HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 73 SEPTEMBER 2016
ISSN 1366-5278

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NHS
National Institute for Health Research

DOI 10.3310/hta20730

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Declared competing interests of authors: Jayant S Vaidya has received a research grant from Photoelectron Corp. (1996–9) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK) and has subsequently received honoraria. Jayant S Vaidya also has a patent for the use of the word TARGIT for TARGeted Intraoperative radioTherapy. Frederik Wenz has received a research grant from Carl Zeiss for supporting radiobiological research. Frederik Wenz also has patents for US 8,724,775B2, US 2013/058460 A, PCT/EP2011/057518, DE/18.12.09/DEA10200905877 and DE/17.12.09/DEA10200905058581, all issues to Wenz/Zeiss. Chris Brew-Graves, Ingrid Potyka and Norman R Williams report that the Clinical Trials Group was paid an unrestricted grant from 1 November 2001 to 31 October 2010. Michael Baum was on the scientific advisory board of Carl Zeiss and was paid monthly consultancy fees until 2010. In addition, Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Christobel Saunders and Michael Baum report that Carl Zeiss sponsors most of the travel and accommodation for meetings of the International Steering Committee and Data Monitoring Committee and, when necessary, for conferences where a presentation about targeted intraoperative radiotherapy is being made for all authors.

Published September 2016
DOI: 10.3310/hta20730

This report should be referenced as follows:

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, *et al*. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess* 2016;**20**(73).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

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

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 07/60/49. The contractual start date was in September 2009. The draft report began editorial review in October 2014 and was accepted for publication in June 2016. 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.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial)

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Background: Based on our laboratory work and clinical trials we hypothesised that radiotherapy after lumpectomy for breast cancer could be restricted to the tumour bed. In collaboration with the industry we developed a new radiotherapy device and a new surgical operation for delivering single-dose radiation to the tumour bed – the tissues at highest risk of local recurrence. We named it TARGeted Intraoperative radioTherapy (TARGIT). From 1998 we confirmed its feasibility and safety in pilot studies.

Objective: To compare TARGIT within a risk-adapted approach with whole-breast external beam radiotherapy (EBRT) over several weeks.

Design: The TARGeted Intraoperative radioTherapy Alone (TARGIT-A) trial was a pragmatic, prospective, international, multicentre, non-inferiority, non-blinded, randomised (1 : 1 ratio) clinical trial. Originally, randomisation occurred *before* initial lumpectomy (prepathology) and, if allocated TARGIT, the patient received it during the lumpectomy. Subsequently, the postpathology stratum was added in which randomisation occurred *after* initial lumpectomy, allowing potentially easier logistics and a more stringent case selection, but which needed a reoperation to reopen the wound to give TARGIT as a delayed procedure. The risk-adapted approach meant that, in the experimental arm, if pre-specified unsuspected adverse factors were found postoperatively after receiving TARGIT, EBRT was recommended. Pragmatically, this reflected how TARGIT would be practised in the real world.

Setting: Thirty-three centres in 11 countries.

Participants: Women who were aged ≥ 45 years with unifocal invasive ductal carcinoma preferably ≤ 3.5 cm in size.

Interventions: TARGIT within a risk-adapted approach and whole-breast EBRT.

Main outcome measures: The primary outcome measure was absolute difference in local recurrence, with a non-inferiority margin of 2.5%. Secondary outcome measures included toxicity and breast cancer-specific and non-breast-cancer mortality.

Results: In total, 3451 patients were recruited between March 2000 and June 2012. The following values are 5-year Kaplan–Meier rates for TARGIT compared with EBRT. There was no statistically significant difference in local recurrence between TARGIT and EBRT. TARGIT was non-inferior to EBRT overall [TARGIT 3.3%, 95% confidence interval (CI) 2.1% to 5.1% vs. EBRT 1.3%, 95% CI 0.7% to 2.5%; $p = 0.04$; $P_{\text{non-inferiority}} = 0.00000012$] and in the prepathology stratum ($n = 2298$) when TARGIT was given concurrently with lumpectomy (TARGIT 2.1%, 95% CI 1.1% to 4.2% vs. EBRT 1.1%, 95% CI 0.5% to 2.5%; $p = 0.31$; $P_{\text{non-inferiority}} = 0.0000000013$). With delayed TARGIT postpathology ($n = 1153$), the between-group difference was larger than 2.5% and non-inferiority was not established for this stratum (TARGIT 5.4%, 95% CI 3.0% to 9.7% vs. EBRT 1.7%, 95% CI 0.6% to 4.9%; $p = 0.069$; $P_{\text{non-inferiority}} = 0.06640$]. The local recurrence-free survival was 93.9% (95% CI 90.9% to 95.9%) when TARGIT was given with lumpectomy compared with 92.5% (95% CI 89.7% to 94.6%) for EBRT ($p = 0.35$). In a planned subgroup analysis, progesterone receptor (PgR) status was found to be the only predictor of outcome: hormone-responsive patients (PgR positive) had similar 5-year local recurrence with TARGIT during lumpectomy (1.4%, 95% CI 0.5% to 3.9%) as with EBRT (1.2%, 95% CI 0.5% to 2.9%; $p = 0.77$). Grade 3 or 4 radiotherapy toxicity was significantly reduced with TARGIT. Overall, breast cancer mortality was much the same between groups (TARGIT 2.6%, 95% CI 1.5% to 4.3% vs. EBRT 1.9%, 95% CI 1.1% to 3.2%; $p = 0.56$) but there were significantly fewer non-breast-cancer deaths with TARGIT (1.4%, 95% CI 0.8% to 2.5% vs. 3.5%, 95% CI 2.3% to 5.2%; $p = 0.0086$), attributable to fewer deaths from cardiovascular causes and other cancers, leading to a trend in reduced overall mortality in the TARGIT arm (3.9%, 95% CI 2.7% to 5.8% vs. 5.3%, 95% CI 3.9% to 7.3%; $p = 0.099$]. Health economic analyses suggest that TARGIT was statistically significantly less costly than EBRT, produced similar quality-adjusted life-years, had a positive incremental net monetary benefit that was borderline statistically significantly different from zero and had a probability of > 90% of being cost-effective. There appears to be little uncertainty in the point estimates, based on deterministic and probabilistic sensitivity analyses. If TARGIT were given instead of EBRT in suitable patients, it might potentially reduce costs to the health-care providers in the UK by £8–9.1 million each year. This does not include environmental, patient and societal costs.

Limitations: The number of local recurrences is small but the number of events for local recurrence-free survival is not as small (TARGIT 57 vs. EBRT 59); occurrence of so few events (< 3.5%) also implies that both treatments are effective and any difference is unlikely to be large. Not all 3451 patients were followed up for 5 years; however, more than the number of patients required to answer the main trial question ($n = 585$) were followed up for > 5 years.

