



OPEN ACCESS



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

Jayant S Vaidya,¹ Max Bulsara,² Michael Baum,¹ Frederik Wenz,³ Samuele Massarut,⁴ Steffi Pigorsch,⁵ Michael Alvarado,⁶ Michael Douek,⁷ Christobel Saunders,⁸ Henrik L Flyger,⁹ Wolfgang Eiermann,⁵ Chris Brew-Graves,¹ Norman R Williams,¹ Ingrid Potyka,¹ Nicholas Roberts,¹ Marcelle Bernstein,¹⁰ Douglas Brown,¹¹ Elena Sperk,³ Siobhan Laws,¹² Marc Sütterlin,¹³ Tammy Corica,¹⁴ Steinar Lundgren,^{15,16} Dennis Holmes,¹⁷ Lorenzo Vinante,¹⁸ Fernando Bozza,¹⁹ Montserrat Pazos,²⁰ Magali Le Blanc-Onfroy,²¹ Günther Gruber,²² Wojciech Polkowski,²³ Konstantin J Dedes,²⁴ Marcus Niewald,²⁵ Jens Blohmer,²⁶ David McCready,²⁷ Richard Hofer,²⁸ Pond Kelemen,²⁹ Gloria Petralia,³⁰ Mary Falzon,³¹ David J Joseph,¹⁴ Jeffrey S Tobias³²

For numbered affiliations see end of the article.

Correspondence to: J S Vaidya jayantvaidya@gmail.com (or @jsvaidya on Twitter ORCID 0000-0003-1760-1278)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2020;370:m2836 <http://dx.doi.org/10.1136/bmj.m2836>

Accepted: 17 June 2020

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, cNO-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 series⁹ 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 results¹¹⁻¹³ 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 \leq 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 survival³¹; 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 DATECAN³³ and STEEP³⁴ 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.

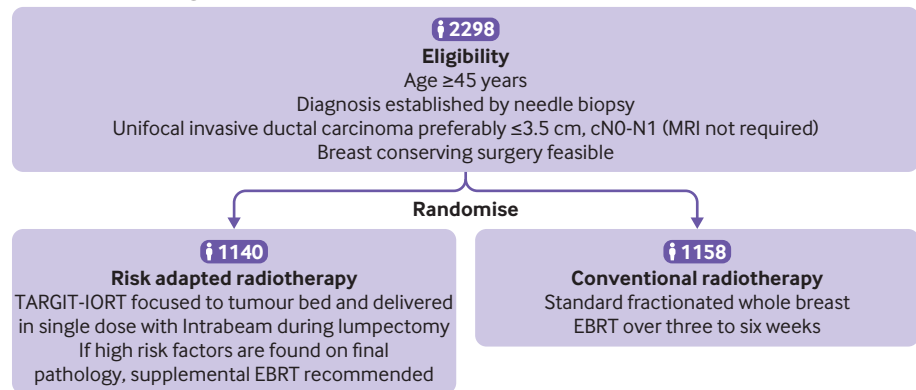
With long term follow-up (median 8.6 years, maximum 18.9 years, interquartile range 7.0-10.6), no statistically significant difference was found between immediate TARGIT-IORT and EBRT for the following outcomes: local recurrence-free survival (167 v 147 events, hazard ratio 1.13, 95% confidence interval 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

Flow chart outlining TARGIT-A recruitment



CONSORT diagram

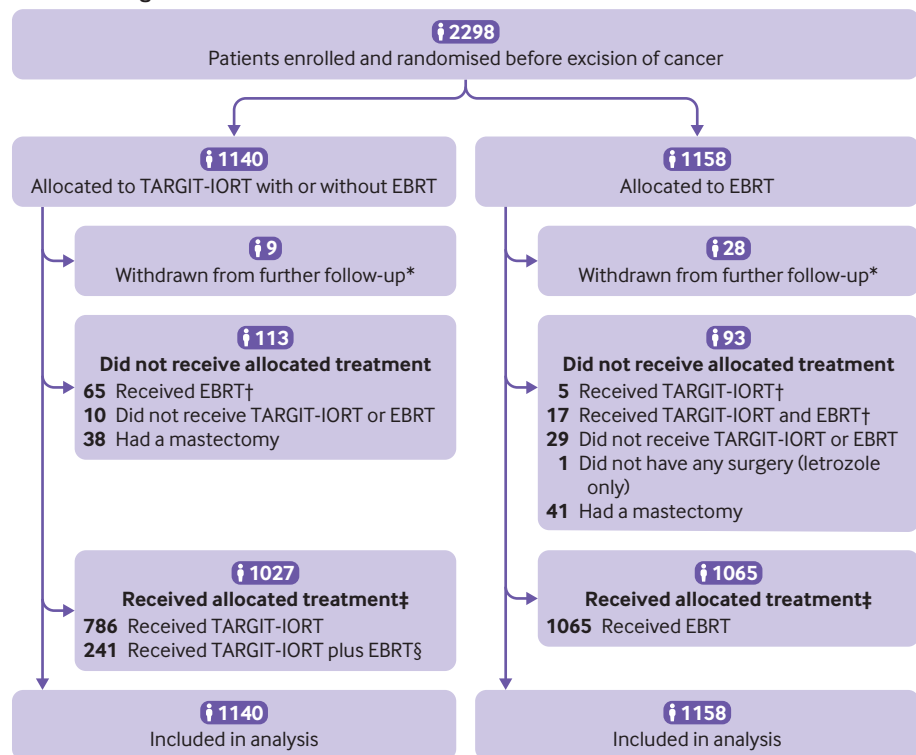


Fig 1 | Flowchart outlining TARGIT-A recruitment and CONSORT (consolidated standards of reporting trials) diagram. *Difference in number withdrawn was statistically significant ($P=0.002$). †Crossovers: 65/1140 (5.7%) allocated TARGIT-IORT received EBRT, and 22/1158 (1.9%) allocated EBRT received TARGIT-IORT. ‡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

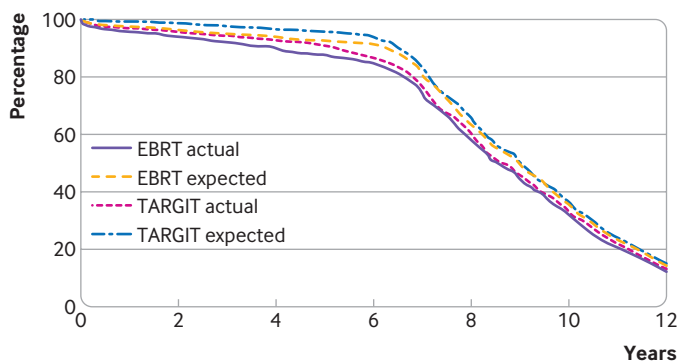
was found to have advantages for the patient, such as convenience, reduced travel and personal costs, improved quality of life, and fewer side effects.⁴³⁻⁴⁷ However, the international community has been waiting for the long term follow-up outcomes before this approach is more widely adopted.

