primary breast cancer and local recurrence, it applied a lower utility value in the 'any other recurrence' state and it did not apply a disutility associated with mastectomy. The manufacturer applied in its model higher utility values than the ones assumed by the Assessment Group. The Assessment Group noted that utilities in the manufacturer's model were obtained with the standard gamble technique and were not obtained from the general population; however the utility values applied in the Assessment Group's model were obtained with EQ-5D and valued with the UK tariff. One consultee noted that it was questionable to assign a lower utility value to the 'any other recurrence' state. What is the Committee's view on the most plausible utility values?
- The manufacturer assumed in its model that the cost of EBRT was reflected by the HRG code for 'other radiotherapy treatment'. The Assessment Group, however, considered that it was more appropriate to use the HRG code for 'deliver a fraction of radiotherapy on a megavoltage machine' which included 'external beam radiotherapy delivered by linear accelerator'. The Assessment Group included the cost of 1 hour in operating theatre and additional staff time cost for Intrabeam based on NHS pay bands of surgical consultant and 8b, 7 and 5. The Assessment Group did not include costs associated with adverse events in the model or post-progression costs. Comments from consultation on the Assessment Group's report highlighted that therapeutic radiographers should be included because they are core staff for the delivery of high quality radiotherapy, training costs should not be defined as considerable because non-surgical radiotherapy team are already trained in the core requirements of radiotherapy and would only require technical updates in the process and practice associated with Intrabeam, and that the additional time in the operating theatre with Intrabeam is on average 30 minutes because sentinel lymph node evaluation is carried out at the same time.

  What is the Committee's view on the most appropriate costing assumptions? Does the Committee consider it appropriate to not include the costs associated with adverse events and post-progression costs in the model?

- The manufacturer's cost-effectiveness analysis showed that Intrabeam was a dominant strategy (that is, it had lower costs and better outcomes) compared with EBRT. The results of the Assessment Group's cost-effectiveness analysis of Intrabeam compared with EBRT showed that Intrabeam cost £140 less and provided 0.088 less QALYs compared with EBRT resulting in an ICER of £1569 saved per QALY lost. The Assessment Group noted that in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. What is the Committee's view on the most plausible ICER of Intrabeam compared with EBRT?
- The Assessment Group undertook several sensitivity analyses and found that the parameters that had the highest impact on the cost-effectiveness results were
  - the probability of any other recurrence
  - the probability of death from breast cancer in the Intrabeam group and
  - changes in parameter values considered for the beta coefficient for the Intrabeam group in the log-normal model of time to local recurrence.

  Changes between higher and lower values for these parameters changed the consideration of the most cost-effective alternative at a maximum acceptable ICER of £20,000 per QALY gained. The results of the probabilistic sensitivity analysis also showed that the degree of uncertainty around the cost-effectiveness results was high and the cost-effectiveness plane showed that simulations of the ICER of Intrabeam compared with EBRT fell in the 4 quadrants. The Assessment Group also conducted scenario analyses varying the main assumptions on the model. What is the Committee's view on the degree of uncertainty around the Assessment Group's cost-effectiveness results?
- The Assessment Group highlighted some factors relevant to the NHS and other parties:
  - the increased need for radiotherapy during the next years
  - the high investment associated with Intrabeam if it becomes widely available in the NHS: capital cost, staff training and additional operating theatre time
  - the potential of Intrabeam for freeing-up radiotherapy resources

- the impact of changes in UK clinical practice associated with radiotherapy delivery as a result of the ongoing FAST-Forward trial, which investigates the potential to provide a shorter course of treatment with EBRT, and the potential of identifying a subset of patients who would not need to receive EBRT treatment.

What is the Committee's view on the issues raised by the Assessment Group as relevant to the NHS and other parties?

1 Background: clinical need and practice

1.1 Breast cancer is the most common cancer in the UK accounting for about 1 in 3 of all cancers in women. A breast lump is often the first symptom of breast cancer.

1.2 There are 2 main forms of early breast cancer: in situ disease predominantly in the form of ductal carcinoma in situ (DCIS) and invasive cancer. In DCIS, cancer cells have developed inside milk ducts but have not spread beyond the ducts. For invasive cancer to be categorised as early breast cancer the tumour should not have spread beyond the breast or the lymph nodes (which remain mobile) in the armpit ipsilateral to (on the same side as) the affected breast. When the cancer spreads outside the lining of the ducts, this is considered to be invasive early breast cancer and classified as stage I and II (or operable breast cancer).

1.3 In 2011, there were 41,826 people diagnosed with invasive breast cancer in England. There are not incidence statistics available for in situ breast cancer for 2011 but there were 4937 people diagnosed in 2010 in England. Over 9700 people died in England as a result of breast cancer in 2011. Breast cancer incidence rates generally increase with age; with over 80% of new diagnoses in women aged over 50 years. It is estimated that 95% of women are expected to survive their disease for at least 1 year and 85% of women survive 5 years or more.

1.4 Treatment for early disease can be divided into primary treatment, which is surgical (removal of the tumour), and adjuvant treatment, which can

include radiotherapy, hormone therapy, biological therapies, or chemotherapy after removal of the primary cancer by surgery.

1.5 Surgery is usually the first treatment option for early breast cancer. Preoperative assessment of the breast and axilla determines the size of the primary tumour relevant to the volume of breast and this information is used to decide whether wide local excision of the tumour or lumpectomy is possible, allowing breast conserving surgery instead of mastectomy. Patients who have a mastectomy can have immediate breast reconstruction (carried out at the same time as the mastectomy) or delayed breast reconstruction. After surgical removal of the primary tumour, the breast cancer multidisciplinary team plans subsequent treatment using the information on prognostic and predictive factors obtained by histological examination, the outcome of tests for oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status, and other patient and tumour characteristics. NICE clinical guideline 80 on early and locally advanced breast cancer recommends adjuvant chemotherapy or radiotherapy for people with early breast cancer following successful breast conserving surgery (that is, removal of tumour with clear margins) to prevent loco-regional recurrences. Adjuvant radiotherapy is currently delivered in UK clinical practice by external beam radiotherapy (EBRT) using a linear accelerator and may be supplemented with an external beam tumour bed boost. Whole breast EBRT is delivered either within 4-6 weeks of surgery or 4-6 months later following completion of cytotoxic therapies. Standard practice is to give 40 Gy in 15 fractions, typically over 3-5 weeks, and this may be followed by a boost dose (12 Gy in 4 fractions, 10 Gy in 5 fractions, or 16 Gy in 8 fractions) to the tumour bed over 1 or 2 weeks in patients considered to be at a higher risk of local recurrence. NICE interventional procedures guidance 268 on Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision only recommends brachytherapy as an adjuvant treatment in the context of research.

2 The technology

2.1 Intrabeam Radiotherapy System (Carl Zeiss UK) is a mobile irradiation system designed to deliver a single dose of targeted low energy x-ray radiation directly to the tumour bed while limiting healthy tissue exposure to radiation. Because it delivers a low energy x-ray radiation, it can be used in an ordinary operating theatre at the time of surgery. Intrabeam system provides a source of 50 kV energy x-rays at the centre of a spherical applicator of 1.5 to 5.0 cm diameter. The applicator is surgically placed in the tumour bed by an inserted purse-string suture that ensures that breast tissues at risk of local recurrence receive the prescribed dose while skin and deeper structures are protected. Radiation is delivered over 20 to 45 minutes to the tumour bed. The surface of the tumour bed typically receives 20 Gy that attenuates to 5 to 7 Gy at 1cm depth. Intrabeam was granted a CE (Conformité Européene) mark in 1999 for use in radiotherapy.

2.2 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). The intraoperative radiotherapy with Intrabeam is given as a single fraction with a high dose directly to the tumour bed and possibly remaining tumour cells. In the case of the EBRT system, the whole breast is irradiated administering the prescribed dose in small fractions over a period of 3 to 5 weeks, starting some weeks after lumpectomy. EBRT is finished with a boost given in small fractions focused on the region of the tumour bed. In the case that intraoperative radiotherapy is given as a boost treatment with Intrabeam and the treatment is followed by EBRT, there is no need for further external boost treatment. Six centres in the UK have experience using Intrabeam for the adjuvant treatment of early breast cancer.

2.3 Adverse reactions are mostly related to wound-related complications and radiotherapy-related complications. For details of adverse reactions recorded in the clinical trial (TARGIT-A) please see section 4.8.

2.4 The manufacturer notified that the cost of the Intrabeam system (including the set with spherical applicators) is £435,000 (excluding VAT, Carl Zeiss UK personal notification). The manufacturer estimated that the device maintenance and servicing costs per year are approximately £35,000. Costs may vary in different settings because of negotiated procurement discounts.

Table 1 Summary description of technology

Proprietary name	Intrabeam
Manufacturer	Carl Zeiss UK
Dose	
Acquisition cost (including the set with spherical applicators)	£435,000
Spherical applicator cost (replacement needed after 100 treatments)	£3170
X-drapes radio protection shields (for a pack of 10 (5 treatments)*	£1041
Sterile plastic drape pack costs (pack of 5, 5 treatments)	£96
Maintenance and servicing cost (per year)	£35,000

Note: *the manufacturer noted that this is not needed everywhere in the UK

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of the Intrabeam Radiotherapy System for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Population	People with early operable breast cancer	People with early operable breast cancer (as defined by the trials). People with a local recurrence are excluded.

