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A 5-min summary of the results of TARGIT-A trial given at the National Cancer Research Institute (NCRI) conference, UK, Nov 2021: https://youtu.be/ygPOaN3AO7s

A short video explaining this paper: https://youtu.be/5Xby04NBanY
A companion blog: https://blogs.bmj.com/bmj/2020/08/20/targeted-intraoperative-radiotherapy-for-early-breast-cancer-new-evidence/

Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer

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Study question Can risk adapted targeted intraoperative radiotherapy (TARGIT-IORT) delivered as a single dose during lumpectomy effectively replace postoperative whole breast external beam radiotherapy (EBRT) for early breast cancer, and what are the long term outcomes?

Methods The TARGIT-A international randomised controlled trial (32 centres in 10 countries in the United Kingdom, Europe, Australia, and North America) recruited 2298 women aged 45 years and older with invasive ductal carcinoma up to 3.5 cm (lymph node stage cN0-N1) who were eligible for breast conservation. Participants were randomised before lumpectomy to either single dose TARGIT-IORT or EBRT (standard daily fractionated course over three to six weeks). The main outcome measures were non-inferiority at a margin of 2.5% for five year local recurrence rate, and long term survival.

Study answer and limitations 1140 patients were randomised to TARGIT-IORT and 1158 to EBRT. The study found that TARGIT-IORT was non-inferior to EBRT for local recurrence. At five year complete follow-up the local recurrence risk was 2.11% (24/1140) for TARGIT-IORT compared with 0.95% (11/1158) for EBRT (difference 1.16%, 90% confidence interval 0.32% to 1.99%). 14 fewer deaths occurred with TARGIT-IORT than with EBRT (42/1140 *v* 56/1158). With long term follow-up (median 8.6 years) no statistically significant difference in any breast cancer outcome was found (such as local recurrence-free survival, mastectomy-free survival, and breast cancer mortality), and mortality from other causes was significantly lower in the TARGIT-IORT arm (45 *v* 74 deaths, hazard ratio 0.59, 95% confidence interval 0.40 to 0.86, P=0.005). Two major risk factors for cardiovascular disease and malignant disease were collected (age and body mass index), and they were well balanced between the two randomised arms of this large trial.

What this study adds For most patients with early breast cancer, immediate single dose TARGIT-IORT during lumpectomy was an effective alternative to EBRT, with comparable long term efficacy for cancer control and lower non-breast cancer mortality. TARGIT-IORT should be discussed with eligible patients when breast conserving surgery is planned.

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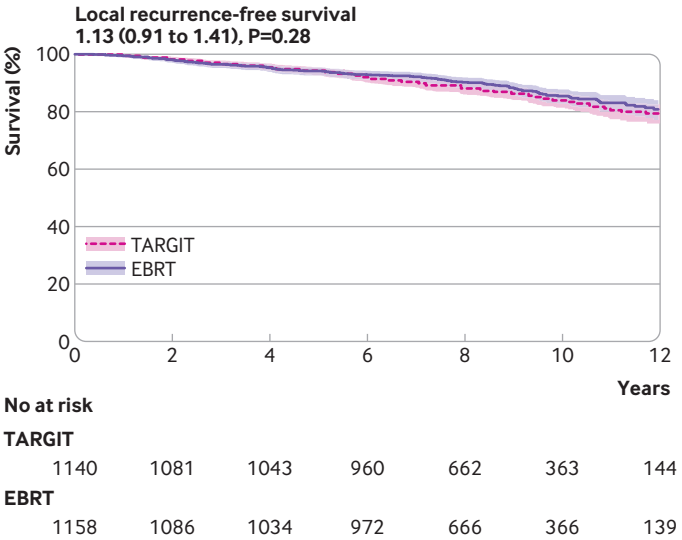
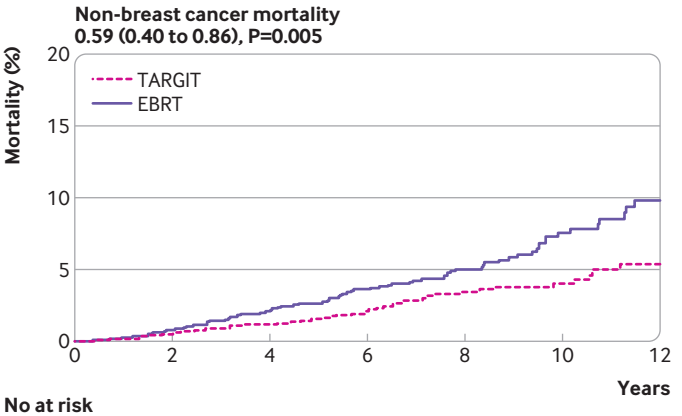
Trial registration ISRCTN34086741, NCT00983684.



No at risk							
TARGIT	1140	1081	1043	960	662	363	144
EBRT	1158	1086	1034	972	666	366	139



No at risk							
TARGIT	1140	1089	1059	989	689	378	152
EBRT	1158	1088	1041	978	672	371	143

Long term outcomes of the randomised TARGIT-A trial comparing risk adapted targeted intraoperative radiotherapy (TARGIT) delivered as single dose during lumpectomy with postoperative whole breast external beam radiotherapy (EBRT) for early breast cancer. Data under titles are hazard ratios (95% confidence intervals) and log rank test P values

Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial

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ABSTRACT

OBJECTIVE
To determine whether risk adapted intraoperative radiotherapy, delivered as a single dose during lumpectomy, can effectively replace postoperative whole breast external beam radiotherapy for early breast cancer.

DESIGN
Prospective, open label, randomised controlled clinical trial.

SETTING
32 centres in 10 countries in the United Kingdom, Europe, Australia, the United States, and Canada.

PARTICIPANTS
2298 women aged 45 years and older with invasive ductal carcinoma up to 3.5 cm in size, cN0-N1, eligible for breast conservation and randomised before lumpectomy (1:1 ratio, blocks stratified by centre) to either risk adapted targeted intraoperative radiotherapy (TARGIT-IORT) or external beam radiotherapy (EBRT).

INTERVENTIONS
Random allocation was to the EBRT arm, which consisted of a standard daily fractionated course (three to six weeks) of whole breast radiotherapy, or the TARGIT-IORT arm. TARGIT-IORT was given immediately after lumpectomy under the same anaesthetic and was the only radiotherapy for most patients (around 80%). TARGIT-IORT was supplemented by EBRT when postoperative histopathology found unsuspected higher risk factors (around 20% of patients).

MAIN OUTCOME MEASURES
Non-inferiority with a margin of 2.5% for the absolute difference between the five year local recurrence rates of the two arms, and long term survival outcomes.

RESULTS
Between 24 March 2000 and 25 June 2012, 1140 patients were randomised to TARGIT-IORT and 1158 to EBRT. TARGIT-IORT was non-inferior to EBRT: the local recurrence risk at five year complete follow-up was 2.11% for TARGIT-IORT compared with 0.95% for EBRT (difference 1.16%, 90% confidence interval 0.32 to 1.99). In the first five years, 13 additional local recurrences were reported (24/1140 *v* 11/1158) but 14 fewer deaths (42/1140 *v* 56/1158) for TARGIT-IORT compared with EBRT. With long term follow-up (median 8.6 years, maximum 18.90 years, interquartile range 7.0-10.6) no statistically significant difference was found for local recurrence-free survival (hazard ratio 1.13, 95% confidence interval 0.91 to 1.41, P=0.28), mastectomy-free survival (0.96, 0.78 to 1.19, P=0.74), distant disease-free survival (0.88, 0.69 to 1.12, P=0.30), overall survival (0.82, 0.63 to 1.05, P=0.13), and breast cancer mortality (1.12, 0.78 to 1.60, P=0.54). Mortality from other causes was significantly lower (0.59, 0.40 to 0.86, P=0.005).

CONCLUSION
For patients with early breast cancer who met our trial selection criteria, risk adapted immediate single dose TARGIT-IORT during lumpectomy was an

WHAT IS ALREADY KNOWN ON THIS TOPIC

When early breast cancer is treated with breast conserving surgery (lumpectomy) rather than mastectomy, adjuvant whole breast postoperative external beam radiotherapy, given as multiple doses over several days, reduces the risk of local recurrence

Restricting radiotherapy to only the area around the tumour by using intraoperative radiotherapy has the benefits of precision and immediacy, and avoids the inevitable delay in starting postoperative radiotherapy

Early results of using single dose targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy indicate this approach has many advantages for the patient, such as less travelling for treatment, improved quality of life, and fewer side effects

WHAT THIS STUDY ADDS

The results of the TARGIT-A trial show that TARGIT-IORT has similar long term local control and cancer survival outcomes to whole breast radiotherapy

Mortality from other causes was lower in the TARGIT-IORT arm

Single dose TARGIT-IORT during lumpectomy should be accessible to healthcare providers and discussed with patients when surgery for breast cancer is being planned

effective alternative to EBRT, with comparable long term efficacy for cancer control and lower non-breast cancer mortality. TARGIT-IORT should be discussed with eligible patients when breast conserving surgery is planned.

TRIAL REGISTRATION
ISRCTN34086741, NCT00983684.

Introduction

In 2018, two million patients were diagnosed as having breast cancer worldwide and 626 000 patients died from the disease.[1] Treatment with breast conserving surgery and adjuvant radiotherapy rather than total mastectomy is suitable for most patients. Most local recurrences occur close to the primary tumour site despite the frequent presence of microscopic cancer foci in other quadrants.[2 3] Based on the hypothesis that adjuvant radiotherapy for women with early breast cancer could be limited to the tumour bed and given immediately during breast conserving surgery (lumpectomy), we developed the concept of targeted intraoperative radiotherapy (TARGIT-IORT).[4-7] When the TARGIT-A trial protocol was published in 1999,[8] restricting radiotherapy to only the area around the tumour had been explored in small patient series[9] and one randomised trial,[10] which had reported inferior results. At that time whole breast radiotherapy was the standard of care, and it remains so today, despite the publication of our initial results[11-13] and several other approaches.[14-21]

TARGIT-IORT provides a well positioned and rapid form of tumour bed irradiation focused on the target tissues alone, while sparing normal tissues and organs such as heart, lung, skin, and chest wall structures.[22] We designed the TARGIT-A randomised trial to compare risk adapted TARGIT-IORT with conventional whole breast external beam radiotherapy (EBRT) over several weeks.[4 11 13] The study received ethics approval from the Joint University College London and University College London Hospital committees of ethics of human research. Recruitment began in March 2000 and was completed in June 2012.

In 2004, four years after recruitment began for the main TARGIT-A trial and at the request of centres with potentially high numbers of patients, we sought additional ethics approval and opened a parallel study. This study was previously referred to as the post-pathology stratum and recruited 1153 patients by using a separate randomisation table. These patients were randomised after their initial surgery to have either conventional fractionated whole breast radiotherapy (n=572) or a further operation to deliver delayed radiotherapy to the wound by reopening the original incision (n=581). The trial was initiated mainly because of easier scheduling of delayed TARGIT-IORT in operating theatres. This delayed radiotherapy was not intraoperative radiotherapy given during the cancer operation; treatment was performed a median of 37 days after the first excision. The 2013 analysis found that this delayed second procedure crossed the 2.5% margin of non-inferiority. Therefore, we recommended that immediate TARGIT-IORT should be the preferred treatment over delayed TARGIT-IORT,[13] and delayed treatment was no longer used. As specified in the statistical analysis plan, which was signed off before unblinding for this analysis, we have addressed the long term outcomes for this parallel trial in a separate paper.

This paper reports the findings of the TARGIT-A trial, in which 2298 patients were randomised after their needle biopsy and before any surgical excision of the cancer to receive either risk adapted TARGIT-IORT delivered during the initial excision of cancer or postoperative whole breast external beam radiotherapy (EBRT). We investigated whether immediate TARGIT-IORT was non-inferior to EBRT at five year complete follow-up in terms of local recurrence, and also compared their long term survival outcomes.

Methods

TARGIT-A was a pragmatic, prospective, international, multicentre, open label, randomised, phase III trial that compared risk adapted TARGIT-IORT with the conventional treatment of whole breast EBRT. The trial protocol (https://njl-admin.nihr.ac.uk/document/download/2006598), including details of sample size calculations and the random allocation process, has been previously described.[11 13] In brief, women with early breast cancer were eligible if they were aged 45 years or older, diagnosed by needle biopsy, and suitable for wide local excision of invasive ductal carcinoma that was unifocal on conventional examination and imaging (cT1 and small cT2 ≤3.5 cm, cN0-N1, M0, as confirmed by cytology or histology). Breast magnetic resonance imaging was not required and only 5.6% of patients in the trial had a scan.

Eligible patients were randomly assigned before their surgery (in a 1:1 ratio) to receive either a risk adapted approach that used single dose TARGIT-IORT or EBRT according to standard schedules over several weeks, with randomisation blocks stratified by centre. The randomisation schedules were generated centrally by computer (securely kept in trial centres in Perth for Australian centres and London, United Kingdom, for all other centres). Requests for randomisation were through telephone or fax to the trial office (Perth or London), where a trained member of staff checked patient eligibility. Treatment was allocated from a preprinted randomisation schedule available to authorised staff only. Written confirmation of randomisation was sent by fax to the site.

All patients gave written informed consent and needed to be available for regular follow-up for at least 10 years. Follow-up clinical examination was at least six monthly for the first five years and annually thereafter, including a mammogram once a year.

The experimental arm was risk adapted radiotherapy. If the final pathology report showed prespecified unpredicted features, EBRT was recommended in addition to TARGIT-IORT, with TARGIT-IORT (already received during surgery) serving as the tumour bed boost. In the core protocol, EBRT was recommended

to supplement TARGIT-IORT within the experimental arm if the tumour-free margin was less than 1 mm, if there was an extensive in situ component (>25%), or if unexpected invasive lobular carcinoma was found in the postoperative final microscopic histopathological examination of the primary tumour excision. Additionally, individual centres prespecified any other final postoperative histopathology criteria (such as grade 3 tumour, node positivity, lymphovascular invasion) that would prompt supplemental EBRT to be recommended. These criteria were recorded in the centre's treatment policy document before their trial recruitment started.

The trial was a comparison of two policies: whole breast radiotherapy without selection versus individualised risk adapted radiotherapy; a proportion of patients who received TARGIT-IORT were also given supplemental EBRT by using prespecified criteria. These patients were not crossovers, but were offered individualised risk adapted radiotherapy according to the experimental treatment policy, which was designed to reflect the real world scenario.

The TARGIT-IORT technique using the Intrabeam device (Carl Zeiss Meditec, Oberkochen, Germany)[5-7] enables a patient to potentially receive all the required radiation in a single treatment under the same anaesthetic as the primary surgery (efig 1).[5-7 23-26] Radiation is delivered from a point source of 50 kV energy x rays at the centre of a spherical applicator over 20-50 minutes. The appropriately sized (1.5-5 cm diameter) applicator is surgically positioned in the tumour bed so that breast tissues at risk of local recurrence receive the prescribed dose while skin and other organs are protected. The surface of the tumour bed typically receives 20 Gy that attenuates to 5-7 Gy at 1 cm depth. Further details and a video are available online (www.targit.org.uk; https://goo.gl/iuF9ZR). The patients in the conventional arm underwent standard EBRT which always included fractionated whole breast radiotherapy for three to six weeks, with or without an EBRT tumour bed boost, as determined by local criteria prespecified by the collaborating centre.

We designed the trial as a non-inferiority trial. Non-inferiority trials in cancer are performed to test new treatments that have obvious non-oncological advantages, such as better access, convenience, or quality of life for the patient, or reduced costs for the healthcare system. The non-inferiority statistical test for such a comparison is not meant to check for superiority, but to assess if the difference is within an acceptable margin and the experimental treatment is not meaningfully worse than the control. Therefore, whether the difference seen between the two randomised arms is statistically significant is not relevant here. As long as the absolute difference is not clinically significant, the new treatment would be deemed non-inferior.[27] Any chosen non-inferiority margin must be one that clinicians and patients agree is an acceptable difference for the sake of the other benefits. These benefits might include lower toxicity, better cosmetic outcome, better quality of life, and overall patient preference. Therefore, in the original protocol, non-inferiority was specified as being achieved if the difference in the binomial proportions of local recurrence rate at five years did not cross a stringent margin of 2.5% in absolute terms; that is, local recurrence risk with TARGIT-IORT minus local recurrence risk with EBRT should not be more than 0.025 (2.5%). In the 2013 analysis, an even more rigorous criterion was used, specifying that the upper 90% confidence interval of the absolute difference must not exceed 0.025 (2.5%).