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 data⁴⁸⁻⁵² 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

| Local recurrence and death | TARGIT-IORT (n=1140) | | EBRT (n=1158) | |
|---|----------------------|-------------|---------------|-------------|
| | ≤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.

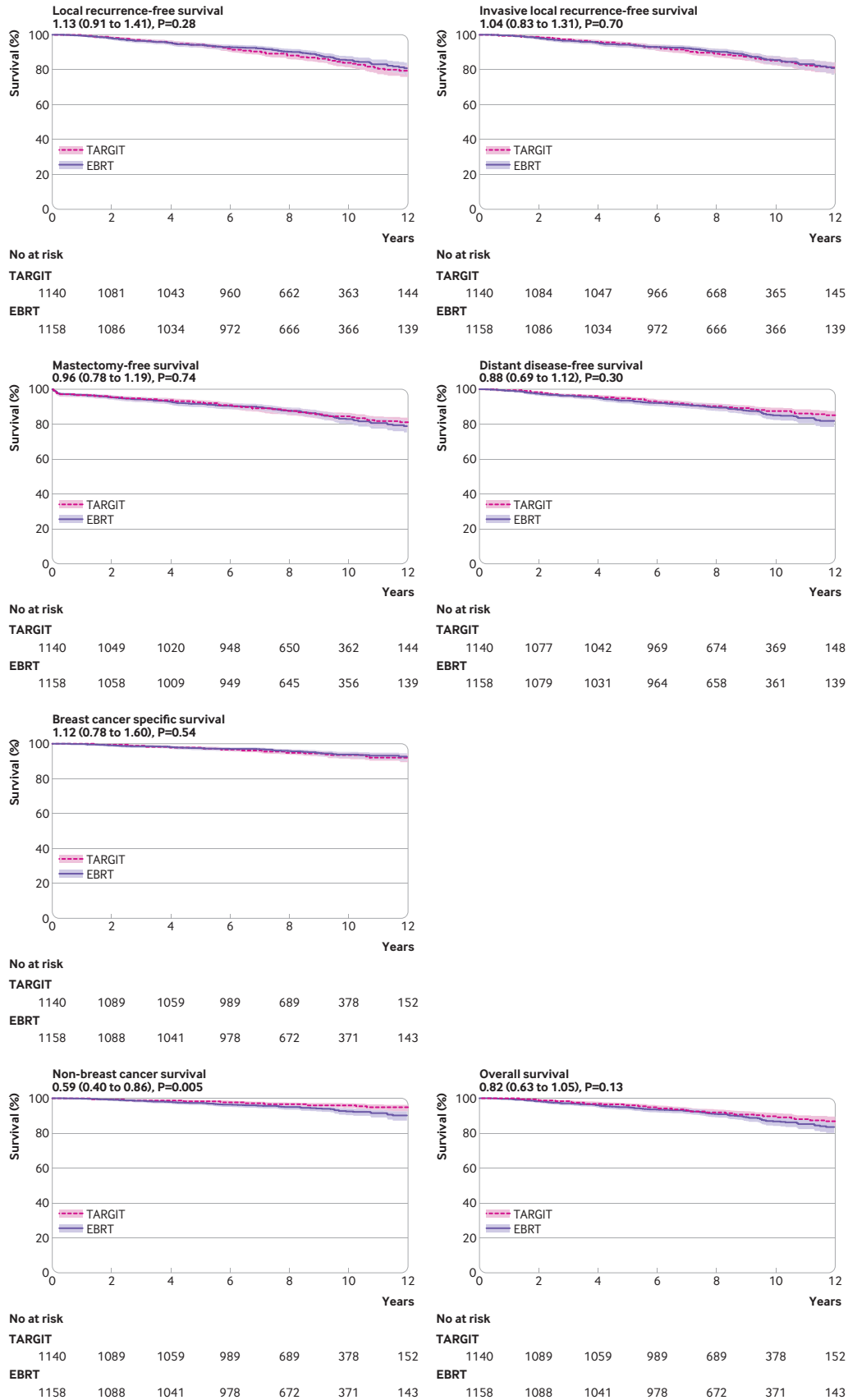


Fig 3 | Kaplan-Meier estimates and curves for the following outcomes for TARGIT-IORT versus EBRT in the TARGIT-A trial: local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival, breast cancer specific survival, non-breast cancer 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