The Assessment Group noted that the population included in the report was people with early operable breast cancer who are eligible for wide local excision of the

tumour followed by whole breast radiotherapy. They also stated that early operable breast cancer includes people with ductal carcinoma in situ (DCIS) and those with invasive early breast cancer. The Assessment Group clarified that the use of Intrabeam in people with a local recurrence of breast cancer was not considered in line with the NICE scope.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Intervention	INTRABEAM Photon Radiotherapy System with or without external beam radiotherapy	
Comparators	External beam radiotherapy delivered by linear accelerator	

The Assessment Group noted that NICE did not include other intra-operative techniques as comparators in the scope because they are not currently in use in clinical practice. These techniques were also not included as interventions alongside Intrabeam because their use was not considered sufficiently comparable.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Outcomes	• overall survival • progression-free survival • ipsilateral local recurrence • adverse effects of treatment • health-related quality of life	• overall survival • disease-free survival • ipsilateral local recurrence • adverse effects of treatment • health-related quality of life

The Assessment Group did not include data on disease-free survival. It noted that the initial TARGIT-A publication (2010) reported disease-free survival results but that this endpoint was not reported in the last trial publication (2014).

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**

Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness (such as incremental cost per QALY gained)

3.2 NICE clinical guideline on early and locally advanced breast cancer (NICE clinical guideline 80) recommends surgery followed by adjuvant systemic therapy for people with early invasive breast cancer. After breast conserving surgery or mastectomy patients should have breast radiotherapy with EBRT, giving 40 Gy in 15 fractions as standard practice. For people at high risk of local recurrence, an additional external beam boost to the site of local excision should be offered (NICE pathway Early and locally advanced breast cancer: adjuvant therapy). Intrabeam could be used in the same place as EBRT in the treatment pathway as an alternative to whole breast radiation or as a boost before whole breast radiation with EBRT is provided.

4 Clinical-effectiveness evidence

4.1 The manufacturer presented evidence from its literature review on the clinical effectiveness of Intrabeam separately depending on the treatment protocol: used as a single method or treatment and used as a boost during surgery followed by external beam radiotherapy (EBRT). The manufacturer noted that it only included literature published after year

2007 because literature published before this year did not represent current clinical practice. It also noted that substantial follow-up experience (more than 5 years) with the use of Intrabeam would not be available before 2007 because Intrabeam became available in 2000.

4.2 The manufacturer primarily based its submission on TARGIT-A, a prospective randomised, non-inferiority clinical trial conducted in 33 centres in 11 different countries including UK. Patients were treated either with Intrabeam as a single method of treatment or with conventional EBRT (typically 40 – 56 Gy with or without a boost of 10 – 16 Gy). The pathology of the disease was assessed and further treatment with EBRT was considered in patients who received treatment with Intrabeam alone depending on the outcome of the pathology (people with tumour-free margin smaller than 1mm, extensive in-situ component or unexpected invasive lobular carcinoma). After a protocol amendment, some patients were allowed to receive treatment with Intrabeam as a second intervention after evaluation of final pathology (post-pathology group). The dose of radiation was administered during a second surgical procedure by opening the wound and administrating radiation. The manufacturer stated that median time of delivery was 37 days after the first surgery and that the protocol amendment led to separate strata, equivalent to 2 trials run in parallel.

4.3 The Assessment Group stated that the manufacturer did not conduct a formal systematic review of the clinical effectiveness of Intrabeam and highlighted that it did not indicate how the results of its search were screened to identify relevant studies, it did not include detailed inclusion and exclusion criteria and it did not present a quality assessment of the included studies. The Assessment Group carried out a systematic literature review in which inclusion and exclusion criteria were derived from the final NICE scope. The systematic review identified 1 randomised controlled trial (TARGIT-A) as relevant for inclusion in line with the manufacturer's search. The Assessment Group considered TARGIT-A to be of good methodological quality with a low risk of bias.

4.4 Women aged 45 years or older were randomised in a 1:1 ratio to receive either risk-adapted approach using single-dose Intrabeam or EBRT as per standard schedule over several weeks. In total, 3451 patients were recruited in TARGIT-A between 2000 and 2012, of which 1721 patients were randomised to receive treatment with Intrabeam and 1730 patients were randomised to receive EBRT. There were 2298 and 1135 patients randomised in the pre-pathology group and post-pathology group respectively. Among patients actually receiving treatment with Intrabeam (1571 patients after accounting for patient withdrawals), 15.2% (239 of 1571 patients) received treatment with Intrabeam and EBRT, 21.6% in the pre-pathology group (219 of 1012 patients) and 3.6% (20 of 559 patients) in the post-pathology group. The overall median follow-up in the trial was 2 years and 5 months and 35% of the patients (1222 of 3451) reached a median follow-up of 5 years. The Assessment Group stated that 77% of the patients in the trial were aged between 51 and 70 years, approximately 33%, 50% and 15% of the patients had grade 1, 2 and 3 tumours respectively. It noted that approximately 67% of the patients were receiving hormonal therapy as adjuvant systemic therapy and approximately 12% of the patients were receiving chemotherapy. The primary outcome measure was the absolute difference in local recurrence in the conserved breast and secondary outcomes were toxicity and overall survival.

4.5 Analysis of the primary outcome, local recurrence in the conserved breast, including all patients in TARGIT-A showed that the difference in local recurrence between Intrabeam and EBRT did not exceed the non-inferiority margin of 2.5%. Statistical significance levels were set at $p<0.01$ for this outcome. The 5-year risk of local recurrence in the conserved breast was 3.3% and 1.3% in people receiving treatment with Intrabeam and EBRT respectively ($p=0.042$). Local recurrence in the pre-pathology group was 2.1% in people receiving Intrabeam and 1.1% in people receiving EBRT ($p=0.31$) (see figure 1). Local recurrence in the post-pathology group was 5.4% and 1.7% in people receiving treatment with

Intrabeam and EBRT respectively (p=0.069) (see table 2 for complete results on local recurrence). The manufacturer stated that as a result of this analysis, the authors of TARGIT-A noted that caution should be taken and that they suggested that Intrabeam should only be used at the same time as lumpectomy and therefore, the post-pathology was not recommended further. The manufacturer noted that the post-pathology group had the same or even less risk factors than the pre-pathology group and that the difference in the results were not related to a variance in the patient population. It also stated that the difference in the results could be explained by the delayed application of radiotherapy. The Assessment Group noted that when the non-inferiority statistic was analysed for local recurrence, Intrabeam met the criteria (non-inferiority margin of 2.5%) to be considered non-inferior to EBRT for the whole population (absolute difference in binomial proportions 0.72%, 90% CI 0.2 to 1.3, $p_{non\text{-}inferiority}$<0.0001) and for the pre-pathology group (0.37%, 90% CI -0.2 to 1.0, $p_{non\text{-}inferiority}$ <0.0001). Non-inferiority was not established for the post-pathology group (1.39%, 90% CI 0 to 2.8, $p_{non\text{-}inferiority}$ =0.0664).

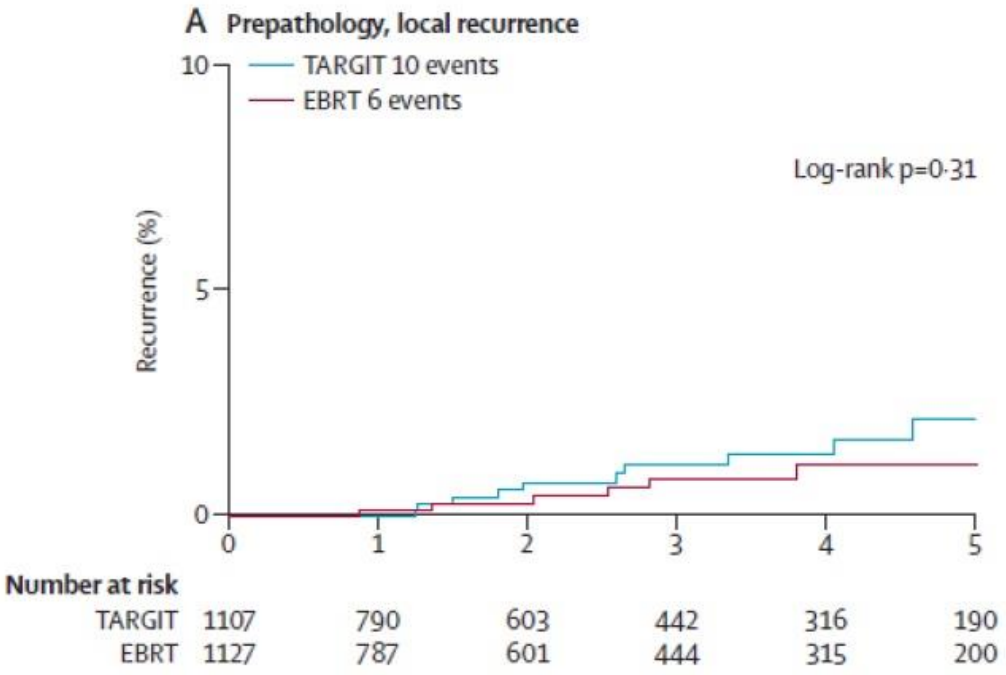
Table 2 5-year cumulative risk of local recurrence in TARGIT-A

Local recurrence Events/N; 5-year cumulative risk % (95% CI)	INTRABEAM	EBRT	Absolute difference; p-value
Whole group (n=3375)[a]	23/1679 3.3% (2.1-5.1)	11/1696 1.3% (0.7-2.5)	12 (2.0%); p=0.042
Pre-pathology stratum (n=2234)	10/1107 2.1% (1.1 to 4.2)	6/1127 1·1% (0.5 to 2.5)	4 (1.0%); p=0.31
Post-pathology stratum (n=1141)	13/572 5.4% (3.0 to 9.7)	5/569 1.7% (0.6 to 4.9)	8 (3.7%), p=0.069

[a] Patients who had undergone a mastectomy were not included in the analysis of local recurrence (n= 76 mastectomies in the whole group, n=64 in the pre-pathology stratum, n=12 in the post-pathology stratum).