The 2.5% non-inferiority margin in the TARGIT-A trial is a relevant, relatively stringent margin. Patient preference studies in the United States, Australia, and Europe suggest that 2.5% is an acceptable margin.[28-30] Importantly, it is widely regarded as a safe margin because it is well established that a local recurrence difference of less than 10% at five years does not worsen breast cancer survival[31]; that is, when the risk in arm A minus the risk in arm B is less than 0.1 (10%). A large increase in local recurrences (>10% at five years) is required to lead to increased mortality because they can be effectively treated. For example, a 20% increase in local recurrence (a risk increase by 0.2) would cause a 5% increase in deaths (a mortality risk increase by 0.05)[31]; this was the basis for the ethics approval of this trial. In the ELIOT trial, which also investigated intraoperative radiotherapy, the non-inferiority margin was set at 7%.[15] In recently reported trials of systemic therapy, the margin of a 3% difference in disease-free survival was considered acceptable.[32]

Analysis of conventional longer term outcomes in breast cancer trials needs to include deaths as events for two reasons. Firstly, deaths are one of the most important clinical outcomes. Secondly, longer follow-up in an older population with early breast cancer means that death becomes much more common than local recurrence. Importantly, if toxicity of treatment leads to a difference in mortality then it needs to be reflected in the results. The statistical analysis plan for this long term analysis was signed off by the chair of the independent steering committee and an independent senior statistician before the unblinded data were sent to the trial statistician for the current analysis. The plan specified the primary outcome was local recurrence-free survival. This outcome is consistent with the DATECAN[33] and STEEP[34] guidelines for clinical events to be included in the definitions of time-to-event end points in randomised clinical trials assessing treatments for breast cancer. Local recurrence-free survival is clinically meaningful because it measures the chance of a patient being alive without local recurrence. Therefore, this outcome includes local recurrence or death as events; that is, patients who had died were not censored. Clinicians and patients need to know the chance of being alive without a local recurrence, which is given by local recurrence-free survival. The other important outcomes were invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival, overall survival, breast cancer mortality, and non-breast cancer mortality.

We performed statistical analysis by using established methods.[27 35 36] Hazard ratios were calculated by using the Cox proportional hazard model with TARGIT-IORT as the numerator. We carried out censoring appropriately for each outcome; for example, for survival outcomes, patients were censored at the time of last follow-up, or the date of withdrawal. Kaplan-Meier graphs for these long term outcomes were presented according to Pocock and colleagues,[37] who recommended that the x axis should be extended until 10-20% of patients are at risk of an event. This approach also ensures that any long term trends (positive or negative) are not missed. We used the log rank test to compare differences between survival functions and to obtain P values. All analyses were by intention to treat according to the randomisation arm.

Each centre specified the cause of death. If the cause of death was specified as a non-breast cancer event and no distant disease was recorded, it was defined as a non-breast cancer death. If the death was recorded by the centre to be related to breast cancer, or as per convention, if breast cancer was present at the time of death, or if the cause of death was recorded as unknown or uncertain, it was presumed to be a breast cancer death.

The reference date for completeness was 2 May 2018, eight years after the first data lock. We considered patients to have complete follow-up if they were seen for the specified duration of follow-up, if they were seen within one year of the reference date, if they had died, or if they had withdrawn from the trial. Because the last patient was randomised in 2012, the statistical analysis plan specified that the five year follow-up would be considered complete if 95% of patients had complete follow-up. The plan also specified that a 10 year follow-up would be considered complete if the patient had at least 10 years of follow-up, had been seen within one year of the reference date, or had died or withdrawn from the study; the 10 year follow-up would be considered complete if this was achieved by 90% of patients. The interim analysis confirmed the safety of TARGIT-IORT, but the follow-up was relatively short. Therefore, the independent data monitoring committee recommended that we continue recruitment while accruing the required follow-up. There was no specific trial funding for individual centres and so return of follow-up relied on individual investigators and the efforts of their teams, enthused by the trial centre team. The trial statistician and the chief investigator produced reports of completeness of follow-up by using blinded databases on a regular basis.

Once the thresholds set in the statistical analysis plan were reached, the database was unblinded for analysis. The reference date for analysis was 3 July 2019, so that all events up until 2 July 2019 were included for analysis. We used Stata version 16.0 for data compilation, validation, and analysis. The trial steering and data monitoring committees each included a patient advocate as a member. Since the last analysis, the trial oversight has been provided by an independent steering committee, appointed by the Health Technology Assessment (HTA) programme of the National Institute of Health Research, Department of Health and Social Care, UK, which also includes a patient as a member.

Patient and public involvement

Patients have been involved as members of the steering committee from the start. Patients were not involved in the initial design of the study in 1999-2000, but they were involved from the time the trial started. However, it was the serious concern about patients' welfare that inspired the study design. The pragmatic nature of this trial was designed to suit the patient's perspective. The non-inferiority margin has been validated with patient preference studies,[28-30] which included asking patients about their priorities. Patients were involved in recruitment to and conduct of the study as members of the steering committee and on several occasions as commentators in the national press, TV, and radio. Patients assessed the burden of intervention and the time required to participate. Unlike most other studies, participating in the trial was the main pathway through which patients could access TARGIT-IORT and reduce the burden of treatment (that is, they were likely to avoid external beam radiotherapy) in the 50% of the group randomised to receive the TARGIT-IORT arm rather than the EBRT arm. A patient has been involved during the development of the statistical analysis plan, interpretation of the results and writing of the manuscript, and is an author of the paper.

Results

Between 24 March 2000 and 25 June 2012, 2298 patients were recruited to the study: 1140 patients were randomised to receive risk adapted immediate TARGIT-IORT during lumpectomy and 1158 patients were randomised to receive EBRT. Table 1 presents patient and tumour characteristics, which were well matched between the randomised arms.

Complete follow-up to the prespecified level of 95% at five years was achieved by mid-2019. Figure 1 presents the flow and CONSORT (consolidated standards of reporting trials) diagrams. Figure 2 shows the completeness of follow-up and illustrates that the observed follow-up is close to the expected follow-up in each arm of the trial. The follow-up duration of the two arms did not differ (log rank P=0.22).

For the protocol specified primary outcome of non-inferiority at five years, we found that immediate TARGIT-IORT was non-inferior to EBRT for local control (table 2): at five year complete follow-up, the number of local recurrences was 24 (including six ductal carcinoma in situ) of 1140 (2.11%) for TARGIT-IORT versus 11 (including one ductal carcinoma in situ) of 1158 (0.95%) for EBRT. The difference in local recurrence rate was 0.0116 (1.16%) and the 90% confidence interval was 0.0032 to 0.0199 (0.32% to 1.99%), establishing non-inferiority. Testing for non-inferiority by using five year Kaplan-Meier estimates also confirmed that immediate TARGIT-IORT is non-inferior to EBRT (difference 1.21%, 90% confidence interval 0.47% to 1.95%). We also confirmed non-

Table 1 | Patient and tumour characteristics in the TARGIT-IORT and EBRT arms

Characteristics	TARGIT-IORT (n=1140)	EBRT (n=1158)
Age (years)		
≤50	117 (10.3)	99 (8.6)
51-60	362 (31.8)	375 (32.4)
61-70	481 (42.2)	524 (45.3)
>70	180 (15.8)	160 (13.8)
Body mass index		
Normal (<25)	408 (41.0)	420 (42.2)
Overweight (25-29.9)	375 (37.7)	329 (33.1)
Obese (≥30)	212 (21.3)	246 (23.7)
Unknown	145 (12.7)	163 (14.1)
Specimen weight (g)		
Median (interquartile range)	40 (25-65)	40 (24-70)
Pathological tumour size (mm; P=0.70)		
≤10	369 (33.1)	370 (33.1)
11-20	571 (51.2)	557 (49.9)
>20	176 (15.8)	190 (17.0)
Unknown	24 (2.1)	41 (3.5)
Grade		
1	275 (24.5)	286 (25.6)
2	621 (55.4)	615 (55.0)
3	226 (20.1)	217 (19.4)
Unknown	18 (1.6)	40 (3.5)
Margin		
Free	1007 (89.4)	993 (88.2)
Ductal carcinoma in situ only	54 (4.8)	60 (5.3)
Invasive	65 (5.8)	73 (6.5)
Unknown	14 (1.2)	32 (2.8)
Re-excision	76 (6.7)	97 (8.4)
Lymphovascular invasion		
Absent	931 (83.4)	946 (84.6)
Present	185 (16.6)	172 (15.4)
Unknown	24 (2.1)	40 (3.5)
Lymph nodes involved		
0	872 (77.4)	893 (79.2)
1-3	213 (18.9)	205 (18.2)
>3	41 (3.6)	29 (2.6)
Unknown	14 (1.2)	31 (2.7)
Estrogen receptor status		
Positive	1005 (89.8)	1030 (91.7)
Negative	114 (10.2)	93 (8.3)
Unknown	21 (1.8)	35 (3.0)
Progesterone receptor status		
Positive	895 (80.3)	921 (82.7)
Negative	220 (19.7)	193 (17.3)
Unknown	25 (2.2)	44 (3.8)
Human epidermal growth factor receptor 2 status		
Positive	156 (14.5)	164 (15.1)
Negative	920 (85.5)	925 (84.9)
Unknown	64 (5.6)	69 (6.0)
Method of presentation		
Screen detected	739 (67.0)	755 (68.0)
Symptomatic	364 (33.0)	355 (32.0)
Unknown	37 (3.3)	48 (4.2)
Endocrine therapy		
Received	897 (81.5)	894 (81.1)
Did not receive	204 (18.5)	209 (18.9)
Unknown	39 (3.4)	55 (4.8)
Chemotherapy		
Received	239 (21.7)	218 (19.7)
Did not receive	863 (78.3)	887 (80.3)
Unknown	38 (3.3)	53 (4.6)

EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy.
Data are numbers (percentages). For percentage calculation, the denominator for unknown percentages is the total number randomised (1140 and 1158) and the denominator for each category is the total number of known patients. No imbalance was found for any of these characteristics between the two randomised arms.

inferiority when 95% confidence intervals were used, and when per protocol analysis was performed with 90% and 95% confidence intervals. The number of deaths was 42 of 1140 for TARGIT-IORT versus 56 of 1158 for EBRT.

With long term follow-up (median 8.6 years, maximum 18.9 years, interquartile range 7.0-10.6), no statistically significant difference was found between immediate TARGIT-IORT and EBRT for the following outcomes: local recurrence-free survival (167 *v* 147 events, hazard ratio 1.13, 95% confidence interval 0.91 to 1.41, P=0.28), invasive local recurrence-free survival (154 *v* 146 events, 1.04, 0.83 to 1.31, P=0.70), mastectomy-free survival (170 *v* 175 events, 0.96, 0.78 to 1.19, P=0.74), distant disease-free survival (133 *v* 148 events, 0.88, 0.69 to 1.12, P=0.30), overall survival (110 *v* 131 events, 0.82, 0.63 to 1.05, P=0.13), and breast cancer mortality (65 *v* 57 events, 1.12, 0.78 to 1.60, P=0.54). Mortality from other causes was significantly lower (45 *v* 74 events, 0.59, 0.40 to 0.86, P=0.005). Analysis according to treatment received found that local recurrence-free survival was no different from EBRT for the following comparisons: TARGIT-IORT plus EBRT (n=241) versus EBRT (n=1065): hazard ratio 1.25, 95% confidence interval 0.87 to 1.80, P=0.24; and TARGIT-IORT alone (n=786) versus EBRT (n=1065): 1.22, 0.95 to 1.57, P=0.11. We used Schoenfeld residuals to confirm that the proportionality assumption was not violated (P=0.87 for local recurrence-free survival and P=0.81 for mortality). We also confirmed that there was no heterogeneity between countries (efig 2). The number of patients who died with uncontrolled local recurrence at the time of death was similar in the two arms of the trial (4/1140 for TARGIT-IORT and 5/1158 for EBRT, P=0.76). Table 3 gives the number of events and absolute event rates for local recurrence and mortality up to five years, and beyond five years. Figure 3 shows the Kaplan-Meier curves and figure 4 shows magnified Kaplan-Meier curves. Table 4 gives the causes of death.

Discussion

We based the TARGIT-IORT approach on the clinical observation that local recurrence after breast conserving surgery, with or without whole breast irradiation, occurs predominantly within the index quadrant.[23] This observation holds true despite the fact that more than 60% of patients for whom breast conservation is a treatment have foci of the disease outside the index quadrant.[23 38] Using this observation that most local recurrences occur in the index quadrant as the rationale for partial breast irradiation has also been reiterated by subsequent investigators.[15 17 19] The propensity of tumour recurrence in the index quadrant could be owing to a tumour promoting effect of the microenvironment of the surgical wound,[39-41] a risk that seems to be favourably influenced by TARGIT-IORT to the fresh tumour bed.[39 41 42]

Early results of using single dose TARGIT-IORT during lumpectomy were promising, and the treatment

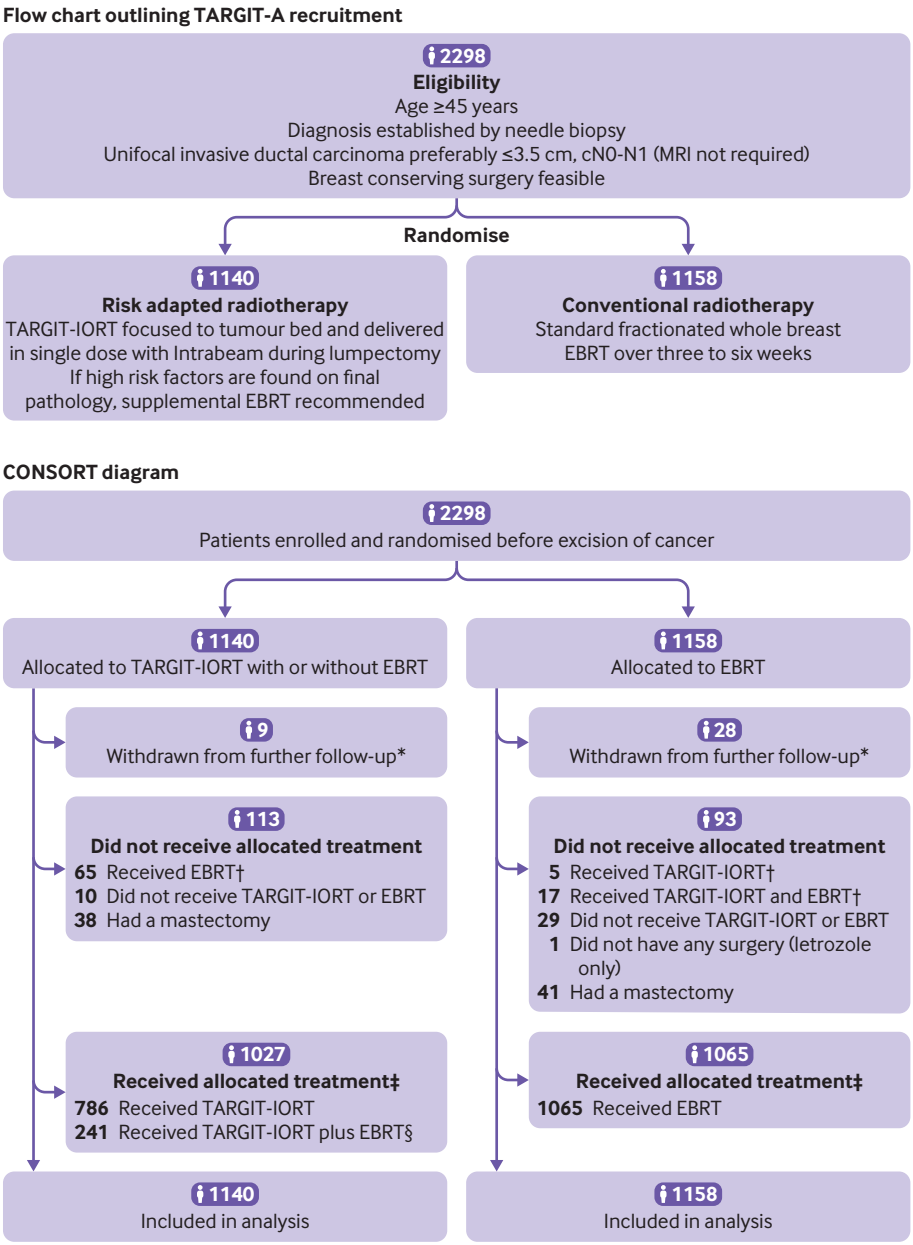


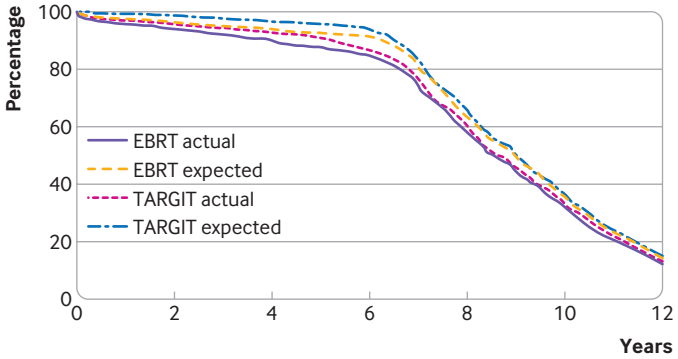
Fig 1 | Flowchart outlining TARGIT-A recruitment and CONSORT (consolidated standards of reporting trials) diagram. *Difference in number withdrawn was statistically significant (P=0.002). †Crossovers: 65/1140 (5.7%) allocated TARGIT-IORT received EBRT, and 22/1158 (1.9%) allocated EBRT received TARGIT-IORT. ‡1027/1140 (91%) allocated TARGIT-IORT and 1065/1158 (92%) allocated EBRT received allocated treatment. §As per protocol, 241/1140 (21.1%) patients allocated TARGIT-IORT received EBRT after TARGIT-IORT. EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

was found to have advantages for the patient, such as convenience, reduced travel and personal costs, improved quality of life, and fewer side effects.[43-47] However, the international community has been waiting for the long term follow-up outcomes before this approach is more widely adopted.