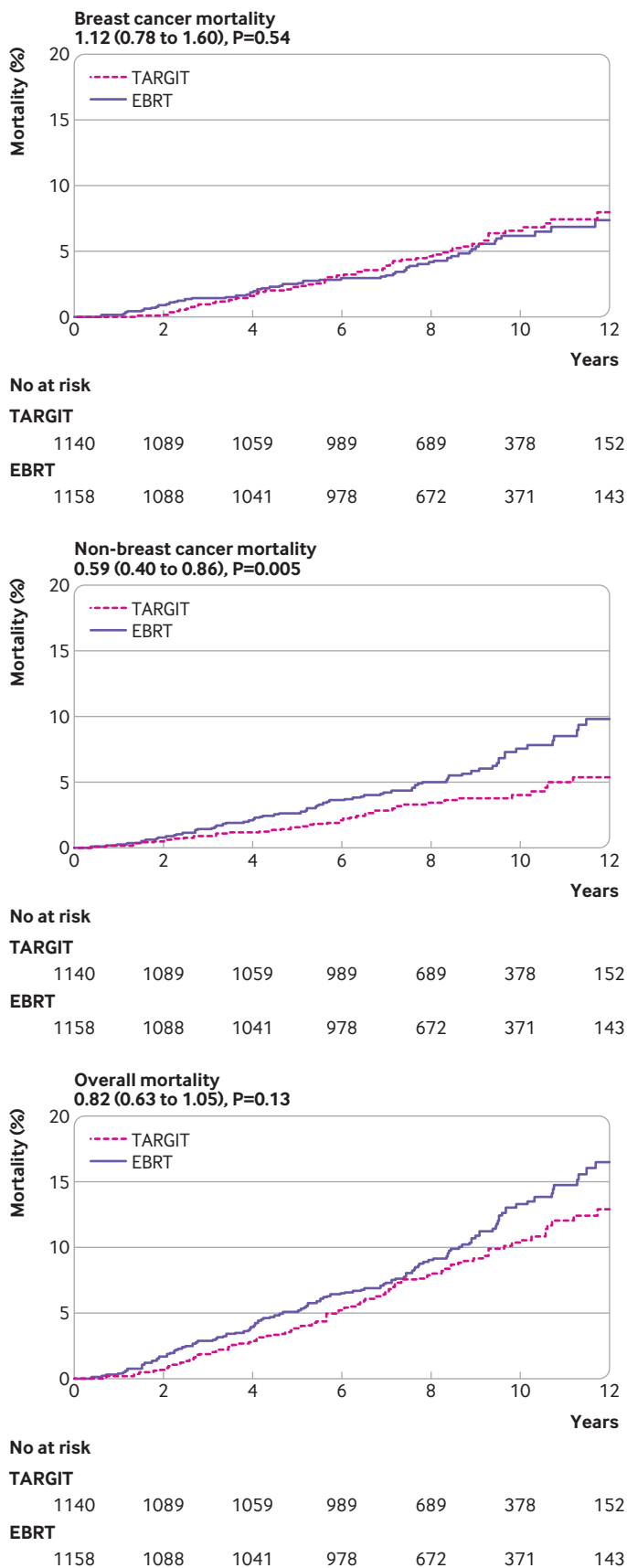


Fig 4 | Kaplan-Meier curves showing differences in breast cancer mortality, non-breast cancer mortality, and overall mortality in TARGIT-A trial for TARGIT-IORT v EBRT. Figures under titles are hazard ratios (95% confidence intervals) and log rank test P values. EBRT=external beam radiotherapy; TARGIT-IORT=targeted 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 disease⁵⁵ and malignant disease⁵⁶ 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 standard¹² 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 2016⁵⁷ 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 | TARGET-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; TARGET-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 trial¹⁹ 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 (1023⁵⁸ and 233¹⁷ 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,

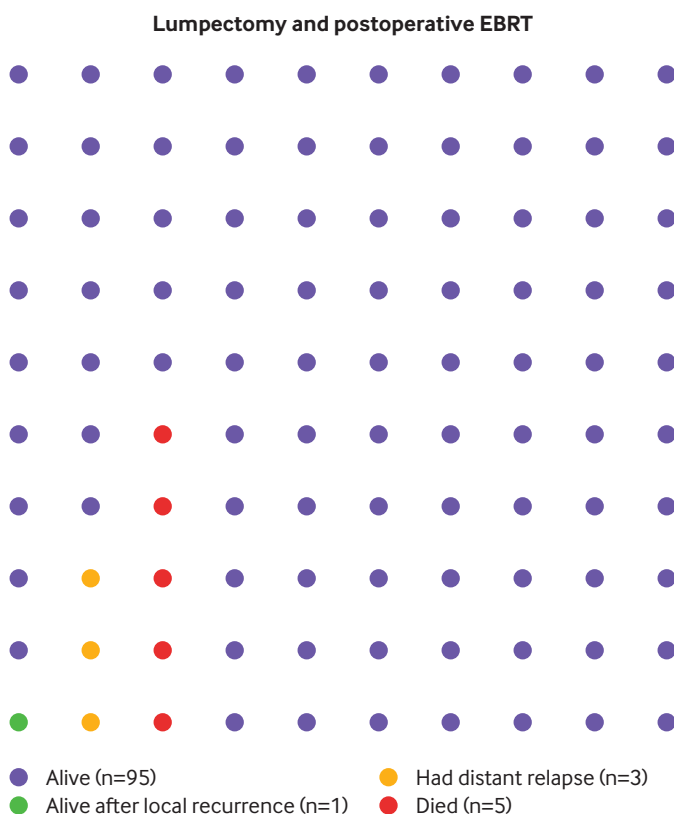
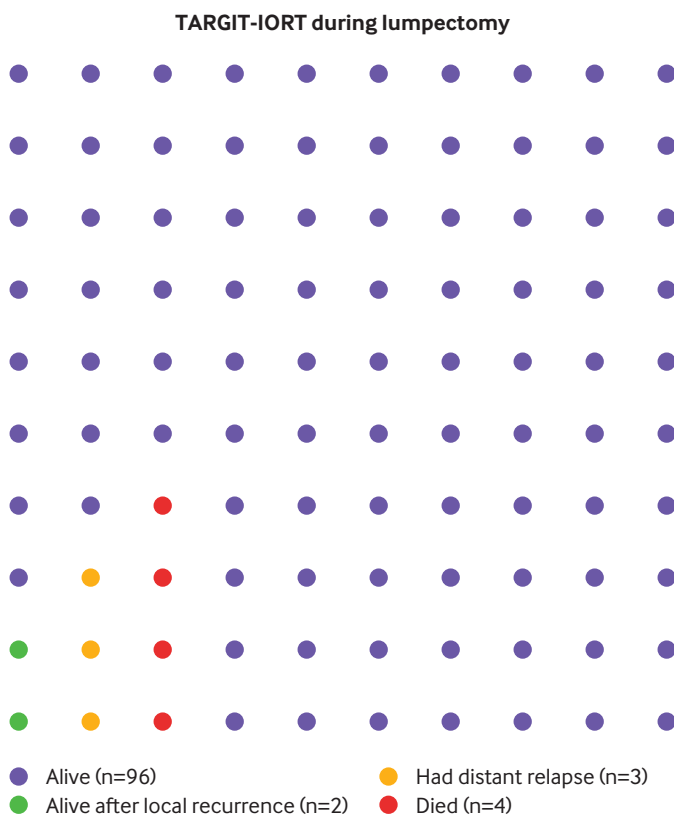


Fig 5 | Pictogram showing outcomes in TARGIT-A trial of TARGIT-IORT v EBRT for breast cancer. Complete follow-up is available for five years. Each dot represents a patient. Absolute numbers of patients who had local recurrences, distant disease, and died (TARGIT-IORT: 24/1140 local recurrences, 34/1140 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 | |
| TARGET-A (immediate TARGIT-IORT) | 2298 | 2048 | 1967 | 1736 | 1361 | 1035 | 749 | 587 | 295 | |
| TARGET-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 (2x5 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

