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"For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks."

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Partial breast irradiation: new standard for selected patients

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Routine whole-breast radiotherapy comprises 50 Gy in daily fractions for 5 weeks.[1] The additional application of an external boost of 10–16 Gy to the tumour bed leads to excellent local tumour control, with local recurrence rates around 6% after a median of 10-years' follow-up.[2] However, in view of the low and focal local recurrence rates, the concept of accelerated partial-breast irradiation has gained widespread interest with various methods.

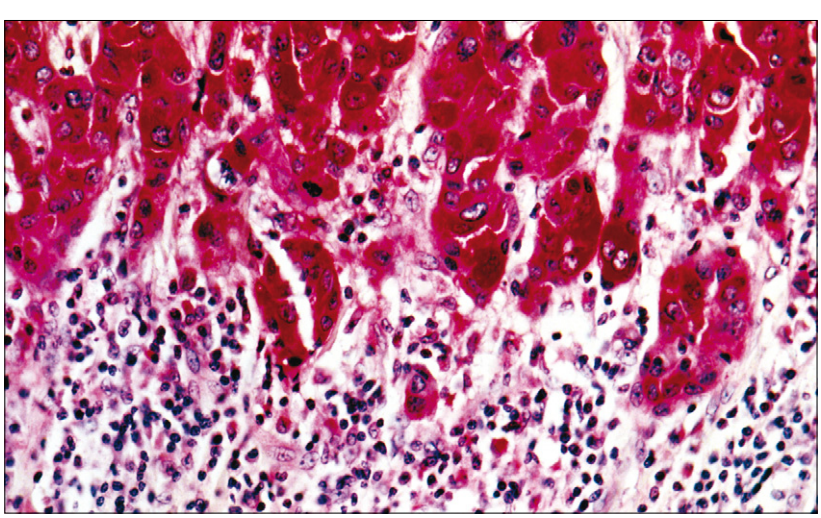
Intraoperative radiotherapy is one method that might offer the advantage of excellent delineation of the tumour bed under visual control, very good dose-homogeneity, and high sparing of normal tissue.[3,4] These advantages were one of the goals of the TARGIT-A randomised phase 3 trial presented in *The Lancet* today.[5] The investigators compared targeted with whole-breast radiotherapy in women with invasive ductal carcinoma who were undergoing breast-conserving surgery. Non-inferiority was shown in the targeted group with less grade 3 acute toxicity but with more wound seroma than in the whole-breast irradiated group. This trial presents major new data for the next decades. There is no doubt that many national health systems will encourage rapid and less expensive adjuvant breast treatments. Such targeted radiotherapy might be such a method, delivering a sufficient dose within the tumour bed and protecting surrounding normal tissues with the unique advantage of a "one-shot" procedure that includes surgery and radiotherapy at the same time.

Nevertheless, this technique has been criticised since it was first developed. The technical limitation is depth of dose due to the 50 kV x-ray delivery. For instance, a dose of 15 Gy prescribed at 2 mm with a typical applicator of 3·5 cm diameter will deliver 10·6 Gy at a depth of 5 mm. The risk is that insufficient breast volume is irradiated and therefore more local recurrences could occur. Clearly, today's TARGIT-A trial contradicts this hypothesis. Additionally, targeted radiotherapy might resolve the problem of cardiac and lung irradiation and the risk of late sequelae.

The oncological keypoint is the selection of the population who will best benefit from this technique. This question does not only apply to the targeted technique but also to all use of accelerated partial-breast irradiation. The ASTRO task force[6] has proposed suitable patients for accelerated partial-breast irradiation if several criteria are present, especially age 60 years or older, tumour size 2 cm or less, and invasive ductal carcinoma that is T1N0 and oestrogen-receptor positive. By contrast, TARGIT-A accepted women with early breast cancer if they were aged 45 years or older and had undergone wide local-excision for invasive ductal carcinoma. Nevertheless, when looking at the characteristics of the tumour and patient in TARGIT-A, the median age was 63 years (IQR 57–69), 86% of the tumours were smaller than 2 cm, nearly 90% expressed oestrogen receptors, and 83% of the nodes were uninvolved. Overall, this profile fits well with the international recommendation.

Additionally, it has been suggested that tamoxifen alone will be sufficient for patients aged 70 years or older.[7] Local or regional recurrences at 5 years were significantly higher in the tamoxifen group than in the tamoxifen plus radiotherapy group. Accelerated partial-breast irradiation is therefore a better alternative than no irradiation at all, and should be widely proposed to these patients. Similarly, the technique could be proposed when: the tumour is less than 1 cm, as suggested by the results of the randomised trial published many years ago by Fisher and colleagues;[8] in patients with oligometastases who have an encouraging response to first-line chemotherapy;[9] or in patients who are hypersensitive to radiation and who present with small tumours.[10]

Frozen-section analysis is clearly one of the limiting aspects of the targeted technique, because the definitive



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Light micrograph of section through ductal cancer cells in female breast

pathology findings might contradict those obtained intraoperatively. This technique thus requires a very close partnership between surgeons, pathologists, radiation oncologists, and physicists. Indeed, in TARGIT-A, 14% of patients received targeted intraoperative radiotherapy plus external-beam radiotherapy. Mixed-modality 3D-conformal accelerated partial-breast irradiation with opposed mini-tangent photon fields and en-face electrons is a promising alternative.[11]

We still await long-term follow-up and the results of another randomised trial from the National Surgical Adjuvant Breast and Bowel Project B-39.[12] Nevertheless, in elderly patients, we are already convinced that accelerated partial-breast irradiation is the new standard and intraoperative radiotherapy an excellent approach.

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We declare that we have no conflicts of interest.

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Preventing type 2 diabetes with low-dose combinations

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The past decade has seen major advances in clinical trial evidence to support improved care in diabetes. One important area is prevention of type 2 diabetes. Several trials have tested single interventions for their ability to reduce the incidence of diabetes in high-risk individuals.[1–6] Lifestyle interventions aimed at reducing bodyweight, and use of metformin, thiazolidinediones, acarbose, and orlistat, reduce the risk of diabetes by 25–60% over 3–6 years. Generallly, interventions aimed at reducing body fat or its adverse metabolic effects show the best evidence for slowing or stopping progression to diabetes.[7] Indeed, the insulin secretagogue, nateglinide, had no effect in reducing diabetes risk.[8] Despite the positive outcomes of these trials, it remains unclear whether prevention is superior to early treatment in terms of long-term health. Additionally, concerns about cost and side-effects have limited recommendations for use of drugs to prevent type 2 diabetes.

In *The Lancet* today, Bernard Zinman and colleagues[9] report the CANOE trial, the first to test low-dose combination drug therapy for diabetes prevention. During a median follow-up of 3·9 years, metformin and rosiglitazone at about half-maximum doses caused a 66% reduction in the risk of diabetes compared with placebo. Importantly, the treated group had no increase in weight gain, heart failure, fractures, or myocardial infarction. Diarrhoea was infrequent, but occurred more often in the treated group. Circulating concentrations of LDL cholesterol, C-reactive protein, and serum alanine aminotransferase fell more, while HDL cholesterol rose more, in the treated group. The investigators concluded that combination treatment with low-dose metformin and rosiglitazone could

Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

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Summary

Background After breast-conserving surgery, 90% of local recurrences occur within the index quadrant despite the presence of multicentric cancers elsewhere in the breast. Thus, restriction of radiation therapy to the tumour bed during surgery might be adequate for selected patients. We compared targeted intraoperative radiotherapy with the conventional policy of whole breast external beam radiotherapy.