Statement of principal findings

The data presented here confirm that TARGIT-IORT is non-inferior to EBRT in terms of local control at protocol specified five year complete follow-up (local recurrence risk 2.11% for TARGIT-IORT *v* 0.95% for EBRT). Additionally, fewer deaths occurred with TARGIT-IORT. When we compared 1140 patients treated with TARGIT-IORT with 1158 patients treated with EBRT, 13 more local recurrences and 14 fewer deaths were reported. Figure 5 shows these raw data apportioned to 100 patients.

The Kaplan-Meier curves illustrate the long term results up to 12 years. These data confirm the comparable effectiveness of TARGIT-IORT versus EBRT in terms of cancer control, with no difference in local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, or distant disease-



No at risk							
EBRT actual							
	1158	1088	1041	978	672	371	143
EBRT expected							
	1158	1113	1087	1056	735	411	164
TARGIT actual							
	1140	1089	1059	988	688	378	152
TARGIT expected							
	1140	1125	1102	1068	752	415	169

Fig 2 | Completeness of follow-up. Curves for actual follow-up and how close they are to curves for expected follow-up. Expected is presumed equal to actual if patients have withdrawn or died. No significant difference in follow-up duration between TARGIT-IORT and EBRT (log rank P=0.22). EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

free survival for at least 12 years from randomisation (fig 3).

Breast cancer specific mortality was similar for both arms, however far fewer deaths were reported from causes other than breast cancer in the TARGIT-IORT arm. Even modern radiotherapy increases cardiac and lung cancer mortality and the results are consistent with our previously published data[48-52] and a meta-analysis of randomised trials.[53 54] Furthermore, the Kaplan-Meier curve for overall survival for TARGIT-IORT always remains above EBRT, with the curves continuing to separate further well beyond 10 years.

Strengths and weaknesses of the study

The pragmatic trial design is a major strength because the experimental arm simulated the potential future real world practice. Patients would get TARGIT-IORT during their initial cancer operation, and if found to have high risk factors, they would receive supplemental whole breast radiotherapy, making the results more clinically applicable. The international setting and broad inclusion criteria mean that the results are generalisable across relatively broad eligibility criteria and across various continents, even though centres of excellence participated in the trial.

Patients were randomised between 2000 and 2012. Substantial effort along with close collaboration from each centre enabled a high level of completeness of long term data. Consequently, another strength of the TARGIT-A trial is that it has more long term follow-up data than other published trials comparing individual techniques of partial breast irradiation with whole breast irradiation for invasive breast cancer (table 5, fig 6). Additionally, figure 2 shows that actual follow-up time is close to the follow-up time expected from the date patients were recruited, which means that substantial unknown data are unlikely. The long duration and high level of completeness of follow-up mean that the trial outcome is reliable and robust,

Table 2 | Analysis of non-inferiority by using binomial proportions and Kaplan-Meier estimates

Analysis	TARGIT-IORT	EBRT
Intention-to-treat analysis (n=1140; n=1158)		
Binomial proportions of five year local recurrence (%)	2.11	0.95
Difference (%; 90% CI; 95% CI)	1.16 (0.32 to 1.99; 0.15 to 2.16)	
Kaplan-Meier estimates of local recurrence at five year complete follow-up (%; SE)	2.23 (0.45)	1.02 (0.31)
Difference (%; 90% CI; 95% CI)	1.21 (0.47 to 1.95; 0.33 to 2.09)	
Per protocol analysis (n=1027; n=1065)		
Binomial proportions of five year local recurrence (%)	2.24	0.94
Difference (%; 90% CI; 95% CI)	1.30 (0.40 to 2.20; 0.23 to 2.38)	
Kaplan-Meier estimates of local recurrence at five year complete follow-up (%; SE)	2.36 (0.49)	0.99 (0.31)
Difference (%; 90% CI; 95% CI)	1.37 (0.56 to 2.18; 0.41 to 2.33)	

EBRT=external beam radiotherapy; SE=standard error; TARGIT-IORT=targeted intraoperative radiotherapy.
The protocol specified that the non-inferiority test should be performed with a prespecified margin of 2.5% at five years. The statistical analysis plan stated that analysis of non-inferiority should be performed by calculating difference in binomial proportion of local recurrence rates at five years, and that non-inferiority would be considered as established if upper 90% confidence interval of difference did not cross 0.025 (2.5%). Local recurrence risk and difference in this risk are depicted as absolute percentage (eg, difference in risk of 0.0116 is depicted as 1.16%). For completeness, test for non-inferiority was performed by using five year Kaplan-Meier estimates of local recurrence and per protocol analysis. Results show that TARGIT-IORT remains non-inferior to EBRT.

Table 3 | Number of events and absolute event rates (percentages) of local recurrence and death

	TARGIT-IORT (n=1140)		EBRT (n=1158)	
Local recurrence and death	**≤5 years**	**>5-19 years**	**≤5 years**	**>5-19 years**
Local recurrence was invasive with or without DCIS	15 (1.3)	17 (1.5)	9 (0.8)	10 (0.9)
Local recurrence was only DCIS	6 (0.5)	6 (0.5)	1 (0.1)	0
Local recurrence type was unknown* (assumed as invasive for analysis)	3 (0.3)	13 (1.1)	1 (0.1)	3 (0.3)
No of deaths	42 (3.7)	68 (5.9)	56 (4.8)	75 (6.5)

DCIS=ductal carcinoma in situ; EBRT=external beam radiotherapy; SE=standard error; TARGIT-IORT=targeted intraoperative radiotherapy.
There is complete follow-up at five years and maximum follow-up at 18.9 years. This table gives the number of events up to five years and beyond five years. The protocol specified that number of local recurrences (all types) at five years should be used for calculation of non-inferiority at 2.5% margin and all types of local recurrences were included.
*Local recurrence of unknown type was included as invasive local recurrence in long term invasive local recurrence-free survival analysis.

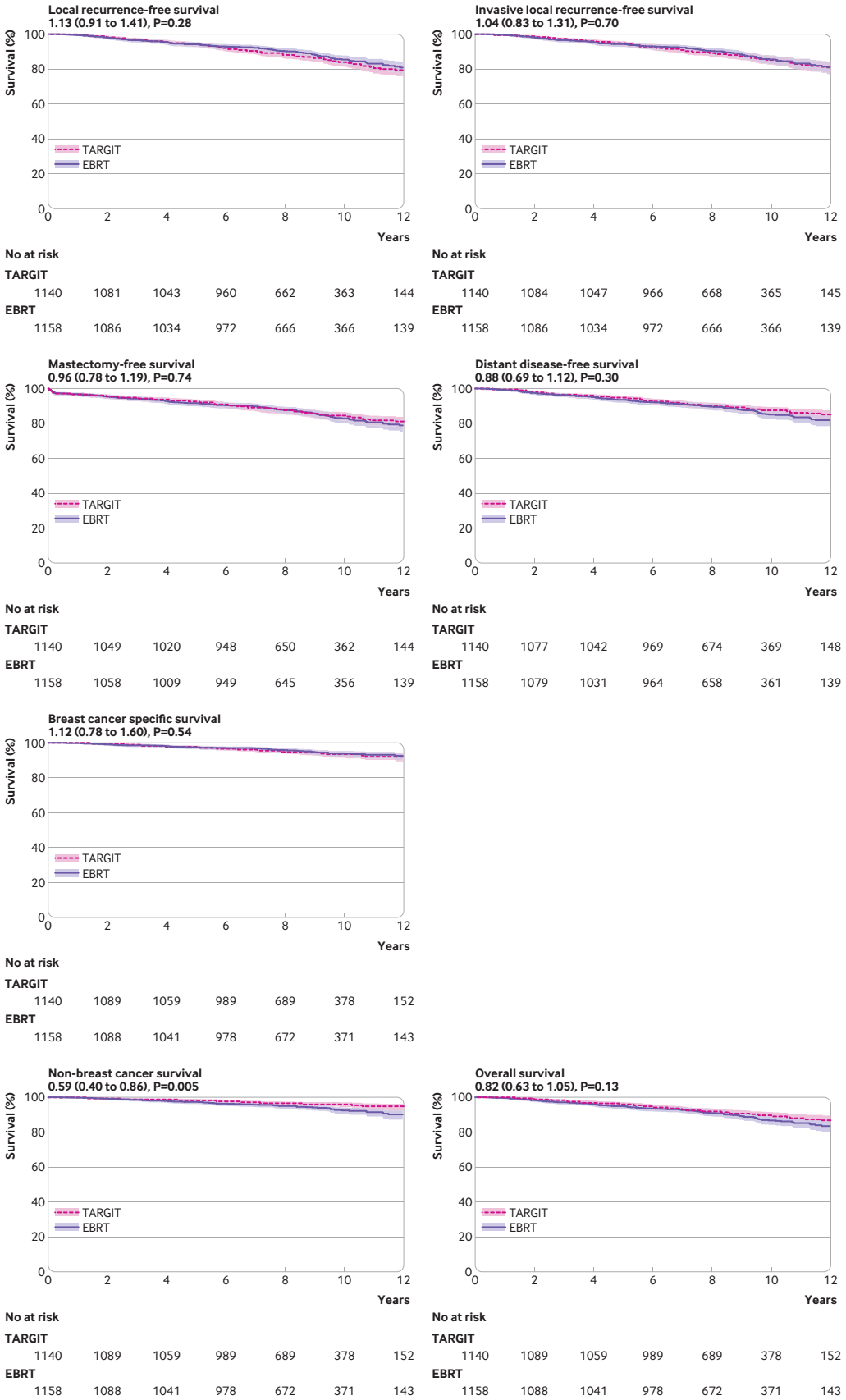


Fig 3 | Kaplan-Meier estimates and curves for the following outcomes for TARGIT-IORT versus EBRT in the TARGIT-A trial: local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival, breast cancer specific survival, non-breast cancer survival, and overall survival. Figures under titles are hazard ratios (95% confidence intervals) and log rank test P values. EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

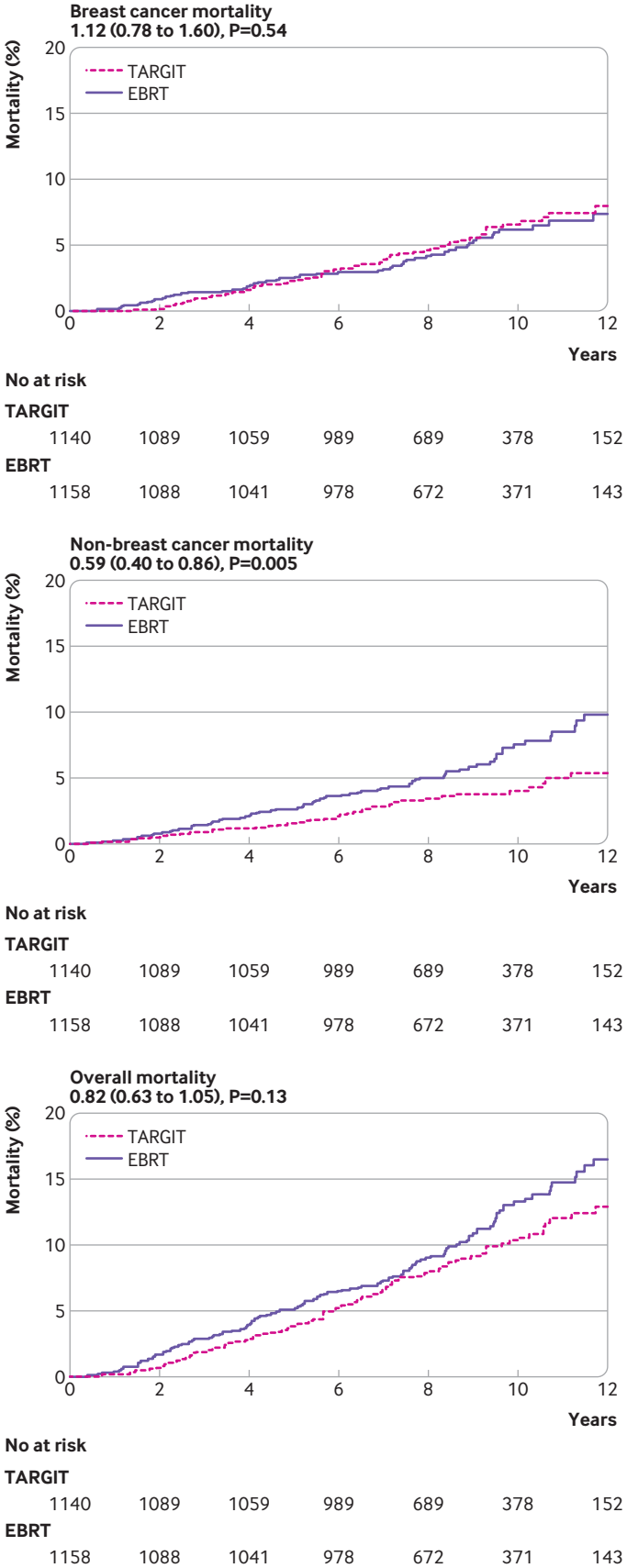


Fig 4 | Kaplan-Meier curves showing differences in breast cancer mortality, non-breast cancer mortality, and overall mortality in TARGIT-A trial for TARGIT-IORT *v* EBRT. Figures under titles are hazard ratios (95% confidence intervals) and log rank test P values. EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

and with 2298 participants, this trial is one of the largest in the field (table 5, fig 6). The trial was a result of an academic insight and was investigator initiated and funded by the HTA programme of the UK Department of Health and Social Care, rather than by industry sponsorship. The investigative team was multidisciplinary and consisted of patients and experts in surgical oncology, radiation oncology, clinical oncology, radiation physics, medical statistics, psycho-oncology, health economics, and clinical trial management.

The ratio of ductal carcinoma in situ to invasive recurrence was higher in the TARGIT-IORT arm (12:32) compared with the EBRT arm (1:19; table 3). One limitation of this study is that we do not know if this finding is owing to overdiagnosis and ascertainment bias because of potentially more frequent use of mammography in patients randomised to TARGIT-IORT, or if it is a real effect. However, this increase in diagnosis of ductal carcinoma in situ in the TARGIT-IORT arm did not lead to a reduction in mastectomy-free survival.

Another limitation of the study was that we did not collect all the background risk factors for deaths from non-breast cancer causes. However, the major risk factors for cardiovascular disease[55] and malignant disease[56] that were formally collected during the trial were age and body mass index, and these factors were distributed evenly between the two randomised arms. While smoking history and other common risk factors were not collected, it is unlikely that their incidence would be imbalanced in such a large randomised trial. Additionally, cause of death could not be determined for every patient. Therefore, patients were deemed to have died of causes other than breast cancer only if the local principal investigator had clearly specified that the cause of death was not breast cancer and breast cancer was not present, and only when there was no record of the patient having had any relapse of breast cancer.

The perspective in relation to other studies investigating partial breast irradiation

Partial breast irradiation was heralded as a new standard[12] at the time of the first publication of the TARGIT-A trial.[11] Several other supporting trials have since been published, including the ELIOT trial,[15] and studies examining brachytherapy,[18] and partial breast EBRT.[17 19] The TARGIT-A and ELIOT trials differ considerably in their inclusion criteria, and most importantly, have entirely different surgical and radiotherapeutic techniques, and so are not comparable. A Cochrane meta-analysis published in 2016[57] included all diverse methods of partial breast irradiation, but could not make definitive conclusions because of data limitations. Our own meta-analysis that only examined mortality (initially published in 2016 and updated in 2018)[53 54] found that partial breast irradiation has no impact on breast cancer mortality but reduces non-breast cancer mortality and overall mortality.

Table 4 | Number of deaths from breast cancer and other causes

Causes of death	TARGIT-IORT	EBRT	Total
Death from breast cancer			
Breast cancer*	35	32	—
Breast cancer present at time of death*	6	7	—
Unknown or uncertain*	24	18	—
Total breast cancer deaths	65	57	122
Death from other causes*			
Other cancers	15	21	—
Cardiovascular causes	8	20	—
Pulmonary causes	4	9	—
Other causes/exact cause not given	18	24	—
Total non-breast cancer deaths	45	74	119
Total	110	131	241

EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy.
*Case record form for death completed by centre stipulated classification of deaths as one of the following: breast cancer; breast cancer present at time of death including previously reported distant disease; not breast cancer and breast cancer not present; unknown or uncertain. As per convention, only deaths classified as not breast cancer and breast cancer not present were classified as non-breast cancer deaths.

