Multiple Technology Appraisal (MTA): INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer [ID618]

Professional organisation statement on behalf of the NCRI Breast Clinical Studies (CSG) Group, Royal College of Physicians (RCP) and Association of Cancer Physicians (ACP)

Summary statement:

Our experts recognise the need for patient choice, but do not recommend the use of the INTRABEAM Photon Radiosurgery System for the adjuvant treatment of early breast cancer outside a research study with the appropriate ethical approval. The overriding reason for this is the inadequate median follow up of the whole TARGIT trial group, which questions the validity of the reported results.

Response to specific questions:

What is the expected place of the technology in current practice?

The INTRABEAM Photon Radiosurgery System may have a place for the treatment of partial breast radiotherapy and breast boost radiotherapy in the future. Currently, partial breast radiotherapy is not recommended as standard practice in the UK using ANY technology as the mature results (at least 5 years median follow up and ideally 10 years) of randomised trials are still required. Adequate follow up is particularly pertinent these group patients at lower risk of recurrence, as the local recurrence rates has been shown to be similar in the 5-10 years after treatment as the initial 5 years (Rakha, E.A., et al. J Clin Oncol, 2008 and Hughes K.S et al. J Clin Oncol, 2013).

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Early breast cancer following breast conserving surgery is currently treated with whole breast radiotherapy ± boost to the tumour bed using external beam radiotherapy (EBRT). All radiotherapy centres in the UK have access to EBRT equipment. The advantages of the current practice are that it is accessible to all patients, it is relatively cheap and there is a huge workforce trained in its use (radiographers, physicists & oncologists).

EBRT can also be used easily to deliver partial breast radiotherapy as well as whole breast RT ± boost, if this becomes standard practice in the future. Standard whole breast radiotherapy using EBRT consists of 15 fractions of treatment over 3 weeks, but current trials are recruiting ahead of schedule to test a 1 week treatment (just 5 treatments) within the national FAST Forward study.

In the future, it is likely that a group of patients with very low risk of recurrence will be reliably identified, in whom radiotherapy can be omitted completely (thus the possible side effects and cost of radiotherapy are avoided). This is suggested by the mature of randomised trials comparing breast conservation surgery with and without radiotherapy:

Firstly, the BASO II trialists have recently reported the 10 year outcomes following radiotherapy and/or tamoxifen after BCS for breast cancers of excellent prognosis (defined as primary invasive cancer <2cm, grade 1 or good prognosis special type, node negative with clear margins following BCS). Actuarial analysis of patients entered into the four-way randomisation showed that local relapse after wide local excision alone was 1.9% per annum compared with 0.7% after WLE followed by radiotherapy alone and 0.8% when followed by tamoxifen alone. None of the 98 women randomised to both treatments experienced a local recurrence. Analysis by treatment received showed local relapse at 2.2% per annum for surgery alone versus 0.8% for either adjuvant radiotherapy or tamoxifen and 0.2% for both treatments. However, there were only 213 patients in the tamoxifen group (no radiotherapy), so comparisons are under powered to reliably detect or exclude clinically meaningful differences in outcome.

Secondly, the CALGB C9343 evaluated radiotherapy in low risk patients ≥70 years: local relapse rates at 5 years were 1% and 4% (p<0.001) with and without radiotherapy. At median follow up of 10.5 years, the difference in local relapse widened in favour of radiotherapy: 2% versus 9% with and without radiotherapy respectively. However, the study lacks the statistical power to carry out a subgroup analysis to identify a lower risk group with more favourable histology. Despite the small excess of local relapse without radiotherapy, there were no differences in the mastectomy, metastases or overall survival rates at 10 years following primary surgery.

Lastly, the PRIME II trial randomised 1479 good prognosis breast cancer patients (defined as aged ≥65 years with primary invasive cancer ≤3cm, grade 1/2, node negative with clear margins following BCS). Recent early results shows 1.3% and 4.1% local relapse rates by 5 years with and without radiotherapy (San Antonio Breast Symposium, 2013). The authors state that mature 10 year data will be presented in due course, which will add to the growing body of evidence suggesting that avoidance of breast radiotherapy in certain subgroups of patients is a safe alternative to radiotherapy. It is likely that further studies will be required in order to show definitively which patients can avoid radiotherapy.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Breast cancer patients with early disease have a large variation in prognosis, but the current recommendations (NICE 2009) are for whole breast radiotherapy ± boost for all patients following breast conservation surgery. It is likely in the future that lower risk patients may benefit from just partial breast radiotherapy or even no radiotherapy (see above), but these non-standard treatments should currently be within research studies.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The INTRABEAM Photon Radiosurgery System could be used within the tertiary care setting (oncology centres). Additional training would be required for breast surgeons, oncologists, physicists and radiographers.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

The INTRABEAM Photon Radiosurgery System should currently only be used as part of ethically approved research studies.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Clinical guidelines are part of the TARGIT trial protocol (see below).