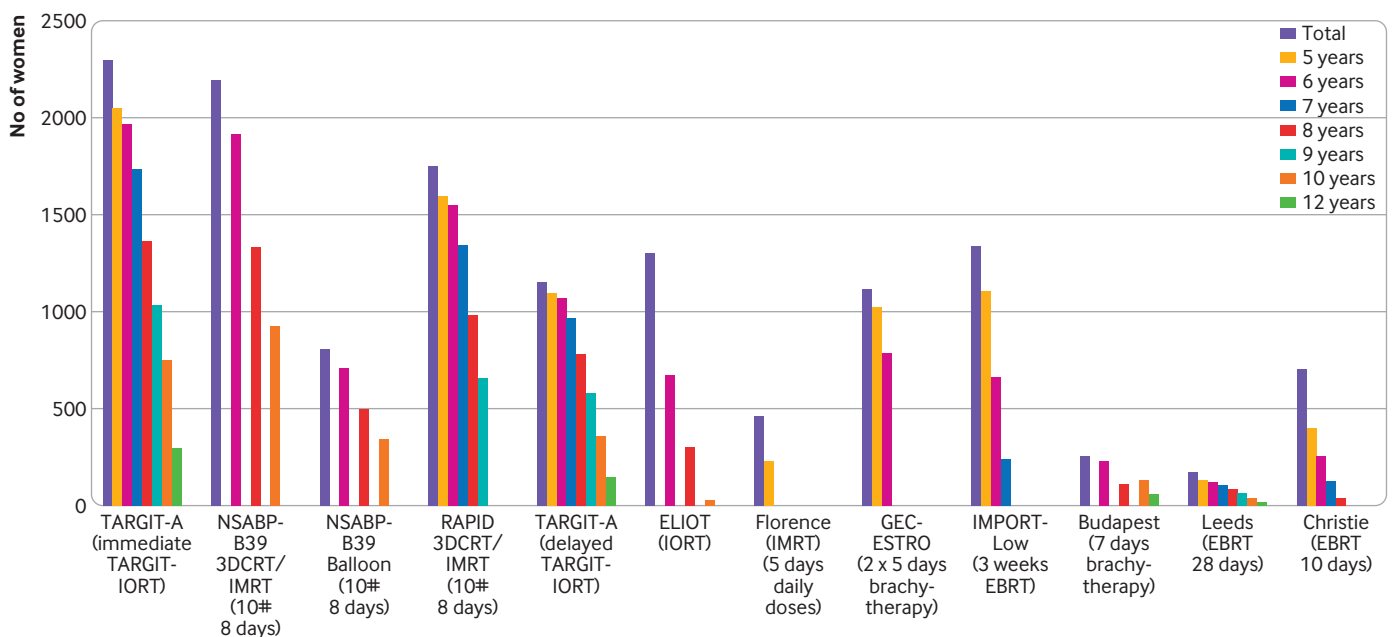


Fig 6 | Amount of data in randomised trials of different techniques of partial breast irradiation for invasive breast cancer. 10# 8 days=10 fractions in eight days; EBRT=external beam radiotherapy; IMRT=intensity modulated radiotherapy; IORT=intraoperative radiotherapy; TARGIT-IORT=targeted intraoperative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

AUTHOR AFFILIATIONS

¹Division of Surgery and Interventional Science, University College London, 43-45 Foley Street, London W1W 7JN, UK

²Department of Biostatistics, University of Notre Dame, Fremantle, WA, Australia

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

⁴Department of Surgery, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy

⁵Department of Gynaecology and Obstetrics, Red Cross Hospital, Technical University of Munich, Munich, Germany

⁶Department of Surgery, University of California, San Francisco, CA, USA

⁷Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

⁸School of Surgery, University of Western Australia, Crawley, WA, Australia

⁹Department of Breast Surgery, University of Copenhagen, Copenhagen, Denmark

¹⁰London, UK

¹¹Department of Surgery, Ninewells Hospital, Dundee, UK

¹²Department of Surgery, Royal Hampshire County Hospital, Winchester, UK

¹³Department of Gynaecology and Obstetrics, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany

¹⁴Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia

¹⁵Department of Oncology, St Olav's University Hospital, Trondheim, Norway

¹⁶Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

¹⁷University of Southern California, John Wayne Cancer Institute & Helen Rey Breast Cancer Foundation, Los Angeles, CA, USA

¹⁸Department of Radiation Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy

¹⁹Istituto Oncologico Veneto, Padoa, Italy

²⁰Department of Radiation Oncology, University Hospital, The Ludwig Maximilian University of Munich, Munich, Germany

²¹Radiotherapy-Oncology, Western Cancer Institute, Nantes, France

²²Breast Centre Seefeld, Zurich, Switzerland

²³Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland

²⁴Breast Centre, University Hospital Zurich, Zurich, Switzerland

²⁵Saarland University Medical Center, Homburg, Germany

²⁶Sankt Gertrauden Hospital, Charité, Medical University of Berlin, Berlin, Germany

²⁷Princess Margaret Cancer Centre, Toronto, Ontario, Canada

²⁸Sentara Surgery Specialists, Hampton, VA, USA

²⁹Ashikari Breast Center, New York Medical College, New York, NY, USA

³⁰Department of Surgery, University College London Hospitals, London, UK

³¹Department of Pathology, University College London Hospitals, London, UK

³²Department of Clinical Oncology, University College London Hospitals, London, UK

We thank the Independent Steering Committee for providing trial oversight. The members were appointed by the Health Technology Assessment programme of the National Institute of Health Research, Department of Health and Social Care, UK. Independent members: Freddie Hamdy (Nuffield Department of Surgical Sciences, University of Oxford), Ian Fentiman (Guy's and St Thomas' Hospital, London), Mangesh Thorat (Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London), Carolyn Murphy (King's Clinical Trials Unit, Kings College London), Ann Millman (Oxford), Martin Bland (Department of Health Sciences, University of York), David Domett (Southend University Hospital NHS Foundation Trust), David Morgan (Nottingham). Jayant S Vaidya and Max Bulsara were appointed as non-independent members of this committee.

We thank Michael D O'Shea (Woodward Informatics, Oxfordshire, UK) for database development, Julie Lindsay (Ninewells Hospital, Dundee, UK) for help in data collection, Uma J Vaidya for help with the figures, tables, and editing of the manuscript, Nathan Coombs for helpful critic and suggestions, and several contributors who have now left the individual centres. Travel and accommodation for meetings of the international steering committee and data monitoring committee were provided by Carl Zeiss. Individual centres were self-financed. We thank all the patients who kindly participated in the trial. Manuscript preparation was helped by the trial operations staff and their respective families.