In general, the other trials of partial breast irradiation with EBRT have included patients with cancer with considerably better prognosis. For example, when we compared the IMPORT-Low trial[19] patient population with that of the TARGIT-A trial, 3% versus 22% had node positivity, and 9% versus 20% had grade 3 tumours. Furthermore, this new analysis of long term data suggests that the greater proportion of patients with higher risk disease has not jeopardised the outcome in the TARGIT-A trial. We recommend that risk adapted TARGIT-IORT should be used in patients who would have been eligible for the TARGIT-A trial. Partial breast irradiation with EBRT still requires up to three weeks of daily radiation with about 16 hospital visits.[19] Although newer brachytherapy or some intensity modulated radiotherapy regimens could be completed in 10 fractions over five days, these trials had much smaller numbers of patients (1023[58] and 233[17] patients with five years of follow-up compared with 2048 in immediate TARGIT-A *v* EBRT; table 5, fig 6). Most of these techniques have adverse physical, social, financial,[59-61] and environmental impacts,[43] and do not substantially reduce the heavy workload of radiotherapy departments. Conversely, TARGIT-IORT delivered during the operation enables four fifths of patients to avoid visiting the radiotherapy centre at all.

Meaning of the study and implications for clinicians and policy makers

The long term results of this trial have shown that risk adapted single dose TARGIT-IORT given during lumpectomy can effectively replace the mandatory use of several weeks of daily postoperative whole breast radiotherapy in patients with breast cancer undergoing breast conservation. Crucially, 80% of patients required no additional radiotherapy after TARGIT-IORT. Additionally, TARGIT-IORT reduced non-breast cancer mortality. The advantage to the patient of avoiding postoperative radiotherapy could be considered obvious. Furthermore, formal studies have also been performed and have reported quality of life and patient reported outcomes such as cosmesis, breast related quality of life, and breast pain to be superior with TARGIT-IORT in the first five years.[44-47] Additionally, patients prefer this approach even when faced with a potentially higher local recurrence risk.[28-30] Moreover, 80% of patients, many of whom live a considerable distance from the radiotherapy centre,[43 57] avoid the need for daily hospital visits for three to six weeks, which would be required for established radiotherapy techniques. For such patients, TARGIT-IORT provides the opportunity for breast conservation rather than being obliged to choose mastectomy.[62] Even as recently as 2015, in a modern urban community (New Jersey, US), patients who lived more than 9.2 miles from the radiation facility (or more than 19 minutes away by car) compared with less than 9.2 miles away were 36-44% more likely to receive a mastectomy than breast conservation.[63]

Another important advantage is the major cost savings for the health services reported in previously published studies of health economics of the TARGIT-A trial.[59-61] All these factors are important when considering a change of policy and determining which treatments should be funded at the national level by organisations such as the NHS in the UK and Medicare or Medicaid in the US. While the payers will save scarce healthcare resources by using TARGIT-IORT, the providers will also want to use this approach when the payment model is changed to be value based rather than activity based.

Another important aspect is the well recognised phenomenon of overdiagnosis of breast cancer because of systematic population screening. This is a difficult problem because the potential of reduced breast cancer mortality needs to be balanced against the definite harms of overtreatment of women who might not have had a diagnosis of breast cancer if it were not for the screening programme. TARGIT-IORT could largely reduce the burden of treatment on such patients, and has been recommended by the Marmot committee.[64]

Implications for patients

When these results are expressed from the patient's perspective, without any definitions of non-inferiority, they would read as follows: "I understand from your explanation that if I choose to have intraoperative radiotherapy during my lumpectomy operation, the whole treatment will probably be completed in one go. I understand that the chance of avoiding a full course of traditional whole breast radiotherapy is about 80%, which requires several daily visits to complete. The results of this study have reassured me that choosing intraoperative radiotherapy doesn't reduce my long term chances of survival or keeping my breast, and remaining cancer free. You have also told me that there will be fewer long term side effects, a better quality of life and that the cosmetic result is likely to be better. I am also reassured to learn that this treatment does in fact reduce my chance of death from causes other than breast cancer."

Patients are entitled to choose which approach is right for them, based on effectiveness, convenience,

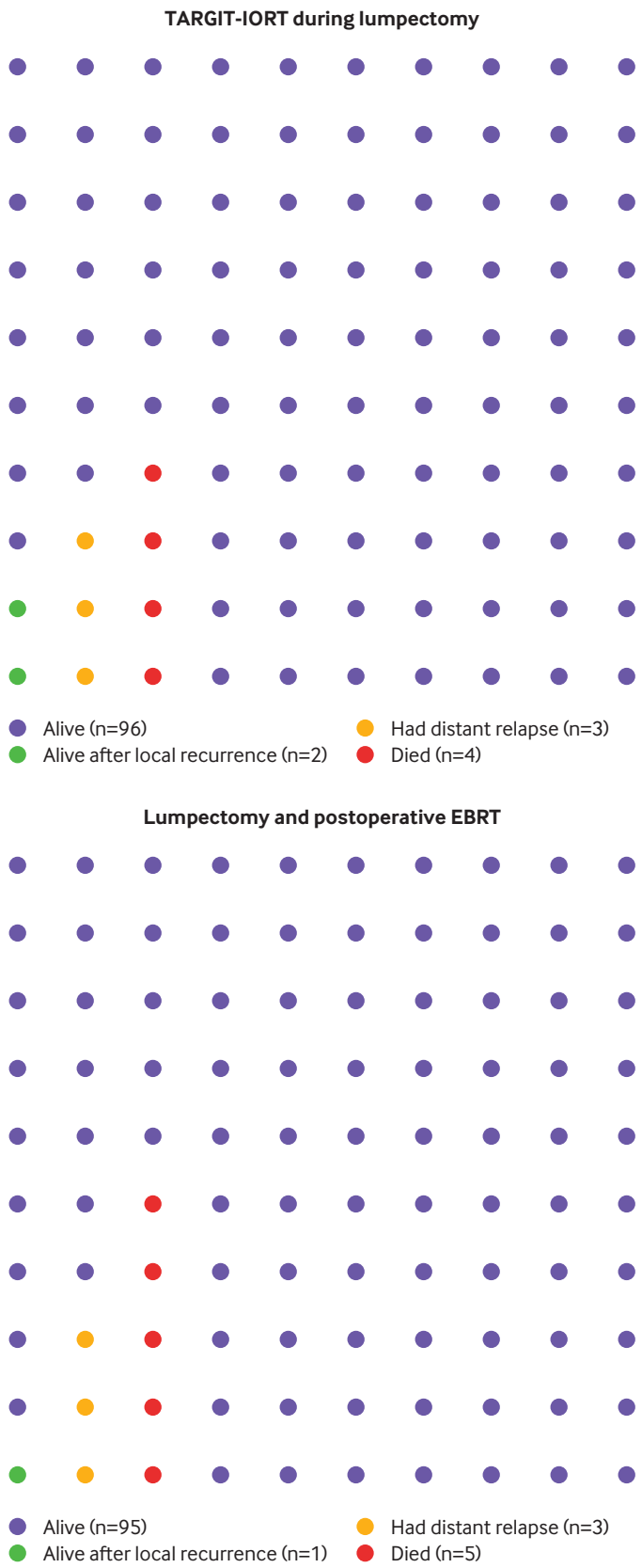


Fig 5 | Pictogram showing outcomes in TARGIT-A trial of TARGIT-IORT *v* EBRT for breast cancer. Complete follow-up is available for five years. Each dot represents a patient. Absolute numbers of patients who had local recurrences, distant disease, and died (TARGIT-IORT: 24/1140 local recurrences, 34/1140 distant disease, and 42/1140 deaths; EBRT: 11/1158 local recurrences, 31 distant disease, and 56/1158 deaths) are apportioned per 100 patients for each treatment type. At five years, one more local recurrence and one less death were reported per 100 patients. EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

Table 5 | Number of patients at risk at various time points in published randomised trials that use different techniques of partial breast irradiation for invasive breast cancer

Study	Total	No of patients at risk*							
		5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
TARGIT-A (immediate TARGIT-IORT)	2298	2048	1967	1736	1361	1035	749	587	295
TARGIT-A (delayed TARGIT-IORT)	1153	1097	1068	967	781	582	364	227	146
ELIOT (IORt)[15]	1305	—	676	—	305	—	29	—	—
Florence (IMRT; 5 days daily doses)[17]	465	233		—	—	—	—	—	—
GEC-ESTRO (2×5 days brachytherapy)[18]	1120	1023	784	—	—	—	—	—	—
IMPORT-Low (3 weeks EBRT)[19]	1343	1119	661	239	—	—	—	—	—
Budapest (7 days brachytherapy)[16]	258	—	231	—	113	—	134	—	57
NSABP-B39 3DCRT/IMRT (10# 8 days†)[20]	2193	—	1915	—	1335	—	930	—	—
NSABP-B39 Balloon (10# 8 days†)[20]	811	—	708	—	494	—	344	—	—
RAPID 3DCRT/IMRT (10# 8 days†)[21]	1754	1593	1548	1344	986	654	—	—	—
Leeds (EBRT 28 days)[14]	174	130	120	106	88	64	40	27	16
Christie (EBRT 10 days)[10]	708	400	250	127	40	—	—	—	—

10# 8 days=10 fractions in eight days; EBRT=external beam radiotherapy; IMRT=intensity modulated radiotherapy; IORT=intraoperative radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy.
Values are shown graphically in figure 6. Proportion of invasive cancer: 100% for TARGIT-A, ELIOT, IMPORT-Low, Budapest, Leeds, and Christie, 73% for NSABP-B39, 82% for RAPID, 89% for Florence, and 95% for GEC-ESTRO.
*Follow-up durations shown in Kaplan-Meier plots.

personal cost, quality of life, and side effects. To allow a truly informed patient to make the choice between a risk adapted TARGIT-IORT policy and conventional EBRT, we need to supply the data using absolute numbers in an easily accessible and comprehensible way.[65] A pictographic display (fig 5), based on the raw numerical data, is a transparent and accurate way of supporting the patient to make an informed choice.

We believe that the long term data presented in this paper, together with many benefits for the patient, provide compelling evidence in favour of TARGIT-IORT as an effective alternative for this large group of patients with early breast cancer who are suitable for breast conservation. Ultimately the treatment patients receive should be their choice and they should be provided with the data in a format which is transparent, straightforward, and easily understood.

Future and ongoing work

Additional work based on these results includes subgroup analysis, an analysis of local recurrence as a hazard for distant disease, and an analysis exploring the mechanisms behind the differences in non-breast cancer mortality seen in the trial. We will also present a web based tool to allow clinicians to use the risk adapted approach. The inputs for this tool include individual patient data, and the output gives the probability of a patient needing supplemental EBRT after TARGIT-IORT within the TARGIT-A trial. Further investigation into the nature of local recurrences will

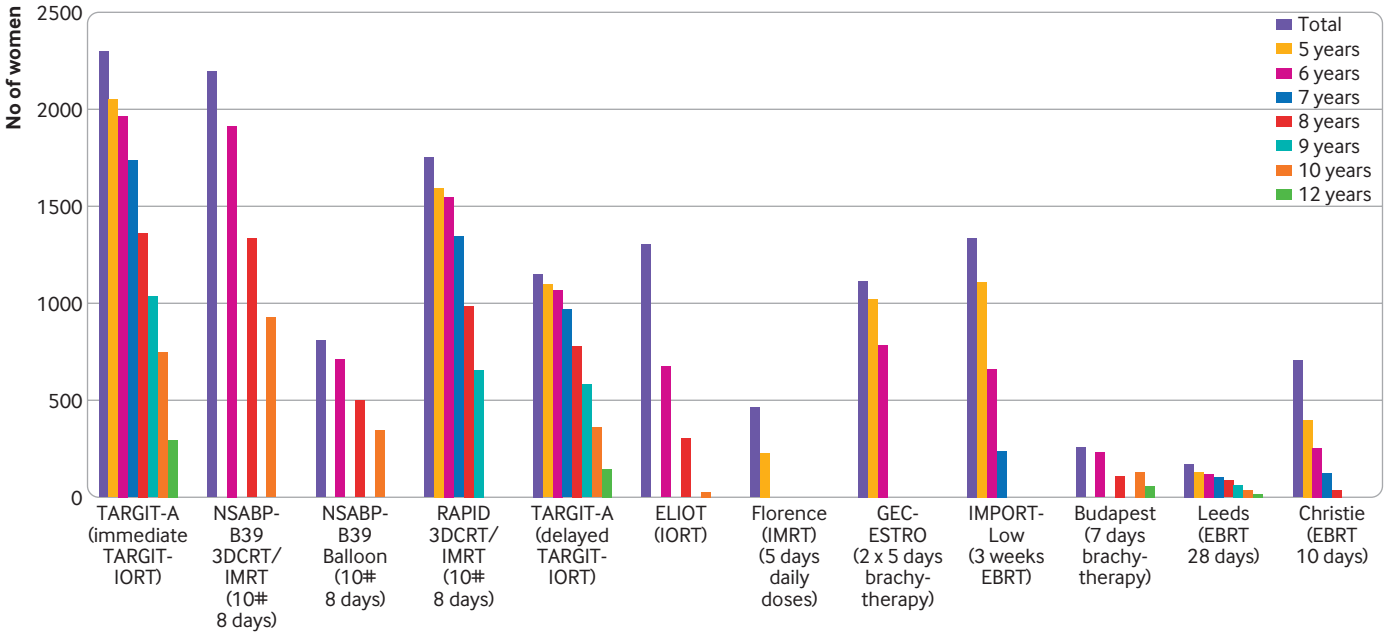


Fig 6 | Amount of data in randomised trials of different techniques of partial breast irradiation for invasive breast cancer. 10# 8 days=10 fractions in eight days; EBRT=external beam radiotherapy; IMRT=intensity modulated radiotherapy; IORT=intraoperative radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy

include molecular markers and the location within the breast.

In the extended follow-up of the TARGIT-A trial (TARGIT-Ex; funded by the HTA programme of the National Institute for Health Research, Department of Health and Social Care in the UK, HTA 14/49/13) we will use new methods such as direct patient contact and linkage with the Office for National Statistics. We are also currently inviting women who would fall outside the eligibility criteria of the TARGIT-A trial to participate in the TARGIT-B(oost) trial (funded by HTA 10/104/07), already opened in 36 centres internationally, which is comparing TARGIT-IORT as a tumour bed boost with EBRT boost in younger women or women who have higher risk disease to test for superiority in terms of local control and survival.

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Web appendix: e-Figures

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ARTICLE
Clinical Studies

New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer

Jayant S. Vaidya et al.

BACKGROUND: The TARGIT-A trial reported risk-adapted targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy for breast cancer to be as effective as whole-breast external beam radiotherapy (EBRT). Here, we present further detailed analyses.
METHODS: In total, 2298 women (≥45 years, invasive ductal carcinoma ≤3.5 cm, cN0–N1) were randomised. We investigated the impact of tumour size, grade, ER, PgR, HER2 and lymph node status on local recurrence-free survival, and of local recurrence on distant relapse and mortality. We analysed the predictive factors for recommending supplemental EBRT after TARGIT-IORT as part of the risk-adapted approach, using regression modelling. Non-breast cancer mortality was compared between TARGIT-IORT plus EBRT vs. EBRT.
RESULTS: Local recurrence-free survival was no different between TARGIT-IORT and EBRT, in every tumour subgroup. Unlike in the EBRT arm, local recurrence in the TARGIT-IORT arm was not a predictor of a higher risk of distant relapse or death. Our new predictive tool for recommending supplemental EBRT after TARGIT-IORT is at https://targit.org.uk/addrt. Non-breast cancer mortality was significantly lower in the TARGIT-IORT arm, even when patients received supplemental EBRT, HR 0.38 (95% CI 0.17–0.88) $P = 0.0091$.
CONCLUSION: TARGIT-IORT is as effective as EBRT in all subgroups. Local recurrence after TARGIT-IORT, unlike after EBRT, has a good prognosis. TARGIT-IORT might have a beneficial abscopal effect.
TRIAL REGISTRATION: ISRCTN34086741 (21/7/2004), NCT00983684 (24/9/2009).

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INTRODUCTION

Most patients with breast cancer are suitable for treatment with breast-conserving surgery and adjuvant radiotherapy, rather than total mastectomy. Based on the hypothesis that adjuvant radiotherapy for women with early breast cancer could be limited to the tumour bed and given immediately during breast-conserving surgery (lumpectomy), we developed the concept of TARGeted Intraoperative radioTherapy (TARGIT-IORT).[1–6]

TARGIT-IORT aims to achieve an accurately-positioned and rapid form of tumour-bed irradiation, focussed on the target tissues alone, sparing normal tissues and organs such as heart, lung, skin and chest wall structures from unnecessary and potentially damaging radiation treatment. We designed the TARGIT-A randomised trial to test this concept by comparing risk-adapted TARGIT-IORT with conventional whole-breast external beam radiotherapy over several weeks (EBRT).[3,7,8] The study received ethics approval from the Joint University College London and University College London Hospital committees of ethics of human research (99/0307). The accrual was from March 2000 to June 2012. The long-term results of the trial are described separately and show that TARGIT-IORT is as effective as whole-breast external beam radiotherapy (EBRT) for all breast cancer outcomes, with a significant reduction in mortality from causes other than breast cancer.[9]

The trial eligibility was not confined to low-risk patients: they needed to be 45 years or older, with invasive ductal carcinoma that was suitable for breast conservation and preferably less than 3.5 cm in size and unifocal on clinical examination and conventional imaging. Having a grade 3 cancer, involved nodes or higher risk receptor status, did not exclude the patient from participating. Therefore, a large number of patients in each category of higher risk were included, allowing meaningful subgroup analysis. In addition, the follow-up of the TARGIT-A trial was long, with a large number of patients having follow-up for at least 5 years ($n = 2048$) and 10 years ($n = 741$). So, the number of events for local recurrences and deaths after long-term follow-up were expected to be large enough to assess the prognostic significance of local recurrence.