Source: Assessment Group's report, table 9, page 44

Figure 1 5-year cumulative risk of local recurrence in the pre-pathology group from TARGIT-A



TARGIT: Targeted intraoperative radiotherapy with Intrabeam

Source: Manufacturer's submission, figure 1, page 10

4.6 The manufacturer and the Assessment Group did not include data on disease-free survival. The Assessment Group noted that the initial TARGIT-A publication (2010) reported disease-free survival results, however this outcome was not considered in the last publication (2014).

4.7 For the analysis of overall survival, statistical significance levels were set at $p<0.05$. The results showed that the 5-year risk of mortality was 3.9% (37 of 1721 patients) in the Intrabeam group compared with 5.3% (51 of 1730 patients) in the EBRT group and that the difference in overall survival between groups was not statistically significant ($p=0.099$). The breast cancer mortality rate was higher in people that received Intrabeam (2.6%) than in people that received EBRT (1.9%) but the difference between treatment groups was not statistically significant ($p=0.56$). There

were statistically significant fewer non-breast cancer deaths in the Intrabeam group (1.4%) than in the EBRT group (3.5%) (p=0.0086). The Assessment Group noted however that these data were based on a small number of events (in the pre-pathology group, 12 non-breast cancer deaths in the Intrabeam group and 27 in the EBRT group). It commented that the TARGIT-A publication showed that the higher number of non-breast cancer deaths in the EBRT group could be because of cardiovascular causes and other cancers and that it was improbable that there was a substantial imbalance in baseline comorbidities between the 2 treatment groups. The Assessment Group also commented that patients included in the EBRT group were slightly older at baseline (the Assessment Group calculated a mean age of 62.5 years for the EBRT group and of 62 years for the Intrabeam group). The Assessment Group has also compared the annual probabilities of death in 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 Assessment Group did not consider that there was an excess of deaths in the EBRT group but a shortfall of deaths in the Intrabeam group because of chance or the slightly younger mean age of patients in this group. Results in the pre-pathology group were similar to the results in the whole population (see figure 2). Results in the post-pathology group showed that the number of deaths between treatment groups were similar (see table 3). The causes of non-breast cancer deaths are included in table 4.

Table 3 5-year mortality cumulative risk in TARGIT-A

Mortality Events/N; 5-year cumulative risk % (95% CI)	INTRABEAM	EBRT	Absolute difference; p-value
Overall mortality:			
All patients (n=3451)	37/1721 3.9% (2.7 to 5.8)	51/1730 5.3% (3.9 to 7.3)	-14 (-1.4%); p=0.099
Pre-pathology stratum (n=2298)	29/1140 4.6% (1.8 to 6.0)	42/1158 6.9% (4.3 to 9.6)	-13 (-2.3%); p=NR
Post-pathology stratum (n=1153)	8/581 2.8% (1.3 to 5.9)	9/572 2.3% (1.0 to 5.2)	-1 (0.5%); p=NR

Breast cancer mortality:			
All patients (n=3451)	20/1721 2.6% (1.5 to 4.3)	16/1730 1.9% (1.1 to 3.2)	p=0.56
Pre-pathology stratum (n=2298)	17/1140 3.3% (1.9 to 5.8)	15/1158 2.7% (1.5 to 4.6)	p=0.72
Post-pathology stratum (n=1153)	3/581 1.2% (0.4 to 4.2)	1/572 0.5% (0.1 to 3.5)	p=0.35
Non-breast cancer mortality:			
All patients (n=3451)	17/1721 1.4% (0.8 to 2.5)	35/1730 3.5% (2.3 to 5.2)	p=0.0086
Pre-pathology stratum (n=2298)	12/1140 1.3% (0.7 to 2.8)	27/1158 4.4% (2.8 to 6.9)	p=0.016
Post-pathology stratum (n=1153)	5/581 1.58% (0.62 to 3.97)	8/572 1.76% (0.7 to 4.4)	p=0.32

Source: Assessment Group's report, table 1, page 47

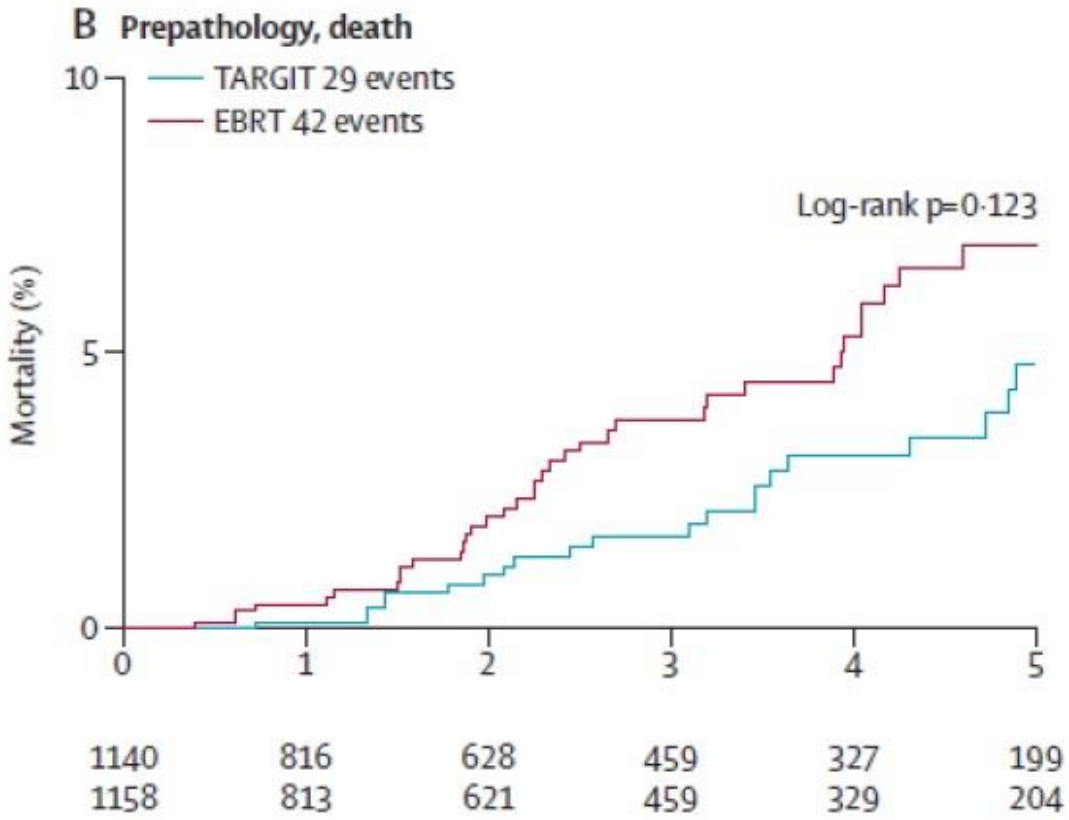
Table 4 Non-breast cancer mortality, causes of death (all patients)

Non-breast cancer mortality, causes of death	Intrabeam n=1721	EBRT n=1730
Other cancers	8	16
Cardiovascular causes		
Cardiac[d]	2	8
Stroke	0	2
Ischemic bowel	0	1
Other[e]	7	8
Total	17	35

Note: [d] Included one "sudden death at home" in the EBRT group. [e] Targit: 2 diabetes, 1 renal failure, 1 liver failure, 1 sepsis, 1 Alzheimer's disease, 1 unknown; EBRT: 1 myelopathy, 1 perforated bowel, 1 pneumonia, 1 old age, 4 unknown.

Source: Assessment Group's report, appendix 4, page 163

Figure 2 5-year mortality cumulative risk in the pre-pathology group from TARGIT-A



TARGIT: Targeted intraoperative radiotherapy with Intrabeam

Source: Manufacturer's submission, figure 1, page 10

4.8 The manufacturer noted that the results of the safety analysis showed that there were statistically significant fewer grade 3 and 4 radiotherapy-related complications in the Intrabeam group compared with the EBRT group. The Assessment Group provided further details of the complications in the form of local toxicity and morbidity. It noted that the incidence of any early complication was similar between treatment groups. Wound seroma requiring more than 3 aspirations occurred more frequently in people receiving Intrabeam (2.1%) than in people receiving EBRT (0.8%, p=0.012) and radiotherapy-related complications, RTOG toxicity scope of grade 3 or 4, was less frequent in people receiving Intrabeam (0.5%) compared with people receiving EBRT (2.1%, p=0.002). The Assessment Group further noted that the incidence of complications

arising 6 months after randomisation was lower than the incidence of early complications in both treatment groups but highlighted that it was not clear whether these complications occurred in any of the same patients reporting early complications. Table 5 shows a summary of toxicity and morbidity results in both treatment groups.