Conclusions: For patients with breast cancer (women who are aged ≥ 45 years with hormone-sensitive invasive ductal carcinoma that is up to 3.5 cm in size), TARGIT concurrent with lumpectomy within a risk-adapted approach is as effective as, safer than and less expensive than postoperative EBRT.

Future work: The analyses will be repeated with longer follow-up. Although this may not change the primary result, the larger number of events may confirm the effect on overall mortality and allow more detailed subgroup analyses. The TARGeted Intraoperative radioTherapy Boost (TARGIT-B) trial is testing whether or not a tumour bed boost given intraoperatively (TARGIT) boost is superior to a tumour bed boost given as part of postoperative EBRT.

Trial registration: Current Controlled Trials ISRCTN34086741 and ClinicalTrials.gov NCT00983684.

Funding: University College London Hospitals (UCLH)/University College London (UCL) Comprehensive Biomedical Research Centre, UCLH Charities, Ninewells Cancer Campaign, National Health and Medical Research Council and German Federal Ministry of Education and Research (BMBF). From September 2009 this project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 73. See the NIHR Journals Library website for further project information.

Chapter 6 Cost–utility analysis of external beam radiotherapy compared with targeted intraoperative radiotherapy in breast cancer

Background

There is limited evidence about the cost-effectiveness of TARGIT. Picot *et al.*[72] recently undertook a systematic review of published economic evaluations and found two primary studies.[73,74] Both were modelling studies using aggregate data from the TARGIT-A trial supplemented with data from other sources. Alvarado *et al.*[73] found that TARGIT was less costly and produced more quality-adjusted life-years (QALYs) than EBRT and concluded that TARGIT was the dominant strategy. Based on the results of a cost-minimisation analysis,[72] TARGIT was associated with substantial cost savings compared with whole-breast irradiation delivered using three-dimensional conformal radiotherapy or accelerated PBI delivered with intensity-modulated radiotherapy. Both studies were based in the USA and because of differences in treatment practices and patients the results are unlikely to be applicable to the UK.

Picot *et al.*[72] undertook a UK-based cost–utility analysis of TARGIT using data from the TARGIT-A trial supplemented with data from other sources. They found that TARGIT was less costly than EBRT and also less effective, producing fewer QALYs. This is more relevant than the studies by Alvarado *et al.*[73] and Shah *et al.*[74] because it is a UK-based study, but it is a modelling study using aggregate data from the TARGIT-A trial. Hence, we undertook a cost–utility analysis of TARGIT compared with EBRT using patient-level data from the TARGIT-A trial.

Methods

Patients

The analysis was based on costs and outcomes for the 817 patients randomised in the 'earliest cohort' in the prepathology stratum of the TARGIT-A trial. Several issues were considered when deciding which cohort of patients to include in the cost–utility analysis:

1. We did not include the postpathology stratum from the earliest cohort because the results in this group were less favourable than those of the prepathology stratum. Hence, it is highly unlikely that TARGIT would be adopted in clinical practice for this group. As patients from this stratum were not included in the analysis, the results cannot be applied to this group.
2. The number of participants needed to prove non-inferiority was calculated to be 585 and therefore the earliest cohort of 817 patients had enough power to draw reliable conclusions.
3. The earliest cohort was randomised between 2000 and 2008 and the average follow-up was 5 years, permitting a reasonable follow-up period without a large number of missing data. The complete prepathology stratum from TARGIT-A consisted of 2298 patients, with an average follow-up of 2 years 4 months. Hence, by including the full cohort we would have substantially increased the proportion of missing data in the sample if we wanted to use a 5-year time horizon or we would have had to use a shorter time horizon.

We therefore balanced the number of patients in the whole cohort compared with the number in the earliest cohort against the duration of follow-up in the two cohorts against the fact that the earliest cohort had enough statistical power to draw reliable conclusions and decided to base our analysis on the 817 patients randomised in the earliest cohort of the TARGIT-A trial in the prepathology stratum. In this cohort,

as in the mature cohort in the prepathology stratum and all patients in the prepathology stratum, TARGIT was non-inferior to EBRT with respect to local recurrence and the 5-year estimated risks of local recurrence were not statistically different between the treatment groups.

Overview of the cost–utility analysis

We undertook a cost–utility analysis to compare the costs and outcomes associated with TARGIT compared with EBRT in the prepathology stratum of the TARGIT-A trial. The outcome measure was QALYs, which combine length of life and quality of life, consistent with NICE guidelines.[75] Cost-effectiveness was expressed as incremental net monetary benefits.[75] The analysis took a UK NHS and personal social services (PSS) perspective.[75] Resource use data were included from all participating centres and UK unit costs were applied. Costs are presented in 2013/14 UK pounds. The time horizon was 5 years, reflecting the average follow-up in the earliest cohort in the prepathology stratum of the TARGIT-A trial. Extrapolation beyond the end of the trial using decision-analytical modelling was not undertaken because the within-trial analysis found no evidence of significant differences in QALYs between the groups. This probably reflects the main finding from the TARGIT-A trial that TARGIT was non-inferior to EBRT with regard to local recurrence. Although there was some evidence of differences in costs, these differences were accrued during the first year, with no evidence of significant differences in costs beyond the first year. Hence, the 5-year time horizon was long enough to reflect all important differences in costs or outcomes between the two treatments. An annual discount rate of 3.5% was applied to costs and outcomes.[75]

Resource use and costs

Cost components

We calculated the costs incurred by every patient during the 5-year time horizon using resource use and event data collected prospectively in the trial. The following costs were included: TARGIT, EBRT, index procedure, additional procedures, chemotherapy, mastectomy, complications, recurrence-free survival, local recurrence, distant recurrence, breast cancer deaths and non-breast-cancer deaths. Unit costs were obtained from published sources[72,76–80] (*Table 12*), inflated when appropriate[82] and multiplied by resource use. Annual costs were calculated for every patient for each year of the 5-year time horizon. These were discounted and summed across all 5 years to calculate total costs per patient over the whole period.