As specified in the protocol, treatment was given using a risk-adapted approach, which meant that patients allocated to receive TARGIT-IORT were recommended to also receive supplemental EBRT, if they were postoperatively found to have specific unsuspected tumour characteristics, in which case the TARGIT-IORT served as a tumour-bed boost. The protocol specified three such factors—an unexpected diagnosis of invasive lobular carcinoma, presence of extensive intraductal component (>25%) and positive margins. Pragmatically, each centre was allowed to pre-specify such criteria and they recorded them in the 'treatment

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policy document' before they started recruitment. Therefore, for an individual case, the use of supplemental EBRT depended on a combination of several factors discussed in the post-operative multidisciplinary team meeting (tumour board). Having known the use of supplemental EBRT within the trial (about 20% of cases) and with the knowledge of the tumour factors, a regression model could be created.

This risk-adapted approach also offers an opportunity for another type of analysis investigating the mechanism of the difference we found in non-breast cancer mortality during the main analysis.[9] One needs to recognise that the use of supplemental EBRT after TARGIT-IORT was prompted by specific features of the primary breast cancer. Therefore, there should be no reason for the risk of non-breast cancer mortality to be different between patients who received TARGIT + EBRT vs. those who received EBRT. Since both groups received EBRT, and if the difference was because of EBRT toxicity alone, there should be no difference found in non-breast cancer mortality in this comparison.

This paper addresses four important aspects of the trial of TARGIT-IORT vs. EBRT, in which 2298 patients were randomised after their needle biopsy and before any surgical excision of cancer to receive either risk-adapted TARGIT-IORT delivered during the initial excision of cancer, or EBRT. These are: (a) outcome as per well-recognised tumour subgroups, (b) prognostic importance of local recurrence, (c) a predictive model for the use of supplemental EBRT after TARGIT-IORT and (d) an exploration seeking explanation for the differences in non-breast cancer mortality found between the two randomised arms.

METHODS

Data from the TARGIT-A trial ($n = 2298$) comparing risk-adapted TARGIT-IORT given during lumpectomy vs. EBRT were used for these analyses.[9]

The TARGIT-A trial protocol (https://njl-admin.nihr.ac.uk/document/download/2006598), including the details of eligibility, methodology and statistical methods, sample size calculations, the process of random allocation, has been previously described.[7,8,9] Eligible patients diagnosed with invasive malignancy by needle biopsy were randomly assigned before their surgery, in a 1:1 ratio, to receive either a risk-adapted approach using single-dose TARGIT-IORT or EBRT as per standard schedules over several weeks, with randomisation blocks stratified by centre. Therefore, the trial was a comparison of two policies—whole-breast radiotherapy without selection vs. individualised risk-adapted radiotherapy—in which a proportion of patients who received TARGIT-IORT were also given supplemental EBRT if they were found to have any pre-specified tumour factors.

The sites participating in the trial were all centres of excellence (almost all were University teaching hospitals) with their own routine quality assurance in place. Every patient was treated as per the treatment guidelines and quality assurance laid down by each of the participating radiotherapy centres. While the collection of specific data relating to quality assurance was not mandatory, the schedule of treatment, total dose, dose per fraction and number of fractions for the EBRT (and the boost when given) were always collected. In the UK, the most widely used dose-fractionation regimen recommended during the time of the study was 40.05 Gy/15 fractions over 3 weeks, i.e., daily dose 2.67 Gy per fraction. In the USA, the commonest recommendation was 50 Gy/25 fractions over 5 weeks. For boost doses, institutional standards were once again routinely employed—mostly 10 Gy/5 fractions.

The statistical analysis plan (SAP, submitted with the manuscript) was signed off by the chair of the independent steering committee and an independent senior statistician, before the data were unblinded and sent to the trial statistician for analysis. It specified the primary outcome as local recurrence-free survival. This outcome measured the chance of a patient being alive without local recurrence (any type of local recurrence in the ipsilateral breast) and therefore included local recurrence or death as events, i.e., patients who had died were not censored, which is consistent with the DATECAN[10] and STEEP[11] guidelines for clinical events to be included in the definitions of time-to-event endpoints in randomised clinical trials assessing treatments for breast cancer[12]. All analyses were by intention-to-treat as per the randomisation arm.

Firstly, we performed a subgroup analysis for the primary outcome of local recurrence-free survival for the tumour factors such as size, grade, lymph node involvement, ER status, PgR status and HER2 status.

Secondly, the concern that a difference in local recurrence might increase long-term mortality prompted us to investigate the assumption that local recurrence is a harbinger of distant disease and ultimately of death. We, therefore, performed Cox regression analysis using local recurrence as a time-dependent covariate, and estimated its interaction for the hazards of distant disease, breast cancer mortality in the two randomised arms. We also assessed this for overall mortality in order to take away any bias from the misclassification of the cause of death.

Thirdly, we prepared a regression model using established high-risk factors to predict the use of supplemental EBRT in patients randomised to TARGIT-IORT. Significant factors from the model were used to create an interactive tool that would simulate how patients were treated in the TARGIT-A trial and whether they received supplemental EBRT. Such a tool should help clinicians decide which patients would have received such supplemental EBRT and enable them to translate the risk-adapted approach used within the randomised trial into day-to-day clinical practice.

Finally, we explored the reason for the statistically significant difference in non-breast cancer mortality already seen between the two randomised arms. We compared non-breast cancer mortality between those who had received TARGIT-IORT followed by supplemental EBRT vs. EBRT. Any difference between these two groups would be indicative of a *beneficial* effect of TARGIT-IORT because both groups had received EBRT.

The first patient was randomised in March 2000, and the last in June 2012. The reference date for completeness of follow-up was May 2, 2018. The reference date for analysis was July 3, 2019, so that all events in the entire population up until July 2, 2019 were included for analysis of hazard ratios. Point estimates are given for 5 years, at which point the follow-up is complete, and hazard ratios are estimated for the full length of the follow-up period, i.e., the length of time from randomisation to the date of the latest follow-up, for each individual patient. STATA version 16.0 was used for data compilation, validation and analysis. The chief investigator/corresponding author and the trial statistician had access to all data sent by the trial centre for the analysis; all authors were responsible for the decision to submit the manuscript. Since the last analysis, the trial oversight has been provided by an independent steering committee, appointed by the Health Technology Assessment Programme of the National Institute of Health Research, Department of Health, UK.

RESULTS

In total, 1140 patients were randomised to TARGIT-IORT and 1158 to whole-breast radiotherapy. Patients were recruited from ten countries (24.7% from UK, 65.1% Europe, 9.4% USA/Canada and 0.8% others). Supplementary Table 1 shows the characteristics of trial patients.

As previously published,[9] there was no statistically significant difference in local recurrence-free survival (events 167 vs. 147, hazard ratio 1.13, 95% confidence interval 0.91–1.41, $P = 0.28$), distant disease-free survival (133 vs. 148 events, HR 0.88, 0.69–1.12, $P = 0.30$), mastectomy-free survival (170 vs. 175 events, 0.96, 0.78–1.19, $P = 0.74$) or breast cancer mortality (65 vs. 57

Table 1. Subgroup analysis: number of events for local recurrence and deaths and point estimates for local recurrence-free survival are given for 5 years when the follow-up is complete, as per protocol.

			TARGIT-IORT			EBRT			TARGIT-IORT	EBRT	Long-term local control TARGIT-IORT vs EBRT	
Subgroup	Category	No. of cases	No. of cases	LR	Deaths	No. of cases	LR	Deaths	Alive without local recurrence	Alive without local recurrence	Hazard ratio	95% confidence interval of hazard ratio
Tumour size	<=10 mm	739	369	10	8	370	2	10	94.9%	96.7%	1.35	0.86–2.10
	11–20 mm	1128	571	11	16	557	5	25	95.5%	94.6%	0.99	0.71–1.37
	>20 mm	366	176	2	18	190	3	20	88.5%	88.2%	1.22	0.80–1.80
Tumour grade	Grade 1 or 2	1797	914	17	25	914	7	39	94.9%	96.7%	1.08	0.83–1.40
	Grade 3	443	226	7	17	217	4	17	90.1%	91.1%	1.26	0.82–1.94
ER status	ER+	2035	1005	15	35	1030	9	46	94.9%	94.7%	1.12	0.87–1.42
	ER−	207	114	8	6	105	2	10	89.2%	87.7%	0.95	0.55–1.65
PgR status	PgR+	1816	895	13	29	921	9	40	95.1%	94.7%	1.09	0.84–1.41
	PgR−	413	220	10	12	193	2	16	90.7%	90.9%	1.08	0.69–1.70
HER2 status	HER2−	1845	920	19	35	925	8	39	94.2%	95.0%	1.12	0.87–1.44
	HER2+	320	156	3	6	164	3	16	94.0%	88.7%	1.36	0.81–2.27
Lymph node status	LN−	1765	872	20	27	893	9	42	94.4%	94.4%	1.14	0.88–1.46
	LN+	488	254	4	15	234	2	14	93.0%	93.2%	1.07	0.68–1.70
Overall	**All patients**	**2298**	**1140**	**24**	**42**	**1158**	**11**	**56**	**94.2%**	**94.2%**	**1.13**	**0.91–1.41**

LR local recurrence.
The hazard ratio for local recurrence-free survival is given for the whole follow-up period and shows that in every subgroup, there was no significant difference in local control (i.e., the probability remaining local recurrence-free) between TARGIT-IORT and EBRT, and 95% CI of the hazard ratio for local recurrence-free survival crossed 1.0, as represented in Fig. 1.
Patients in whom the specific pathological detail was not known were, —for local recurrence: one in each arm for tumour size, in TARGIT-IORT arm 1 ER/PgR status, 2 HER status and, —for death: one in EBRT arm for tumour size, one in TARGIT-IORT arm for ER/PgR/HER2 status.

events, HR 1.12, 0.78–1.60, $P = 0.54$). There was a significant reduction in non-breast cancer mortality with TARGIT-IORT (45 vs. 74 events, HR 0.59, 0.40–0.86, $P = 0.005$).

In addition, no difference was found in local recurrence-free survival when the following comparisons were made: EBRT patients vs. TARGIT-IORT patients who received additional EBRT (HR 1.19, 0.83–1.71, $P = 0.3422$) and EBRT patients vs. TARGIT-IORT patients who did not receive additional EBRT (HR 1.12, 0.88–1.41, $P = 0.3661$) (Supplementary Fig. 1).

The new analysis presented in this paper examines four specific aspects of the data accrued from this large, randomised trial.

Firstly, the difference in the primary outcome of survival without local recurrence between TARGIT-IORT and EBRT was not significant for any of the tumour subgroups viz pathological tumour size, grade, ER status, PgR status, HER2 status and lymph node status (Table 1 and Fig. 1). Prompted by comments from reviewers, we created subgroups using combinations of factors and performed the following analyses. The most substantial of these include 1468 (64%) 'lower-risk' patients in whom the tumours were not >2 cm, or grade 3 or ER-negative, irrespective of age or lymph node status (59% were <65 years old and 17% were node-positive). The remaining 830 patients ('not-lower-risk') would have at least one of these risk factors.

Analysis within each of these two subgroups found no difference in local control between the randomised arms TARGIT-IORT vs. EBRT by intention-to-treat, ('lower-risk' $n = 1468$, HR 1.05 (95% CI 0.77–1.44, $P = 0.7450$ and 'not-lower-risk' $n = 830$, HR 1.24 95% CI 0.91– 1.70, $P = 0.1715$), or after excluding those who received supplemental EBRT after TARGIT-IORT ($n = 1331$, 'lower-risk' HR 1.02 (0.73–1.43), $P = 0.8859$ and 'not-lower-risk' $n = 726$, HR 1.28 (0.92–1.79), $P = 0.1404$). Similarly, no difference was found for the higher-risk subgroup of with triple-negative breast cancers by intention-to-treat ($n = 143$, HR 0.87 (0.45–1.67), $P = 0.6840$) or after excluding those who received supplemental EBRT ($n = 131$, HR 0.84 (0.43–1.66), $P = 0.6300$)), or those with HER2-negative tumours which were either ER- or PR-negative by intention-to-treat ($n = 317$, HR 1.01 (0.60–1.69), $P = 0.9730$), or after excluding those who received supplemental EBRT ($n = 281$, HR 1.03 (0.60–1.78), $P = 0.9039$). However, for those 1468 'lower-risk' patients (not > 2 cm, or grade 3 or ER-negative), overall survival with TARGIT-IORT was 4.2% better at 12 years (TARGIT-IORT 91.7% vs. EBRT 87.3%, HR 0.65 (95% CI 0.44–0.96), $P = 0.0308$). Figure 1 also shows the overall survival outcomes in each main subgroup. The overall survival was significantly better by 4.4% (89.3 vs. 84.9%) at 12 years with TARGIT-IORT compared with EBRT in those with grade 1 or 2 cancers, (Fig. 2, $n = 1797$, HR 0.72, 95% CI 0.53–0.98, $P = 0.0361$). We recognise of course that these are subgroup analyses, with all the usual caveats.

Secondly, the analysis of an interaction between local recurrence and mortality found that the prognostic significance of local recurrence in the EBRT arm was different to that of local recurrence in the TARGIT-IORT arm. Local recurrence in the EBRT arm but not in the TARGIT-IORT arm predicted a higher risk of distant disease (P value for interaction $P = 0.008$, Fig. 3a), breast cancer mortality (P value for interaction $P = 0.003$, Fig. 3b), and overall mortality (P value for interaction $P = 0.020$, Fig. 3c). This interaction might be better appreciated when seen in terms of the raw numbers of long-term deaths amongst those who had local recurrence within 5 years: 3/24 (13%) died in the TARGIT-IORT vs. 7/11 (63%) died in the EBRT arm. The mean survival duration of patients who had early local recurrence in the TARGIT arm was 8.7 years (SD 3.1) vs. EBRT 6.1 years (SD 3.3).

Thirdly, the proportion of patients who ultimately received supplemental EBRT in addition to TARGIT-IORT for each prognostic subgroup is given in Table 2, which also gives the local recurrence and mortality events, cumulative incidence of local recurrence, and local control rates as per treatment received. The regression model (sensitivity 71%, specificity 67%, correct classification in 68% of cases) for predicting the use of supplemental EBRT in an individual patient is available on the web and can be best understood with direct interaction. We urge the readers to click on the link https://targit.org.uk/addrt and input some numbers for a

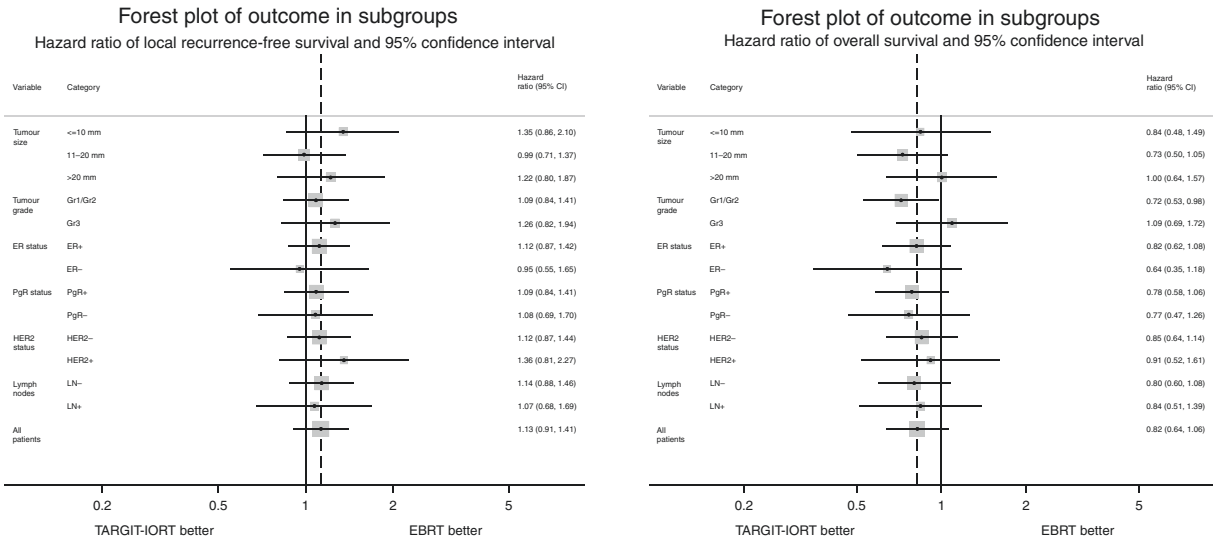

Fig. 1 Forest plot showing local recurrence-free survival and overall survival as per tumour subgroups. Each box represents the amount of the data and horizontal lines show the 95% confidence interval. The dashed vertical line is through the hazard ratio for all patients.