Table 5 Toxicity and morbidity from TARGIT-A

Early[a] complications	INTRABEAM (n=1113)	EBRT (n=1119)	p-value
No. of complications per patient:			
0			
1	917/1113 (82.4%)	946/1119 (84.5%)	NR
2	151/1113 (13.6%)	139/1119 (12.4%)	NR
3	29/1113 (2.6%)	27/1119 (2.4%)	NR
4	11/1113 (1.0%)	5/1119 (0.4%)	NR
5	3/1113 (0.3%)	0/1119	NR
6	2/1113 (0.2%)	0/1119	NR
Any complication[a]	0/1113	3/1119 (0.3%)	NR
	196/1113 (17.6%)	174/1119 (15.5%)	$\chi 2$ 1.74,p=0.19[b]
Clinically significant complications:[a]	INTRABEAM (n=1113)	EBRT (n=1119)	p-value
Haematoma needing surgical evacuation	11/1113 (1.0%)	7/1119 (0.6%)	0.338
Seroma needing >3 aspirations	23/1113 (2.1%)	9/1119 (0.8%)	0.012
Infection needing i.v. antibiotics or surgical intervention	20/1113 (1.8%)	14/1119 (1.3%)	0.292
Skin breakdown or delayed wound healing[c]	31/1113 (2.8%)	21/1119 (1.9%)	0.155
RTOG toxicity grade 3 or 4[d]	6/1113 (0.5%)	23/1119 (2.1%)	0.002
Major toxicity[e]	37/1113 (3.3%)	44/1119 (3.9%)	0.443
Wound-related complications arising 6 months after randomisation:	INTRABEAM (n=1721)	EBRT (n=1730)	p-value
Haematoma/seroma needing >3 aspirations	4/1721 (0.2%)[f]	2/1730 (0.1%)[f]	NR
Infection needing i.v. antibiotics or surgery	12/1721 (0.7%)[f]	9/1730 (0.5%)[f]	NR
Skin breakdown or delayed wound healing	3/1721 (0.2%)[f]	5/1730 (0.3%)[f]	NR
Total	19/1721 (1.1%)	16/1730 (0.9%)	0.599
Radiotherapy-related complications:			
RTOG toxicity grade 3 or 4	4/1721 (0.2%)	13/1730 (0.8%)	0.029

NR, not reported; RTOG, Radiation Therapy Oncology Group. Data are number of patients (%). [a]The 2010 paper does not indicate the time period over which these complications arose but the 2014 paper describes them as 'early complications'. [b]TARGIT (TARGIT: Targeted intraoperative radiotherapy with Intrabeam)vs EBRT for no complications vs any number of complications, degree of freedom = 1. [c]Some patients in first three rows could be included in the 4th row. [d]No patient had grade 4 toxicity. [e]Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4. [f] Percentages calculated by reviewer.

Source: Assessment Group's report, table 12, page 49

4.9 The manufacturer also included information from different studies including people who received treatment with Intrabeam as a boost followed by EBRT. The manufacturer stated that the results published from these studies demonstrated that Intrabeam given as a boost followed by EBRT led to good results, it was clinically feasible and it was associated with low toxicity and complications rates. The manufacturer also presented data from additional studies for the efficacy and safety of Intrabeam and EBRT. The Assessment Group noted that these studies did not meet the inclusion criteria in its systematic review mostly because of study design.

4.10 The manufacturer included data on quality of life and preferences from people who received treatment with Intrabeam as a boost followed by EBRT. Based on a study by Welzel et al. (2013) which analysed a subset of patients (2.5%) included in TARGIT-A and which assessed quality of life using the EORTC – QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) and the QLQ-BR-23 (Breast Cancer module), the manufacturer concluded that patients receiving Intrabeam showed ability to carry out more professional and other daily activities, and had fewer general pain symptoms compared with patients receiving EBRT. The Assessment Group further noted that the study by Welz et al. included results from an ITT analysis and an as-treated analysis (in which 5 patients from the Intrabeam group were removed, of which 4 were moved to the EBRT group because it was the actual treatment they received and 1 patient was excluded from the analysis because they refused to receive EBRT). The results from the ITT analysis did not show any statistically significant difference between treatment groups in any quality of life measure (statistically significance

set at p<0.01). The as-treated analysis showed a statistically significant benefit for Intrabeam in daily activities, general pain, breast symptoms and arm symptoms compared with EBRT. The Assessment Group noted that these data should be interpreted with caution because the small number of patients included in the analyses and because the non-randomised nature of these data. The manufacturer also included results from a preference study conducted to determine the trade-off preferences of women for a single treatment delivered intraoperative by Alvarado et al. (2013). The results showed that patients preferred treatment with Intrabeam rather with EBRT at an equivalent risk of local recurrence.

4.11 The Assessment Group also included information about ongoing studies using Intrabeam. It identified 1 RCT (TARGIT-B) that compared Intrabeam with EBRT after breast conserving surgery in women with high risk of local recurrence, and 1 single-arm trial (TARGIT-E) that investigated the efficacy of Intrabeam followed by EBRT only when risk factors were present in older people with low risk factors. It also identified 3 registry studies (TARGIT-R, TARGIT-BQR and TARGIT-US) that collect long-term and follow-up data of people receiving treatment with Intrabeam.

5 Comments from other consultees

5.1 The professional and patient groups agreed that treatment for early breast cancer consists of surgery (either lumpectomy or mastectomy which may be followed by breast reconstruction), radiotherapy and chemotherapy, and that some people might be eligible to receive targeted treatments and/or hormonal therapy. The current established adjuvant treatment for early breast cancer is whole breast radiotherapy and a possible boost to the tumour bed delivered by external beam radiotherapy (EBRT) with linear accelerators by 15 fractions of treatment over 3 weeks. The professional groups highlighted that currently, partial breast radiotherapy is not recommended as standard practice in the UK using any technology because there is lack of robust clinical evidence on this use. The professional groups noted that all radiotherapy centres in the UK have

access to EBRT which has a relatively low cost and there are many clinical specialists trained in its use (radiographers, physicists and oncologists). The professional groups also noted that there are clinical trials in development studying the reduction of the scheduled treatment with EBRT from over 3 weeks to a 1 week treatment and other trials studying whether radiotherapy could be completely omitted in people with very low risk of recurrence.

5.2 Patient groups highlighted that although early breast cancer is treatable it might recur and spread to other parts of the body. They noted that the psychological burden of the disease is high for the patient and its family and that people want to ensure that they have the best chance of ensuring that they have a future free from cancer. Patients groups highlighted that current radiotherapy practice requires continuous hospital appointments which implies inconvenient and disruptive travelling times to and from hospital and additional costs. Patient groups highlighted that Intrabeam would be particularly beneficial for patients because it is given at the same time as surgery and therefore would remove the need for hospital visits. Patient groups noted that administering radiotherapy treatment during surgery will lessen the impact that the treatment has on both the patients and their family and friends.

5.3 The professional and patient groups noted that the available clinical evidence suggests that Intrabeam is as effective as EBRT. The professional groups noted that the safety profile of Intrabeam is similar to EBRT and highlighted that radiotherapy specific toxicity seems to be lower with the use of Intrabeam compared with EBRT because of the smaller volume of breast treated to a lower dose with Intrabeam. A professional group highlighted that in TARGIT-A, the quality control of the EBRT group was minimal and that variations in protocol commonly affect outcomes impacting on the differences between treatment groups (e.g. increased toxicity in the EBRT group).

5.4 A professional group highlighted that they would not recommend the use of Intrabeam radiotherapy system outside the context of a clinical trial because of the lack of robustness and immaturity of its clinical evidence. Patient groups raised the importance of collecting long term data on the benefits and risks of Intrabeam. The professional groups noted that the available clinical evidence suggests that Intrabeam is associated with a high level of toxicity when used as a boost treatment in combination with whole breast radiotherapy compared with an EBRT boost, particularly in terms of high levels of late normal tissue fibrosis. The professional groups also noted that it is not possible to confirm whether there would be any difference between Intrabeam and EBRT in terms of non-breast cancer deaths and highlighted that, although the results from TARGIT-A showed statistically significant differences between treatment groups, the excess of non-breast cancer deaths with EBRT compared with Intrabeam could not be explained by a radiation or treatment exposure with EBRT. The professional group noted that for example, based on the expected median radiation dose to the heart in TARGIT-A, EBRT could only be considered the cause of 1 of the 11 cardiovascular deaths and that any excess in the number of cardiovascular deaths could be explained by imbalance between treatment groups in the relevant risk factors at presentation or under-reporting of cardiovascular deaths. They also noted that TARGIT-A did not provide information about the tumour site causing other cancer deaths in the trial and about the interval from randomisation to second cancer diagnosis. The professional group concluded that the follow-up in the trial was too short to show any induction of cancer by EBRT.

5.5 Patient groups were concerned about the 2 different methods of delivery of treatment with Intrabeam (as an alternative to whole breast radiation and as a boost prior to whole breast radiation), and highlighted that it is highly important that these methods are clearly and thoroughly explained to the patient prior to surgery avoiding the confusion about the need of further treatment and the exacerbation of fear and anxiety about recurrence and prognosis.

5.6 The professional groups noted that the Intrabeam radiotherapy system is currently only available in a small number of centres compared with the total number of UK centres delivering radiotherapy. They also noted that if Intrabeam would be implemented widely it would have a considerable negative impact on surgical theatre time as each treatment takes around 30 minutes and the costs per hour associated with running a surgical theatre are high regardless of whether time is spent operating or not. They highlighted that the use of Intrabeam may also increase waiting times for breast cancer surgery and that it would be unlikely that Intrabeam would replace the need for EBRT because many people with early breast cancer are likely to still need whole breast radiotherapy in the future. The professional groups also added that additional training on the use of Intrabeam would be required for breast surgeons, oncologists, physicists and radiographers. A professional group noted that the multi-disciplinary team legally required for the delivery of radiotherapy includes medical physics experts to provide independent verification of treatment parameters. In contrast, another professional group highlighted that treatment with Intrabeam has the potential of taking radiotherapy out of the major centres into smaller hospitals with no prior infrastructure for radiotherapy treatment. Patient groups highlighted that whilst initial investment will be required to purchase the device, Intrabeam would reduce the need for radiotherapy appointments which, in turn, would save clinical specialists time and would allow more people with the disease to be treated. A professional group noted that although radiotherapy treatment delivered with Intrabeam would take approximately 25 to 40 minutes, the multi-professional team would need to be available for approximately 2 to 3 hours per patient.