Methods Having safely piloted the new technique of single-dose targeted intraoperative radiotherapy with Intrabeam, we launched the TARGIT-A trial on March 24, 2000. In this prospective, randomised, non-inferiority trial, women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 28 centres in nine countries. Patients were randomly assigned in a 1:1 ratio to receive targeted intraoperative radiotherapy or whole breast external beam radiotherapy, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy. Neither patients nor investigators or their teams were masked to treatment assignment. Postoperative discovery of predefined factors (eg, lobular carcinoma) could trigger addition of external beam radiotherapy to targeted intraoperative radiotherapy (in an expected 15% of patients). The primary outcome was local recurrence in the conserved breast. The predefined non-inferiority margin was an absolute difference of 2·5% in the primary endpoint. All randomised patients were included in the intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00983684.

Findings 1113 patients were randomly allocated to targeted intraoperative radiotherapy and 1119 were allocated to external beam radiotherapy. Of 996 patients who received the allocated treatment in the targeted intraoperative radiotherapy group, 854 (86%) received targeted intraoperative radiotherapy only and 142 (14%) received targeted intraoperative radiotherapy plus external beam radiotherapy. 1025 (92%) patients in the external beam radiotherapy group received the allocated treatment. At 4 years, there were six local recurrences in the intraoperative radiotherapy group and five in the external beam radiotherapy group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1·20% (95% CI 0·53–2·71) in the targeted intraoperative radiotherapy and 0·95% (0·39–2·31) in the external beam radiotherapy group (difference between groups 0·25%, –1·04 to 1·54; p=0·41). The frequency of any complications and major toxicity was similar in the two groups (for major toxicity, targeted intraoperative radiotherapy, 37 [3·3%] of 1113 *vs* external beam radiotherapy, 44 [3·9%] of 1119; p=0·44). Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted intraoperative radiotherapy group (six patients [0·5%]) than in the external beam radiotherapy group (23 patients [2·1%]; p=0·002).

Interpretation For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks.

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Introduction

During the past 50 years, the conceptual approach to breast cancer treatment has shifted from radical mastectomy[1] to local treatment that preserves the breast and axillary lymph nodes along with adjuvant systemic therapy. Breast-conserving surgery followed by postoperative whole breast external beam radiotherapy is now the standard of care for suitable patients with early breast cancer.

External beam radiotherapy is a safe and effective treatment; the risk of side-effects is low, but since breast

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For an **outline of the protocol for this trial** see http://www.thelancet.com/protocol-reviews/99PRT-47

For **the full protocol for this trial** see http://www.hta.ac.uk/project/1981.asp

cancer is common, the absolute number of women with complications and side-effects is large. More importantly, the 3–7 weeks of a typical postoperative radiotherapy schedule is at best inconvenient for working women or exhausting and often untenable for elderly women. Although many studies[2–4] have failed to identify a subgroup of patients in whom radiotherapy can be completely avoided, whether irradiation of the whole breast is necessary in all or a subgroup of patients remains unclear.

Many observational studies and randomised clinical trials have shown that more than 90% of recurrent disease occurring in the breast is within the index quadrant,[5–13] which is by contrast with the findings of three-dimensional analysis of mastectomy specimens that show that 63% of breasts harbour occult cancer foci, with 80% of these situated remote from the index quadrant.[14–16] These widespread and occult multifocal or multicentric cancers in other quadrants of the breast therefore appear to remain dormant for many years or even decades, and have a low risk of causing clinical tumours. Thus, irradiation of the immediate vicinity of the primary tumour might be adequate for achieving local control of cancer.[14–16]

The TARGIT-A trial was designed to test the hypothesis that in selected patients, substituting the policy of whole breast radiotherapy after breast-conserving surgery with a policy of targeted intraoperative radiotherapy (also known as TARGIT) to the tumour bed with additional whole breast radiotherapy in a subgroup of patients (around 15%) with poor features on final pathology would not lead to inferior local control of breast cancer.

Methods

Study design and participants

TARGIT-A was a pragmatic, prospective, international, multicentre, randomised, phase 3 trial that compared targeted intraoperative radiotherapy with the conventional policy of whole breast external beam radiotherapy. An outline of the protocol and the full protocol are available online. Women with early breast cancer were eligible for enrolment if they were aged 45 years or older and were suitable for wide local excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging (MRI was not necessary for confirming unifocality). Preoperative diagnosis of lobular carcinoma was an exclusion criterion. Patients gave written informed consent to join the trial. The protocol was approved by the appropriate regulatory and ethics authorities for each centre before enrolment could begin.

The initial trial plan was developed in University College London (UCL), London, UK. Management of the trial was coordinated and supervised by the international steering committee (ISC) with advice from the data monitoring committee (DMC). Representatives from the manufacturer of the Intrabeam equipment (Carl Zeiss, Oberkochen, Germany) attended the ISC meetings as observers. The trial statistician supervised all data analyses. The interpretation of the analyses, presentation of data at meetings, and preparation of manuscripts for publication are all responsibilities of the ISC. The TARGIT Trials Operations Office is located at UCL and is responsible for randomisations, data collection, data management, and servicing of the ISC and DMC. No changes were made to the methods after commencement of the trial.

Before centres were allowed to participate, the team was trained and audited by a member of the ISC. Each centre was allowed to restrict the inclusion criteria beyond the core protocol, and to stipulate local policy for giving external beam radiotherapy (typically 40–56 Gy with or without a boost of 10–16 Gy, standard tangents, etc) both in the external beam radiotherapy group and as an additional dose in the targeted intraoperative radiotherapy group, in a site-specific treatment policy document that was reviewed and signed off by the ISC before randomisation could begin.

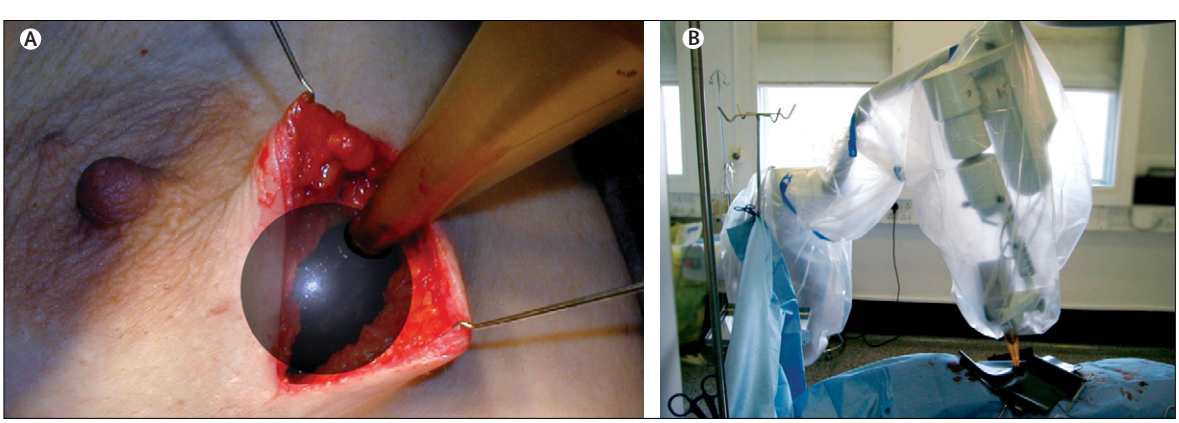

Figure 1: **Targeted intraoperative radiotherapy technique with the Intrabeam system**
(A) The applicator being placed in the tumour bed. (B) The x-ray source is delivered to the tumour bed by use of a surgical support stand. The sterile applicator is joined with a sterile drape that is used to cover the stand during treatment delivery.