Individuals from each centre whose help has been invaluable are listed below, in order of the date of randomisation of the first patient (acknowledgments are also due to those who no longer work in the respective departments and those who might not have been named below): Surgical Interventional Trials Unit, Division of Surgery and Interventional Science, University College London (Chris Brew-Graves, Ingrid Potyka, Nicholas Roberts, Norman Williams, Haroon Miah, Cinzia Baldini, Bina Shah, Danielle Maas, Charlene Carvalho, Rachael Sarpong, Jack Grierson, Neil McCartan, Charlie Mizon, Morteza Ali, Cindy Li, Alex Shirley, Joanna Hadley, Fatima Akbar, Muhammad Hammed, Daryl Hagan, Olive Murphy, Tina Lennon, Joan Houghton); University College London Hospital, London, UK (Jayant S Vaidya, Jeffrey S Tobias, Michael Baum, Mohammed Keshtgar, Glen Blackman, Chris Brew-Graves, Michael Douek, Mary Falzon, Gloria Petralia, Norman R Williams); Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany (Frederik Wenz, Elena Sperk, Mark Suetterlin, M Bohrer, S Clausen, B Hermann, R Hildenbrand, Anke Keller, Uta Kraus-Tiefenbacher, B Kuepper, A Marx, F Melchert, D Neumann, F Schneider, V Steil, M Trunk, Frank A. Giordano); Sir Charles Gairdner Hospital, Perth, WA, Australia (Christobel Saunders, David J Joseph, Tammy Corica, Elizabeth Kernutt, Mandy Taylor, Eva Vosikova, Claire Haworth); Centro di Riferimento Oncologico, Aviano, Italy (Samuele Massarut, Lorenzo Vinante, M Arcicasa, E Bidoli, E Cadiani, E Capra, M Oliva, T Perin, S Reccanello, M Roncadin, G Sartor, G Tabaro, M Trovo, R Volpe Mario Mileto, Erica Piccoli, Antonella Spada); Ninewells Hospital, Dundee, UK (DC Brown, Julie Lidsay, M Adams, DJA Adamson, K Armoogum, J Bosch, JA Dewar, S Edwards, J Gardner, A Gunning, M Hawkes, LB Jordan, A Lee, G Little, C Mackay, AJ Munro, J Parry, CA Purdie, MM Reis, V Walker, RAB Wood); University of California, San Francisco Medical Center, San Francisco, CA, USA (Michael Alvarado, Laura Esserman, Alfred Au, Alison Bevan, Jay Connolly, Cheryl Ewing, Clark Fisher, Shelley Hwang, K Lane, Christina Minami, Michelle Oboite, Cathy Park, Jean Pouliot, Theadora Sakata, Aron Mohan, Brittany Harrison, Albert Chan, Mitchell Hayes); Frauenklinik vom Roten Kreuz, Munich in cooperation with Technical University of Munich, Department of RadioOncology, Germany (Wolfgang Eiermann, Steffi Pigorsch, Stephanie E Combs, Beyhan Ataseven, C Becker, B Hoegel, P Kneschaurek, A Lackermeier, M Molls, Carsten Nieder, Markus Oechsner, Barbara Röper, Sabine Schill, Ralf Wehrmann, Brigitte Werner, Christopher Wolf); University of Southern California, Los Angeles, CA, USA (Dennis R Holmes, Melvin Astrahan, Carryl Dubois, Jacqueline Majors, Sylvia Villegas Mendez, Afshin Rashtian, Ronald Rivera, Howard Silberman, Melvin Silverstein, Rashida Soni, Oscar E Streeter Jr, Lina Wang, Heather Macdonald, Stephen Sener, America Casillas); Ospedale San Giuseppe di Empoli, Empoli, Italy (Gianmaria Fiorentini, Carli Ballola Adele, Rafaella Barca, Mauro Biancalani, Giampaolo Biti, Enrico Cellai, Antonella Compagnucci, Claudio Caponi,