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The current evidence for the use of this technology is: Vaidya JS et al; on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2013 Nov 8. pii: S0140-6736(13)61950-9. doi: 10.1016/S0140-6736(13)61950-9. [Epub ahead of print].

This manuscript suggests non-inferiority for local recurrence at 5 years using this technology, but median follow-up in the trial overall is only 2 years 5 months and only 611/3451 patients have ≥5 years of follow-up. Local recurrence risk continues for many years following breast cancer treatment, so a median follow up of 5 years for the whole cohort would be a *minimum* requirement to assess the efficacy of this technology.

In addition, there are major criticisms of the statistical analyses, which are also likely to affect the validity of the presented results. In summary:

1. **Survival analysis has been used to test inferiority of local recurrence, but the median follow-up for the trial is only 2 years and 7 months.**
2. **Comparison of binominal proportions has also been used to test inferiority of local recurrence, but due to the inadequate follow up, the number of relapses are likely to be considerably less than expected with a median follow up of 5 years.**
3. **The authors try to address the issue of inadequate follow up by presenting results for 3 cohorts of patients with varying lengths of median follow-up: it is stated that the results illustrate the stability of the treatment effect over time. This is flawed as the cohorts are nested within each other and so in effect, the patients with the longest follow-up have been analysed three times.**

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The frequency of any complications and major toxicity was similar in the two groups in the TARGIT trial (Vaidya JS et al, lancet 2010). For major toxicity, targeted intraoperative radiotherapy, 37 [3·3%] of 1113 *vs* EBRT, 44 [3·9%] of 1119; p=0·44). Radiotherapy specific toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted intraoperative radiotherapy group (six patients [0·5%]) than in the EBRT group (23 patients [2·1%]; p=0·002). This is to be expected due to the much smaller volume of breast treated to a much lower dose in the targeted intraoperative radiotherapy group. However, the combination of targeted intraoperative radiotherapy and whole breast radiotherapy produced extremely high levels of late normal tissue fibrosis: in the sub-analysis (Arm A IORT vs. Arm A IORT + WBRT vs. Arm B WBRT), fibrosis had a cumulative rate of 5.9 versus 37.5 versus 18.4 %, respectively at 3 years (Sperk E et al, Breast Cancer Res Treat 2012). This high level of toxicity raises concerns about the use of targeted intraoperative radiotherapy as a boost treatment in combination with whole breast radiotherapy compared with an EBRT boost (Bartelink H et al, Journal of Clin Oncol 2007).

The recent Lancet 2013 publication suggests that the standard EBRT treatment arm causes a "very large excess" of non-breast cancer deaths compared with the targeted intraoperative radiotherapy group. Radiation exposure as causation is very unlikely, despite the p-value. Darby et al (NEJM 2013), report that major cardiac event (MCE) risk was shown to increase by 7% per Gy of mean heart dose, with no lower dose threshold. Based on expected median heart doses in the TARGIT standard group, EBRT cannot explain more than 1 of the 11 cardiovascular deaths (8 cardiac deaths, 2 strokes and 1 ischaemic bowel). This is the case even if all cardiac deaths occurred in patients with left-sided cancers (this information is not provided). The explanation for excess cardiovascular deaths is either imbalance between groups in relevant risk factors at presentation or under-reporting of cardiovascular deaths in the test group.

It is also not credible to attribute the excess number of cancer deaths in the EBRT group (16 vs. 8) to treatment. For example, the National Surgical Adjuvant Breast Protocols B-04 and B-06, testing radiotherapy after surgery for early breast cancer followed up

1665 patients for a median of 21.4 years after randomisation +/- locoregional radiotherapy after mastectomy. This study confirmed a small excess (n=6) of primary lung cancer up to 25 years after EBRT (this effect took 10 years to emerge). The excess was attributed to large anterior radiotherapy beams used to treat axilla and supraclavicular fossa (not used in the TARGIT trial). No excess of primary lung cancers was seen among 1261 patients in the B-06 trial at a median of 19 years after randomisation +/- whole breast EBRT following tumour excision. The TARGIT authors offered no information on tumour site (lung is by the commonest breast radiation-induced cancer) or interval from randomisation to second cancer diagnosis. Finally, follow-up in the TARGIT trial is likely to be far too short for induction of cancer by EBRT.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

The INTRABEAM Photon Radiosurgery System is currently only available in a small number of centres compared with the total number of UK radiotherapy centres. The INTRABEAM Photon Radiosurgery System, if implemented widely, would have a considerable negative impact on surgical theatre time as each treatment takes around 30 minutes. This is likely to be expensive given the amount of personnel required to run each theatre (average theatre cost £800 per hour: Cambridge University Hospitals NHS Foundation Trust) regardless of whether time is spent operating or not. It may also increase waiting times for breast cancer surgery. It is unrealistic that this system would replace the need for EBRT as the majority of early breast cancer patients are likely to still need whole breast radiotherapy in the future. Therefore, one new type of technology would not simply replace another.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Considerable additional training would be required for breast surgeons, oncologists, physicists and radiographers at each centre.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No