TABLE 12 Unit costs

Cost item	Unit cost[a]	Notes/source
TARGIT	£1882 per patient	Picot *et al.*[72] Base-case value calculated assuming 126 procedures performed per year and a 10-year lifetime of the INTRABEAM device
EBRT	£123 per fraction	Department of Health[76] – Currency code SC23Z. Outpatients
	£769 for planning meeting	Department of Health[76] – Currency code SC52Z. Outpatients
EBRT boost	£126 per fraction	Department of Health[76] – Currency code SC23Z. Outpatients
	£769 for planning meeting	Department of Health[76] – Currency code SC52Z. Outpatients
NHS patient transport	£68 per return journey	Department of Health[77] – Currency code PTS. Outpatients
Index procedure	£1128 per procedure	Department of Health[76] – Currency code JA09G. Combined day case/ordinary elective spell

TABLE 12 Unit costs (*continued*)

Cost item	Unit cost[a]	Notes/source
Overnight stay related to index procedure	£227 per additional overnight stay	Department of Health[76] – Currency code JA09G. Long stay for days exceeding time point
Mastectomy with breast reconstruction	£6504 per procedure	Department of Health[76] – Currency code JA16Z. Combined day case/ordinary elective spell
Additional procedures (excision of positive margins, axillary dissection or clearance)	£1128 per procedure	Department of Health[76] – Currency code JA09G. Combined day case/ordinary elective spell
Chemotherapy	£2087 per course of treatment	NICE[78] – docetaxel infusion every 21 days (six cycles). Department of Health[76] – Currency code first attendance SB14Z, subsequent attendance SB15Z. Outpatient
Complications		
Surgical evacuation of haematoma	£362 per procedure	Department of Health[76] – Currency Code JA12C. Day case
Aspiration for seroma	£397 per complication	Department of Health[76] – treatment function 370, consultant led WF01B for first and WF01A for second and third aspirations. Only applied each time three aspirations of seroma noted. Outpatient
Wound infection requiring oral antibiotics	£2.60 per course of treatment	*British National Formulary*[79] – treatment using flucloxacillin 500 mg, £2.60 for a 28-tablet pack (1 week)
Wound infection requiring intravenous antibiotics	£362 per course of treatment	Department of Health[76] – Currency code JA12C. Day case
Skin breakdown/delayed wound healing	£29 per course of treatment	*British National Formulary*[79] – soft non-woven dressing impregnated with Intrasite® (Smith & Nephew, London, UK) gel, 10 cm × 10 cm, £1.70 (2 weeks) = £23.80 plus flucloxacillin 500 mg, £2.60 for a 28-tablet pack (2 weeks) = £5.20
RTOG toxicity grade 3	£5 per course of treatment	*British National Formulary*[79] – aqueous cream 500 g
RTOG toxicity grade 4	£23.80 per course of treatment	*British National Formulary*[79] – soft non-woven dressing impregnated with Intrasite® gel, 10 cm × 10 cm, £1.70 (2 weeks) = £23.80
Pain in the irradiated field	£3 per course of treatment	*British National Formulary*[79] – paracetamol 500 mg, 100-tablet pack
Events		
Recurrence free	£1057 per year	Hind *et al.*[81] – one oncologist visit per year for 5 years, one mammogram per year for 5 years, 5 years of anstrozole/tamoxifen (70 : 30) hormonal therapy
Local recurrence	Mean £4956 (SD £3953) per recurrence	Mean (SD) from patient-level costing
Distant recurrence	£1040 per month	Hind *et al.*[81] – monthly cost of supportive care for metastatic breast cancer
Breast cancer death	£3659 per death	Hind *et al.*[81] – cost of death from breast cancer
Non-breast-cancer death	£3659 per death	Hind *et al.*[81] – assumed to be the same as cost of death from breast cancer

SD, standard deviation.
a Costs are in 2013/14 UK pounds.

Targeted intraoperative radiotherapy

A fixed cost per patient was assumed for TARGIT, based on recently published calculations by Picot *et al.*[72] This cost includes one-off capital costs and annual maintenance costs associated with the INTRABEAM device; one-off, annual and per-treatment costs requiring additional staff resources; the cost of consumables required for each use of the device; and the cost of additional operating theatre time for each use of the device. The capital and one-off costs were annualised using a device lifetime of 10 years. These costs and the annual costs were assigned to individual treatments assuming that each device was used to undertake 126 procedures per year. On this basis Picot *et al.*[72] calculate the unit cost per patient to be £1882 (2013/14 prices), which is the value that we used in our analysis for the base case. This was varied in sensitivity analysis.

External beam radiotherapy

Patient-level data were collected in the TARGIT-A trial on the number of fractions of EBRT received by each patient. A proportion of patients randomised to TARGIT also received EBRT and these were also included in the analysis. The mean [standard deviation (SD)] number of fractions given to patients in the trial who received EBRT was 23 (5). This is higher than current recommendations stating that 15 fractions are required to complete a course of treatment for patients with early invasive breast cancer after breast-conserving surgery or mastectomy.[78] In our base case we therefore assumed that all patients in the TARGIT-A trial who received EBRT received a fixed number of 15 fractions. We applied a unit cost per fraction plus a one-off cost for a planning meeting (see *Table 12*). In sensitivity analyses we estimated cost-effectiveness based on the actual number of fractions of EBRT received in the trial.

Standard treatment of breast cancer includes an EBRT boost as part of the course of whole-breast radiotherapy; however, it is sometimes omitted in patients at a lower risk of local recurrence.[83–85] In the TARGIT-A trial, patient-level data were also recorded on whether or not patients received an EBRT boost and if so the number of fractions received. These were included in our base case. We applied a unit cost per fraction plus a one-off cost for an additional planning meeting (see *Table 12*). In sensitivity analysis we estimated cost-effectiveness assuming no EBRT boost.

External beam radiotherapy requires several trips to hospital for treatment, incurring time and travel costs for patients and their families. Our analysis was undertaken from a NHS and PSS perspective and so we did not include these costs. However, some patients use NHS patient transport to travel to hospital for EBRT, which is a cost incurred by the NHS. We were unable to find any pre-existing evidence on the proportion of EBRT patients who use NHS patient transport and so we undertook a short survey at two sites. The first site was Great Western Hospital in Swindon, where patients receiving EBRT typically travel to radiotherapy centres at the John Radcliffe Hospital, Oxford, the Royal United Hospital, Bath, or Cheltenham General Hospital for treatment. The second was Princess Alexandra Hospital, Harlow, where patients typically travel to North Middlesex Hospital, Enfield, for treatment. Patients were asked to indicate their method of transport to the radiotherapy centre, with possible responses being by car, by hospital transport or by public transport. We received 37 responses (17 from patients at Great Western Hospital and 20 from patients at Princess Alexandra Hospital), with five (13.5%) patients reporting using hospital transport. In our base case we therefore assumed that 13.5% of patients receiving EBRT use NHS patient transport over the course of their treatment and applied a unit cost per return journey (see *Table 12*). We varied the proportion of patients using NHS patient transport to travel to hospital for EBRT in sensitivity analysis.

Other cost components

The cost of the index procedure included the cost of the lumpectomy procedure itself plus the cost of any associated hospital stay, which was recorded in the trial. Any additional procedures related to excision of margins or axillary dissection and/or clearance were recorded, as well as whether or not the patient received chemotherapy and had a mastectomy. For the index procedure, additional procedures and mastectomies, unit costs based on NHS reference costs[76] were applied. Costs for a course of chemotherapy were based on current treatment recommendations.[78]

Data were recorded in the trial on the number of the following complications: haematoma requiring surgical evacuation; seroma requiring three or more aspirations; infection requiring oral or intravenous antibiotics or surgical intervention; skin breakdown or delayed wound healing; and RTOG toxicity of grade 3 or 4. Details were recorded on how each individual complication was treated and these were costed separately and included in the analysis (see *Table 12*).