5.7 A professional group suggested that if Intrabeam would be introduced as a standard in the NHS, it would be advisable to maintain the organisational model applied during the TARGIT-A trial in clinical practice. This includes a registered clinical scientist (radiotherapy physics) on site and a medical physics expert. The professional group also noted that an

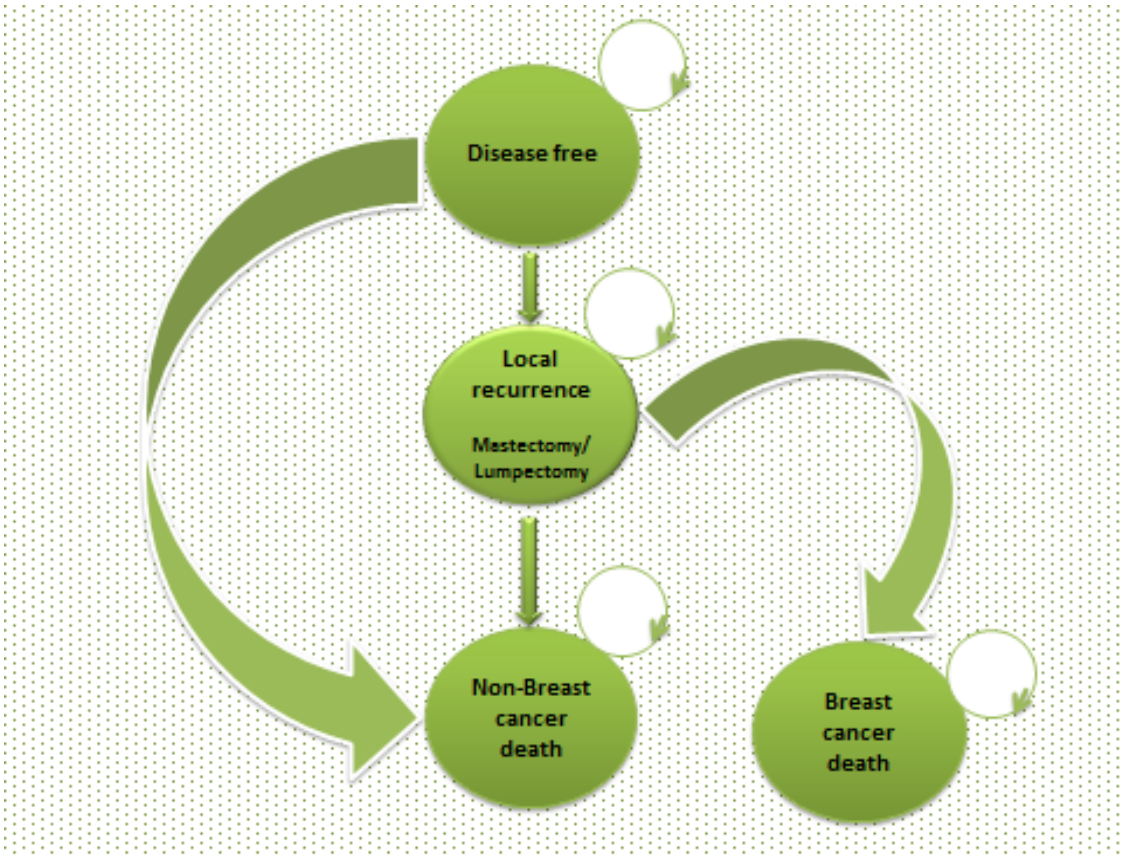
independent verification of dosimetry of radiotherapy systems is implemented, as it is recommended that there is an agreed programme of technical commissioning including independent measurement equipment to ensure consistent, accurate and safe treatment, incurring resource implications. The professional group noted that the introduction of Intrabeam would require either local physics support or a service level agreement with existing radiotherapy providers which, in turn, would require an increase in radiotherapy physics staff numbers.

6 Cost-effectiveness evidence

The manufacturer's economic model

6.1 The manufacturer submitted an economic model to assess the cost effectiveness of Intrabeam as a single dose radiation treatment compared with radiotherapy given over 3 to 6 weeks with external beam radiotherapy treatment (EBRT). The model structure was a Markov model with 4 states: disease free; local recurrence (mastectomy/lumpectomy); non-breast cancer death and breast cancer death (see figure 3). The cost-effectiveness analysis was conducted from the NHS perspective, costs and outcomes were discounted at a rate of 3.5% per annum, the cycle duration was 1 year and the time horizon was 20 years.

Figure 3 Manufacturer's model structure



Source: Manufacturer's economic model

6.2 The manufacturer did not provide details on how the parameters were implemented in the model. It used public sources for the cost of EBRT, the cost of lumpectomy and the cost of mastectomy. The manufacturer assumed that the number of annual procedures with Intrabeam was 100 and that the average number of fractions with EBRT was 23. It also assumed that Intrabeam was given concurrently with initial lumpectomy, that patients will have lumpectomy after local recurrence with Intrabeam and mastectomy after local recurrence with EBRT. The transition probabilities were derived from the TARGIT-A trial and the utilities in the model were taken from a study of Hayman et al. (1997) (see table 6). The mortality rate in the disease-free patients was equal to the mortality rate in the general population. The manufacturer did not provide further details on assumptions applied in the economic model.

Table 6 Manufacturer's model inputs

Model input	Value	Source
EBRT fraction cost	£327	HRG code SC29Z
Average EBRT fractions delivered	23	Clinical practice
Cost of EBRT	£7521	HRG code SC29Z
Cost of Intrabeam	£2165	Expert opinion
Cost of treating post Intrabeam local recurrence (lumpectomy)	£1558	HRG code JA09H
Cost of treating post EBRT local recurrence (mastectomy)	£6504	HRG code JA16Z
Annual disease-free follow up care	£892	Wolowacz (2008)
Utility in disease-free state	0.92	Hayman et al (1997)
Utility in lumpectomy post local recurrence	0.87	Hayman et al (1997)
Utility in mastectomy post local recurrence	0.82	Hayman et al (1997)

Source: Manufacturer's economic model

6.3 The results of the manufacturer's base-case analysis showed that Intrabeam was a dominant strategy (that is, it had lower costs and better outcomes) compared with EBRT. Intrabeam provided an additional 0.007 quality-adjusted life years (QALYs) and cost £6465 less than EBRT. The manufacturer conducted probabilistic sensitivity analysis to assess uncertainty in the model parameters applying the beta pert distribution to the costs and the beta distribution to the transition probabilities and utilities. It concluded that the model results were robust to parameter uncertainty as they yielded to similar results to the deterministic analysis. The manufacturer stated that Intrabeam was a cost-effective strategy compared with EBRT at various maximum acceptable incremental cost-effectiveness ratios (ICER).

6.4 The Assessment Group noted that the manufacturer did not conduct a systematic review of economic evaluations and that the information provided about the manufacturer's model was limited. It also noted that

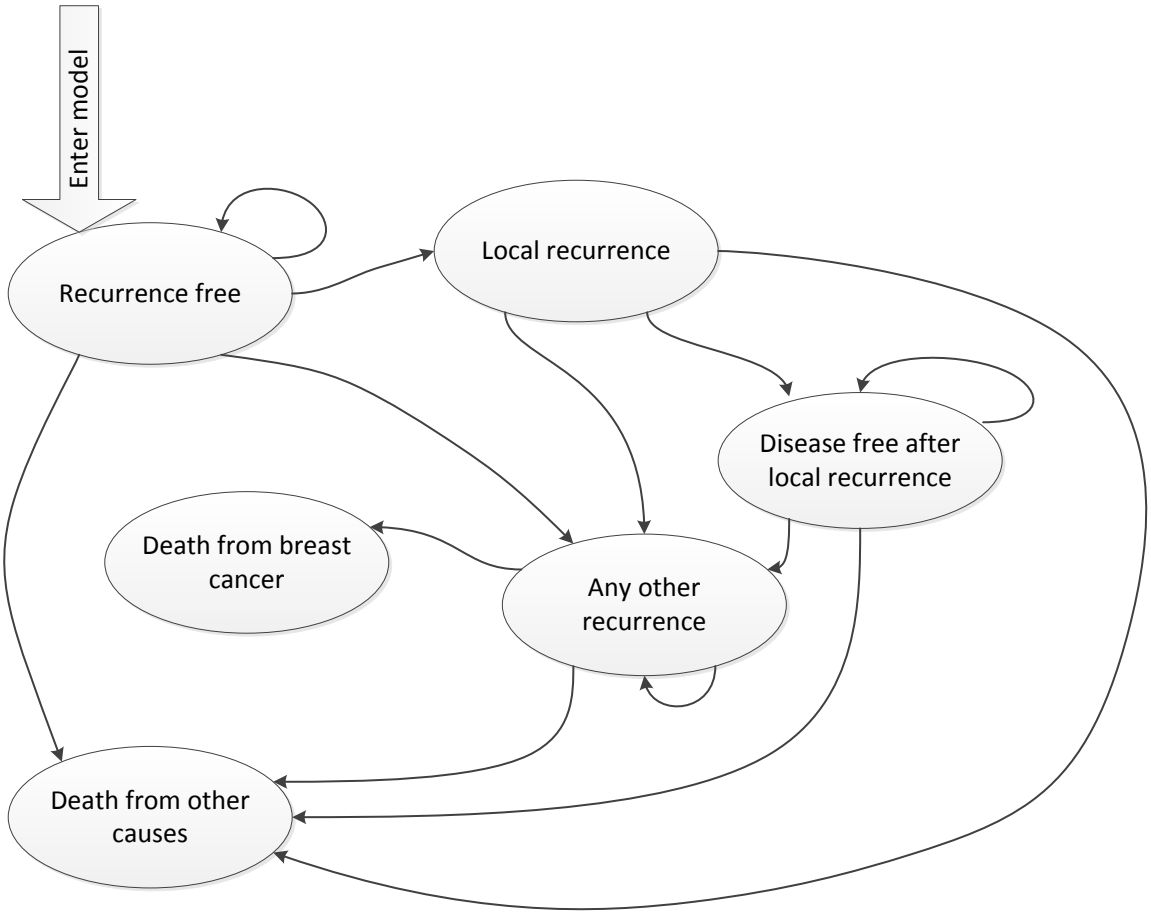
some of the manufacturer's assumptions in the model were not in line with UK clinical practice. The Assessment Group noted that the manufacturer assumed that people receiving Intrabeam would have lumpectomy after local recurrence but in the UK most patients would have mastectomy after local recurrence instead. The Assessment Group also highlighted that in contrast with the manufacturer's assumption, not all patients who have mastectomy would also have breast reconstruction and that the cost of mastectomy following local recurrence with EBRT in the manufacturer's model appears to include the cost of breast reconstruction for all patients. It noted that in the UK, only approximately 31% of the patients undergoing mastectomy would have breast reconstruction. It also noted that in the UK, the average number of fractions with EBRT is 15 instead of the 23 fractions assumed in the manufacturer's model. The Assessment Group also considered that the structure of the manufacturer's model was simplified and that it would have been more appropriate to include an additional state for progressed disease. It also considered that a time horizon of 20 years used by the manufacturer was too short to reflect the entire follow-up period of the disease and that the exponential distribution applied by the manufacturer to extrapolate the local recurrence and survival data beyond the 5 years of TARGIT-A did not provide the best fit. Instead, the Assessment Group considered that the log-normal distribution provided a best fit. The Assessment Group also noted that the cost of EBRT which the manufacturer used in its model was inappropriate because it reflected 'other radiotherapy treatment'. It considered that it was more appropriate to use the code that was described as 'deliver a fraction of radiotherapy on a megavoltage machine' which included 'external beam radiotherapy delivered by linear accelerator'. It also stated that the manufacturer was inconsistent with the source of costs used in the model because the cost following local recurrence with Intrabeam (lumpectomy) and the cost of following local recurrence with EBRT (mastectomy) were obtained from Payments by Results tariff 2013-14 and the cost of EBRT was obtained from the NHS Reference Costs 2012-13. The Assessment Group concluded that overall, the results of the

