The INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published August 2015
DOI: 10.3310/hta19690

Scientific summary

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Health Technology Assessment 2015; Vol. 19: No. 69
DOI: 10.3310/hta19690

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Breast cancer is the most common cancer in women in England, with 41,523 new diagnoses in 2011. Earlier detection and improved treatment for breast cancer in women have led to a rise in survival, with 3-year net survival in early breast cancer now 99.3% for patients with tumour node metastasis (TNM) stage I disease and 92.4% for patients with TNM stage 2 disease.

The focus of this assessment is the treatment of early breast cancer. Definitions vary, but for the purposes of this assessment early breast cancer includes early invasive cancer for which the tumour has not spread beyond the breast or the lymph nodes (which remain mobile) in the armpit on the same side as the affected breast. The first treatment option for early breast cancer is usually surgery, which may be wide local excision (WLE) of the tumour [breast-conserving surgery (BCS)] instead of mastectomy. Post-operative whole-breast external beam radiotherapy (WB-EBRT) is the standard of care for all patients with early invasive breast cancer after BCS, because it substantially reduces the risk of recurrence and moderately reduces the risk of breast cancer death.

A potential alternative to post-operative WB-EBRT is treatment with the INTRABEAM® Photon Radiotherapy System (Carl Zeiss, Oberkochen, Germany). The INTRABEAM device can be used to deliver intraoperative radiation therapy to the tissue adjacent to the resection cavity in an ordinary operating theatre at the time of surgery.

Objectives

To assess the clinical effectiveness and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Methods

Data sources

Electronic resources including MEDLINE, EMBASE, The Cochrane Library and Web of Science were searched for published studies and ongoing research from inception to March 2014 for English-language articles. Bibliographies of included articles, systematic reviews, clinical guidelines and the manufacturer's submission to National Institute for Health and Care Excellence were also searched for additional studies. An advisory group was contacted to identify additional published and unpublished evidence.

Study selection

Titles and abstracts were screened for eligibility by two reviewers independently. Inclusion criteria were applied to full texts by one reviewer and checked by a second reviewer. Inclusion criteria were as follows:

- Intervention – INTRABEAM device with or without post-operative WB-EBRT.
- Comparator – WB-EBRT delivered by linear accelerator.
- Population – people with early operable breast cancer; people with a local recurrence were excluded. For the systematic review of health-related quality of life (HRQoL), the population was not limited to early-stage breast cancer.
- Outcomes – overall survival, disease-free survival, ipsilateral local recurrence, adverse effects of treatment, HRQoL, cost-effectiveness [expressed in units such as life-years gained or quality-adjusted life-years (QALYs) gained or in monetary units].

- Study design – randomised controlled trials (RCTs) [good-quality controlled clinical trials could be considered if the data from RCTs were incomplete (e.g. absence of data on outcomes of interest)] for the review of clinical effectiveness; full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses for the systematic review of cost-effectiveness; primary research studies based in the UK, Europe, North America and Australasia for the systematic review of quality of life (QoL).

Abstracts or conference presentations were eligible for inclusion only if sufficient details were presented.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved by discussion at each stage.

Data synthesis

Data were synthesised through narrative reviews with full tabulation of the results of included studies.

Economic model

A cost–utility decision-analytic model was developed to estimate the costs, benefits and cost-effectiveness of INTRABEAM compared with WB-EBRT for early operable breast cancer. The intervention effects and characteristics of the modelled patient population were obtained from RCT data identified by the clinical effectiveness systematic review. The perspective of the analysis was that of the NHS and Personal Social Services in the UK. A lifetime (40-year) horizon was used to estimate costs and benefits from each treatment. Future costs and benefits were discounted at 3.5% per annum and the outcomes were reported as the cost saved per QALY lost.

Results

Systematic review of clinical effectiveness

From 655 records screened, 44 references were retrieved for consideration. One non-inferiority RCT, the TARGeted Intraoperative radioTherapy Alone (TARGIT-A) trial, which evaluated whether or not INTRABEAM treatment was no worse than WB-EBRT, met the inclusion criteria. The trial was judged to be at a low risk of bias. Results were reported for the whole trial population ($n = 3451$) and separately for the pre-pathology stratum ($n = 2298$ randomisation to INTRABEAM or WB-EBRT prior to WLE of the primary tumour) and the post-pathology stratum ($n = 1153$ randomisation after initial surgery to either INTRABEAM as a second procedure or WB-EBRT). Median follow-up was 2 years 5 months, with 35% of participants achieving median follow-up of 5 years.