We included the costs of remaining recurrence free, local recurrence, distant recurrence, breast cancer death and non-breast-cancer death. Unit costs were taken from a published source[81] and applied to patient-level data from the trial. Treatments for local recurrence were recorded in the trial and were costed on an individual patient basis. Treatments for local recurrence included mastectomy, TARGIT, EBRT, hormone therapy and chemotherapy. The mean (SD) cost per patient of local recurrence was £4956 (£3953; see *Table 12*).

Utilities and quality-adjusted life-years

The outcome measure in our cost–utility analysis was QALYs, which combine length of life and quality of life, the latter being measured by utility scores. A utility score of 1 represents full health and a score of 0 denotes death; negative values represent states worse than death.

Utility data were not collected in the TARGIT-A trial. Patient-level data on the timing of events were collected and for every patient we created a data set describing the health state that they were in during every day of the 5-year time horizon. Utility values from published sources were then applied to each health state. These were used to construct five 1-year utility profiles for every patient covering the 5-year time horizon. QALYs for every patient for each year were calculated as the area under the utility profile for that year. These were discounted and summed across all 5 years to calculate QALYs per patient over the whole period.

The health states included in the cost–utility analysis were recurrence free, local recurrence, distant recurrence, breast cancer death and non-breast-cancer death. A review of the *Cost-Effectiveness Analysis Registry*[86] was undertaken using the search term 'breast cancer' to identify studies reporting relevant utility scores and 1291 results (utility scores) were identified. Picot *et al.*[72] recently undertook an extensive literature search of studies providing utility values for such patients and identified nine suitable studies. The criteria for the values that they selected in their analysis were that they would ideally be based on EQ-5D scores, would ideally have been derived from UK patients and these patients would ideally reflect the younger age range of patients in the TARGIT-A trial. The values that they selected, from studies by Turnbull *et al.*[87] and Lidgren *et al.*,[88] were as follows:

- recurrence free in first year: 0.7728
- recurrence free after first year: 0.8112
- local recurrence: 0.8112
- recurrence free after local recurrence: 0.8112
- distant recurrence: 0.658.

We used these values in our base case. The values imply that the utility associated with local recurrence is the same as the utility associated with being recurrence free after the first year and the utility associated with being recurrence free after local recurrence. We undertook a sensitivity analysis using values from an alternative study by Hayman *et al.*,[89,90] which have been used in previous studies, as follows:

- recurrence free: 0.92
- local recurrence: 0.87
- recurrence free after local recurrence: 0.92
- distant recurrence: 0.70.

Patients who died in the TARGIT-A trial (either from breast cancer or from other causes) were assigned a utility value of 0 at their date of death until the end of the 5-year time horizon.

In the cost–utility analysis we did not incorporate utility losses associated with additional procedures, chemotherapy, mastectomy or complications. Given the low incidence of these events, that they were evenly distributed between treatment groups and that the time period affected is likely to be short, this is unlikely to affect the QALYs associated with each treatment group. We also did not include any utility losses associated with EBRT. Therefore, this would make our estimates more conservative because such an omission would work against TARGIT.

Missing data

There were some missing data on patient follow-up, meaning that for some patients we did not know whether or not they had experienced events. This affected both the total costs incurred by each patient and the total QALYs. Multiple imputation was used to impute missing data separately for costs in years 1–5, total costs, QALYs in years 1–5 and total QALYs. The following variables were included in the imputation models as additional explanatory variables: cost of EBRT, cost of the index procedure, cost of additional procedures, cost of chemotherapy, cost of mastectomy, whether or not the patient had each type of complication, age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre, year of randomisation and treatment allocation. We used multivariate normal regression to impute missing values and generated 20 imputed data sets. We repeated the multiple imputation several times using different random number seeds to investigate whether or not the conclusions of the analysis changed.

Statistical methods

Mean costs, outcomes and net monetary benefits were compared between all patients randomly assigned to EBRT and TARGIT, irrespective of which treatment was administered and whether or not patients received additional therapies of either type. We calculated differences in mean costs and QALYs and incremental net monetary benefits between groups. Net monetary benefits for EBRT and TARGiT were calculated as the mean QALYs per patient multiplied by the maximum willingness to pay for a QALY minus the mean cost per patient. Incremental net monetary benefits were calculated as the difference in mean QALYs per patient with TARGIT compared with EBRT multiplied by the maximum willingness to pay for a QALY minus the difference in mean costs per patient. We used the cost-effectiveness threshold range recommended by NICE of £20,000–30,000[75] as the lower and upper limits of the maximum willingness to pay for a QALY. If the incremental net monetary benefit is positive (negative) then TARGIT (EBRT) is preferred on cost-effectiveness grounds. The QALYs gained and incremental costs were adjusted for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation. For each of the 20 imputed data sets we ran 1000 bootstrap replications and combined the results using equations described by Briggs *et al.*[91] to calculate standard errors (SEs) around mean values accounting for uncertainty in the imputed values, the skewed nature of the cost data and utility values and sampling variation. SEs were used to calculate 95% CIs around point estimates. A similar analytical approach has been used previously.[92]

Sensitivity analyses

We undertook deterministic sensitivity analyses to evaluate the impact of uncertainty in the following components. In each case the changes made were applied one at a time to the base case.

- No adjustment for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation.

- Complete case analysis without imputing missing values.
- Complete case analysis without imputing missing values plus with no adjustment for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation.
- EBRT costs based on number of fractions received in the trial [mean (SD) number of fractions administered per patient who received EBRT in the trial was 23 (5)].
- No EBRT boost.
- Costs of EBRT per fraction of £101 and £154, based on the lower and upper values of the IQR of the NHS reference costs.[76]
- Costs of TARGIT of £1300, £1500, £1700, £1900, £2100, £2300, £2500 and £2700. The value of £1300 corresponds to the minimum value in Picot *et al.*,[72] in which the capital and one-off costs were annualised using a device lifetime of 10 years and these costs and the annual costs were assigned to individual treatments assuming that each device was used to undertake 631 procedures per year. The value of £2500 corresponds to the maximum value in Picot *et al.*,[72] with a device lifetime of 5 years and 100 procedures per year.
- Percentage of patients using NHS transport for EBRT of 0% (no patients use NHS transport) and 30%.
- Health states valued using utilities from Hayman *et al.*[89,90]

A cost-effectiveness acceptability curve[93] showing the probability that TARGIT was cost-effective compared with EBRT at a range of values for the maximum willingness to pay for a QALY was generated based on the proportion of the bootstrap replications across all 20 imputed data sets with positive incremental net monetary benefits.[94] The probability that TARGIT was cost-effective at a maximum willingness to pay for a QALY of £20,000 and £30,000 was reported, based on the proportion of bootstrap replications with positive incremental net monetary benefits at these values.