Vito Maria Fontanarosa, Roberta Ghezzi, Alessandro Ghirelli, Gloria Giustarini, Barbara Grilli Leonulli, Francesca Littori, Maurizio Pertici, Visna Petrina, Paola Raffaele, Francesca Righi, Serenella Russo, Michele de Simone, Gina Turrisi, Giuditta Zipoli); Sankt Gertrauden-Krankenhaus, Berlin, Germany (Jens-Uwe Blohmer, Petra Feyer, J Gross, G Jautzke, K Luebbert, Michaela Platzer, Joerg Preussler, D Puppe, Esther Wiedemann); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Michael Henderson, David Blakey, Boon Chua, Ram Das, Roslyn Drummond, Annette Haworth, Penny Fogg, Stephen Fox, Jodi Lynch, Jane O'Brien, Catherine Poliness, Ann-Marie Power, David Speakman, Tina Thorpe, Melanie Walker); Ludwig Maximilians Universität, Munich, Germany (Montserrat Pazos, Wolfgang Janni, Ulrich Andergassen, C Balka, Darius Dian, Sylvia Dondl, Klaus Friese, Julia Jueckstock, Thomas Kirchner, Klaus Krimmel, Doris Mayr, Susanne Reinhard, Dr Schaffer, Christian Schindlbeck, Harald Sommer, Justus Well); Universität Frankfurt am Main, Frankfurt, Germany (M Kaufmann, H Boettcher, J Moog, Achim Rody, Claus Rödel, S Schopohl, Christian Weiss, Inge Fraunholz, Ulla Ramm, Martin-Leo Hansmann, R Strohmeier); Herlev/Rigs Hospitals, Copenhagen, Denmark (Henrik Flyger, Eva Balslev, Niels Bentzon, Paul Geertsen, Helle Holtveg, Claus Kamby, Niels Kroman, Faisal Mahmood, Fritz Rank, Birgitte Bruun Rasmussen, Lone Gry Schäfer, Peter Michael Vestlev, Vera Timmermans Wielenga, Eva Wilken); Medical University of Lublin, Lublin, Poland (Wojciech P Polkowski, Malgorzata Jankiewicz, Andrzej Kurylcio, Jerzy Mielko, Magdalena Skorzevska, Bogumila Cisel, Monika Lewicka, Edyta Matejek, Jaroslaw Romanek, Andrzej Stanislawek, Jadwiga Sierocinska-Sawa, Zofia Siezieniewska, Rafal Smyk, Andrzej Bedonski); Royal Free Hospital, London, UK (Mohammed Keshtgar, Katherine Pigott, Tim Davidson, Jayant S Vaidya, Debasis Ghosh, Sarah Needleman, Jawad Keshtgar, Samia Shah, Katia Pasciuti, Neil Dancer, Kashmira Metha, Benjamin Earner, Stephan Duck, David Woolf); Whittington Hospital, London, UK (Jayant S Vaidya, Jeffrey S Tobias, Alan Wilson, Glen Blackman, Rashika Rajakumar, Renata Rowicka, Veronica Conteh, Su Ramachandra, Lucy Harbin, R Chaudhuri, Ros Crooks, Francesca Peters, Tom Connors, George Stasinou, Melissa Hickson, Alison Jones, Mulyati Mohamed, Tim Crook, Vivienne Maidens, Sylvia Grieve, Elizabeth Tamufor, Lucy Mavriano, Lotta Jonsson, Ciara McNulty); Lafayette Surgical Clinic, Lafayette, IN, USA (Thomas L Summer, Mario Contreras, Paul M DesRosiers, Irene Gordon, Kazumi Chino, Bedatri Sinha, Cindy McDowell, Mike Ringer, Tammy Spurlock, Lisa Ramsey); Sentara Surgery Specialists, Hampton, VA, USA (Richard A Hoefler, Mary Berry, Michael Miller, Song Kang); Uniklinikum des Saarlandes, Homburg, Germany (Erich Solomayer, K Abel, S Baum, Rainer Allgayer, R M Bohle, Mustafa Deryal, J Fleckenstein, R Grobholz, Jeanett Koehn, Anja Martin-Riedheimer, Marcus Niewald, J Radosa, J Friedmann, Markus Promnik, Christian Ruebe, W Schmidt); Princess Margaret Cancer Centre, Toronto, ON, Canada (David McCready, Akbar Beiki-Ardakani, John Cho, Susan Done, Jamie Escallon, Anthony W Fyles, Wilfred Levin, Alex Vitkin, Marie Vranic); Royal Hampshire County Hospital, Winchester, UK (Siobhan Laws, Dick Rainsbury, Claire Birch, Lyn Booth, Caroline Cross, Alan Gately, Virginia Hall, Kevin Harris, Sanjay Raj, Balvinder Shoker, Virginia Straker, Jennifer Wilson); Brust Zentrum Seefeld, Zurich, Switzerland (Christopher Rageth, Uwe Gneveckow, Elisabeth Grob, Guenther Gruber, Baerbel Pappasotiropoulos, Barbara Tausch, C Tausch, Zsuzsanna Varga, Iris Vergin); Breast Centre, Universitätsspital Zurich, Zurich, Switzerland (Claudia Hutzli, Konstantin J Dedes, Yvonne Burgstaller, Rosemary Caduff, Daniel Fink, Guntram Kunz, Claudia Linsenmeier, Yousef Najafi, Natalie Gabriel, Cornelia Betschart, Eleftherios Samartzis, Ana-Maria Schmidt, Tino Streller, Z Varga, Madeleine Wick, Cornelia Leo, Zsuzsanna Varga, Leila Kocan); St Olav's University Hospital, Trondheim, Norway (Steinar Lundgren, Anne Beate Marthinsen Langeland, Marianne Brekke, Hans E Fjosne, Jomar Frengen, Kristen Helset, Jarle Karlsen); University of Nebraska Medical Center, Omaha, NE, USA (James Edney, Aaron Sasson, Debra Spence, Robert Thompson, William W West, Sumin Zhou); Guy's and St Thomas' Hospital, London, UK (Michael Douek, Sarah Aldridge, Ashutosh Kothari, Nick Beechey-Newman, Charles Deehan, Ian Fentiman, Hisham Hamed, Sarah Harris, Hardeep Johal, Sarah Pinder, Arnie Purushotham, Vernie Ramalingam, Chris Stacey); Vassar Brothers Medical Center, Poughkeepsie, NY, USA (Angela Keleher, Eileen Abate, Nicole Cappillino, Laszlo Csury, Edward Farhangi, Anne Kim, Sutini Ngadiman, Dimitrios Papadopoulos, Dan Pavord, P Hank Schmidt, Camilo Torres, Erika Mednick); Ashikari Breast Center, New York Medical College, New York, NY, USA (P Kelemen, Andrew Ashikari, Ulrich Hermat, Helen Li, Demetrious Makrides, Mike Malamed, Wanda Rivera, Yadita Samnarain, Alfred Tinger, Raphael Yankelevich, Yasmin Yusuf); Medizinische Hochschule Hannover, Germany (Tjong-Won Park-Simon, Peter Hillemans, Ursula Hille, Michael Bremer, Frank Bruns, Frank Rudolf, Hans Grundtke, Jorg Fruhauf, HH Kreipe, Florian Laenger, Adelheid Klein); Centre Rene Gauducheau,

Nantes, France (Magali Le Blanc-Onfroy, Maud Aumont, Francois Dravet, Magali Dejode, Albert Lisbona, Delphine Loussouarn, Christine Sagan, Nicolas Rougé, Stephanie Gaudaine-Josset); Instituto Oncologico Veneto (Michele Pignataro, Fernando Bozza, Raffaello Grigoletto, Silvia Michieletto, Stefano Valente, Tania Saibene, Franco Berti, Ornella Lora, Marta Pausio, Sonia Reccanello, Davide Canonico, Enrico Orvieto, Marcello Lo Mele, Liliana Spangaro); Hospital of St John and St Elizabeth, London, UK (Katharine Pigott, Punita Vyas, Catherine O'Connor, Donna Gibbs, Simon Stevens, Ashley Richmond, Tabasom Ghaus, Thomas Ashford, Deborah Waters, Mohammed Keshtgar); Institut Bergonie, Bordeaux, France (Marion Fournier, Christine Tunon De Lara, Christelle Breton-Callu, Philippe Lagarde, Sarah Belhomme, Gaetan MacGrogan, Beatrice Gonzalves, Mickael Antoine).

Contributors: JSV, MBa, and JST were responsible for trial concept, trial design, trial management, data interpretation, and writing of the manuscript. FW, DJJ, JST, MBa, and JSV contributed to trial concept, trial design, trial management, training and accreditation of centres, patient accrual and treatment, data collection, data interpretation, and writing of the manuscript. JSV, FW, JST, MBa, SM, HLF, MD, ES, MS, and MA contributed to training and accreditation of centres, patient accrual and treatment, data collection, and writing of the manuscript. JSV, MBa, MBu, and NRW designed the statistical analysis plan and contributed to statistical analysis, trial coordination, data collection, data interpretation, and writing of the manuscript. CS and TC contributed to trial design, patient accrual, patient treatment, data interpretation, and writing of the manuscript. WE, MD, LV, FB, MP, GG, WP, KJD, MN, JB, GP, and MS contributed to patient accrual, patient treatment, data collection, and data interpretation. SM, WE, SP, JSV, ES, MS, MLB, DH, SLa, SLu, DM, RH, PK, and DB contributed to setting up their centres, patient accrual, treatment, and data collection. JSV was involved with design and preclinical tests of the Intrabeam system. CB-G, NR, and IP contributed to training, trial coordination, trial management, data collection, and writing of the manuscript. MF advised about pathological aspects of the trial. MBa reviewed the results and their interpretation, provided patient perspective and contributed to the manuscript. The authors take full responsibility for the manuscript. The initial draft was written by JSV, MBu, JST, and MBa, who revised it by following comments from all other authors and are the guarantors. The chief investigator/corresponding author and the trial statistician had access to all data sent by the trial centre for analysis; all authors were responsible for decision to submit the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The trial was initiated by an academic insight and collaboration with the industry was solely for the development of the device. The manufacturers of the Intrabeam device (Carl Zeiss) did not have any part in concept, design, or management of the trial, or in data analysis, data interpretation, or writing of the report. The study was sponsored by University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre. Funding was provided by UCLH Charities, National Institute for Health Research (NIHR) Health Technology Assessment programme (HTA 07/60/49), Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research (BMBF) FKZ 01ZP0508. The infrastructure of the trial operations office in London, UK was supported by core funding from Cancer Research Campaign (now Cancer Research UK) when the trial was initiated. The funding organisations had no role in concept, design, analysis or writing of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, Ninewells Cancer Campaign, National Health and Medical Research Council, German Federal Ministry of Education and Research (BMBF), and Cancer Research Campaign (now Cancer Research UK) for the submitted work; JSV has received a research grant from Photoelectron Corp (1996-99) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK, 2004-2008), and has received honorariums. JSV, JST, NRW, IP, CBG, and NR receive funding from HTA, NIHR, Department of Health and Social Care for some activities related to the TARGIT trials. MBa was briefly on the scientific advisory board of Carl Zeiss and was paid consultancy fees before 2010. FW has received a research grant from Carl Zeiss for supporting radiobiological research. Carl Zeiss sponsors some of the travel and accommodation for meetings of the international steering committee and data monitoring committee and when necessary for conferences where a presentation about targeted