Local recurrence

Local recurrence in the conserved breast (primary outcome) for the whole trial population was higher in the INTRABEAM group than in the WB-EBRT group (3.3% vs. 1.3%); however, the absolute difference in 5-year risk of local recurrence did not exceed the 2.5% non-inferiority margin. A similar result was observed for the pre-pathology stratum. In the post-pathology stratum, the non-inferiority margin was exceeded and non-inferiority was not established.

Overall survival

Overall survival (secondary outcome) for the whole trial population did not differ statistically significantly between INTRABEAM and WB-EBRT arms (3.9% vs. 5.3%; $p = 0.099$). Rates of breast cancer deaths were similar but there were significantly fewer non-breast cancer deaths in the INTRABEAM group than in the WB-EBRT group. In the pre-pathology stratum, lower overall mortality was observed in the INTRABEAM group because there were significantly fewer non-breast cancer deaths. In the post-pathology stratum, overall mortality, breast cancer mortality and non-breast cancer mortality were similar between treatment groups.

Complications

Wound seroma requiring more than three aspirations occurred more frequently in the INTRABEAM group (2.1% vs. 0.8%; $p = 0.012$), whereas a Radiation Therapy Oncology Group toxicity score of grade 3 or 4 was less frequent in the INTRABEAM group (0.5% vs. 2.1%; $p = 0.002$). These were the only statistically significant differences in complications.

Health-related quality-of-life substudy

One small single-centre substudy ($n = 88$) did not identify any statistically significant differences in QoL measures between the study arms.

Systematic review of cost-effectiveness

From 184 citations screened, 10 references were retrieved for consideration. Three publications were included, two on the same economic model. Outcomes from both models suggested that INTRABEAM was a cost-effective option when compared with WB-EBRT. In one model, the incremental cost-effectiveness ratio (ICER) showed that INTRABEAM dominated WB-EBRT by being both cheaper and more clinically effective. In the other model, the costs per QALY for WB-EBRT compared with INTRABEAM ranged from $89,234 to $108,735 depending on the difference in whole-breast irradiation rates.

Systematic review of health-related quality of life

From 939 records screened, 65 studies were retrieved for consideration. Nine studies were included which provided European Quality of Life–5 Dimensions data for five out of seven health states potentially relevant for the independent model.

Manufacturer's economic evaluation

The manufacturer's submitted model indicates that INTRABEAM is associated with higher QALY gains and lower costs, with the incremental analysis showing dominance of INTRABEAM over WB-EBRT. A probabilistic sensitivity analysis (PSA) found that INTRABEAM had a 100% probability of being cost-effective, at both the £20,000 and £30,000 thresholds.

Independent economic evaluation

The assessment group's model finds INTRABEAM to be less expensive but also less effective than WB-EBRT because it is associated with lower total costs but fewer total QALYs gained. The base-case ICER to replace WB-EBRT with intraoperative radiation therapy is £1596 saved per QALY lost. INTRABEAM is therefore not cost-effective compared with WB-EBRT at a willingness-to-pay (WTP) threshold of £20,000 per QALY. The PSA indicates that WB-EBRT has a greater probability than INTRABEAM of being cost-effective at the £20,000 and £30,000 per QALY WTP thresholds. INTRABEAM has a higher probability of being cost-effective than WB-EBRT at thresholds of around £5000 per QALY or less. Deterministic sensitivity analysis finds four parameters for which the difference between upper and lower values causes a switch in the treatment option, which is considered cost-effective at the £20,000 per QALY threshold. The parameters to which the model is most sensitive are the probability of any other recurrence assumed for WB-EBRT and INTRABEAM, the beta coefficient for the time to local recurrence (INTRABEAM) and the probability of death from breast cancer (INTRABEAM).

Discussion

Systematic reviews and an economic evaluation have been carried out independent of any vested interest. A de novo economic model was developed following recognised guidelines and systematic searches were conducted to identify data inputs for the model.

Limitations

The base-case result is subject to uncertainty because the disease progression parameters are largely drawn from the single available RCT. This RCT has a median follow-up of 2 years 5 months, which may be inadequate, particularly as numbers of participants experiencing a local recurrence in the pre-pathology stratum are small. The model is particularly sensitive to this parameter.

Conclusions

A significant investment in INTRABEAM equipment and staff training (clinical and non-clinical) would be required to make this technology available across the NHS. Longer-term follow-up data from the TARGIT-A trial and analysis of registry data are required as results are currently based on a small number of events and economic modelling results are uncertain.

Study registration

This study is registered as PROSPERO CRD42013006720.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research. Note that the economic model associated with this document is protected by intellectual property rights, which are owned by the University of Southampton. Anyone wishing to modify, adapt, translate, reverse engineer, decompile, dismantle or create derivative work based on the economic model must first seek the agreement of the property owners.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

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Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 12/69/01. The protocol was agreed in September 2013. The assessment report began editorial review in April 2014 and was accepted for publication in September 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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