Results

Resource use and costs

In total, 15.2% of patients randomised to TARGIT also received EBRT (*Table 13*). We assumed that every patient receiving EBRT received 15 fractions. In total, 38% of patients randomised to EBRT also received an EBRT boost [mean (SD) 5 (2) fractions]. We assumed that 13.5% of all EBRT patients used NHS transport to travel to hospital for their radiotherapy treatment. The mean (median) number of nights in hospital for the initial procedure was 4 (3) for both TARGIT and EBRT patients. A total of 19% of EBRT patients received additional procedures, compared with 12% of TARGIT patients. In total, 20% of EBRT patients received chemotherapy and 4% had a mastectomy; for TARGIT the figures were 23% and 3%, respectively. The incidence of complications was low in both treatment groups. The number of events for TARGIT and EBRT were local recurrences (6 vs. 3), distant recurrences (21 vs. 18), breast cancer deaths (13 vs. 11) and non-breast-cancer deaths (7 vs. 18).

Accounting for missing data using multiple imputation, mean total costs per patient (95% CI) were £11,840 (£11,422 to £12,259) in the EBRT group ($n = 416$) and £11,404 (£10,800 to £12,008) in the TARGIT group ($n = 401$; *Table 14*). The mean radiotherapy cost per patient (summing the cost of TARGIT plus EBRT plus EBRT boost plus NHS transport for EBRT) was £3373 in the EBRT group and £2307 in the TARGIT group. Other costs were similar for EBRT and TARGIT. Values were similar for complete cases (*Table 15*).

Quality-adjusted life-years

Accounting for missing data using multiple imputation, mean QALYs per year were similar for the two groups and there was a decline over time. Mean QALYs per patient (95% CI) fell from 0.810 (0.808 to 0.812) in the EBRT group in year 1 to 0.657 (0.640 to 0.674) in year 5. In the TARGIT group the values were 0.811 (0.810 to 0.811) and 0.674 (0.660 to 0.689), respectively. Mean total QALYs per patient over

TABLE 13 Summary of data used in the cost–utility analysis

Resource	EBRT ($n = 416$)	TARGIT ($n = 401$)
EBRT, %	100	15.2
Fractions of EBRT, *n*	15	15
EBRT boost, %	38	0
Boost fractions, mean (SD)	5 (2)	–
NHS transport for EBRT, %	13.5	13.5
Index procedure, number of nights		
Mean (SD)	4 (4)	4 (4)
Median (IQR)	3 (1–6)	3 (1–6)
Additional procedures, *n* (%)		
0	338 (81)	353 (88)
1	72 (17)	46 (11)
2	5 (1)	1 (0)
3	1 (0)	1 (0)
Chemotherapy, *n* (%)	84 (20)	93 (23)
Mastectomy, *n* (%)	17 (4)	13 (3)
Complications, *n* (%)		
Haematoma requiring surgical evacuation or seroma needing three or more aspirations	1 (0)	1 (0)
Infection requiring oral or intravenous antibiotics or surgical intervention	5 (1)	5 (1)
Skin breakdown or delayed wound healing, number (%)	3 (1)	2 (0)
RTOG toxicity grade 3 or 4	9 (2)	2 (0)
Events, *n*		
Local recurrence	3	6
Distant recurrence	18	21
Breast cancer death	11	13
Non breast cancer death	18	7

the 5-year period were 3.663 (3.614 to 3.713) in the EBRT group and 3.704 (3.664 to 3.744) in the TARGIT group (see *Table 14*). QALYs were similar for complete cases (see *Table 15*).

Cost–utility analysis

Accounting for missing data using multiple imputation, the mean net monetary benefits for EBRT and TARGIT were £61,426 (95% CI £60,299 to £62,544) and £62,678 (95% CI £61,542 to £63,762) at a maximum willingness to pay for a QALY of £20,000 and £98,059 (95% CI £96,470 to £99,644) and £99,720 (95% CI £98,228 to £101,147) at a maximum willingness to pay for a QALY of £30,000 (see *Table 14*).

TABLE 14 Mean QALYs, costs and net monetary benefits: multiple imputation

	EBRT ($n = 416$)		TARGIT ($n = 401$)	
Variable	Mean	95% CI	Mean	95% CI
Costs (£)[a]				
TARGIT	0	[b]	1882	[b]
EBRT	2659	[b]	405	[b]
EBRT boost	557	487 to 628	0	[b]
NHS transport for EBRT	157	154 to 160	21	[b]
Total EBRT	3373	3300 to 3447	425	[b]
Total EBRT plus TARGIT	3373	3300 to 3447	2307	[b]
Index operation	2069	1986 to 2153	2101	2009 to 2193
Additional procedures	230	182 to 279	143	103 to 184
Chemotherapy	421	341 to 502	484	397 to 571
Mastectomy	266	142 to 390	211	98 to 324
Costs associated with health status[c]				
Year 1	1099	1063 to 1135	1124	1052 to 1196
Year 2	1176	1073 to 1278	1254	1123 to 1384
Year 3	1126	1014 to 1237	1265	1108 to 1423
Year 4	1059	945 to 1173	1269	1099 to 1438
Year 5	1020	879 to 1161	1246	1072 to 1420
Total costs	11,840	11,422 to 12,259	11,404	10,800 to 12,008
QALYs				
Year 1	0.810	0.808 to 0.8120	0.811	0.810 to 0.811
Year 2	0.774	0.766 to 0.781	0.777	0.772 to 0.782
Year 3	0.728	0.714 to 0.742	0.738	0.727 to 0.749
Year 4	0.695	0.679 to 0.710	0.704	0.691 to 0.717
Year 5	0.657	0.640 to 0.674	0.674	0.660 to 0.689
Total QALYs	3.663	3.614 to 3.713	3.704	3.664 to 3.744
Net monetary benefits (£)				
£20,000	61,426	60,299 to 62,544	62,678	61,542 to 63,762
£30,000	98,059	96,470 to 99,644	99,720	98,228 to 101,147

a Costs are in 2013/14 UK pounds.
b Values do not vary by patient.
c Costs associated with being disease free, local recurrence, distant recurrence, breast cancer death, non-breast-cancer death and complications.

Notes
Data include values imputed using multiple imputation (see *Missing data* and *Statistical methods*). The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets (see *Missing data* and *Statistical methods*). The net monetary benefit is calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.