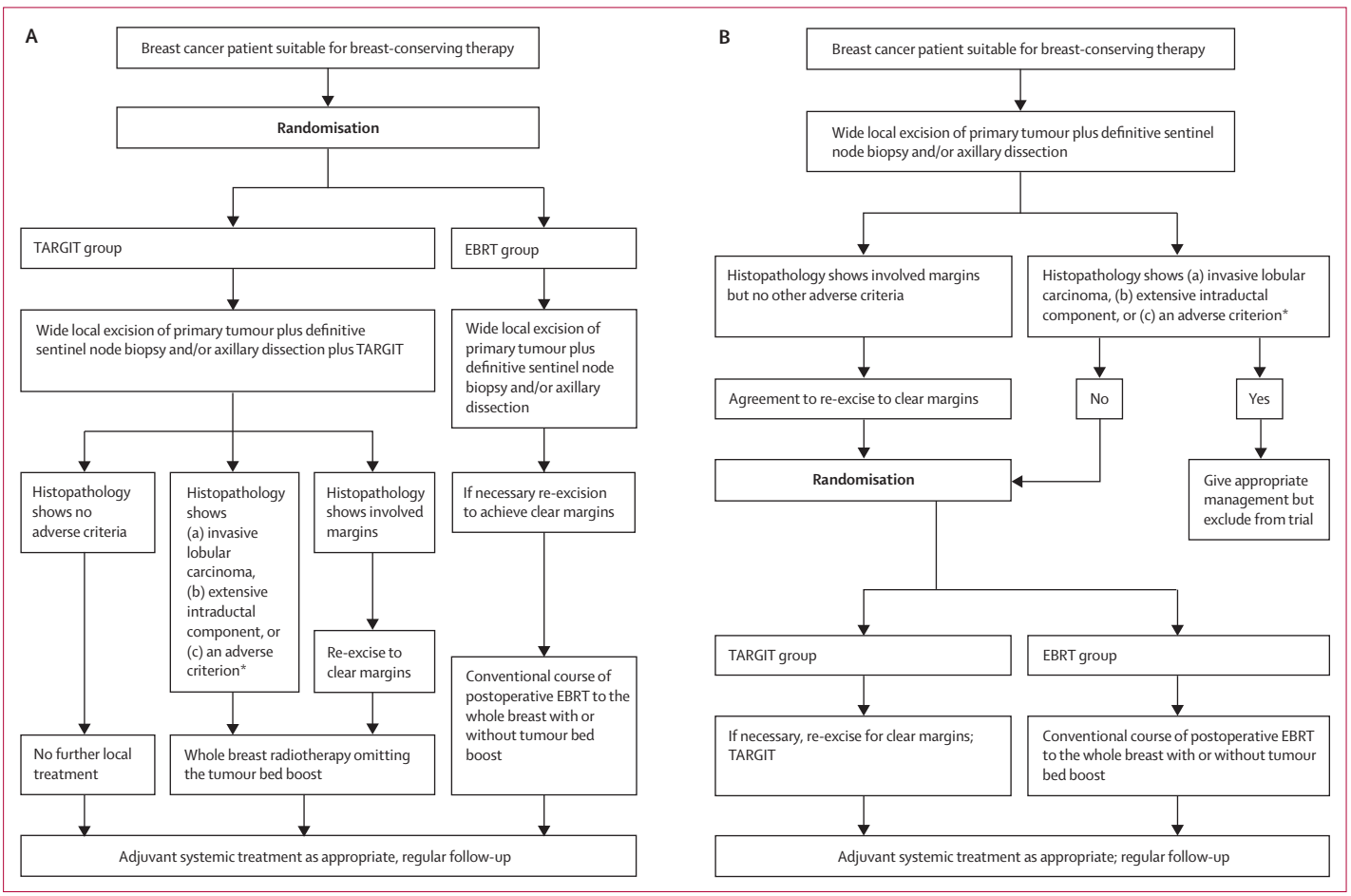

Figure 2: **Randomisation strata**
TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. (A) Prepathology entry. Randomisation was done before the definitive surgical removal of the tumour. Characteristics that would prompt addition of EBRT were predefined (eg, unexpected lobular carcinoma, extensive intraductal component, positive margins at first excision, in addition to others by individual centre). (B) Postpathology entry/TARGIT as a second procedure. Postpathology entry allowed for patients randomised for entry to the trial only once the pathological characteristics of the tumour had been reported. If allocated to TARGIT the wound was opened, the applicator inserted, and TARGIT given as a second surgical procedure. *Decided by each centre at the outset—eg, grade 3, node involvement, lymphovascular invasion.

Procedures

The concept and technique of targeted intraoperative radiotherapy, which was pioneered by our group,[17–19] is designed to allow the patient to receive all required radiation in a single fraction before she awakes from surgery. The clinicopathological rationale, the technology of the device, surgical technique (figure 1), radiobiology, and acute and long-term toxicity have been previously described.[5,14–24]

Briefly, the Intrabeam device provides a point source of low energy x-rays (50 kV maximum) at the tip of a 3·2 mm diameter tube that is placed at the centre of a spherical tumour bed applicator. After surgically positioning the appropriately sized applicator in the tumour bed, radiation is switched on for 20–35 min to target the tissues that are at highest risk of local recurrence. The surface of the tumour bed typically receives 20 Gy that attenuates to 5–7 Gy at 1 cm depth. We established the safety and tolerability of the technique in phase 2 studies started in July, 1998,[17,20] in which targeted intraoperative radiotherapy was delivered as a substitute for tumour bed boost, followed by standard external beam radiotherapy to the whole breast. The most recent update, in 300 patients, has a median follow-up of 60·5 months and the 5-year Kaplan-Meier estimate for ipsilateral recurrence was 1·74% (SE 0·77).[25]

In this trial, we compared the conventional policy of whole breast external beam radiotherapy with the experimental policy of targeted intraoperative radiotherapy given in a single dose. We recognised that because of unfavourable features found subsequently in the pathological examination of the excised lesion (eg, lobular carcinoma), some patients (around 15%) assigned to targeted intraoperative radiotherapy will need to have external beam therapy in addition (without the boost that would already have been provided by the targeted intraoperative dose).

For more information about **targeted intraoperative radiotherapy** see http://www.targit.org.uk

	Prepathology	Postpathology	Contralateral	Total
University College London, London, UK	144	29	10	183
Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany	145	0	7	152
Sir Charles Gairdner Hospital, Perth, WA, Australia	34	246	7	287
Centro di Riferimento Oncologico, Aviano, Italy	219	4	16	239
Ninewells Hospital, Dundee, UK	129	34	6	169
University of California, San Francisco, CA, USA	78	12	3	93
Frauenklinik vom Roten Kreuz, Munich, Germany	195	0	5	200
University of Southern California, Los Angeles, CA, USA	51	10	7	68
Ospedale San Giuseppe di Empoli, Empoli, Italy	53	1	0	54
Sankt Gertrauden-Krankenhaus, Berlin, Germany	47	0	0	47
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia	0	9	0	9
Ludwig Maximilians Universität, Munich, Germany	68	0	1	69
Universität Frankfurt am Main, Frankfurt, Germany	33	0	2	35
Herlev/Rigs Hospitals, Copenhagen, Denmark	0	292	10	302
Medical University of Lublin, Lublin, Poland	41	0	0	41
Royal Free/Whittington Hospitals, London, UK	49	4	0	53
Lafayette Surgical Clinic, Lafayette, IN, USA	4	6	2	12
Sentara Surgery Specialists, Hampton, VA, USA	8	0	0	8
Uniklinikum des Saarlandes, Homburg, Germany	46	0	1	47
Princess Margaret Hospital, Toronto, ON, Canada	13	0	0	13
Royal Hampshire County Hospital, Winchester, UK	50	10	0	60
Brust Zentrum Seefeld, Zurich, Switzerland	26	0	0	26
Universitäts Spital Zurich, Zurich, Switzerland	14	0	0	14
St Olav's Hospital, Trondheim, Norway	20	0	1	21
University of Nebraska Medical Center, Omaha, NE, USA	0	11	0	11
Guy's Hospital, London, UK	0	4	0	4
Poughkeepsie, NY, USA	12	0	0	12
Dobbs Ferry, NY, USA	3	0	0	3
Total	1482	672	78	2232

Centres are listed in the order that they joined the trial. The patients randomised from each country were: UK 469 (21%), Germany 571 (26%), Denmark 302 (14%), Australia 296 (13%), Italy 293 (13%), USA 207 (9%), Poland 41 (2%), Switzerland 40 (2%), Canada 13 (1%).