intraoperative radiotherapy is being made for all authors apart from WE who declares that he has no conflicts of interest. All other authors declare that they have no conflicts of interest.

Ethical approval: The study received ethics approval from the joint University College London and University College London Hospital committees of ethics of human research (99/0307).

Data sharing: University College London 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 and 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 and statistical code 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 acknowledgment of the TARGIT Trialists' Group, investigators, the sponsor, and funders.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to widely disseminate the published paper. We shall use all modern media and engage patients and our own institutional public relations departments.

This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <http://creativecommons.org/licenses/by/4.0/>.

- Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019;144:1941-53. doi:10.1002/ijc.31937
- Baum M, Vaidya JS, Mitra I. Multicentricity and recurrence of breast cancer. *Lancet* 1997;349:208. doi:10.1016/S0140-6736(05)60950-6
- Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mitra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 1996;74:820-4. doi:10.1038/bjc.1996.442
- Vaidya JS, Baum M, Tobias JS, et al. Targeted Intraoperative Radiotherapy (TARGIT)-trial protocol. *Lancet* 1999. <https://www.thelancet.com/protocol-reviews/99PRT-47>.
- Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001;12:1075-80. doi:10.1023/A:1011609401132
- Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *Eur J Surg Oncol* 2002;28:447-54. doi:10.1053/ejso.2002.1275
- Vaidya JS. A novel approach for local treatment of early breast cancer. *PhD Thesis, University College London, University of London* 2002 <https://www.ucl.ac.uk/~rmhkjsv/papers/thesis.htm>
- Vaidya JS, Tobias JS, Baum M. *The TARGIT-A trial protocol* 1999; <https://njl-admin.nihr.ac.uk/document/download/2006598>
- Dirbas FM, Jeffrey SS, Goffinet DR. The evolution of accelerated, partial breast irradiation as a potential treatment option for women with newly diagnosed breast cancer considering breast conservation. *Cancer Biother Radiopharm* 2004;19:673-705. doi:10.1089/cbr.2004.19.673
- Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS. The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol (R Coll Radiol)* 1993;5:278-83. doi:10.1016/S0936-6555(05)80900-8
- Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010;376:91-102. doi:10.1016/S0140-6736(10)60837-9
- Azria D, Bourgiere C. Partial breast irradiation: new standard for selected patients. *Lancet* 2010;376:71-2. doi:10.1016/S0140-6736(10)60898-7
- Vaidya JS, Wenz F, Bulsara M, et al. TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383:603-13. doi:10.1016/S0140-6736(13)61950-9
- Dodwell DJ, Dyker K, Brown J, et al. A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. *Clin Oncol (R Coll Radiol)* 2005;17:618-22. doi:10.1016/j.clon.2005.07.018
- Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013;14:1269-77. doi:10.1016/S1470-2045(13)70497-2
- Polgár C, Fodor J, Major T, Sulyok Z, Kásler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202. doi:10.1016/j.radonc.2013.05.008
- Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015;51:451-63. doi:10.1016/j.ejca.2014.12.013
- Strnad V, Ott OJ, Hildebrandt G, et al. Groupe Européen de Curiothérapie de European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016;387:229-38. doi:10.1016/S0140-6736(15)00471-7
- Coles CE, Griffin CL, Kirby AM, et al. IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017;390:1048-60. doi:10.1016/S0140-6736(17)31145-5
- Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet* 2019;394:2155-64. doi:10.1016/S0140-6736(19)32514-0
- Whelan TJ, Julian JA, Berrang TS, et al. RAPID Trial Investigators. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet* 2019;394:2165-72. doi:10.1016/S0140-6736(19)32515-2
- Aziz MH, Schneider F, Clausen S, et al. Can the risk of secondary cancer induction after breast conserving therapy be reduced using intraoperative radiotherapy (IORT) with low-energy x-rays? *Radiat Oncol* 2011;6:174. doi:10.1186/1748-717X-6-174
- Tobias JS, Vaidya JS, Keshitgar M, D'Souza DP, Baum M. Reducing radiotherapy dose in early breast cancer: the concept of conformal intraoperative brachytherapy. *Br J Radiol* 2004;77:279-84. doi:10.1259/bjr/17186381
- Herskind C, Steil V, Kraus-Tiefenbacher U, Wenz F. Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X rays for early-stage breast cancer. *Radiat Res* 2005;163:208-15. doi:10.1667/RR3292
- Enderling H, Chaplain MA, Anderson AR, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. *J Theor Biol* 2007;246:245-59. doi:10.1016/j.jtbi.2006.12.010
- Herskind C, Wenz F. Radiobiological comparison of hypofractionated accelerated partial-breast irradiation (APB) and single-dose intraoperative radiotherapy (IORT) with 50-kV X-rays. *Strahlenther Oncol* 2010;186:444-51. doi:10.1007/s00066-010-2147-9
- Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and noninferiority testing. *Biol Blood Marrow Transplant* 2009;15(Suppl):120-7. doi:10.1016/j.bbmt.2008.10.004
- Alvarado MD, Conolly J, Park C, et al. Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. *Breast Cancer Res Treat* 2014;143:135-40. doi:10.1007/s10549-013-2782-9
- Corica T, Joseph D, Saunders C, Bulsara M, Nowak AK. Intraoperative radiotherapy for early breast cancer: do health professionals choose convenience or risk? *Radiat Oncol* 2014;9:33. doi:10.1186/1748-717X-9-33
- Spaich S, Krickeberg S, Hetjens S, Wenz F, Gerhardt A, Sütterlin M. Patient preferences regarding intraoperative versus external beam radiotherapy for early breast cancer and the impact of socio-demographic factors. *Arch Gynecol Obstet* 2019;299:1121-30. doi:10.1007/s00404-018-5025-9
- Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-106. doi:10.1016/S0140-6736(05)67887-7
- Earl HM, Hiller L, Vallier A-L, et al. PERSEPHONE Steering Committee and Trial Investigators. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-