TABLE 15 Mean QALYs, costs and net monetary benefits: complete cases

	EBRT			TARGIT		
Variable	Mean	SD	*n*	Mean	SD	*n*
Costs (£)[a]						
TARGIT	0	0	416	1882	0	401
EBRT	2659	0	416	405	0	401
EBRT boost	557	733	416	0	0	401
NHS transport for EBRT	157	28	416	21	0	401
Total EBRT	3373	760	416	425	0	401
Total EBRT plus TARGIT	3373	760	416	2307	0	401
Index operation	2069	865	416	2101	937	401
Additional procedures	230	506	416	143	409	401
Chemotherapy	421	839	416	484	882	401
Mastectomy	266	1289	416	211	1153	401
Costs associated with health status[b]						
Year 1	1099	347	406	1125	730	393
Year 2	1184	1040	395	1261	1325	388
Year 3	1129	1130	387	1264	1600	382
Year 4	1052	1113	360	1279	1771	354
Year 5	1057	1301	266	1260	1916	233
Total costs	11,956	4656	266	11,789	7301	233
QALYs						
Year 1	0.810	0.019	406	0.811	0.006	393
Year 2	0.773	0.078	395	0.777	0.052	388
Year 3	0.726	0.143	387	0.737	0.110	382
Year 4	0.689	0.167	360	0.700	0.136	354
Year 5	0.631	0.214	266	0.651	0.183	231
Total QALYs	3.593	0.620	266	3.642	0.518	231

a Costs are in 2013/14 UK pounds.
b Costs associated with being disease free, local recurrence, distant recurrence, breast cancer death, non-breast-cancer death and complications.

In the base-case analysis TARGIT was less costly than EBRT (mean incremental cost –£685) and produced slightly more QALYs than EBRT (mean QALYs gained 0.034; *Table 16*). The difference in costs between the two groups was statistically significant (mean incremental cost for TARGIT vs. EBRT –£685, 95% CI –£1131 to –£63) but the difference in QALYs was not (mean QALYs gained 0.034, 95% CI –0.026 to 0.095). The incremental net monetary benefit for TARGIT compared with EBRT was positive indicating that TARGIT was cost-effective: at a maximum willingness to pay for a QALY of £20,000 or £30,000 the mean incremental net monetary benefit was £1363 and £1730 (see *Table 16*). The incremental net monetary benefit was not significantly different from zero at a maximum willingness to pay for a QALY of £20,000 (mean £1363, 95% CI –£66 to £2838) or £30,000 (mean £1730, 95% CI –£284 to £3740). However, the incremental net monetary benefit for TARGIT compared with EBRT was borderline significantly different from zero: at a maximum willingness to pay for a QALY of £20,000 the 90% CI was £175 to £2818 and at £30,000 it was

TABLE 16 Incremental cost-effectiveness of TARGIT compared with EBRT: base case

Parameter	Mean	95% CI
Incremental costs (£),[a] TARGIT vs. EBRT	–685	–1341 to –63
QALYs gained, TARGIT vs. EBRT	0.034	–0.026 to 0.095
Incremental net monetary benefits (£), TARGIT vs. EBRT		
£20,000	1363	–66 to 2838
£30,000	1703	–284 to 3740
Probability TARGIT cost-effective	***p*-value**	
£20,000	0.965	
£30,000	0.950	

a Costs are in 2013/14 UK pounds.

Notes

Data include values imputed using multiple imputation (see *Missing data* and *Statistical methods*). The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets (see *Missing data* and *Statistical methods*). The QALYs gained and incremental costs are adjusted for age, tumour size, ER status and PgR status at baseline, whether the cancer was detected by screening or not, contralateral breast cancer or not, year of randomisation and centre. The incremental net monetary benefit and the probability that TARGIT is cost-effective are based on the adjusted QALYs gained and incremental costs and calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.

£38 to £3746. In a hypothesis test, this would indicate that against a null hypothesis the incremental net monetary benefit equals zero; the *p*-value for rejecting the null hypothesis would be between 0.05 and 0.1.

We repeated the analysis several times using alternative versions of the multiple imputation process using different random number seeds to investigate whether or not the conclusions of the analysis changed; in every case the results were qualitatively the same.

Sensitivity analyses

In all but one of the scenarios tested in the deterministic sensitivity analysis TARGIT was less costly than EBRT (*Table 17*). The exception was when the cost of TARGIT was £2700 per patient, which is higher than the maximum value in Picot *et al.*[72] (£2500). The costs were statistically significantly lower for TARGIT compared with EBRT (the 95% CI did not cross zero) when EBRT costs were based on the number of fractions received in the trial, the unit cost per fraction of EBRT was £154 (the upper quartile unit cost in the NHS reference costs[76]), the cost of TARGIT was ≤ £1900 per patient and the alternative utility values were used.

In every case the QALYs gained were small, positive and non-significant. Note that these were unlikely to change given that the parameters varied in the deterministic sensitivity analysis were mainly cost parameters.

In all cases tested the incremental net monetary benefits for TARGIT compared with EBRT were positive at a maximum willingness to pay for a QALY of £20,000 and £30,000. The incremental net monetary benefits were significantly greater than zero (the 95% CI did not cross zero) when EBRT costs were based on the number of fractions received in the trial, the unit cost per fraction of EBRT was £154 and the cost of TARGIT was ≤ £1700 per patient at a maximum willingness to pay for a QALY of £20,000 or ≤ £1300 per patient at a maximum willingness to pay for a QALY of £30,000.

The probability that EBRT is cost-effective is equal to 1 minus the probability that TARGIT is cost-effective at each value of the maximum willingness to pay for a QALY. The cost-effectiveness acceptability curve shows that, at a maximum willingness to pay for a QALY of £20,000 (£30,000), the probability that TARGIT was cost-effective was 0.965 (0.950) in the base case (*Figure 30* and see *Table 17*). In the deterministic sensitivity analyses the probability that TARGIT was cost-effective at a maximum willingness

TABLE 17 Incremental cost-effectiveness of TARGIT compared with EBRT: deterministic sensitivity analysis

	QALYs gained		Incremental costs (£)[a]		Incremental net monetary benefits (£)				Probability TARGIT cost-effective	
					£20,000		£30,000			
Analysis	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	£20,000	£30,000
Base case[b]	0.034	–0.026 to 0.095	–685	–1341 to –63	1363	–66 to 2838	1703	–284 to 3740	0.965	0.950
Unadjusted[c]	0.041	–0.022 to 0.102	–436	–1185 to 323	1253	–335 to 2796	1661	–502 to 3762	0.941	0.937
Complete case analysis adjusted[d]	0.029	–0.072 to 0.125	–583	–1549 to 315	1159	–1199 to 3498	1446	–1860 to 4691	0.834	0.803
Complete case analysis unadjusted[e]	0.049	–0.052 to 0.149	–167	–1272 to 926	1138	–1367 to 3650	1623	–1818 to 5069	0.817	0.824
EBRT costs based on number of fractions received in the trial[f]	0.034	–0.029 to 0.095	–1377	–2026 to –771	2055	562 to 3569	2394	313 to 4485	0.998	0.987
No EBRT boost	0.034	–0.028 to 0.095	–90	–733 to 519	766	–676 to 2226	1104	–913 to 3132	0.787	0.829
Costs of EBRT per fraction (£)										
101	0.034	–0.026 to 0.095	–366	–1009 to 271	1041	–387 to 2504	1379	–607 to 3413	0.926	0.917
154	0.034	–0.028 to 0.093	–1042	–1664 to –443	1715	267 to 3149	2052	28 to 4043	0.989	0.978
Costs of TARGIT (£)										
1300	0.034	–0.032 to 0.096	–1267	–1896 to –680	1940	420 to 3452	2276	141 to 4378	0.996	0.986
1500	0.034	–0.029 to 0.097	–1064	–1705 to –444	1738	247 to 3261	2075	–7 to 4194	0.994	0.980
1700	0.034	–0.026 to 0.095	–869	–1516 to –281	1544	150 to 3018	1881	–72 to 3924	0.979	0.963
1900	0.034	–0.025 to 0.092	–667	–1304 to –73	1342	–59 to 2765	1679	–271 to 3642	0.968	0.954
2100	0.034	–0.029 to 0.094	– 471	–1130 to 146	1147	–336 to 2623	1486	–584 to 3524	0.936	0.920
2300	0.034	–0.025 to 0.094	– 264	–910 to 329	944	–433 to 2395	1284	–638 to 3292	0.909	0.904
2500	0.034	–0.027 to 0.096	– 65	–702 to 515	740	–695 to 2264	1078	–927 to 3186	0.855	0.863
2700	0.034	–0.023 to 0.092	135	–496 to 748	540	–840 to 1966	877	–1032 to 2847	0.785	0.818

Analysis	QALYs gained		Incremental costs (£)[a]		Incremental net monetary benefits (£)				Probability TARGIT cost-effective	
					£20,000		£30,000			
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	£20,000	£30,000
Patients using NHS transport for EBRT (%)										
0	0.034	–0.028 to 0.096	–546	–1205 to 52	1220	–202 to 2728	1557	–437 to 3649	0.951	0.935
30	0.034	–0.025 to 0.097	–852	–1484 to –262	1530	176 to 3000	1868	–34 to 3924	0.990	0.981
Health statuses valued using utilities from Hayman *et al.*[89,90]	0.033	–0.040 to 0.104	–686	–1338 to –67	1347	–367 to 3051	1678	–737 to 4061	0.912	0.903

a Costs are in 2013/14 UK pounds.
b Data include values imputed using multiple imputation (see *Missing data* and *Statistical methods*). The QALYs gained, incremental costs and incremental net monetary benefits are for TARGIT minus EBRT. The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets (see *Missing data* and *Statistical methods*). The QALYs gained and incremental costs are adjusted for age, tumour size, ER status and PgR status at baseline, whether the cancer was detected by screening or not, contralateral breast cancer or not, year of randomisation and centre. The incremental net monetary benefits and the probability that TARGIT is cost-effective are based on the adjusted QALYs gained and incremental costs and calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.
c As for the base-case analysis except that the QALYs gained and the incremental costs are unadjusted.
d As for the base-case analysis except that there is no multiple imputation of missing values and the 95% CIs were derived from 20,000 bootstrap replications of a single data set containing the 233 TARGIT patients and 266 EBRT patients with no missing values.
e As for the complete case analysis adjusted except that the QALYs gained and the incremental costs are unadjusted.
f The mean (SD) number of fractions administered per patient who received EBRT was 23 (5).

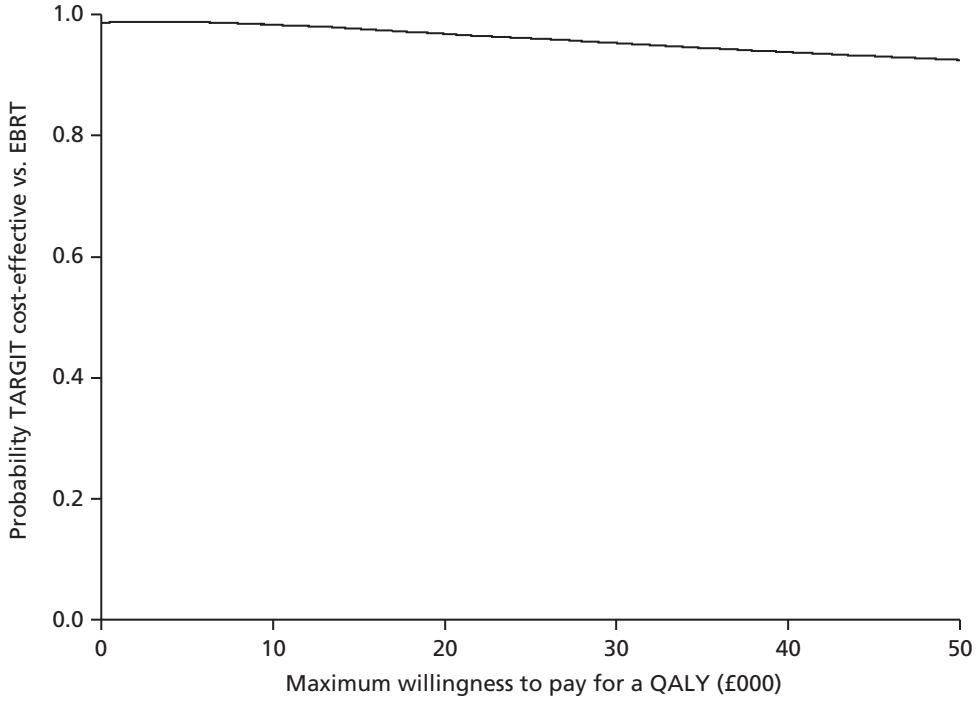

FIGURE 30 Cost-effectiveness acceptability curve showing the probability that TARGIT is cost-effective compared with EBRT at different values of the maximum willingness to pay for a QALY.

to pay for a QALY of £20,000 was > 0.75 in every case. At a maximum willingness to pay for a QALY of £30,000 the probability that TARGIT was cost-effective was > 0.80 in every case.

Potential budget impact

The cost savings per patient found in our base case could translate into cost savings per year for the NHS if TARGIT was carried our routinely instead of EBRT in eligible patients. The latest available evidence suggests that in 2011 there were 49,936 new cases of breast cancer in the UK.[95] Figures from Germany[96] based on 1108 new cases of breast cancer treated at a single centre between 2003 and 2009 suggest that 258 patients (23.3% cases) would have met the eligibility criteria for participation in the TARGIT-C trial (ClinicalTrials.gov NCT02290782),[97] which has similar but more restrictive inclusion and exclusion criteria than the TARGIT-A trial (e.g. age ≥ 50 years rather than ≥ 45 years, tumour size ≤ 2 cm rather than ≤ 3.5 cm). This conservatively suggests that around 49,936 × 23.3% = 11,600 patients may be eligible for TARGIT in the UK each year. Applying the cost saving per patient in our base case to this estimate suggests that the NHS might save around 11,600 × –£685 = £8 million a year.