manufacturer's model should be considered with caution because of methodological and reporting limitations.

The Assessment Group's model

6.5 The Assessment Group developed an independent de-novo economic model to estimate the cost effectiveness of Intrabeam compared with EBRT for the adjuvant treatment of early operable breast cancer. The Assessment Group used a Markov model structure with 6 states: recurrence-free, local recurrence, disease-free after local recurrence, any other recurrence, death from breast cancer and death from other causes (see figure 4). Data from the pre-pathology group from TARGIT-A were used to guide the model inputs because the conclusions from the trial suggested that Intrabeam could be used as an alternative to postoperative EBRT but should not be used postoperatively as an alternative to EBRT. The Assessment Group also noted that in TARGIT-A, non-inferiority was not established for the post-pathology group. The cost-effectiveness analysis was conducted from an NHS and personal social services perspective, costs and outcomes were discounted at 3.5% per annum and a lifetime time horizon that equates to 40 years was used. The cycle length was 1 year and a half-cycle correction was applied. The Assessment Group assumed that all patients entered the model at an age of 62 years which is the median age of diagnosis of breast cancer in women in England.

Figure 4 Assessment Group's model structure



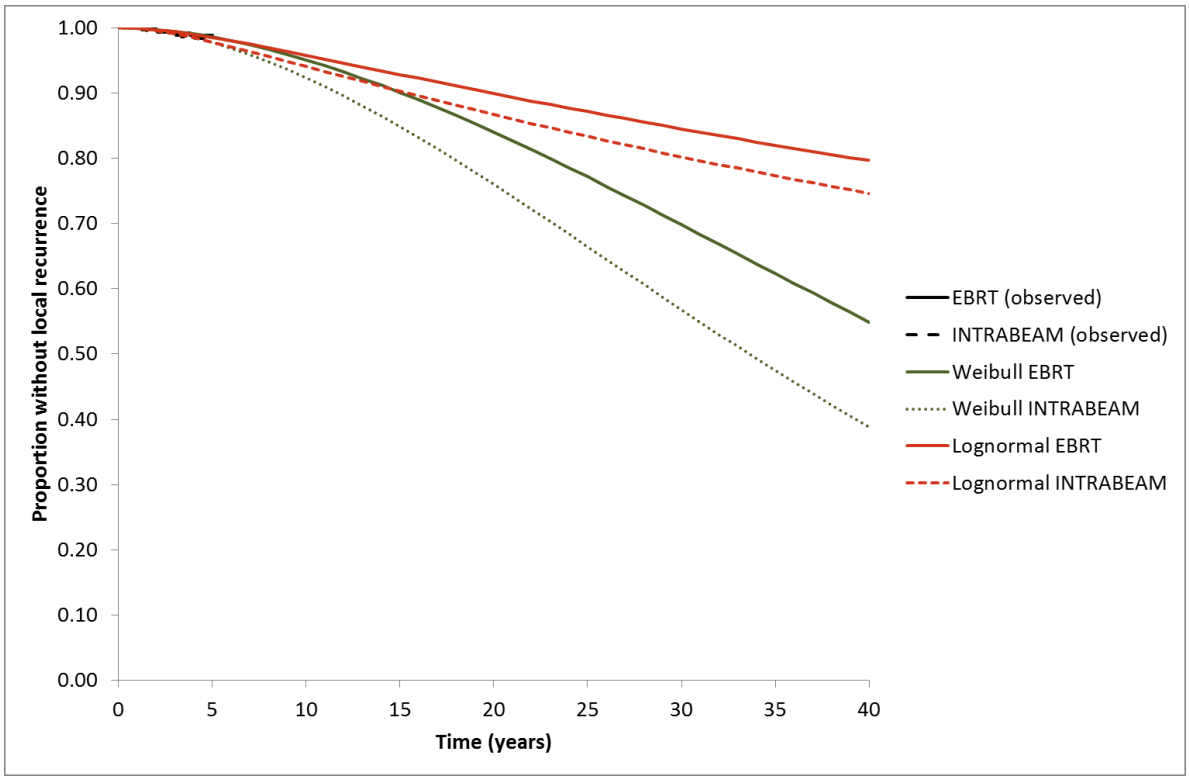
Source: Assessment Group's report, figure 5, page 88

6.6 All patients entered the model in the recurrence-free state and moved to local recurrence, any other recurrence or death from other cancer. The Assessment Group assumed that only 1 local recurrence was possible and that it was only possible to die from breast cancer whilst in the any other recurrence state. Transition probabilities of local recurrence, any other recurrence while recurrence-free, and death from breast cancer were derived from TARGIT-A. The probability of any other recurrence given local recurrence was obtained from Bock et al. (2009) and all-cause mortality adjusted by age was derived from data from the Office of National Statistics.

6.7 Local recurrence probabilities were derived from the Kaplan-Meier data from TARGIT-A for both treatment groups and parametric curves were fitted to extrapolate the data beyond the 5 years duration of the trial. The

Assessment Group investigated the fit of different parametric curves and concluded that the log-normal and Weibull distributions provided the best fit. The Assessment Group noted that its clinical advisers suggested that the risk of local recurrence continues relatively liner over the lifetime of the patient and that the proportion of people with local recurrence after 40 years was much higher with the Weibull distribution compared with the log-normal distribution (see figure 5). Because using the log-normal distribution did not accelerate the rate of local recurrence as steeply as with the Weibull distribution, it thereby showed that median survival was longer, therefore the Assessment Group chose the log-normal distribution for the base-case analysis.

Figure 5 Kaplan-Meier plot of local recurrence in the pre-pathology group of TARGIT-A and fitted distributions over 40 year time horizon



Source: Assessment Group's report, figure 7, page 93

6.8 The probability of any other recurrence from the local recurrence-free state was calculated from TARGIT-A. To estimate the transitions from the local recurrence and disease-free after local recurrence states to the any

other recurrence state, the Assessment Group assumed that the probability of any other recurrence is higher for people who have already experienced a recurrence and, based on a study by de Bock et al. (2009), it derived the transition probabilities for its model.

6.9 The probability of death from breast cancer is conditional to any other recurrence in the Assessment Group's model. The Assessment Group derived these probabilities for both treatment groups from TARGIT-A and it assumed that time to death after any other recurrence was exponentially distributed. Therefore, the mean breast cancer survival after any other recurrence was approximately 21 months for the EBRT group and 17.5 months for the Intrabeam group. For the analysis of overall mortality, the mortality risk was obtained from life tables in England and adjusted by demographics characteristics of women with breast cancer. The Assessment Group noted that although the number of non-breast cancer deaths in TARGIT-A was statistically significant lower in the EBRT group compared with the Intrabeam group, it did not seem that this difference were explained by an excess of deaths in the EBRT group but rather a shortfall of deaths in the Intrabeam group. The Assessment Group considered that this shortfall occurred by chance and because the mean age of patients included in the EBRT group was slightly lower. The Assessment Group confirmed that the annual probability of death in the EBRT group was similar to the one observed in the life tables in England and therefore, it applied the same probability of non-breast cancer death by age to both groups in the model. The Assessment Group applied non-breast cancer mortality rates from TARGIT-A in sensitivity analyses.

6.10 The Assessment Group obtained health-related quality of life data from its systematic review, specifically from the COMICE trial by Turnball et al. (2010) and from a Swedish study by Lidgren et al. (2007). The Assessment Group chose these studies because they included a patient population of similar age and characteristics of those assumed in the economic model and because the utility values were obtained using EQ-5D and valued with the UK tariff. The Assessment Group noted that

utilities in the manufacturer's model were obtained with the standard gamble technique and were not obtained from the general population. According to these studies and based on conclusions from another study by Hildebrandt et al. (2014), the Assessment Group applied the same utility value to the first year after local recurrence and to the second and following years after both primary breast cancer and local recurrence. Table 7 shows a summary of utility values used in the Assessment Group´s model. The Assessment Group did not apply a disutility associated with mastectomy based on the study by Robertson et al. (2012) which reported a higher utility value for people who had mastectomy and breast reconstruction than the utility value from the COMICE trial for wide local excision. The Assessment Group did not either assume any benefit from the initial treatment with Intrabeam compared with the 3-weeks treatment with EBRT because, given the annual cycle length of the model, the benefit associated with the one-off treatment with Intrabeam was likely to be small. Any impact of the treatment in terms of health-related quality of life was assumed to be captured by disease progression.