Table 1: **International centres and accrual in the three main strata, by site and country**

Randomisation and masking

The randomisation schedules were generated centrally by computer (securely kept in trial centres in Perth for Australian centres and London, UK, for all other centres). Requests for randomisation were via telephone or fax to the trials office (Perth or London), where a trained member of staff checked patient eligibility. Treatment was allocated from a pre-printed randomisation schedule available to authorised staff only. Written confirmation of randomisation was sent by fax to the site. Patients were randomly assigned in a 1:1 ratio to receive targeted intraoperative radiotherapy or external beam radiotherapy, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy. Three strata were used to stratify patients by timing of delivery. Details of the first two strata (prepathology entry and postpathology entry/targeted intraoperative radiotherapy as a second procedure) are given in figure 2.

If a patient otherwise suitable for the TARGIT-A trial was found to have a history of previous contralateral breast cancer, we did not exclude them. Such patients were expected to be few and we wished to ensure that their distribution between the two groups remained balanced. Hence they were randomised in a third stratum.

Neither patients nor investigators or their teams were masked to treatment given after randomisation. Individual sites were unblinded to treatment given to their own patients, but they were not given access to these data for other sites. Confidential unblinded reports for the DMC, and blinded reports for the ISC were produced by the trial statistician. Unblinded analyses were done according to a prespecified statistical analysis plan.

Outcomes

Patients' assessments were scheduled at entry, 3 months, and 6 months; thereafter, they were scheduled every 6 months up to 5 years, and then yearly for up to 10 years.

The primary outcome of the trial was pathologically confirmed local recurrence in the conserved breast. The secondary outcome measure of local toxicity or morbidity was assessed from data recorded on the complications form, which contained a prespecified checklist:

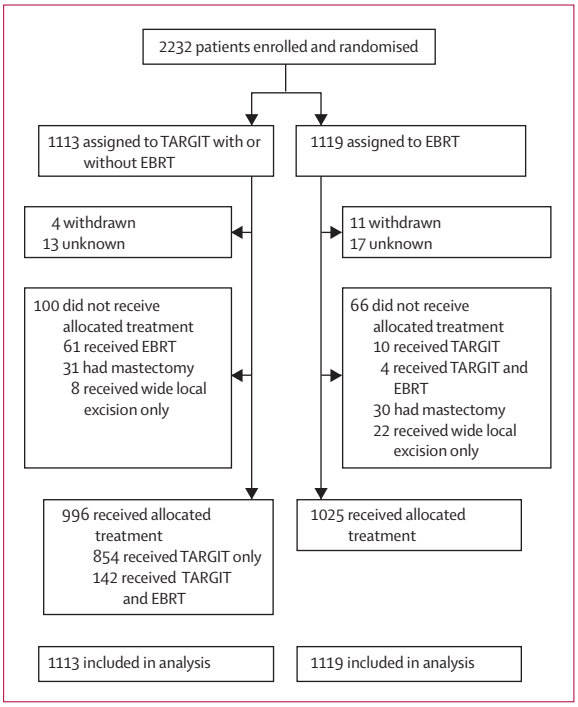

Figure 3: **Trial profile**
TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. Data for number of patients screened for eligibility are not available from all centres.

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
Age (years)		
<45	17/1113 (2%)	10/1119 (1%)
45–54	212/1113 (19%)	167/1119 (15%)
55–64	443/1113 (40%)	464/1119 (41%)
65–74	355/1113 (32%)	381/1119 (34%)
>74	86/1113 (8%)	97/1119 (9%)
Height (cm)	164 (159–168)	163 (159–168)
Weight (kg)	70 (62–80)	70 (62–80)
Pathological tumour size (cm)		
<1	381/1056 (36%)	388/1061 (37%)
1–2	531/1056 (50%)	519/1061 (49%)
>2	144/1056 (14%)	154/1061 (15%)
Unknown	57/1113 (5%)	58/1119 (5%)
Tumour type		
Invasive ductal carcinoma	1012/1070 (95%)	1018/1079 (94%)
Invasive lobular carcinoma	47/1070 (4%)	45/1079 (4%)
Mixed	32/1070 (3%)	35/1079 (3%)
Unknown	43/1113 (4%)	40/1119 (4%)
Tumour grade		
1	341/1040 (33%)	374/1048 (36%)
2	540/1040 (52%)	514/1048 (49%)
3	159/1040 (15%)	160/1048 (15%)
Unknown	73/1113 (7%)	71/1119 (6%)
Lymphovascular invasion		
Absent	881/1022 (86%)	894/1026 (87%)
Present	141/1022 (14%)	132/1026 (13%)
Unknown	91/1113 (8%)	93/1119 (8%)
Ductal carcinoma in situ		
Present	529/1063 (50%)	547/1069 (51%)
Absent	534/1063 (50%)	522/1069 (49%)
Unknown	50/1113 (4%)	50/1119 (4%)
Nodes involved		
0	866/1059 (82%)	898/1070 (84%)
1–3	155/1059 (15%)	149/1070 (14%)
>3	38/1059 (4%)	23/1070 (2%)
Unknown	54/1113 (5%)	49/1119 (4%)
Hormone receptors		
Oestrogen-receptor positive	962/1063 (90%)	981/1060 (93%)
Oestrogen-receptor negative	101/1063 (10%)	79/1060 (7%)
Oestrogen-receptor status unknown	50/1113 (4%)	59/1119 (5%)

(Continues on next page)

haematoma, seroma, wound infection, skin breakdown, delayed wound healing, Radiation Therapy Oncology Group (RTOG version 2.0) toxicity grade 3 or 4 for dermatitis, telangiectasia, pain in irradiated field, or other. We analysed seroma needing more than three aspirations, wound infections needing intravenous antibiotics, any complication needing surgical intervention, or (RTOG) toxicity grade more than 2. Skin breakdown or delayed wound healing or RTOG grade more than 2 were classified as major toxicity.

To compare the extent of local surgery we analysed the specimen weight, margin status, and re-operation for margins. No changes were made to trial outcomes after commencement of the trial.

Statistical analysis

The predefined non-inferiority margin was an absolute difference of 2·5% in the primary endpoint between groups. To test for non-inferiority with a background 5-year recurrence rate of 6%[12,26] and an absolute non-inferiority margin of 2·5%, a total sample size of 2232 patients was calculated for 80% power at a 5% significance level.