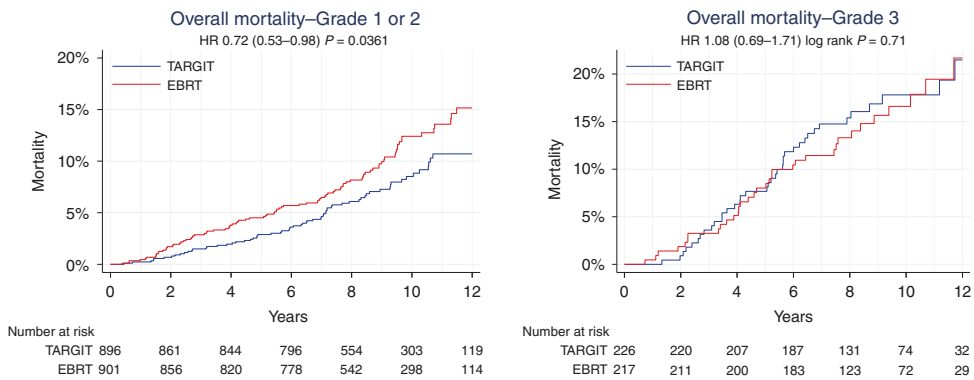

Fig. 2 Subgroup analysis: overall survival in those with grade 1 or 2, $n = 1797$, and those with grade 3 cancers, $n = 443$. In total, 80% of the patients had grade 1 or 2 cancers. Of those with grade 1 or 2 cancers vs. grade 3 cancers, 20 vs. 30% were node-positive, and 4 vs. 29% were ER-negative, respectively. There was no difference in the rate of additional EBRT given after TARGIT-IORT between these groups.

hypothetical patient—this way best illustrates the concept—how a combination of factors influence the decision. Two example cases are illustrated in Supplementary Fig. 2. In order to achieve results similar to those achieved within the trial, clinicians would want to emulate the way the risk-adapted approach was used within the trial. This interactive tool gives the probability of any individual patient's receipt of supplemental EBRT if they had participated in the TARGIT-A trial. Using this information could facilitate an informed decision about recommending supplemental EBRT for an individual patient.

Finally, an exploratory analysis sought an explanation for the difference in non-breast cancer mortality that was found in the main analysis between the two randomised arms (HR 0.59 (0.40–0.86), $P = 0.005$). The numbers of non-breast cancer deaths in those who were randomised to TARGIT were 45/1140 (6/241 amongst those who received additional EBRT and 39/899 amongst the others), and 74/1158 amongst those randomised to EBRT. Most of this difference (79% of the difference in the number of deaths) was contributed to by differences in deaths from pulmonary, cardiovascular causes and other cancers. Two of the major risks for these conditions, age and body mass index, were equally distributed in the two randomised arms (Supplementary Table 2, top). Of the 1140 patients randomised to TARGIT-IORT, 241 patients were deemed to have a higher risk of relapse of breast cancer by the treating multidisciplinary team and therefore were selected to receive supplemental EBRT. While this group would have a higher risk of death from breast cancer, they should not have an increased risk of death from non-breast cancer causes—this was corroborated by the well-balanced distribution of two recorded risk factors (age and BMI, Supplementary Table 2, bottom). We found that patients who had TARGIT-IORT plus EBRT ($n = 241$) had a statistically significant reduction in non-breast cancer mortality (HR 0.38 (95% CI 0.17–0.88), $P = 0.009$) when compared with those randomised to EBRT ($n = 1158$), in addition to the significant difference seen in the remaining 899 patients (HR 0.65 (95% CI 0.44–0.96), $P = 0.0265$) (Fig. 4).

DISCUSSION

The long-term results of the TARGIT-A trial[9] have shown that there was no statistically significant difference between EBRT and the approach of risk-adapted TARGIT-IORT during lumpectomy, for local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival or breast cancer mortality. The mortality from other causes was significantly lower in the TARGIT-IORT arm.

In this paper, we found that the results remain the same for each of the tumour subgroups such that no particular subgroup fares better or worse in terms of the difference in local recurrence-free survival for TARGIT-IORT vs. EBRT. This finding could make it

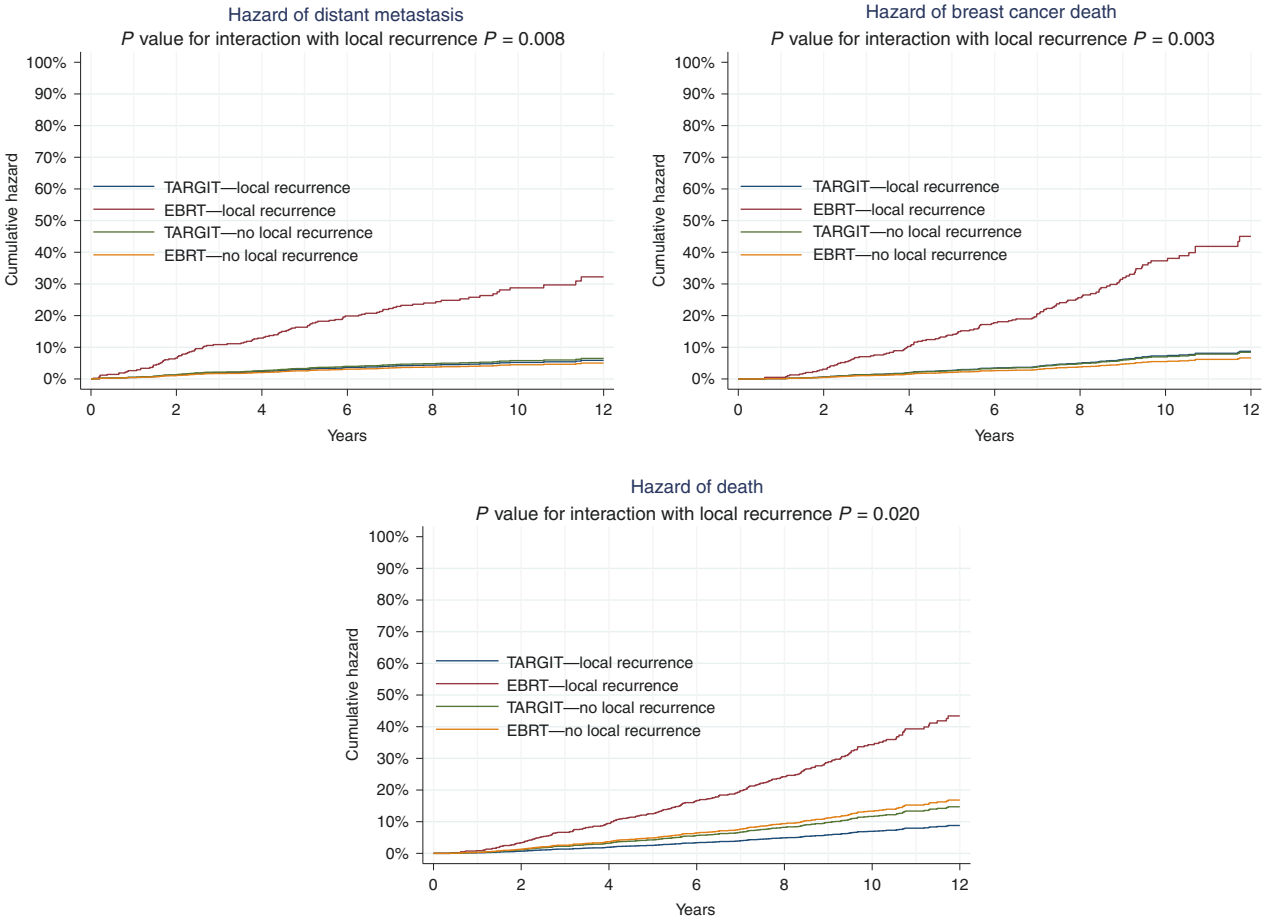

Fig. 3 TARGIT-IORT vs EBRT: Contrasting long-term outcome after local recurrence. The hazard of distant metastasis (top left), breast cancer death (top right) and any death (bottom) —interaction with local recurrence as a time-dependent covariate. The hazards of patients who have local recurrence after EBRT as shown by the rising red line in each graph are significantly higher than those who have local recurrence after TARGIT-IORT, which in turn are the same as those without any local recurrence. Please note that these figures denote cumulative hazards of each interaction groups, whereas the curves in Fig. 4 are Kaplan–Meier estimates of cumulative incidences.

easier for clinicians to select patients. In order to be eligible for risk-adapted TARGIT-IORT, patients simply need to fulfil the eligibility criteria for the TARGIT-A trial (≥45 years of age with invasive ductal carcinoma ≤3.5 cm in size and cN0–N1 and suitable for breast conservation). Once the final histopathology is available postoperatively, the interactive tool based on our regression model could facilitate decision-making about the need for supplemental EBRT: a clinician can input values for characteristics for an individual patient and their tumour in this web-based tool (https://targit.org.uk/addrt), and its output will show the probability that that patient would have received supplemental EBRT after TARGIT-IORT within the TARGIT-A trial. This can help the clinician to make an individualised decision for their patient so that the outcome would be similar to that achieved within the TARGIT-A trial.

An important point that traditionally causes concern is the long-term prognosis of a patient with a local recurrence. A local recurrence has been generally regarded as a harbinger of early death. This idea is supported by the results of the meta-analysis of breast-conserving surgery and whole-breast external beam radiotherapy by the Early Breast Cancer Trialists Collaborative Group,[13] which determined that for every four additional women who had a local recurrence one died from their disease. Consistent with this long-held belief, the analysis in the TARGIT-A trial presented in this paper also found that a local recurrence after EBRT was indeed a powerful predictor of distant metastases, breast cancer mortality and overall mortality. In contrast, a local recurrence after TARGIT-IORT did not have any impact on distant metastases, breast cancer mortality and overall mortality (Fig. 3). We recognise that the number of events is small, but the statistical significance of this finding is very high ($P = 0.003$). This remarkable finding suggests that local recurrences after TARGIT-IORT are not indicative of the expected poor prognosis that is seen with local recurrences after whole-breast external beam radiotherapy. Possible explanations for this important observation need further research, but some suggestions about its mechanisms are the following:

A simple explanation might be that majority of local recurrences after TARGIT-IORT are new primaries that normally do not have a poor prognosis while EBRT may be suppressing these good-prognosis cancers. The corroboration of this idea is seen in the much higher DCIS: Invasive ratio (12:32 vs. 1:19) in the TARGIT-IORT arm compared with EBRT, raising the possibility of over-diagnosis and ascertainment bias because of potentially more frequent use of mammography in those randomised to TARGIT-IORT. This may have led to a higher chance of detection of DCIS or invasive cancers that may not have progressed. However, this detection of such good-prognosis cancers in the TARGIT-IORT arm did not cause any reduction in mastectomy-free survival. We might also speculate that after EBRT, a local recurrence has only very aggressive cells that are a marker of incurable distant disease or consist of metastatic cells that grow in the tumour supportive wound environment. TARGIT-IORT appears to favourably influence wound fluid composition, and this may be a mechanism by which it might have unique radiobiology that somehow mainly allows

Table 2. Total number of patients, total numbers in each arm and proportion of patients receiving supplemental EBRT among those randomised to receive TARGIT-IORT.

	Total no.	Allocated TARGIT-IORT				Allocated EBRT
		Characteristics of 1140 patients in the TARGIT arm	Characteristics of 241 patients allocated TARGIT who received supplemental EBRT	Characteristics of 899 patients allocated TARGIT who did not receive supplemental EBRT	Proportion (%) in TARGIT arm receiving supplemental EBRT	Characteristics of 1158 patients in the EBRT arm
Overall	**2298**	**1140**	**241**	**899**		**1158**
Age (years)						
≤50	216	117	24	93	20.5%	99
51–60	737	362	81	281	22.4%	375
61–70	1005	481	100	381	20.8%	524
>70	340	180	36	144	20.0%	160
Tumour size						
≤10 mm	739	369	58	311	15.7%	370
11–20 mm	1128	571	121	450	21.2%	557
>20 mm	366	176	59	117	33.5%	190
Grade						
Grade 1	561	275	42	233	15.3%	286
Grade 2	1236	621	148	473	23.8%	615
Grade 3	443	226	50	176	22.1%	217
Margins						
Negative	2000	1007	191	816	19.0%	993
Positive	252	119	49	70	41.2%	133
Invasive lobular carcinoma at final histology						
Negative	2112	1053	208	845	19.8%	1059
Positive	120	58	30	28	51.7%	62
Lymphovascular invasion						
Absent	1877	931	172	759	18.5%	946
Present	357	185	63	122	34.1%	172
Nodal status						
Negative	1765	872	147	725	16.9%	893
1–3 nodes	418	213	76	137	35.7%	205
4 or more	70	41	17	24	41.5%	29
ER status						
Positive	2035	1005	218	787	21.7%	1030
Negative	207	114	20	94	17.5%	93
PgR status						
Positive	1816	895	191	704	21.3%	921
Negative	413	220	47	173	21.4%	193
HER2 status						
Positive	320	156	41	115	26.3%	164
Negative	1845	920	188	732	20.4%	925
Method of presentation						
Screen-detected	1494	739	148	591	20.0%	755
Symptomatic	719	364	86	278	23.6%	355
Total number		**1140**	**241**	**899**	**–**	**1158**
Local recurrences (invasive/DCIS/unknown) cumulative incidence		15/6/3 1.3%/0.5%/0.3%	2/1/0 0.8%/0.4%/0%	13/5/3 1.4%/0.6%/0.3%	–	9/1/1 0.8%/0.1%/0.1%
Cumulative incidence of any type of local recurrence		24 2.11%	3 1.24%	21 2.35%		11 0.95%
Deaths (cumulative incidence)		42 (3.7%)	14 (5.8%)	28 (3.1%)	–	56 (4.8%)
Alive without local recurrence		94.15% (92.6–95.4)	93.46% (89.4–96.0)	94.33% (92.6–95.7)	–	94.19% (92.6–94.4)

LRFS local recurrence-free survival.
Of the 1140 randomised to TARGIT-IORT, 241 received supplemental EBRT after TARGIT-IORT during lumpectomy. The local recurrence and mortality and local control values are at complete follow-up of 5 years.

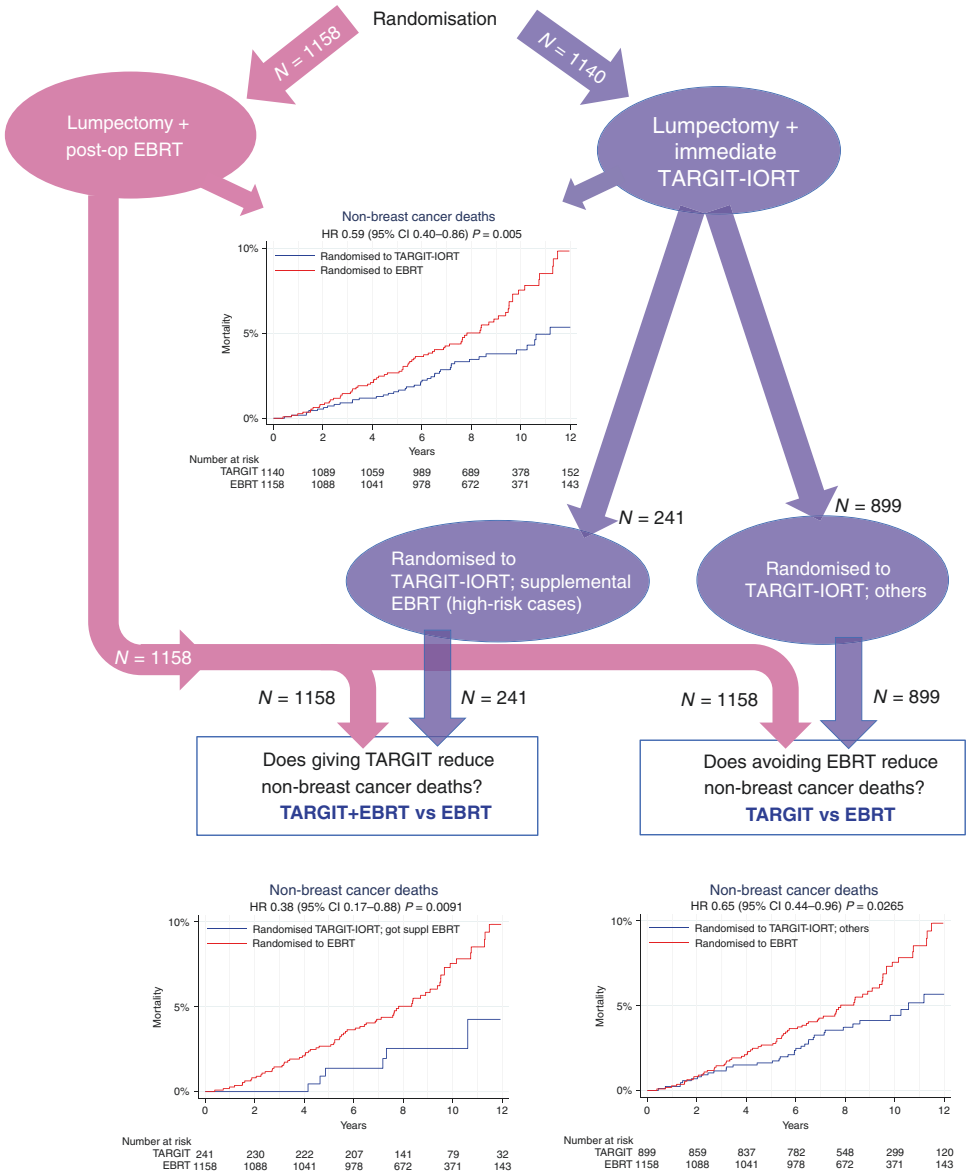

Fig. 4 Randomised comparison of non-breast cancer mortality showing signifcantly fewer deaths in patients randomised to TARGIT-IORT (top graph), and non-randomised comparisons to assess the contribution to the difference seen in the randomised comparison: because of the delivery of TARGIT-IORT (bottom left), and the avoidance of EBRT (bottom right). Please note that 40% of patients in the 1158 EBRT arm also received a tumour-bed boost which was not given to those who had received TARGIT-IORT.

the expression of local recurrences that are curable by earlier surgery and change of systemic (usually endocrine) therapy.