Table 7 Utility values used in the Assessment Group's economic model

Model health state	EQ-5D (SE)	Source
Recurrence free in 1st year	0.7728 (0.0079)	Turnbull et al. no MRI arm 8 weeks post-randomisation time point
Recurrence free after 1st year	0.8112 (0.0072)	Turnbull et al no MRI arm 12 months post-initial surgery
Local recurrence	0.8112 (0.0072)	Turnbull et al no MRI arm 12 months post-initial surgery
Disease-free after local recurrence	0.8112 (0.0072)	Turnbull et al no MRI arm 12 months post-initial surgery
Any other recurrence	0.685 (0.0293)	Lidgren et al

Source: Assessment Group´s report, table 24, page 98

6.11 The Assessment Group stated that its model reflected the UK clinical pathway and based on NICE clinical guideline on Early and locally advanced breast cancer (NICE clinical guideline 80) it assumed that the number of fractions required to complete a course of treatment with EBRT

was 15. It also assumed that 80% of the patients received mastectomy at local recurrence based on advice from its clinical advisers and that 31% of patients who received mastectomy would also receive breast reconstruction based on advice from its clinical advisers and data from the National Mastectomy and Breast Reconstruction Audit (2011). The Assessment Group noted that varying the proportion of patients who have mastectomy after local recurrence and the proportion of patients who have breast reconstruction following mastectomy did not have a big impact on the ICER. The proportion of patients receiving Intrabeam who also received EBRT was assumed to be 15.2% based on TARGIT-A. The Assessment Group assumed that the lifetime of the Intrabeam device was 10 years and conservatively, that all patient receiving treatment with Intrabeam would need a radiation protection shield. Based on a study by Leonardi et al. (2012) and advice from its clinical advisers, the Assessment Group assumed that 16% of the people diagnosed with breast cancer would be eligible to receive treatment with Intrabeam. The Assessment Group applied an alternative proportion of 50% in a sensitivity analysis based on clinical advice. With a hospital catchment of 1,000,000, the number of annual procedures with Intrabeam was assumed to be 126. The Assessment Group noted that varying the proportion of patients eligible to receive Intrabeam did not have a big impact on the ICER.

6.12 Additional staff time cost was estimated based on clinical advice and the associated costs were obtained from the PSSRU Unit Costs of Health and Social Care (2013) using NHS pay bands of surgical consultant and 8b, 7 and 5 (see tables 27 and 28, pages 100 and 101 in the Assessment Group's report for full details). Because delivery of Intrabeam required extra time in the operating theatre, the cost of 1 hour in the operating theatre was obtained from the University Hospitals Southampton Finance Department January (2014). Costs for mastectomy with and without breast reconstruction, wide local excision, and planning and delivery of EBRT were obtained as weighted averages from NHS Reference Costs

(2012-13) (see table 8). With a hospital catchment of 1,000,000 and the number of annual procedures with Intrabeam estimated to be 126, the cost of Intrabeam per procedure was calculated to be £1882. The Assessment Group did not include costs associated with adverse events because the only adverse events which showed a statistically significant difference between treatment groups occurred in less than 3% of the population in TARGIT-A. It did not include any cost of post-progression therapies in the model to avoid potential confounding assumptions and because of lack of data on the type of any other recurrence in the pre-pathology group in TARGIT-A.

Table 8 Costs in the Assessment Group's model

Model input	Value	Source
Cost of mastectomy with reconstruction	£7822	HRG codes JA27Z and JA28Z
Cost of wide local excision	£1542	HRG codes JA24D, JA24E and JA24F
Cost of mastectomy	£2510	HRG codes JA20D, JA20E and JA20F
Cost of delivering a fraction of radiotherapy on a megavoltage machine	£118.44	HRG codes SC22Z and SC23Z
Cost of preparation for simple radiotherapy	£323.65	HRG codes SC45Z, SC46Z, SC47Z and SC48Z
Cost of 1 hour in operating theatre	£569	University Hospitals Southampton Finance Department January 2014

Source: Adapted from Assessment Group's report, tables 30 and 3, pages 102 and 103

6.13 The results of the Assessment Group's cost-effectiveness analysis of Intrabeam compared with EBRT for the adjuvant treatment of early breast cancer showed that Intrabeam cost £140 less and provided 0.088 less quality-adjusted life years (QALY) compared with EBRT resulting in an incremental cost-effectiveness ratio (ICER) of £1596 saved per QALY lost (see table 9). The Assessment Group noted that In situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting

ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes.

Table 9 Base case cost-effectiveness results

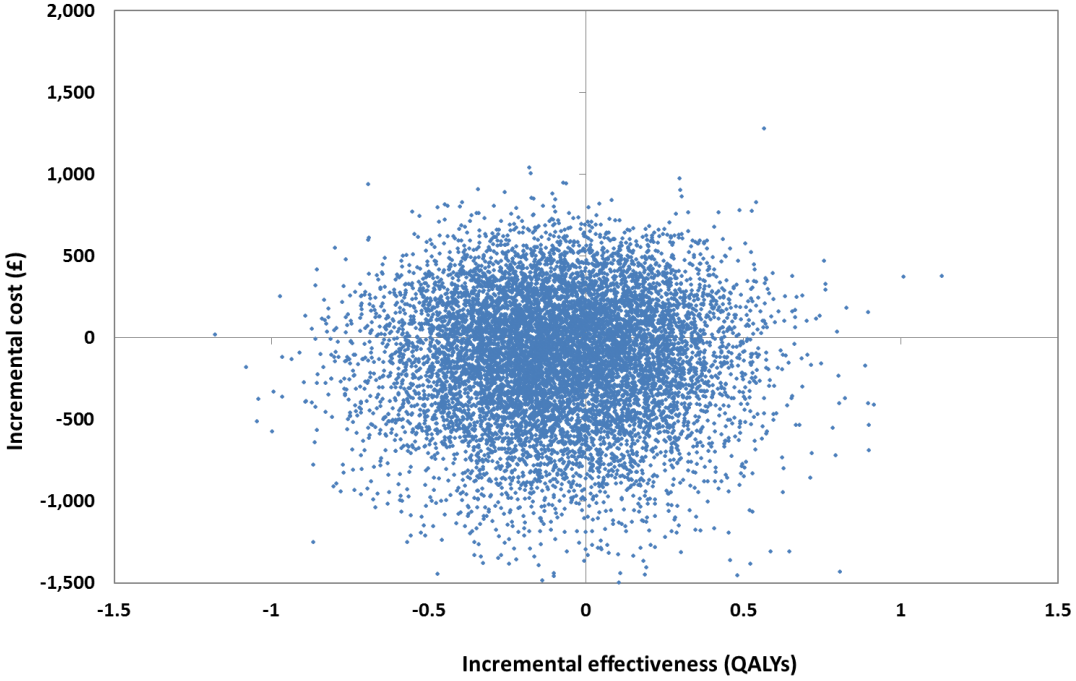
Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,368	20.72	11.329	-	-	-
INTRABEAM	2,227	20.51	11.241	-140	-0.088	1,596*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Source: Assessment Group´s report, table 34, page 108

6.14 The Assessment Group undertook sensitivity analyses to explore the impact of changes in the parameters in the ICER. The results of the deterministic sensitivity analyses showed that the cost-effectiveness results were more sensitive to the probability of any other recurrence for both treatment groups. When a lower probability of any other recurrence was assumed in the Intrabeam group or a higher probability of any other recurrence was assumed in the EBRT group, Intrabeam was a cost-effective treatment compared with Intrabeam for a maximum acceptable ICER of £20,000 per QALY gained. In contrast, when a higher probability of any other recurrence was assumed in the Intrabeam group or a lower probability of any other recurrence was assumed in the EBRT group, EBRT became the most cost-effective alternative at a maximum acceptable ICER of £20,000 per QALY gained. The cost-effectiveness results were also sensitive to the probability of death from breast cancer in the Intrabeam group and to changes in parameter values considered for the beta coefficient for the Intrabeam group in the log-normal model of time to local recurrence. Changes between higher and lower values for these parameters changed the consideration of the most cost-effective alternative at a maximum acceptable ICER of £20,000 per QALY gained. The results of the probabilistic sensitivity analysis also showed that the degree of uncertainty around the cost-effectiveness results was high. The cost-effectiveness plane showed that simulations of the ICER of Intrabeam compared with EBRT fell in the 4 quadrants (see Figure 6).

Figure 6 Cost-effectiveness plane of Intrabeam compared with EBRT



Source: Assessment Group´s report, figure 11, page 116

6.15 The Assessment Group also conducted 5 scenario analyses applying the following assumptions to the model (see table 10):

- Scenario 1: Fitting and applying a Weibull distribution to the 5 years Kaplan-Meier data from TARGIT-A for the probability of non-breast cancer death, and applying mortality rates from the general population based on life tables from England thereafter,
- Scenario 2: Changing the estimated number of patients receiving Intrabeam to 100 patients as per the manufacturer´s model (this equates to a catchment population of a hospital offering treatment with Intrabeam of 795,000 people)
- Scenario 3: Applying a disutility because of mastectomy to the local recurrence and the disease free after local recurrence states
- Scenario 4: Applying a disutility because of mastectomy to the local recurrence state only. The Assessment Group noted that although fewer patients had a mastectomy in the Intrabeam group compared with EBRT at local recurrence, the rate of local recurrence was higher

in the Intrabeam group than in the EBRT group. Therefore, the net effect was that the utility decrement because of mastectomy was greater in the Intrabeam group than in the EBRT group

- Scenario 5: Using alternative utility values from Hind et al. (2007) applied in a previous submission to NICE in which the utility values for the 'local recurrence' (0.61) and 'recurrence-free' (0.78) states were different. The utility values for the 'disease-free after local recurrence' and 'any other recurrence' states were equal to 0.71 and 0.42 respectively. In the study by Hind et al. these utility values were obtained from patients or clinical experts using the time trade-off technique.