The analysis was done in accordance with the CONSORT guidelines.[27] Data lock was on May 2, 2010. All randomised patients were included in the intention-to-treat analysis, which compared the targeted intraoperative radiotherapy group with the external beam radiotherapy group, for efficacy and safety of the strategy. For the analysis of local recurrence in the conserved breast, patients who underwent mastectomy as their definitive surgery (for reasons such as positive margins, patient choice, etc) and patients who died or withdrew consent for further follow-up were censored on that date. All other recurrences in the conserved breast, but not axilla, were analysed and Kaplan-Meier curves were plotted to account for time to event and censoring of the data and included all patients. We also analysed the annual hazards of local recurrence in the conserved breast. When displaying the results, we

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
(Continued from previous page)		
HER2 (ERBB2) receptor status		
Positive	132/991 (13%)	132/1004 (13%)
Negative	859/991 (87%)	872/1004 (87%)
Not done	31/1113 (3%)	33/1119 (3%)
Unknown	91/1113 (8%)	82/1119 (7%)
Adjuvant therapy		
Hormone therapy	727/1113 (65%)	753/1119 (67%)
Chemotherapy	116/1113 (10%)	141/1119 (13%)
Other	48/1113 (4%)	41/1119 (4%)
Unknown	100/1113 (9%)	89/1119 (8%)

Data are n/N (%) or median (IQR). The denominator for unknown percentages is the number of randomised patients and the denominator for each category is the number of known cases. Percentages are rounded, so may not add up to 100%.

Table 2: **Patient and tumour characteristics**

	Targeted intraoperative radiotherapy	External beam radiotherapy
Specimen weight (g)*	46 (28–72)	47 (29–76)
Margins at first excision		
Free	970/1072 (90·5%)	968/1073 (90·2%)
DCIS only	46/1072 (4·3%)	43/1073 (4·0%)
Invasive	56/1072 (5·2%)	62/1073 (5·8%)
Unknown	41/1113 (3·7%)	46/1119 (4·1%)
Re-excision for margins		
Prepathology stratum	52/766 (6·8%)	67/768 (8·72%)
Postpathology stratum	27/347 (7·8%)	36/351 (10·3%)
Total	79/1113 (7·1%)	103/1119 (9·2%)

Data are median (IQR) or n/N (%). DCIS=ductal carcinoma in situ. *Specimen weight was available for 1219 patients (targeted intraoperative therapy, n=614; external beam radiotherapy, n=605). The denominator for unknown percentages is the number of randomised patients and the denominator for each category is the number of known cases.

Table 3: **Extent of surgery**

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
Number of complications per patient		
0	917 (82·4%)	946 (84·5%)
1	151 (13·6%)	139 (12·4%)
2	29 (2·6%)	27 (2·4%)
3	11 (1·0%)	5 (0·4%)
4	3 (0·3%)	0
5	2 (0·2%)	0
6	0	3 (0·3%)
Any complication*	196 (17·6%)	174 (15·5%)

Data are number of patients (%). *χ^2 1·74, p=0·19 comparison between the targeted intraoperative radiotherapy and external beam radiotherapy groups for no complications versus any number of complications, degree of freedom 1.

Table 4: **All complications**

restricted the duration to 4 years as recommended by Pocock and colleagues,[28] since fewer than 420 (<20%) patients had a follow-up beyond this point. The customised trial database was in Microsoft Access 2003; SAS System version 9.2 for Windows XP and STATA version 11.0 were used for data compilation and analysis. Pearson χ^2 test and log-rank test were used to obtain p values.

This trial is registered with ClinicalTrials.gov, number NCT00983684.

Role of the funding source

This was an academically driven trial. The funding bodies had no role in trial design, data analysis, data interpretation, or writing of the report. Carl Zeiss has partly supported a few centres for help in data collection. The corresponding author had full access to all data in the study. All authors had final responsibility for the decision to submit for publication.

Results

The first patient was randomised on March 24, 2000, and the trial recruited patients from 28 centres in nine countries. 1113 patients were randomly allocated to targeted intraoperative radiotherapy and 1119 were allocated to external beam radiotherapy. Table 1 shows the distribution of patients in individual sites and strata.

Figure 3 shows the trial profile. 89% of patients in the targeted intraoperative radiotherapy group and 92% in the external beam radiotherapy group received the allocated treatment. Of those who received the allocated treatment in the targeted intraoperative radiotherapy group, 86% received targeted intraoperative radiotherapy only and 14% received targeted intraoperative radiotherapy plus external beam radiotherapy (figure 3), matching the 15% expectation in the protocol.

Follow-up information was available for 1668 (99%) patients randomised before May 2, 2009, and 1945 (98%) patients randomised before Nov 2, 2009, 12 months and 6 months before the data lock, respectively.

Table 2 shows patient and tumour characteristics. The median age was 63 years (IQR 57–69) and 1834 (82%) patients were younger than 70 years. Tumour sizes were small: 36% were less than 1 cm, 50% were between 1 cm and 2 cm, and 14% were more than 2 cm. Most tumours were grade 1 (34%) or 2 (50%); only 15% were grade 3. Nodes were uninvolved in 83% of patients. 66% of systemic therapy was hormonal and 12% was chemotherapy.

Table 3 shows that the median amount of tissue excised during breast-conserving surgery was similar in the two groups, as was the proportion of first excisions with free margins. The difference in re-excision rates was not significant between the two main strata (prepathology 119 [7·8%] *vs* postpathology 63 [9·0%], p=0·31) or between the two groups (table 3; p=0·07).

The number of patients with any complication (table 4) was similar in the two groups. Table 5 shows the clinically

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)	p value
Haematoma needing surgical evacuation	11 (1·0%)	7 (0·6%)	0·338
Seroma needing more than three aspirations	23 (2·1%)	9 (0·8%)	0·012
Infection needing intravenous antibiotics or surgical intervention	20 (1·8%)	14 (1·3%)	0·292
Skin breakdown or delayed wound healing*	31 (2·8%)	21 (1·9%)	0·155
RTOG toxicity grade of 3 or 4†	6 (0·5%)	23 (2·1%)	0·002
Major toxicity‡	37 (3·3%)	44 (3·9%)	0·443

Data are number of patients (%). RTOG=Radiation Therapy Oncology Group. *Some of the patients in the first three rows (haematoma needing surgical evacuation, seroma needing more than three aspirations, infection needing intravenous antibiotics or surgical intervention) could be included in the fourth row (skin breakdown or delayed wound healing). †No patient had grade 4 toxicity. ‡Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4).

Table 5: **Clinically significant complications**

significant complications, three of which were similar in the two groups. Wound seroma needing more than three aspirations were more frequent in the targeted intraoperative radiotherapy group than in the external beam radiotherapy group, whereas RTOG score of 3 or 4 was more frequent in the external beam radiotherapy group than in the targeted intraoperative radiotherapy group. The total rate of major toxicities was similar in the two groups.

The number of axillary recurrences (targeted intraoperative radiotherapy, four *vs* external beam radiotherapy, three) and uncontrolled local recurrences at the time of death (one in each group) were similar in the two groups.

At 4 years, there were six local recurrences in the intraoperative radiotherapy group and five in the external beam radiotherapy group. Figure 4 shows the results for the primary endpoint of local recurrence. Figure 4A is the Kaplan-Meier plot for the whole cohort and shows narrow 95% CIs. Figure 4B shows the two randomised groups. There was no significant difference in the Kaplan-Meier estimate of local recurrence in the conserved breast between the targeted intraoperative radiotherapy and external beam radiotherapy groups at 4 years (1·20%, 95% CI 0·53–2·71 *vs* 0·95%, 0·39–2·31; difference between groups 0·25%, –1·04 to 1·54; log-rank test, p=0·41). Figure 4C shows the annual hazard of local recurrence in the first 4 years and the expected peak of recurrence in the second and third year with overlapping CIs for the targeted intraoperative radiotherapy and external beam radiotherapy groups.

Discussion

This large, international randomised trial provides robust and mature evidence that substantiates previous findings showing that targeted intraoperative radiotherapy is safe. Rates of overall complications and major complications were similar in the targeted intraoperative radiotherapy and external beam radiotherapy groups. Although there was a higher risk of seroma needing aspiration in patients assigned to targeted intraoperative radiotherapy than in those assigned to conventional treatment, this event was more than compensated for by significantly lower radiotherapy-related complications in the targeted intraoperative radiotherapy group (RTOG toxicity grade 3 or 4).