By corollary, one might argue that avoiding radiotherapy altogether might have even enhanced such effect—but randomised evidence tells us that it does not—in trials of EBRT vs. no EBRT, for every four local recurrences that occur in the absence of EBRT there is one additional death[13]. So TARGIT-IORT may be stopping the growth of local recurrences that have the potential to spread and cause death, whilst allowing those local recurrences that are a marker of curable distant disease to grow and raise an early flag just like the canary in the coal mine. Further research comparing the molecular characteristics of local recurrences between the two arms of the trial could give more insight into the biological nature of these recurrences.

The other striking outcome in the trial was that there was a significant reduction in non-breast cancer mortality in patients randomised to TARGIT-IORT. Now, within those randomised to TARGIT-IORT, there were some patients ($n = 241$) who also had received supplemental EBRT because they had a higher risk of breast cancer relapse. However, their risk of non-breast cancer death should not be any different from those who were randomised to EBRT. Surprisingly, there was a statistically significant difference in non-breast cancer mortality (HR 2.62 (1.14–6.04), $P = 0.0093$) between them, and those allocated to EBRT. As both these groups received EBRT, the reduction in non-breast cancer mortality cannot be attributed to the absence of EBRT, but rather must be attributed to the presence of TARGIT-IORT. There is however one caveat—40% of those in the EBRT arm also received a tumour-bed boost (reminding us that TARGIT-A was a medium-risk cohort), so this higher dose may have contributed to the effect. In any case, the baseline major risk factors for these deaths (age and BMI) were well balanced between these non-randomised groups (Supplementary Table 1). This long-term outcome is consistent with previous reports and prompts the hypothesis that a single large dose of radiation such as TARGIT-IORT given during the trauma of surgery might possibly

have an abscopal effect, i.e., an effect away from the site of irradiation, by influencing the tumour microenvironment or by immunological mechanisms.[14–27,28] Strange as it may seem, such an abscopal effect appears to give long-term protection against deaths from cardiovascular causes and other cancers. The early separation of lines in the K–M curves that starts soon after randomisation also suggests such a 'drug-like' effect, while a separation starting a few years later in the comparison of TARGIT-IORT alone vs. EBRT suggests an effect of avoiding EBRT (Fig. 4). We believe that for the effect of immediate TARGIT-IORT on wound fluid, and its potential abscopal effects, the temporal proximity of TARGIT-IORT to surgery is crucially important. This TARGIT-IORT delivery to the fresh tumour bed immediately after lumpectomy, without any additional trauma, did not happen in the delayed IORT trial.[29] The IORT in the experimental arm in that separate study[29] was delivered at a median of 37 days post-operatively, by re-opening the wound. This difference in timing of radiotherapy may well offer an explanation for the difference in non-breast cancer mortality outcomes. Of course, we need to recognise that these data only generate the hypothesis, and do not prove an abscopal effect. The TARGIT-B superiority trial, in which patients are being recruited from 38 centres in 15 countries, is comparing TARGIT-IORT boost during lumpectomy, in addition to post-operative whole-breast radiotherapy, vs. conventional EBRT (i.e., TARGIT-IORT + EBRT vs. EBRT). It will provide randomised data to assess such putative abscopal effects.

In conclusion, these long-term data from the TARGIT-A trial show that for every subgroup of patients with breast cancer who meet our trial selection criteria, risk-adapted single-dose TARGIT-IORT during lumpectomy is an effective and safe alternative to several weeks' course of post-operative EBRT. The observation that local recurrence after TARGIT-IORT, unlike after EBRT, does not have a poor prognosis is reassuring. The potential beneficial effect of TARGIT-IORT during surgery on non-breast cancer mortality seen in this trial has increased the importance of forthcoming randomised data on non-breast cancer mortality from the TARGIT-B trial.

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Study concept and design: J.S.V., M. Baum, J.S.T., M. Bulsara, F.W. and D.J. Acquisition and interpretation of the data: all authors. Final approval of the manuscript: all authors. Drafting of the manuscript: J.S.V., M. Bulsara, J.S.T. and M. Baum. Critical revision of the manuscript for important intellectual content: J.S.V., M. Bulsara, M. Baum, J.S.T., F.W., S.M., S.P., M.A., M.D., C.S., H.F., W.E., C.B.-G., N.W., I.P., N.R., M. Bernstein, D.B., E.S., S.L., M.S., T.C., S.L., D.H., L.V., F.B., M.P., M.L.B.-O., G.G., W.P., K.J.D., M.N., J.B., D.M., R.H., P.K., G.P., M.F. and D.J. Statistical analysis: M. Bulsara, J.S.V. and N. W. Obtained funding: J.S.V., F.W., N.W. and M. Baum. Administrative, technical or material support: J.S.V., T.C., F.W., S.P., M.D., C.B.-G., N.W., I.P., N.R., D.B., W.P., K.J.D., M. N., J.B., R.H. and M. Baum. Study supervision: J.S.V., M. Bulsara, C.S., H.F., J.S.T., F.W., N. W., D.B., M.P., J.B., P.K., M. Baum and D.J.

ADDITIONAL INFORMATION

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Data sharing statement UCL is supportive of data sharing and will endeavour to assist in requests for data sharing. All requests for data sharing will adhere to the UCL Surgical & Interventional Trials Unit (SITU) data-sharing agreement policy. These data will be held at UCL on secure servers and cannot be released to any third parties. All requests for access to the data will be formally requested through the use of a SITU data request form which will state the purpose, analysis and publication plans together with the named collaborators. All requests are dealt with on a case by case basis. All requests will be logged and those successful will have a data transfer agreement which will specify appropriate security and privacy agreements, and acknowledgement of the TARGIT Trialists' Group, investigators, the sponsor and funders.

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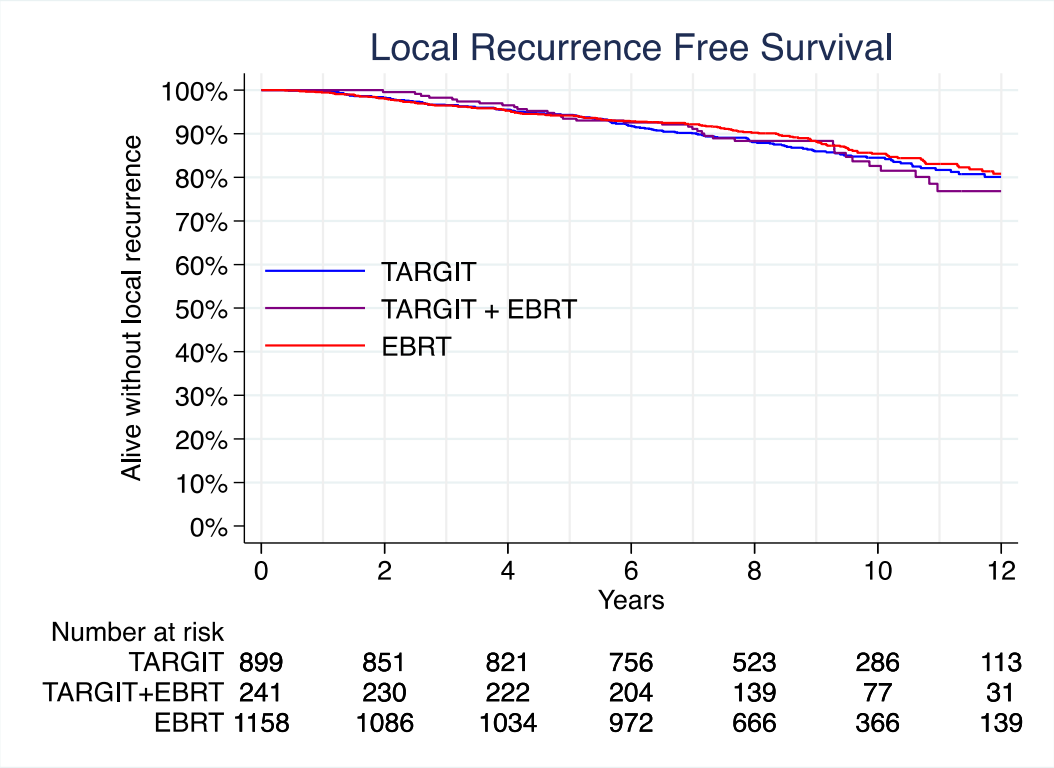
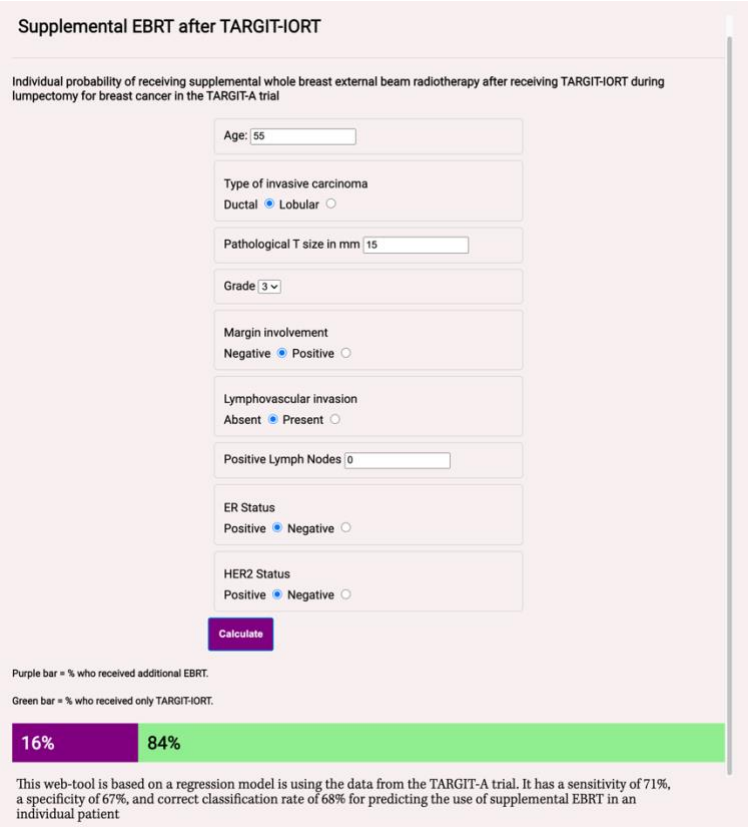
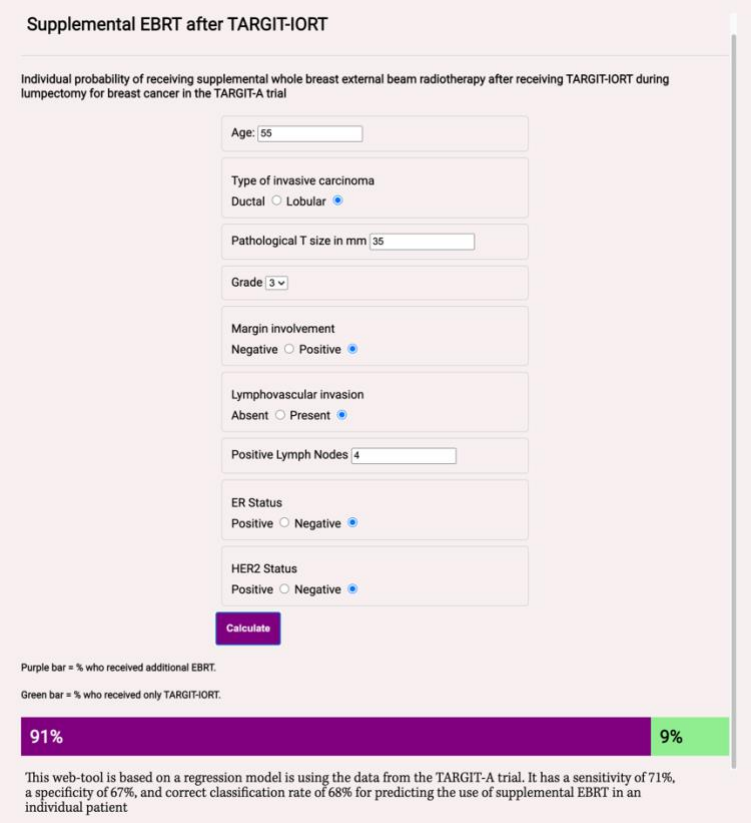
Supplementary figure 1

Kaplan-Meier plot of local recurrence-free survival of those randomised to receive EBRT (red line) along with those randomised to receive TARGIT-IORT separated by those who received additional EBRT (purple line) and those who did not (blue line). No statistically significant difference was found between EBRT and the two latter groups.



Supplementary figure 2 – An illustration of the tool to assess which patient we recommend EBRT after TARGIT-IORT based on the data from the TARGIT-A trial**.** *We urge the readers to please click on the link* https://targit.org.uk/addrt *– and input some numbers for a hypothetical patient to best illustrate the concept.*





Supplementary table 1 – Patient and tumour characteristics

Characteristics	TARGIT-IORT (n=1140)	EBRT (n=1158)
Age (years)		
≤50	117 (10.3)	99 (8.6)
51-60	362 (31.8)	375 (32.4)
61-70	481 (42.2)	524 (45.3)
>70	180 (15.8)	160 (13.8)
Body mass index		
Normal (<25)	408 (41.0)	420 (42.2)
Overweight (25-29.9)	375 (37.7)	329 (33.1)
Obese (≥30)	212 (21.3)	246 (23.7)
Unknown	145 (12.7)	163 (14.1)
Specimen weight (g)		
Median (interquartile range)	40 (25-65)	40 (24-70)
Pathological tumour size (mm; P=0.70)		
≤10	369 (33.1)	370 (33.1)
11-20	571 (51.2)	557 (49.9)
>20	176 (15.8)	190 (17.0)
Unknown	24 (2.1)	41 (3.5)
Grade		
1	275 (24.5)	286 (25.6)
2	621 (55.4)	615 (55.0)
3	226 (20.1)	217 (19.4)
Unknown	18 (1.6)	40 (3.5)
Margin		
Free	1007 (89.4)	993 (88.2)
Ductal carcinoma in situ only	54 (4.8)	60 (5.3)
Invasive	65 (5.8)	73 (6.5)
Unknown	14 (1.2)	32 (2.8)
Re-excision	76 (6.7)	97 (8.4)
Lymphovascular invasion		
Absent	931 (83.4)	946 (84.6)
Present	185 (16.6)	172 (15.4)
Unknown	24 (2.1)	40 (3.5)
Lymph nodes involved		
0	872 (77.4)	893 (79.2)
1-3	213 (18.9)	205 (18.2)
>3	41 (3.6)	29 (2.6)
Unknown	14 (1.2)	31 (2.7)
Estrogen receptor status		
Positive	1005 (89.8)	1030 (91.7)
Negative	114 (10.2)	93 (8.3)
Unknown	21 (1.8)	35 (3.0)

Characteristics	TARGIT-IORT (n=1140)	EBRT (n=1158)
Progesterone receptor status		
Positive	895 (80.3)	921 (82.7)
Negative	220 (19.7)	193 (17.3)
Unknown	25 (2.2)	44 (3.8)
Human epidermal growth factor receptor 2 status		
Positive	156 (14.5)	164 (15.1)
Negative	920 (85.5)	925 (84.9)
Unknown	64 (5.6)	69 (6.0)
Method of presentation		
Screen detected	739 (67.0)	755 (68.0)
Symptomatic	364 (33.0)	355 (32.0)
Unknown	37 (3.3)	48 (4.2)
Endocrine therapy		
Received	897 (81.5)	894 (81.1)
Did not receive	204 (18.5)	209 (18.9)
Unknown	39 (3.4)	55 (4.8)
Chemotherapy		
Received	239 (21.7)	218 (19.7)
Did not receive	863 (78.3)	887 (80.3)
Unknown	38 (3.3)	53 (4.6)

EBRT=external beam radiotherapy; TARGIT-IORT=targeted intraoperative radiotherapy.
Data are numbers (percentages). For percentage calculation, the denominator for unknown percentages is the total number randomised (1140 and 1158) and the denominator for each category is the total number of known patients. No imbalance was found for any of these characteristics between the two randomised arms.