- inferiority trial. *Lancet* 2019;393:2599-612. doi:10.1016/S0140-6736(19)30650-6
- 33 Gourgou-Bourgade S, Cameron D, Poortmans P, et al. Definition for the Assessment of Time-to-event Endpoints in Cancer Trials Initiative. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann Oncol* 2015;26:873-9. doi:10.1093/annonc/mdv106
- 34 Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007;25:2127-32. doi:10.1200/JCO.2006.10.3523
- 35 Laster LL, Johnson MF, Kotler ML. Non-inferiority trials: the 'at least as good as' criterion with dichotomous data. *Stat Med* 2006;25:1115-30. doi:10.1002/sim.2476
- 36 Smits PC, Hofma S, Togni M, et al. Abluminal biodegradable polymer bioluminescent stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet* 2013;381:651-60. doi:10.1016/S0140-6736(12)61852-2
- 37 Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet* 2002;359:1686-9. doi:10.1016/S0140-6736(02)08594-X
- 38 Vaidya JS, Baum M. Clinical and biological implications of the Milan breast conservation trials. *Eur J Cancer* 1998;34:1143-4
- 39 Belletti B, Vaidya JS, D'Andrea S, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clin Cancer Res* 2008;14:1325-32. doi:10.1158/1078-0432.CCR-07-4453
- 40 Segatto I, Berton S, Sonogo M, et al. Surgery-induced wound response promotes stem-like and tumor-initiating features of breast cancer cells, via STAT3 signaling. *Oncotarget* 2014;5:6267-79. doi:10.18632/oncotarget.2195
- 41 Segatto I, Berton S, Sonogo M, et al. p70S6 kinase mediates breast cancer cell survival in response to surgical wound fluid stimulation. *Mol Oncol* 2014;8:766-80. doi:10.1016/j.molonc.2014.02.006
- 42 Fabris L, Berton S, Citron F, et al. Radiotherapy-induced miR-223 prevents relapse of breast cancer by targeting the EGF pathway. *Oncogene* 2016;35:4914-26. doi:10.1038/ncr.2016.23
- 43 Coombs NJ, Coombs JM, Vaidya UJ, et al. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open* 2016;6:e010703. doi:10.1136/bmjopen-2015-010703
- 44 Andersen KG, Gärtner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial. *Breast* 2012;21:46-9. doi:10.1016/j.breast.2011.07.011
- 45 Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiat Oncol* 2013;8:9. doi:10.1186/1748-717X-8-9
- 46 Keshthgar MR, Williams NR, Bulsara M, et al. Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial. *Breast Cancer Res Treat* 2013;140:519-25. doi:10.1007/s10549-013-2641-8
- 47 Corica T, Nowak AK, Saunders CM, et al. Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: a substudy of the TARGIT-A trial. *Int J Radiat Oncol Biol Phys* 2016;96:55-64. doi:10.1016/j.ijrobp.2016.04.024
- 48 Taylor C, Correa C, Duane FK, et al. Early Breast Cancer Trialists' Collaborative Group. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017;35:1641-9. doi:10.1200/JCO.2016.72.0722
- 49 Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-98. doi:10.1056/NEJMoa1209825
- 50 Burt LM, Ying J, Poppe MM, Suneja G, Gaffney DK. Risk of secondary malignancies after radiation therapy for breast cancer: Comprehensive results. *Breast* 2017;35:122-9. doi:10.1016/j.breast.2017.07.004
- 51 Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiother Oncol* 2015;114:56-65. doi:10.1016/j.radonc.2014.10.004
- 52 Bansod S, Desai R. Nationwide prevalence and trends of acute cardiovascular and cerebrovascular events among adult breast cancer survivors with a history of radiation therapy. *Breast Cancer Res Treat* 2020;180:267-8. doi:10.1007/s10549-020-05535-3
- 53 Vaidya JS, Bulsara M, Wenz F, et al. Reduced mortality with partial-breast irradiation for early breast cancer: a meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* 2016;96:259-65. doi:10.1016/j.ijrobp.2016.05.008
- 54 Vaidya JS, Bulsara M, Wenz F, Tobias JS, Joseph D, Baum M. Targeted radiotherapy for early breast cancer. *Lancet* 2018;391:26-7. doi:10.1016/S0140-6736(17)33316-0
- 55 Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006;444:875-80. doi:10.1038/nature05487
- 56 Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. *J Natl Cancer Inst* 2015;107:djv088. doi:10.1093/jnci/djv088
- 57 Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev* 2016;7:CD007077. doi:10.1002/14651858.CD007077.pub3
- 58 Strnad V, Ott OJ, Hildebrandt G, et al. Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016;387:229-38. doi:10.1016/S0140-6736(15)00471-7
- 59 Alvarado M, Ozanne E, Mohan A, et al. Cost-effectiveness of intraoperative radiation therapy for breast conservation. *J Clin Oncol* 2011;29:6081. doi:10.1200/jco.2011.29.15_suppl.6081
- 60 Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare TARGIT Intraoperative Radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). *Health Technol Assess* 2016;20. doi:10.3310/hta20730
- 61 Vaidya A, Vaidya P, Both B, Brew-Graves C, Bulsara M, Vaidya JS. Health economics of targeted intraoperative radiotherapy (TARGIT-IORT) for early breast cancer: a cost-effectiveness analysis in the United Kingdom. *BMJ Open* 2017;7:e014944. doi:10.1136/bmjopen-2016-014944
- 62 Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 2000;92:269-71. doi:10.1093/jnci/92.3.269
- 63 Goyal S, Chandwani S, Haffty BG, Demissie K. Effect of travel distance and time to radiotherapy on likelihood of receiving mastectomy. *Ann Surg Oncol* 2015;22:1095-101. doi:10.1245/s10434-014-4093-8
- 64 Marmot M, Altman G, Cameron DA, Dewar JA, Thompson SG, Wilcox M. Independent UK Panel on Breast Cancer Screening. Independent UK Panel on Breast Cancer Screening replies to Michael Baum. *BMJ* 2013;346:f873. doi:10.1136/bmj.f873
- 65 The Supreme Court U. *Montgomery v Lanarkshire Health Board*. In: Kingdom SCoU, ed. [2015] UKSC 11. United Kingdom: The Supreme Court, 2015:1-37.

Web appendix: e-Figures