When the original sample size of 2232 was calculated, we based our estimate of 5-year local recurrence rate of 6% on the literature available in 1999.[12,26] We chose the non-inferiority margin as an absolute difference of 2·5% because this seemed clinically acceptable to physicians and patients. However, during the past decade recurrence rates have substantially reduced. The recurrence rate in the control group of our trial was 0·95% at 3 years. It would be logical to extrapolate the 5-year local recurrence rate to 1·5%, which is not unexpected. For example, in the UK Standardisation of Breast Radiotherapy (START) trial,[29] patients had a worse prognosis (eg, 36% had a tumour size of more than 2 cm *vs* 14% in TARGIT-A and 22% were node positive *vs* 17% in TARGIT-A) and were treated a few years before patients were in our trial. In the START trial, the recurrence rate at 5 years was 2·3%. Therefore the estimate of 1·5% for our trial is not unrealistic.

The absolute non-inferiority margin of 2·5% could still be deemed reasonable because a 2·5% difference in local recurrence at 5 years would translate into a 0·625% difference in mortality at 15 years (by use of the 4:1 ratio reported in the analysis by the Early Breast Cancer Trialists' Collaborative Group[30]), a magnitude that could be considered acceptable.[31] In fact, two patient preference studies[32,33] have suggested that the median additional increase that would be accepted in exchange for the convenience of a single treatment dose is 2·5%.

Thus, with a background recurrence rate at 5 years of only 1·5%, a trial for testing a non-inferiority margin of 2·5% with 80% power and 95% confidence needs a sample size of only 585 (table 6).[34] In our trial of 2232 patients, the number of patients with a median follow-up of 4 years was 862 and the number with a median follow-up of 3 years was 1514, well above the required 585 who already have a median follow-up of 4·5 years. Studies of temporal distribution of local recurrence suggest that this period covers the peak hazard of local recurrence that occurs between

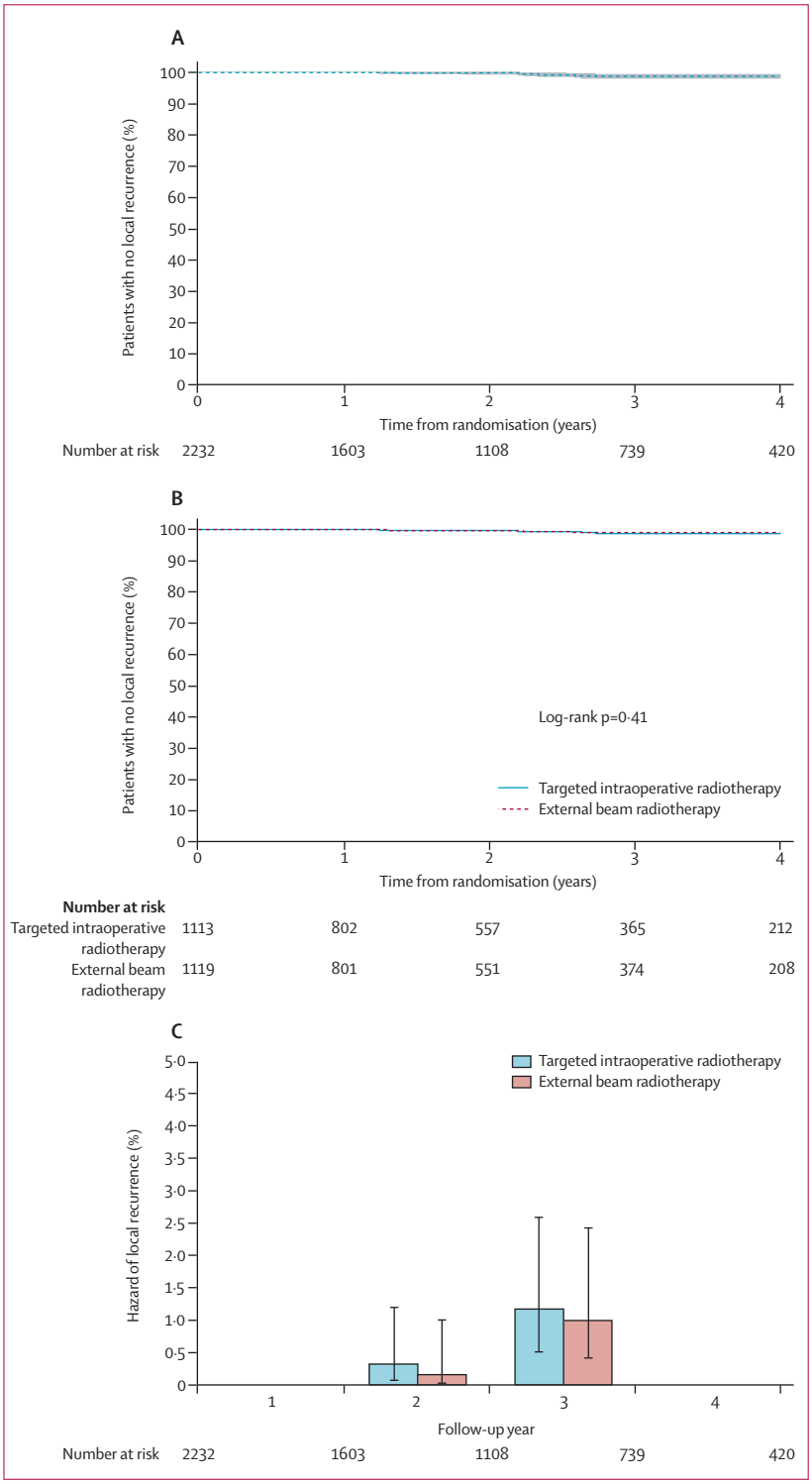

Figure 4: **Local recurrence in the conserved breast**
(A) Survival free of local recurrence in the conserved breast in entire cohort. Shaded area represents 95% CIs. (B) Survival free of local recurrence in the conserved breast; all patients in the two randomised groups. (C) Annual hazards of local recurrence. Error bars represent 95% CIs. There were no recurrences in years 1 or 4. These graphs (A, B, and C) are restricted to 4 years because less than 420 (<20%) patients have a follow-up beyond this point; however, all patients (with a maximum follow-up of 10 years) are included in the analysis, as recommended by Pocock and colleagues.[28]

2–3 years after surgery,[35] thus it is arguable that our results do have the maturity of follow-up in large enough numbers to draw cautious yet reasonable conclusions about efficacy.

The local recurrence rate in the targeted intraoperative radiotherapy group was not significantly different from that in the external beam radiotherapy group (1·2% *vs* 0·95%, p=0·41 at 4 years). As previously mentioned, the number of patients needed for testing a non-inferiority margin of 2·5% with 80% power and 95% confidence (n=585) have indeed completed a median 4·5 years of follow-up (minimum 3·6 years). One could therefore conclude that the targeted intraoperative radiotherapy approach is non-inferior in terms of efficacy to control local recurrence in selected patients covering the period at maximum hazard for such events. Our results have established a clinically relevant non-inferiority with a margin of 1·5%.

Furthermore, in the fourth year, with 739 patients at risk, there was no local recurrence in either group, suggesting that our results are robust. The results conform to the idea that the peak hazard of local recurrence has passed by year 4.