Table 10 Results of the assessment's group scenario analyses

Scenario	Intervention	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1	Intrabeam vs EBRT	-132	0.166	Dominating
Scenario 2	Intrabeam vs EBRT	47	-0.088	Dominated
Scenario 3	Intrabeam vs EBRT	-140	-0.090	1,563*
Scenario 4	Intrabeam vs EBRT	-47	-0.088	1,592*
Scenario 5	Intrabeam vs EBRT	-140	-0.093	1,517*

Note: Dominating: Intrabeam is associated with both less cost and greater benefits than EBRT; Dominated: Intrabeam is associated with both higher cost and less benefits than EBRT; * INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Source: Adapted from Assessment Group´s report, tables 41, 42, 43, 44 and 46, pages 117 – 120.

6.16 The Assessment Group also conducted an illustrative scenario analysis including post-progression therapies (see table 11). Because TARGIT-A did not provide information about the type of recurrence in the pre-pathology group; the Assessment Group assumed that 60% of recurrences in the 'any other recurrence' state were distant recurrences based on TARGIT-A data for the whole population and data from the literature, and that mortality after any other recurrence was the same in both treatment groups. The Assessment Group noted that it assumed the

same mortality after any other recurrence (applying the probability of death for EBRT in the base case) because the data from the trial showed that mortality after any other recurrence was higher in the Intrabeam group and including costs for this state without adjustment would result in additional incremental cost for EBRT. The cost of post-progression therapies were obtained from Hind et al. (2007) and inflated to 2013 using the Hospital and Community Health Services prices index and were equal to £12,122 for the annual cost of metastatic disease (active treatment and supportive care) and £3,669 for the cost of end of life care for a patient with breast cancer.

Table 11 Results of the Assessment Group' scenario analysis including post-progression therapies

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	4,662	20.72	11.329	-	-	-
INTRABEAM	4,652	20.51	11.268	-10	-0.061	157*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Source: amended from Assessment Group´s report, table 47, page 121

6.17 The Assessment Group also included an assessment of factors relevant to the NHS and other parties. It noted that for the year 2011-12, breast cancer accounted for 28% of radiotherapy services delivered by 256 linear accelerators in the UK, and that it is expected that the need for radiotherapy would increase during the next few years, estimating an increase up to 412 linear accelerators by 2016. Because there are only 8 Intrabeam devices currently available in the NHS, it is expected that the investment in Intrabeam equipment would be high if it becomes widely available in the NHS. The Assessment Group noted that in addition to the capital cost, there would also be a need to invest in staff training. The Assessment Group also received comments from its advisory group stating that the additional operating theatre time required with Intrabeam could potentially add pressure to breast cancer clinics although this impact could be mitigated in those clinics where lymph node analysis is

already undertaken intraoperatively using the RD-100i OSNA system because treatment with Intrabeam could be delivered and completed within this time. The Assessment Group also commented on the potential of Intrabeam freeing-up radiotherapy resources. It assumed that the proportion of people with an incident diagnosis of breast cancer that would be eligible to receive treatment with Intrabeam was 16%, and therefore the proportion of radiotherapy services required for treating breast cancer would decrease to 24%. The Assessment Group highlighted that this drop would be expected to be less than 24% because some patients receiving Intrabeam may be at high risk of recurrence and receive additional treatment with EBRT and some patients could experience recurrence and choose to receive local excision and further treatment with EBRT. The Assessment Group also noted the ongoing FAST-Forward trial, which investigates the potential to provide a shorter course of treatment with EBRT (5 fractions compared with the actual 15 fractions given as established practice in the UK), and that the potential impact this could have in freeing-up radiotherapy resources is greater than with the introduction of Intrabeam. It also noted the potential for identifying a subset of patients who would not need to receive EBRT treatment might also free up radiotherapy resources in the future.

7 Comments received during consultation of the Assessment Report

7.1 Summary of the comments received:

- **Clinical practice**: Consultees noted that in clinical practice, the proportion of patients who have mastectomy after local recurrence is lower and the proportion of patients who have breast reconstruction following mastectomy is higher than the proportions assumed by the Assessment Group in its report. It was highlighted that people who received EBRT cannot be treated with conservative lumpectomy and breast conservation after whole breast radiation. It was also noted that

Intrabeam could still be used if there is recurrence after the use of EBRT.

- **TARGIT-A follow-up:** One consultee noted that the follow-up in the trial was long enough to show any effect from surgery or radiation. It stated that the period in which the peak hazard of local recurrence after surgery is observed is 2 – 3 years and that in the TARGIT-A trial 1222 patients had a median follow-up of 5 years and 2232 patients had a median follow-up of nearly 4 years.
- **Extrapolation of trial data**: One consultee stated that it was not appropriate to extrapolate the trial data to 40 years, especially for local recurrence. The consulttee noted that the peak of local recurrence is observed during the first 2 – 3 years after surgery and radiation, and therefore, the trial data should not be extrapolated beyond 5 years. It was also noted that any other recurrence is not affected by the intervention and it is not related to local recurrence and that local recurrence does not have an impact on survival. The consultee considered that it was more appropriate to use disease-free survival in the model.
- **Use of resources, cost and utility assumptions**: Consultees highlighted that therapeutic radiographers are not mentioned in the staff categories considered by the Assessment Group in its report but they are core staff for the delivery of high quality radiotherapy. They also considered that the training costs specified by the Assessment Group should not be defined as considerable because non-surgical radiotherapy teams are already trained in the core requirements of radiotherapy and therefore, they would only require technical updates in the process and practice associated with Intrabeam. It was also noted that the additional time in the operating theatre is on average 30 minutes because sentinel lymph node evaluation is carried out at the same time. It was noted that the NHS radiotherapy equipment is old and needs to be replaced so both increased training and new equipment will be necessary. One consultee highlighted that the Assessment Group did not apply the costs of modern EBRT practices

and noted that this inclusion would lead to higher costs in the EBRT group. It was noted that the proportion of patients eligible to receive treatment with Intrabeam is higher (30 – 50%) and thus, the cost of Intrabeam per patient is lower than the cost assumed by the Assessment Group in its model. One consultee further noted that it was questionable to assign a lower utility value to the 'any other recurrence state'.

- **Non-breast cancer mortality**: Consultees also highlighted that the Assessment Group's conclusion on a lower mortality in the Intrabeam group compared with the EBRT group because of chance or the possible younger age of people in the Intrabeam group was erroneous. They stated that the mean age in both treatment groups was comparable, that the fact that the whole breast radiation is associated with cardiac toxicity and ionizing radiations which increase the subsequent rate of ischemic heart disease was ignored in the Assessment Group's report and that the inclusion of deaths because of ischemic bowel and stroke in the EBRT group would have increased the mortality rate because of cardiovascular death in this group.
- **Adverse effects**: It was raised that, because of the known adverse effects of radiotherapy (damage to organs), it is currently given with the patient lying on their front to protect organs. It was highlighted that less radiotherapy toxicity should be seen as a key consideration, particularly when it is derived by the introduction of a single treatment with Intrabeam compared with a regimen of at least 3-weeks of radiotherapy.
- **Patient needs:** It was noted that although more research is needed to confirm the long-term benefits of Intrabeam, women aged between 40 and 50 years need a fast and effective treatment because a long-term absence from work could be very difficult and expensive for them and their families. Consultees also noted that an older woman may not live long enough to benefit from treatment if further research is requested to allow Intrabeam to be available in the NHS.

8 Equality issues

8.1 No equality issues were identified during scoping consultation or in the evidence submitted.

9 Innovation

9.1 The manufacturer noted that Intrabeam is an innovative technology with important health-related benefits such as a better survival, a better side effects profile and better quality of life independently from the treatment option (as the sole method of treatment or as a boost followed by EBRT). It also highlighted that Intrabeam is particularly beneficial because it is given at the same time as surgery and because the source of radiation is placed directly in the tumour cavity. The manufacturer also highlighted that Intrabeam can be given to patients in whom treatment with EBRT is not advised.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

- Early and locally advanced breast cancer. NICE clinical guideline 80 (2009).
- Hormonal therapies for the adjuvant treatment of early oestrogen-receptor positive breast cancer. NICE technology appraisal 112 (2006).
- Breast reconstruction using lipomodelling after breast cancer treatment. NICE interventional procedure guidance 417 (2012).
- Image-guided radiofrequency excision biopsy of breast lesions. NICE interventional procedure 308 (2009).
- Endoscopic mastectomy and endoscopic wide local excision for breast cancer. NICE interventional procedure 296 (2009).
- Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision. NICE interventional procedure guidance 268 (2008).
- Laparoscopic mobilisation of the greater omentum for breast reconstruction. NICE interventional procedure 253 (2008).
- Endoscopic axillary lymph node retrieval for breast cancer. NICE interventional procedure 147 (2005).
- Interstitial laser therapy for breast cancer. NICE interventional procedure 89 (2004).
- Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. NICE diagnostics guidance 10 (2013).
- Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer. NICE diagnostics guidance 8 (2013).

NICE pathways

- There is a NICE pathway on Early and locally advanced breast cancer, which is available from http://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer