

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)

Jayant S Vaidya,^{1,2*} Frederik Wenz,³ Max Bulsara,⁴
Jeffrey S Tobias,⁵ David J Joseph,⁶
Christobel Saunders,⁷ Chris Brew-Graves,¹
Ingrid Potyka,¹ Stephen Morris,⁸
Hrisheekesh J Vaidya,⁹ Norman R Williams¹
and Michael Baum¹

¹Division of Surgery and Interventional Science, University College London, London, UK

²Department of Surgery, Whittington Hospital, Royal Free Hospital and University College London Hospital, London, UK

³Department of Radiation Oncology, University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany

⁴Department of Biostatistics, University of Notre Dame, Fremantle, WA, Australia

⁵Department of Clinical Oncology, University College London Hospitals, London, UK

⁶Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia

⁷Department of Surgery, University of Western Australia, Perth, WA, Australia

⁸Health Economics Group, Department of Biomedical Engineering, University College London, London, UK

⁹Keble College, Oxford University, Oxford, UK

*Corresponding author

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Scientific summary

The TARGIT-A trial

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Scientific summary

Background

Early local recurrence of breast cancer most commonly (> 90%) occurs at the site of the primary tumour. Whole-organ analysis of mastectomy specimens, on the other hand, reveals that 63% of breasts harbour occult cancer foci and 80% of these are situated remote from the index quadrant. Therefore, these occult cancer foci may not be clinically relevant and it may not be necessary to treat the whole breast with radiotherapy, which is normally given as a 6-week long course of external beam radiotherapy (EBRT). EBRT is effective but can be inconvenient and costly and may cause many women from geographically remote areas to choose mastectomy. In 1995 we suggested that restriction of radiation therapy to the peritumoural area alone might provide adequate local control for selected patients within a risk-adapted design. In collaboration with the industry we developed a device (INTRABEAM®) and a surgical procedure to enable us to give TARGeted Intraoperative radioTherapy (TARGIT) at a dose of about 20 Gy to the surface of the applicator in 20–30 minutes during surgery in a standard operating theatre environment. We then proceeded to test its feasibility and safety in pilot studies between 1998 and 2000 followed by the TARGeted Intraoperative radioTherapy Alone (TARGIT-A) randomised trial.

Methods

The TARGIT-A trial recruited 3451 patients between 24 March 2000 and June 2012. In this prospective, randomised, non-inferiority trial, women aged ≥ 45 years with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 33 centres in 11 countries. Patients were randomly assigned in a 1 : 1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by centre and by timing of delivery of TARGIT. Randomisation occurred either before lumpectomy (prepathology stratum – TARGIT concurrent with lumpectomy) or after lumpectomy (postpathology stratum – TARGIT given subsequently by reopening the wound). Such stratification allowed easier operating theatre logistics and more stringent case selection, but needed a reoperation to reopen the wound to give TARGIT as a delayed procedure. Neither patients nor investigators or their teams were masked to treatment assignment. Postoperative discovery of predefined factors (e.g. lobular carcinoma) could trigger the addition of EBRT (excluding tumour bed boost) to TARGIT (in an expected 15% of patients), making the experimental arm a risk-adapted radiotherapy approach vis-à-vis the control arm, which followed a one-size-fits-all policy of giving whole-breast radiotherapy to all patients. The primary outcome was absolute difference in local recurrence in the conserved breast, with a pre-specified non-inferiority margin of 2.5% at 5 years; pre-specified analyses included outcome according to the timing of randomisation in relation to lumpectomy. Secondary outcomes included complications and mortality. The planned analyses were performed in 2010 after the initial accrual of 2232 patients and again in 2012 after closure of the trial with an accrual of 3451 patients. For the second analysis, standard tests for non-inferiority were performed and at this time for a log-rank test for difference in survival the significance level was set at a *p*-value of 0.01 for local recurrence as this was a second analysis and at a *p*-value of 0.05 for mortality. In 2010 it was calculated that the number of participants needed to prove non-inferiority was 585.

For subgroup analysis, before the data were unblinded for the 2012 analysis, we hypothesised that hormone sensitivity might be predictive of response to TARGIT and therefore analysed whether or not the response to radiotherapy in the TARGIT-A trial was dependent on hormone receptor responsiveness using progesterone receptor (PgR) status as a marker. We assessed the effect of hormone sensitivity using PgR status, timing of randomisation/delivery of TARGIT, age, tumour grade, oestrogen receptor status, human epidermal growth factor receptor-2 (HER2) status, presence of ductal carcinoma in situ (DCIS), margin

status, whether screen detected or not, lymphovascular invasion and node status, on the outcome in a Cox proportional hazard model.

We performed the main analyses on patients in the prepathology stratum who were randomised in the first 8 years of the TARGIT-A trial. We also analysed (1) the effect of omission of EBRT on recurrence of breast cancer in quadrants of the breast other than the index quadrant (the original hypothesis), (2) the effect of omission of EBRT on axillary recurrence, (3) whether or not a beneficial effect of irradiation of the tumour bed on the patient's microenvironment could contribute to the difference in non-breast-cancer mortality, (4) whether or not the higher threshold for margin positivity in the German cohort with regard to adding EBRT improved outcomes and (5) health economics.

Findings

Main findings

In total, 1721 patients were randomised to TARGIT and 1730 to EBRT. Supplemental EBRT after TARGIT was necessary in 15.2% (239/1571) of patients who received TARGIT (21.6% prepathology, 3.6% postpathology). With regard to follow-up, 3451 patients had a median follow-up of 2 years and 5 months (interquartile range 12–52 months), 2020 patients had a median follow-up of 4 years and the first 1222 randomised patients (the earliest cohort) had a median follow-up of 5 years.

First analysis of local recurrence

The first analysis, after completion of the original accrual of 2232 patients (the mature cohort), described the results at 4 years when there were six local recurrences in the intraoperative radiotherapy group and five in the EBRT group. The Kaplan–Meier estimate of local recurrence in the conserved breast at 4 years was 1.20% [95% confidence interval (CI) 0.53% to 2.71%] in the TARGIT group and 0.95% (95% CI 0.39% to 2.31%) in the EBRT group [difference between groups 0.25% (95% CI –1.04% to 1.54%); $p = 0.41$].

Five-year analysis of local recurrence and survival

The test of non-inferiority in terms of control of local recurrence in the conserved breast found that TARGIT was non-inferior to EBRT for the whole trial ($P_{\text{non-inferiority}} = 0.00000012$) and for the prepathology stratum ($P_{\text{non-inferiority}} = 0.000000013$), but not for the postpathology stratum ($P_{\text{non-inferiority}} = 0.06640$).

For the first 1222 patients randomised in the trial the median follow-up was 5 years and the test for non-inferiority found that TARGIT was non-inferior to EBRT in terms of local recurrence in the conserved breast when both strata were taken together ($P_{\text{non-inferiority}} = 0.040$) and for the prepathology stratum ($P_{\text{non-inferiority}} = 0.00914$), but not for the postpathology stratum ($P_{\text{non-inferiority}} = 0.35108$).

The 5-year estimated risk for local recurrence in the conserved breast was 3.3% (95% CI 2.1% to 5.1%) for TARGIT and 1.3% (95% CI 0.7% to 2.5%) for EBRT. TARGIT concurrently with lumpectomy (prepathology, $n = 2298$) had much the same rate of local recurrence in the conserved breast as EBRT (2.1%, 95% CI 1.1% to 4.2% vs. 1.1%, 95% CI 0.5% to 2.5%; $p = 0.31$). With delayed TARGIT (postpathology, $n = 1153$) the between-group difference in local recurrence was larger than 2.5% (TARGIT 5.4%, 95% CI 3.0% to 9.7% vs. EBRT 1.7%, 95% CI 0.6% to 4.9%; $p = 0.069$).

There was no difference in the 5-year estimated local recurrence-free survival between TARGIT and EBRT [all patients: 93.1% (95% CI 90.8% to 94.9%) vs. 93.8% (95% CI 91.7% to 95.4%); $p = 0.81$; prepathology: 93.9% (95% CI 90.9% to 95.9%) vs. 92.5% (95% CI 89.7% to 94.6%); $p = 0.35$].

Overall, breast cancer mortality was similar between the 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. Overall mortality was 3.9% (95% CI 2.7% to 5.8%) for TARGIT compared with 5.3% (95% CI 3.9% to 7.3%) for EBRT ($p = 0.099$).

For the preferred option of using TARGIT during initial lumpectomy, breast cancer mortality was similar between the groups (TARGIT 17 deaths vs. EBRT 15 deaths; 5-year rates 3.3%, 95% CI 1.9% to 5.8% vs. 2.7%, 95% CI 1.5% to 4.6%; $p = 0.72$). Non-breast-cancer mortality was 12 patients for TARGIT and 27 patients for EBRT (1.3%, 95% CI 0.7% to 2.8% vs. 4.4%, 95% CI 2.8% to 6.9%; $p = 0.016$). Overall mortality was numerically lower by 2.3% in the TARGIT group (4.6%, 95% CI 1.8% to 6.0% vs. 6.9%, 95% CI 4.3% to 9.6%; $p = 0.12$).

In total, 817 patients were randomised in the first 8 years of the trial in the prepathology stratum. The median follow-up was 5.01 years. For local recurrence in the conserved breast, TARGIT was non-inferior to EBRT ($P_{\text{non-inferiority}} = 0.00914$). The 5-year Kaplan–Meier estimated risk was not statistically different between the groups for local recurrence (TARGIT 1.8%, 95% CI 0.84% to 4.2% vs. EBRT 0.84%, 95% CI 0.3% to 2.6%; $p = 0.32$) and death from breast cancer (TARGIT 3.9%, 95% CI 2.3% to 6.7% vs. EBRT 3.0%, 95% CI 1.7% to 5.4%; $p = 0.34$). There were significantly fewer deaths from causes other than breast cancer with TARGIT (1.9%, 95% CI 0.9% to 3.9% vs. 5.1%, 95% CI 3.2% to 8.0%; $p = 0.04$). It should be noted that the number needed to prove non-inferiority was calculated to be 585 and therefore this earliest cohort of 817 patients had enough power to draw reliable conclusions.

Local toxicity

The frequency of any complications and major toxicity was similar in the two groups [major toxicity: TARGIT 37/1113 (3.3%) vs. EBRT 44/1119 (3.9%); $p = 0.44$]. Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the TARGIT group (six patients, 0.5%) than in the EBRT group (23 patients, 2.1%; $p = 0.002$). In the second analysis in 2012, among complications 6 months after surgery, wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT (4/1720 vs. 13/1731; $p = 0.029$).

Subgroup analysis

In PgR-positive cases ($n = 2462$) there was no significant difference between the two arms (TARGIT vs. EBRT) in terms of the 5-year risk of local recurrence (2.3%, 95% CI 1.3% to 4.3% vs. 1.49%, 95% CI 0.75% to 3.0%; $p = 0.51$), whereas in PgR-negative cases local recurrence was higher in the TARGIT arm (7.0%, 95% CI 3.5% to 13.6% vs. 0.5%, 95% CI 0.1% to 3.7%; $p = 0.017$). In the large group of 1625 PgR-positive cases in the prepathology stratum, breast cancer control with TARGIT was similar to that with EBRT (5-year risk of local recurrence 1.4%, 95% CI 0.5% to 3.9% vs. 1.2%, 95% CI 0.5% to 2.9%; $p = 0.77$); this was also the case for breast cancer mortality (1.78%, 95% CI 0.7% to 4.4% vs. 1.98%, 95% CI 0.94% to 4.2%; $p = 0.9$) whereas mortality from other causes was reduced with TARGIT (1.59%, 95% CI 0.7% to 3.4% vs. 4.51%, 95% CI 2.8% to 7.3%; $p = 0.04$), leading to a 3.1% reduction in overall mortality (3.3%, 95% CI 1.83% to 6.04% vs. 6.4%, 95% CI 4.3% to 9.6%; $p = 0.08$). Margin status was a predictive factor only in the EBRT arm. Other factors did not influence the outcomes.

Other analyses

1. *Other quadrant recurrences.* In total, 94.4% of cases in the TARGIT-A trial did not have a preoperative magnetic resonance imaging (MRI) scan. A total of 793 patients in the prepathology stratum randomised to TARGIT had only TARGIT as their radiotherapy. With 2098 women-years of follow-up, there were nine recurrences in the conserved breast. The 5-year local recurrence rate in those who received TARGIT alone was 2.7% (95% CI 1.3% to 5.5%), which was not different from the rate in the whole prepathology cohort randomised to TARGIT (2.1%, 95% CI 1.1% to 4.2%). In these 793 patients, one would expect 63% of patients (i.e. $n = 500$) to have additional foci of cancer in their breasts and 80% of these (i.e. $n = 400$) should be in quadrants other than the index quadrant. In reality, seven patients had recurrence in the scar, six had new contralateral cancers and two had cancers growing in other quadrants, implying that the remaining 398 foci had remained dormant.

Among 935 patients who received whole-breast radiotherapy, the same number of cancers ($n = 2$) grew in other quadrants and there were five new contralateral cancers. Therefore, cancer foci in the breast that were away from the site of the primary tumour remained dormant and behaved no differently from those in the contralateral breast. They also appeared to be unaffected by whole-breast radiotherapy. This analysis from the randomised TARGIT-A trial provides further evidence supporting partial breast irradiation.

2. *Axillary recurrence.* We found that omission of EBRT did not increase axillary recurrence when analysed according to treatment received: the number of axillary recurrences was 5 out of 1613 when EBRT was not given compared with 6 out of 1762 when EBRT was given (5-year risk 0.68%, 95% CI 0.28% to 1.6% vs. 0.82%, 95% CI 0.34% to 2.02%; hazard ratio 0.84, 95% CI 0.26 to 2.74; $p = 0.8$).
3. *Reduction in non-breast-cancer mortality: could this be a beneficial effect of TARGIT?* We found that, among the 1730 patients randomised to receive EBRT, eight cardiac deaths were seen in contrast to the 12 estimated based on age, sex and follow-up period. Most interestingly, there were no deaths from non-breast-cancer causes in the TARGIT + EBRT group compared with 24 in the EBRT group (0/218 vs. 24/892; log-rank $p = 0.012$). Although the numbers are small, these data suggest that EBRT toxicity may not be the only possible explanation for the excess of non-breast-cancer deaths; they lead to the hypothesis that the local effect of TARGIT on the tumour bed by inhibiting cancer-stimulating cytokines may spill over to reduce the systemic inflammatory response to trauma and have significant long-term systemic beneficial effects that might be protective against cardiac and cancer mortality.
4. *Adequacy of 1 mm as a threshold for negative margins.* Additional EBRT was given in nearly twice the number of patients in the TARGIT arm in the German centres (prompted by the higher limit of a 10-mm tumour-free margin) compared with the TARGIT arm in the rest of the trial population [31.4% (96/306) vs. 17.4% (123/706)]. However, the 5-year local recurrence rate in the German cohort was not lower than in the rest of the sample (German 2.6%, 95% CI 0.87% to 7.8% vs. rest of the sample 1.9%, 95% CI 0.81% to 4.5%). Therefore, a policy of adding EBRT after TARGIT only when the margin is < 1 mm appears appropriate.
5. *Health economic analyses.* In the base-case analysis TARGIT was less costly than EBRT (mean incremental cost –£685) and produced slightly more quality-adjusted life-years (QALYs) than EBRT (mean QALYs gained 0.034). TARGIT 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. If TARGIT were given instead of EBRT in suitable patients, it might potentially reduce costs to health-care providers by £8–9.1 million each year. This does not include environmental, patient and societal costs.

Interpretation

In cases selected as per the TARGIT-A trial protocol, TARGIT during lumpectomy compared with EBRT was found to have non-inferior local control, similar mortality from breast cancer and significantly lower mortality from non-breast-cancer causes.

Subgroup analysis found that PgR status influenced the outcome of patients overall and those randomised to TARGIT; margin status influenced the outcome of those randomised to EBRT. Other patient or tumour factors had no significant influence on the outcome of patients randomised in the two arms. It appears that hormone receptor positivity identifies a group in whom local control with TARGIT during lumpectomy is very similar to that with EBRT.

Other analyses provide further evidence supporting limited irradiation and suggest new hypotheses as well as demonstrate the cost-effectiveness of TARGIT.

Several large randomised trials of radiotherapy have found that the effect of radiotherapy on local recurrence is in the first 5 years and that a difference seen at 5 years does not increase with longer follow-up of up to 25 years. Therefore, these results are based on a sufficient number of patients whose follow-up is long enough to enable a change of practice. However, as breast cancer is a chronic illness, we are

committed to longer-term follow-up (the protocol aims for a 10-year follow-up of all patients) for ethical, moral, scientific and academic reasons, as a higher number of events, which will accrue with time, could allow for a more in-depth analysis and refinement of our understanding.

Conclusion

For patients with breast cancer selected as per the TARGIT-A trial protocol (women aged ≥ 45 years with unifocal 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 and safer than postoperative EBRT.

Trial registration

This trial is registered as ISRCTN34086741 and ClinicalTrials.gov NCT00983684.

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Editorial contact: nhredit@southampton.ac.uk

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