To cater for a wide level of equipoise, our design was pragmatic with restrictions for age (≥45 years) and tumour size (preferably smaller than 3·5 cm) kept to a minimum, and no restrictions for grade and nodal status. At the outset, each centre specified these options in a treatment policy document. Allowing clinicians to be liberal in their intended inclusion criteria increased appeal and encouraged wider participation, yet led to a fairly homogeneous low risk patient sample, which showed an unsurprising conservatism among participating clinicians in this pragmatic trial.[36]

Biologically, these results challenge two very different dogma, first that whole breast radiotherapy is necessary in this group of patients, and, second, that the traditional radiation dose (much higher than targeted intraoperative radiotherapy) is essential for effective tumour control.

Another interesting biological paradox is that the proportional risk reduction achieved by radiotherapy is the same whether the margins are positive, narrow, or wide, although the absolute reduction differs. Of the breast-conserving trials that have tested the effect of radiotherapy, patients in most trials,[30] including National Surgical Adjuvant Breast and Bowel Project (NSABP) B06,[37] underwent less extensive surgery than did patients in the Milan III trial.[38] The recurrence rate in the control group of the Milan III trial, in which the tumour dimensions were smaller and excision was substantially wider than in other trials, was low (8·8% *vs* 24–27% in other trials). Nevertheless, radiotherapy reduced the recurrence rate even further and at the same proportional rate as it did in other trials. If local recurrence were caused by residual disease only, then radiotherapy should have affected a much larger proportional reduction in those patients with positive margins or less extensive surgery;

but radiotherapy is as effective in patients with negative margins, suggesting that this modality of treatment might have an effect on the tumour microenvironment as well.[5]

The notion that some of the benefit from radiotherapy could result from a favourable effect on the tumour microenvironment[5] has been substantiated by translational research during targeted intraoperative radiotherapy.[39] In this study, the wound fluid collected in the 24 h after surgical-wide local excision of cancer stimulated breast cancer cell lines to proliferate, migrate, and invade into Matrigel (BD Biosciences, San Jose, CA, USA). By contrast, the fluid obtained from wounds that had received targeted intraoperative radiotherapy did not stimulate cancer cells.[39]

A delay in delivery of radiotherapy either because of long waiting lists or because chemotherapy is given first, could jeopardise its effectiveness.[40] A recent large study[41] in 18 050 patients has shown that timeliness does make an important difference. If radiotherapy is delivered intraoperatively, it would avoid a temporal miss[42] and enable the shortest possible interval between surgical resection of the cancer and accurate delivery of radiotherapy.

Mathematical models of radiotherapy[43] suggest that a smaller number of well targeted doses of radiotherapy are probably more effective than fractionated radiotherapy, which accords with the results of the START trial.[29] Additionally, the dose fall-off with the Intrabeam treatment mimics the decreasing tumour cell density with increasing distance from the border of the macroscopic tumour. This dose distribution led to a novel target volume theory, the sphere of equivalence, for targeted intraoperative radiotherapy treatment.[24] The model suggests that within such a sphere of equivalence[24] around the intraoperative radiotherapy applicator, local control should be equivalent to that achieved by a course of fractionated radiotherapy. The beneficial effect of targeted intraoperative radiotherapy on tumour microenvironment might enlarge such a sphere of equivalence.[44]

Although the traditional doses of fractionated radiation are much higher than the dose given with targeted intraoperative radiotherapy, the radiobiology of single doses under these circumstances is interestingly different. First, the radiation from Intrabeam (50 kV) has been shown to have an increased relative biological effectivity (RBE) of 1·5–2·0, so the biological dose is much higher than the physical dose. Also, this RBE paradoxically increases with depth so that the clinically relevant dose fall-off is less steep than is suggested from the mere physical dose distribution.[21,24,45,46] Second, the intraoperative dose is given at the earliest possible time and within a short period. Therefore, there is no loss of dose because of tumour cell proliferation between surgery and the initiation of radiotherapy, and between the fractions of a fractionated course of radiotherapy. We previously reported[24] that within the limits of the currently available radiobiological models, the dose of 20 Gy at the applicator surface is equivalent to a fractionated dose of 70 Gy.

There are several other trials of partial breast irradiation that use various techniques, including the ELIOT,[47] NSABP-B39, GEC ESTRO, and Hungarian trials.[48] The ELIOT trial[47] is the only other trial that uses single fraction intraoperative radiotherapy and a mobile linear accelerator that generates electrons at various energy levels. While the radiotherapy with targeted intraoperative treatment is given from within the breast with minimum additional dissection of the breast, the ELIOT technique[47] requires the breast tissue to be dissected off the skin and the chest wall and brought together for irradiation from outside the breast. The other trials use well-established techniques such as radioactive interstitial implants, intensity modulated and three-dimensional conformal radiotherapy, and interstitial balloon devices. Like TARGIT-A, all these trials are aimed at testing the idea of partial breast irradiation as an alternative to whole breast irradiation.

The implications of our results for day-to-day clinical practice will be affected by emerging data from these trials, as well as the individual circumstances of the patient. Furthermore, we need longer term follow-up of our own trial to monitor the clinical appearance of new primary tumours outside the index quadrant or delayed recurrences inside the index quadrant. If the results of these trials reflect our results then the range of techniques available will mean that clinicians and patients will have a choice and could make individualised decisions based on the evidence available for each technique, patient preference, local resources, and professional expertise. We wish to urge caution while applying these results to clinical practice; although targeted intraoperative radiotherapy

For more information about **the NSABP-B39 trial** see http://www.nsabp.pitt.edu/B-39.asp

For more information about **the GEC ESTRO trial** see http://www.apbi.uni-erlangen.de/outline/outline.html

	Background recurrence rate	Recurrence rate in the experimental group (background plus non-inferiority margin of 2·5%)	Total sample size required for 80% power and 95% confidence	Median follow-up of this sample size in the TARGIT-A trial at present (months)
Expected 10 years ago	6%	8·5%	2232	25·3
Expected following recent publications (eg, START trial[29])	3%	5·5%	1151	43·0
Actually found in the external beam radiotherapy group of the TARGIT-A trial	1·5%	4%	585	54·0

With a background recurrence rate of 1·5%, we need only 585 patients in total, which already have a median follow up of 54 months (4·5 years), long enough to draw reasonable conclusions (reference 35 and EAST, Cytel Statistical Software version 5, 2007).

Table 6: **Sample size calculations for different scenarios**

provides effective local control in the period of peak hazard (first 4 years), the results are valid only for patients with the clinicopathological features similar to those in this trial.

In addition to the obvious benefits of completing all the necessary radiotherapy in a single session at the time of surgery, targeted intraoperative radiotherapy almost completely avoids irradiation of the intrathoracic structures such as the heart, lung, and oesophagus.[21] Consequently, the damage to these structures, which can occur even with modern external beam radiotherapy,[49] will have been avoided. We will monitor late cardiac toxicity in these patients to assess whether it is indeed lower in the targeted intraoperative radiotherapy group than in the external beam radiotherapy group.

A crucial issue in understanding this trial centres on the benefits to the patient and the effect on the workload of a radiotherapy centre. Treatment of patients with breast cancer accounts for about a third of the workload of radiotherapy departments in some parts of the world and contributes substantially to the unacceptable waiting lists seen in many oncology departments worldwide. In countries such as the UK where the waiting list for postoperative radiotherapy could rapidly diminish with use of targeted intraoperative radiotherapy, we estimate savings of around £15 000 000 (US$23 000 000) a year.[5]

When making decisions about which operation to choose, the main factors women are concerned about are tumour recurrence, the need for radiation therapy, and speed of recovery.[50] Consequently, because the definitive treatment with radiation can be completed at the time of the surgery or shortly afterwards in a single session with targeted intraoperative radiotherapy, two of the patients' major concerns are immediately addressed, and perhaps fewer patients should feel obliged to choose mastectomy over breast-conserving surgery either because they live far away from a radiotherapy facility[51] or to avoid prolonging their treatment. Furthermore, since the risk of local recurrence with targeted intraoperative radiotherapy is similar to that with conventional external beam radiotherapy, then this approach should effectively deal with all three of the major concerns of women with breast cancer.