Supplementary table 2 Background risk factors for non-breast-cancer deaths

	TARGIT-IORT (1140)		EBRT (1158)	
Age (Median age is 63)				
<63 years	572	50.18%	578	49.91%
>=63 years	568	49.82%	580	50.09%
Body Mass Index (BMI)				
(Normal <25)	408	41.01%	420	42.21%
Overweight /Obese (>=25)	587	58.99%	575	57.79%

	Patients at higher risk of breast cancer relapse and given TARGIT-IORT plus supplemental EBRT (241)		EBRT (1158)	
Age (Median age is 63)				
<63 years	120	49.79%	578	49.91%
>=63 years	121	50.21%	580	50.09%
Body Mass Index (BMI)				
Normal (<25)	85	40.09%	420	42.21%
Overweight /Obese (>=25)	127	59.91%	575	57.79%

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COMMENT

Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: an innovative patient-centred treatment

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In the randomised TARGIT-A trial, risk-adapted targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy was non-inferior to whole-breast external beam radiotherapy, for local recurrence. In the long-term, no difference was found in any breast cancer outcome, whereas there were fewer deaths from non-breast-cancer causes. TARGIT-IORT should be included in pre-operative consultations with eligible patients.

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MAIN

In 1996, the *British Journal of Cancer* published original work from our group, describing widespread spatial distribution of additional cancer foci in mastectomy specimens of patients who were otherwise suitable for breast conservation.[1] We proposed that these foci may not be clinically relevant because of local recurrence after breast conservation occurs mainly at the site of primary tumour. The TARGIT-A randomised trial[2] was firmly rooted in this initial observation, and compared risk-adapted single-dose targeted intraoperative radiotherapy (TARGIT-IORT) given during lumpectomy vs conventional whole-breast external beam radiotherapy (EBRT) in an international randomised non-inferiority trial.

The long-term results of the randomised TARGIT-A trial were recently published.[3] They confirmed comparable long-term effectiveness of risk-adapted TARGIT-IORT and EBRT in terms of breast cancer control. At 5-years complete follow-up, for the primary outcome of absolute difference in raw local-recurrence rates was 1.16% with the upper 90% confidence limit of 1.99%, confirming non-inferiority at the prespecified margin of 2.5%. With long-term follow-up (median 9 years, maximum 19 years), no statistically significant difference was found in local or distant control of breast cancer, breast-preservation or breast cancer mortality. Deaths from causes other than breast cancer were significantly fewer in the TARGIT-IORT arm—HR 0.59 (0.40–0.86) $P = 0.005$, with 12-year rates being 5.41 vs 9.85%, a reduction of 4.44%.

In this commentary we would like to address a number of critical points.

(1) The first of these is to emphasise that TARGIT-A trial was not restricted only to patients with a very low risk of local recurrence. Participants had a much higher risk profile than with other trials of partial breast irradiation (PBI, Table 1[3–11]). These other trials restricted the trial entry much more stringently, only recruiting patients with the best prognostic features. By contrast, a substantial absolute number of patients in TARGIT-A, just like the Fast-Forward trial of shorter-course whole breast radiotherapy (Table 2)[12] were at higher risk of relapse: 1898 (83%) were younger than 70 years, 366 (16%) had tumours >2 cm in size, 443 (20%) patients had grade 3 cancers, 488 (22%) patients had involved nodes and 426 (19%) had ER- or PgR-negative tumours.

Similarly, patients in the three main trials comparing radiotherapy vs no-radiotherapy (Table 2—CALBG, BASO-II and PRIME-II),[13–16] were again very highly selected for their low-recurrence risk. By contrast with TARGIT-A, they were strictly limited to those older than 65 or 70 years, with smaller, lower grade, node negative and ER-positive tumours. Despite this, the 5-year local-recurrence rates with 'no-radiotherapy' were 2–3 times higher than those seen with TARGIT-IORT (Table 2).

For the record, most patients in the TARGIT-A trial who had high-risk features did not receive supplemental EBRT after TARGIT-IORT as part of the risk-adapted approach. For example, supplemental EBRT was not given to 78% of Grade 3, not given to 82% of ER-negative and not given to 63% of node-positive patients. Rather, the decision regarding use of supplemental EBRT was made for the individual patient by the treating multidisciplinary team, particularly bearing in mind the main indications of unexpected lobular cancer and positive margins. We regard this as a more patient-centred approach, which takes account of the individual patient-specific circumstances, including their preferences.

What does all this add up to? Data from the TARGIT-A trial suggest that PBI using this risk-adapted TARGIT-IORT approach is applicable to a breast cancer population more widely inclusive than those recruited in other PBI or 'no-radiotherapy' trials. By having TARGIT-IORT during their lumpectomy, 8 out of 10 patients complete their radiotherapy right away, and the benefits include avoiding repeated hospital visits,[17] a generally lower toxicity, and an improved quality of life.[18–23]

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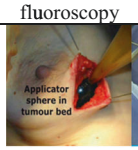
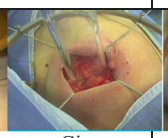
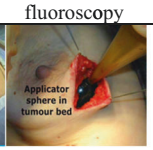
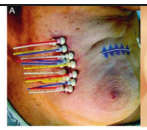
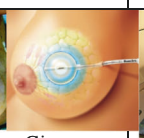
Table 1. Modern trials comparing partial breast irradiation with whole breast radiotherapy.

	Intraoperative		Post-operative 2nd procedure interstitial			Post-operative external beam	
	TARGIT-A Risk-adapted TARGIT-IORT during lumpectomy	**Electron IORT during lumpectomy ELIOT**	**TARGIT-A Delayed second-procedure TARGIT-IORT**	**Interstitial wires x 5 days GEC-ESTRO**	**NSAPB-B039 Balloon (6% of exp. arm)**	**NSAPB-B39/ RAPID /Florence 3DCRT /IMRT**	**IMRT IMPORT-Low**
Patients							
Total	2298	1305	1153	1184	811	2193/ 1754/ 520	1343
At 6-yr FU	**1967**	**676**	**1068**	**784**	**708**	**1915/ 1548/ 503**	**661**
KM curves to	12 years	9 years	12 years	6.5 years	10 years	10/9/10.5 yrs	7 years
Tumours Grade 3 (%) Pos. nodes (%)	Medium risk 20% 22%	Medium risk 20% 26%	Low risk 6% 6.5%	Low risk 9% 0%	Low risk 1% 10%	Low risk 1%/15%/11% 10%/1%/ 10%	Low risk 9% 3%
5-year Local recurrence	2.11% vs. 0.95%	4.4% vs. 0.4%	3.96% vs. 1.05%	1.44% vs.0.92%	2.8% vs. 2.1%	2.8/2.3/2.5% vs 2.1/1.7/1.3%	0.5% vs. 1.1%
Non-inferiority Margin and whether achieved?	2.5% (bkgr 6%) Non-inferior	Equivalence margin 4.5% (bkgr 3%) (4.4% v 0.4%)	2.5% (bkgr 6%) No. Non-inferior in HR+HER-, ET	3% (bkgr 4%) Non-inferior	NA Not equivalent	NA/ 2.75% (bkgr 4%)/ 2% (bkgr 3%) Not equivalent/Non-inferior/Non-inferior	2.5% (bkgr 2.5%) Non-inferior
Breast cancer control similar to WBRT?	Yes	No	Yes	Yes	No	No/Yes/Yes	Yes
Toxicity/ QOL less or more than WBRT?	Less toxicity, better QOL	Not reported	Less toxicity, better QOL	Less toxicity, but wire-entry scarring not reported	More toxicity, QOL not reported	Generally more toxicity, QOL not reported	No major difference
Deaths from other causes different?	Sig. reduced (HR0.59); by 4.4% at 12y	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
Significant scatter radiation to vital organs?	No	Possibly, if lead shield is not properly used	No	Yes	Yes	Yes	Yes
Additional hospital visits and time?	**No additional visits for 80%**; 20% had supplemental WBRT (~16 half days)	**No additional visits**	Additional surgical procedure for 1 dose single dose **1 full day**	Additional procedure 10# over 5 days, 2# /day as inpatient **5 full days**	Additional procedure 10 # over 8 days 2#/ day **5 full days**	10# twice per day over 5-8 days or 5# over 2 weeks **5.5 full days or 6 half days over 2wks**	16 hospital visits **16 half-days**
Where is it done?	Standard OR like c-arm fluoroscopy	Lead-lined walls	Standard OR like c-arm fluoroscopy	Lead-lined walls	Lead-lined walls	Lead lined bunker	Lead lined bunker
How it is done?	 Given during lumpectomy surgery	 Given during lumpectomy surgery. Needs extensive dissection + deep lead shield	 Given as a second-procedure by re-opening the lumpectomy wound	 Given as second-procedure and radioactive wires remain in place for 4 days (in-patient)	 Given as second procedure and the baloon remains in place for 8 days (in-patient)	 Given as twice daily treatments over 8 days or 5 non-consecutive days over 2 weeks	 Given as daily doses for 15 days over 3 weeks

For NSABP-39 overall LR used for balloon. External beam days includes half a day for planning. The very old or small trials with less than 500 patients or those with less than 5-year follow-up—from Leeds (EBRT over 28 days, $n = 174$, published 2005)[38] and Christie (EBRT 10 days, $n = 708$, published 1995)[39] both with worse outcome for PBI, Budapest (interstitial wires twice a day over 7 days, $n = 258$, published 2013) with similar outcome for PBI[40] and trials with no published cancer outcome data[41] are not included in this table. Table reproduced and slightly modified from Vaidya, J.S., Bulsara, M., Baum, M. et al. Intraoperative radiotherapy for breast cancer: powerful evidence to change practice, *Nature Reviews Clinical Oncology*. https://doi.org/10.1038/s41571-021-00471-7 (2021). Numbers are for patients with invasive breast cancer.
bkgr expected background risk in the control arm, *ET* endocrine therapy, *QOL* quality of life.

Table 2. Modern trials of no-radiotherapy, the trial of short course whole-breast radiotherapy and the TARGIT-A trial.

	CALGB No RT vs WBRT	BASO 2 No RT vs WBRT	PRIME 2 No RT vs WBRT	FAST-FORWARD WBRT vs shorter WBRT	TARGIT-A trial risk-adapted single-dose TARGIT-IORT vs WBRT
Number for comparison	636	1135	1326	2562	2298
Number at 6-year follow-up	<500	N/A	<600	1025	1967
Age limits	≥70 0% < 70	≥65 0% < 65	≥65 0% < 65	>18 84% < 70	≥45 60% < 65 85% < 70
T Size limits	≤2 cm	≤2 cm	≤3 cm	T1–T3	≤3.5 cm
Grade limits	No info.	Grade 1	Grade 1 or 2, only 2% grade 3	No restriction 28% grade 3	No restriction 20% grade 3
Nodes limits	Negative	Negative	Negative	N0–N1 19% node positive	No restriction 22% node positive
LV invasion	No info.	Negative	Neg if Gr 3	No restriction	No restriction
ER status	Positive	Positive	Positive	No restriction	No restriction
Additional hospital visits	1	1	1	7–15	None in 80% of cases; WBRT recommended in 20%
5-year local-recurrence rates	4 vs 1%	6 vs 2%	4.1 vs 1.3% Difference 2.9% (upper 95%CI 4.8%)	2.1 vs 1.4% (including 7% post-mastectomy radiotherapy) No difference	2.11 vs. 0.95% Non-inferiority confirmed with complete 5-year follow-up Difference 1.16% Upper 90% CI 1.99%
Long-term outcomes, more than 5 years	10-yr OS 67 vs 66%; LR 8 vs 2%; 10-yr LRFS ~53 vs ~61%	10-yr LRFS ~89 vs ~97%	10-yr LR 9.8% vs 0.9%. Binomial 10-year Non-breast cancer deaths 3.9% vs 6.1% and total deaths 13.2% vs 12%	Not available	At median follow-up of 9 years (max 19 years): No difference in local/distant control/breast preservation/breast cancer mortality Significantly fewer deaths from other causes (5.41% vs 9.85% at 12 years)
Significant scattered radiation to vital organs?	No	No	No	Yes	No
Mortality	No difference	No difference	No difference	No difference	Significantly reduced non-BC mortality with TARGIT-IORT No difference in BC mortality
Toxicity in experimental arm	Not reported	Not reported	Not reported	Higher (e.g. breast induration/ hardness)	Reduced
Quality of life with experimental treatment	Not reported	Not reported	Higher insomnia No improvement in QOL	Not reported	Improved breast related QOL Improved cosmetic outcome Reduced pain

(2) An important statistical point relates to the use of Kaplan–Meier (K–M) curves. These are very informative if properly computed. The first step for estimating the risk of any event (e.g. local recurrence), is to categorise each patient into either having the event or not. The time-to-event is then used to plot a graph. This would work well if everyone's follow-up was the same and no one died, but this of course is never the case because patients are never recruited all at the same instant in any trial. The K–M model therefore uses a method called 'censoring', which means that a patient's data are used until the point when they were last seen. The assumption is that they are alive after they were last seen and continue to have a risk of having local recurrence. But, sadly, some patients die during follow-up, at which point this assumption is of course no longer true. So, when plotting K–M estimates for local recurrence, one should not categorise patients who have died as 'censored'. Such a plot *must include death* as an event.[3] Both the plot and any estimate in which the dead have been censored are set in an imaginary world where there is a continual risk of local recurrence after death. Unfortunately, such graphs have frequently been published and are inevitably misleading to readers.

Here is an example to make this clearer. Let's look at the NSABP-B39 data.[24] Their K–M graph of local recurrence shows that the chance of having local recurrence with PBI at 10 years is 4.6%, therefore 95.4% of patients can be expected to be local-recurrence free. This immediately leads to a paradox because in fact, only 90.6% are alive at 10 years, so how can a larger number of patients (95.4%) be around (alive) to be local-recurrence free? A further example comes from the CALGB trial,[14] in which over 90% patients are estimated to be alive without local recurrence at 10 years, when in fact only 60% are actually alive. Thus, such a K–M graph allegedly depicting local control over time is misleading.

For this reason both DATECAN[25] (European) and STEEP[26] (American) guidelines, rightly insist that death and local recurrence should both be included as clinical events for assessing local treatments for breast cancer.

Most importantly of all, patients naturally need to know the local control achieved by any new approach compared with the previous standard, which is precisely provided by the outcome of local-recurrence-free survival.

(3) Next, we would like to discuss the persistent finding of fewer non-breast cancer deaths with TARGIT-IORT, compared with whole-breast radiotherapy. The reduction was mainly due to fewer deaths from cardiovascular or lung problems and from other cancers and was not small in magnitude: 41% in relative terms and 4.4% at 12 years in absolute terms.

Randomisation, especially when the trial size is large, ensures that both known and unknown factors are well balanced. In the TARGIT-A trial, all known prognostic factors[3] were well balanced, as well as age and body mass index (BMI),[3] relevant for risks of cardiovascular[27] and malignant disease.[28]

This somewhat surprising observation is in fact consistent with the results of meta-analyses of randomised trials comparing partial breast irradiation with whole-breast irradiation.[29,30] It is well to remember that even modern

radiotherapy increases cardiac and lung cancer mortality.[31–35] This is particularly important in current or ex-smokers,[31] in which a survival decrement of 6% is estimated over a 30 year period. This detriment is likely to outweigh any possible survival benefit from radiotherapy for these patients with early breast cancer.[36]

Perhaps even more important nowadays, in patients with screen-detected cancer, where the dangers of overtreatment are now so well recognised,[37] we argue that it is both logical and in the patient's interest to use TARGIT-IORT, in order to minimise side effects.

(4) Finally, it is obvious that this work has special relevance during the current COVID-19 pandemic during which additional visits for radiotherapy consultations, planning and treatment all raise the risks to a vulnerable population as well as adding to pressures on an overstretched hospital system. TARGIT-IORT could help reduce these risks and save precious resources.

Conclusion

Using the approach of risk-adapted TARGIT-IORT in patients with early breast cancer avoids the inconvenience and toxicity of whole-breast radiotherapy in 8 out of every 10 patients. When compared with whole-breast radiotherapy in the randomised TARGIT-A trial, now with long-term follow up, no difference was found for any breast cancer outcomes, but there was a reduction in non-breast cancer mortality with TARGIT-IORT. Previous studies have shown that the other advantages include reduced breast pain, a better quality of life,[18–23] a cosmetically superior outcome and reduced travelling time for the patient.[17]

Clinicians and patients in 38 countries (260 centres) have been adopting TARGIT-IORT since the publication of the first results, and over 45,000 patients have been treated so far. We believe that the long-term data,[3] taken together with the many obvious benefits for the patient, provide compelling evidence to roll this out further.

Finally, all doctors in the UK are now obliged to follow the recently published GMC guidelines which underline the essential nature of adequate patient information—i.e. what they can reasonably expect to be told—in order to provide valid consent (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent). This powerful principle is now fully enshrined in UK law (Montgomery v Lanarkshire Health Board, 2015).

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J.S.V. wrote the first draft, made important intellectual contribution to the conceptualisation, data analysis, data interpretation, writing and editing the manuscript and agreed with the final version. M.Bu. made important intellectual contributions towards conceptualisation, data analysis, data interpretation, writing and editing. M.Ba. and J.S.T. made important intellectual contribution towards conceptualisation, data interpretation, writing and editing. J.S.V., M.Bu., M.Ba. and J.S.T. agreed with the final version of the manuscript.

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