Figures from France[98] based on two cohorts of patients between 1980 and 2008 indicate that, across a combined total of 12,025 patients receiving breast-conserving surgery, 5545 patients (46%) would have been eligible for TARGIT according to the eligibility criteria of the TARGIT-A trial. Approximately 58% of newly diagnosed patients with breast cancer in the UK undergo lumpectomy.[99] Therefore, according to these figures, around 49,936 × 58% × 46% = 13,300 patients may be eligible for TARGIT in the UK each year. Applying the cost saving per patient in our base case to this estimate suggests that the NHS might save around 13,300 × £685 = £9.1 million a year.

Combined, these calculations suggest that if TARGIT was carried our routinely instead of EBRT in eligible patients the potential cost savings to the NHS would be around £8–9.1 million each year.

Discussion

Summary

We undertook a cost–utility analysis comparing TARGIT versus EBRT in the prepathology stratum of the earliest cohort of the TARGIT-A trial. In our base case TARGIT was statistically significantly less costly than EBRT, produced similar QALYs, had a positive incremental net monetary benefit that was borderline statistically significantly different from zero and had a probability of > 90% of being cost-effective. Although there appears to be some uncertainty about the statistical significance of the differences in costs and whether or not the incremental net monetary benefit is different from zero, the appears to be little uncertainty in the point estimates, based on deterministic and probabilistic sensitivity analyses.

Comparison with other studies

Alvarado *et al.*[73] found that TARGIT dominated EBRT (was less costly and more effective) in that it resulted in a QALY gain of 0.00026 compared with EBRT and cost US$5191 less. Based on their analysis using TARGIT-A trial data, Shah *et al.*[74] reported that use of TARGIT was associated with cost savings of US$3.6–4.3 million per 1000 patients compared with EBRT. Neither study reported CIs around the point estimates and so it is unclear if the QALYs gained or cost savings were significantly different from zero. Our results are qualitatively similar to those of Alvarado *et al.*[73] in that based on the point estimates in our base case we also found a cost saving for TARGIT and a small QALY gain compared with EBRT. Our findings are also qualitatively similar to those of Shah *et al.*[74] in that we also found a cost saving with TARGIT compared with EBRT. However, given that both studies were US based it is difficult to draw close comparisons.

Picot *et al.*[72] found that TARGIT produced a small cost saving compared with EBRT and a small QALY loss; the authors' conclusion was that EBRT was associated with more QALYs than TARGIT at a broadly similar overall cost. The point estimates of the costs saved per QALY lost were < £20,000, indicating that TARGIT was not cost-effective (in cases in which an intervention is less costly and less effective than the comparator then for it to be cost-effective the incremental cost-effectiveness ratio must lie above the threshold value). CIs around the cost and outcome differences and the incremental cost-effectiveness measures were not reported and so it is difficult to make a full comparison of the findings. Other than the use of patient-level data, the main differences between the study by Picot *et al.*[72] and the present study were the time horizon and the range of costs included. Picot *et al.*[72] modelled costs and outcomes using a time horizon of 40 years, whereas the time horizon in the present study was 5 years based on the average length of follow-up in the trial. We did not extrapolate beyond the end of the trial because the within-trial analysis found no evidence of significant differences in QALYs between the groups and, although there was some evidence of differences in costs, these differences were all accrued during the first year. In terms of costs included, there were several differences between the present study and that by Picot *et al.*[72] During the radiotherapy treatment period the present study included the cost of EBRT boost and NHS transport costs for EBRT, which were not included in the study by Picot *et al.*[72] More generally, the total cost per patient in the study by Picot *et al.*[72] over the 40-year period, based on the costs included in the analysis, was around £2300 in both groups. In our study the total cost per patient over the 5-year period, based on the costs included in the analysis, was around £11,600 in both groups, suggesting large differences in the range of cost components included.

Strengths and limitations

The main strength of our analysis is that it is based on a large international multicentre randomised trial with detailed information on resource use and events for a median follow-up period of 5 years.

There are several limitations. First, the time horizon was 5 years. Extrapolation beyond the end of the trial using decision-analytical modelling was not undertaken because the within-trial analysis found no evidence of significant differences in QALYs between groups during the 5-year period. This probably reflects the main finding from the TARGIT-A trial that TARGIT was non-inferior to EBRT with regard to local recurrence. Although there was some evidence of differences in costs these differences were all accrued during the first year; there was no evidence of significant differences in costs beyond the first year. Hence, the 5-year time horizon was long enough to reflect all important differences in costs or outcomes between

the two treatments. Although local recurrence (and other events) are likely to continue to occur over a patient's lifetime, the evidence from the TARGIT-A trial is that TARGIT is non-inferior to EBRT. Hence, taking a longer time horizon is unlikely to have affected the results of the incremental analyses.

Second, utility data were not collected in the TARGIT-A trial. We therefore applied utility values from published sources to the health states experienced by patients in the trial. The utility values that we applied may not reflect the values of patients in the study. Given the relatively small number of events, and that the numbers of events were largely not different between the two groups, the QALY differences between the two groups may not be expected to change much with alternative utility values. This is borne out by our sensitivity analysis, which showed that the results did not change appreciably when we used alternative values. We did not incorporate utility losses associated with additional procedures, chemotherapy, mastectomy or complications in our analysis. Given the low incidence of these events, that they were evenly distributed between treatment groups and that the time period affected is likely to be short this is unlikely to affect the QALYs associated with each treatment group. We also did not include any utility losses associated with EBRT. Therefore, this would make our estimates more conservative because such an omission would work against TARGIT.

Third, the dose of EBRT administered to patients in the TARGIT-A trial does not reflect current UK treatment guidelines. This reflects the multinational nature of the trial, plus that it began recruiting patients in 2000 when treatment recommendations were different. We accounted for this in our base case by assuming that all patients in the TARGIT-A trial who received EBRT received a fixed number of 15 fractions.

Fourth, the analysis took a NHS/PSS perspective on costs. A wider perspective (e.g. societal) could have been taken to measure costs, including impacts on the rest of society, patients, families and businesses. If a wider perspective was taken this should include the additional costs borne by patients and families in terms of time and travel costs associated with additional radiotherapy visits for EBRT compared with TARGIT. If these costs were included it is likely that the cost savings attributable to TARGIT would be greater than demonstrated. Taking the example of the transport costs, we used the figure of 13.5% for the proportion of patients for whom the NHS paid for transport for radiotherapy visits for EBRT. Assuming that the same cost is paid out of pocket by the remaining patients, the difference in costs between TARGIT and EBRT would be increased by £877 to £1562 per patient, taking the total saving to the UK national economy to between 11,600 × £1562 = £18.1 million and 13,400 × £1562 = £20.9 million each year. These are crude estimates and further research to evaluate the wider impacts of TARGIT, including on other costs to the rest of society, would be useful.

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