Our results bring us closer to a scenario in which a patient with early breast cancer might complete all her local treatment, surgical excision, sentinel lymph node biopsy, and radiotherapy at one or two visits, without having to stay overnight in a hospital bed. Together with the developments in adjuvant systemic therapy, these advances could substantially reduce the effect of a breast cancer diagnosis and treatment on a woman's life.

Contributors

JSV, MBa, and JST were responsible for trial concept, trial design, trial management, data interpretation, and writing of the report. DJJ, FW, JST, MBa, and JSV contributed to trial concept, trial design, trial management, training and accreditation of centres, patient accrual and treatment, data collection, data interpretation, and writing of the report. JSV and MA contributed to training and accreditation of centres, patient accrual and treatment, data collection, and writing of the report. JSV and NRW designed the statistical analysis plan and contributed to statistical analysis, trial coordination, data collection, data interpretation, and writing of the report. MBu and JSV did the statistical analyses and contributed to data interpretation and writing of the report. CS, TC, and LE contributed to trial design, patient accrual, patient treatment, data interpretation, and writing of the report. HLF, WE, MK, MR, and MS contributed to patient accrual, patient treament, data collection, and data interpretation. MK contributed to trial management and accreditation of new centres. HLF, SM, WE, MK, JSV, JD, UKT, MS, MR, HMRH, and SP contributed to setting up their centres, patient accrual, treatment, data collection, and approval of the report. JSV and MM were involved with design and preclinical tests of the Intrabeam system. MM was involved with continuing quality assurance and dosimetry analysis, data collection, and approved the report. MF was involved with primary diagnosis and subsequent assessment of the histology from University College London Hospitals. AM reviewed the data generated from the trial and their interpretation and approved the report. All authors apart from HLF, MR, SP, and HMRH attended the ISC meetings as members. The authors take full responsibility for the report. The writing committee consisted of JSV, JST, MBu, FW, CS, MA, and DJJ, and was helped by the trial operations staff and their respective families.

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Conflicts of interest

JSV had received a research grant from Photoelectron Corp (1996–99), and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK) and has subsequently received honoraria. MBa is on the scientific advisory board of Carl Zeiss and is paid monthly consultancy fees. FW has received a research grant from Carl Zeiss for supporting radiobiological research. Carl Zeiss sponsors most of the travel and accommodation for meetings of the ISC and DMC and when necessary for conferences where a presentation about targeted intraoperative radiotherapy is being made for all authors apart from LE, MR, WE, and HMRH. Carl Zeiss paid MM and AM honoraria for attending ISC meetings. MR, WE, and HMRH declare that they have no conflicts of interest.

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The trial was initiated by an academic insight and collaboration with the industry was solely for the development of the device. The manufacturers of the Intrabeam device (Carl Zeiss) did not have any part in concept, design, or management of the trial, or in data analysis, data interpretation, or writing of the report. The study was sponsored by University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre. Funding was provided by UCLH Charities, National Institute for Health Research (NIHR) Health Technology Assessment programme, Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research (BMBF) FKZ 01ZP0508. The infrastructure of the trial operations office in London, UK, was supported by core funding from Cancer Research Campaign (now Cancer Research UK) when the trial was initiated. We thank Michael D O'Shea (Tessella, Abingdon, UK) for database development, Mo Thaha for help in data collection, and Hrisheekesh J Vaidya for help with figure 1A, as well as several contributors who have now left the individual centres. Travel and accommodation for meetings of the international steering committee and data monitoring committee were provided by Carl Zeiss. Funding for the TARGIT Trials Operations Office was provided by the NIHR Health Technology Assessment programme. Individual centres were self-financed. We thank all the patients who kindly participated in the trial.

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A brief description of the TARGIT-A trial by Jayant S Vaidya on behalf of the TARGIT group

For most women with breast cancer, the standard treatment includes surgery, which removes the tumour with a margin of normal tissues (lumpectomy), and radiotherapy, which reduces the chances of the cancer coming back. Radiotherapy is usually given as a 3-6 weeks course (whole breast external beam radiotherapy - EBRT). A new development could significantly change the way breast cancer is treated.

Based on our clinical and pathological studies, we suggested in 1995 that radiotherapy restricted only to the tissues around the original tumour, and given at the time of surgery, may be as effective.

In the late 1990s, we designed a new device (called Intrabeam®) in collaboration with a specialist manufacturer, and developed the operative technique to deliver single-dose radiotherapy either during the lumpectomy or at a second operation soon afterwards. We called this novel approach TARGeted Intra-operative radioTherapy (TARGIT). In this technique, radiation is given directly to the site, the spherical device being placed where the lump was, and over half an hour, radiation is administered to the tissues that surrounded the tumour – the 'tumour bed', from within the breast.

We first treated a breast cancer patient with this technique on 2 July 1998. Our initial study of 25 women was expanded to 300 cases. TARGIT was given as a substitute for the usual tumour bed boost and all patients also received a shorter course of EBRT. TARGIT boost was found to be feasible, safe, and according to a recent analysis may even yield a better clinical outcome.

In March 2000 we launched a large international randomised clinical study (TARGIT-A trial) that took 10 years to complete and directly compared the TARGIT approach with conventional EBRT given over 3-6 weeks. The TARGIT approach was to give single-dose TARGIT to every patient, and, if a higher than acceptable risk was found (for example many positive lymph nodes) whole breast EBRT was added. The control group consisted of whole breast EBRT over 3-6 weeks for every patient. Patients could also be entered in the trial after the tumour had been removed for example, at another hospital. For such patients, TARGIT was delivered by re-opening the wound as an additional surgical procedure.

It is important to recognise that the TARGIT-A trial compared TARGIT (with added whole breast EBRT as per the individual risk) vs. whole breast EBRT in all. In other words it compared risk-adjusted radiotherapy vs. whole-breast-radiotherapy-for-all. Within the trial, overall, 14% patients who received TARGIT also received EBRT. Amongst those who received TARGIT at the time of the first operation, 21% also received EBRT. Thus nearly 4 out of 5 such patients did not need any further radiotherapy.

In total, 2232 women from 28 centres in 9 countries participated in the trial: 1113 were allocated the TARGIT approach and 1119 the conventional radiotherapy approach. Our manuscript describing the results was fast tracked and published in The Lancet (online first on 5 June and in the print on 9 July 2010)[1]. We found that the local recurrence rates in the two groups were very low and similar at 4 years, by which time the greatest risk of local recurrence had passed (EBRT group 0.95% and TARGIT group 1.2%)*. We also found that the TARGIT approach had less radiotherapy related side effects. We concluded in the Lancet that "For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks"

Given the similar outcome and lower side effects, one cannot overemphasise the obvious advantages to the patient and the healthcare system of completing the radiotherapy in a single session at the time of the cancer operation; in addition the equipment is less expensive and there would be lower greenhouse gas emissions from avoiding 3-6 weeks' of daily trips for EBRT.

*The statistics: The actual difference between the TARGIT and EBRT groups was 0.25% (10 times less than our original acceptable limit of 2.5%) at 4 years. As is usual while reporting clinical trials, not all patients have reached the follow up period of 4 years, so a standard statistical method was used to estimate a range around the 0.25% difference. This range, called 95% confidence interval, was -1% to +1.5%, which means that, with a 95% probability, at worst TARGIT is 1.5% worse than EBRT and at best TARGIT is 1% better than EBRT.

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Further information about the trial and its related publications are available at www.targit.org.uk, www.targittrial.org, and www.targit-research.org

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