Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival

Vaidya, Jayant S.; Bulsara, Max; Saunders, Christobel; Flyger, Henrik; Tobias, Jeffrey S.; Corica, Tammy

Published in:
JAMA Oncology

DOI:
10.1001/jamaoncol.2020.0249

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

JAMA Oncology | Original Investigation

Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival
Long-term Results From the TARGIT-A Randomized Clinical Trial in Early Breast Cancer

Jayant S. Vaidya, MBBS, MS, DNB, PhD; Max Bulsara, PhD; Christobel Saunders, MBBS; Henrik Flyger, MD; Jeffrey S. Tobias, MD; Tammy Corica, PhD; Samuele Massarut, MD; Frederik Wenz, MD; Steffi Pigorsch, MD; Michael Alvarado, MD; Michael Douek, MD; Wolfgang Eiermann, MD; Chris Brew-Graves, MSc; Norman Williams, PhD; Ingrid Potyka, PhD; Nicholas Roberts, BSc; Marcelle Bernstein; Douglas Brown, MD; Elena Sperk, MD; Siobhan Laws, MD; Marc Sütterlin, MD; Steinar Lundgren, MD, PhD; Dennis Holmes, MD; Lorenzo Vinante, MD; Fernando Bozza, MD; Montserrat Pazos, MD; Magali Le Blanc-Onfroy, MD; Günther Gruber, MD; Wojciech Polkowski, MD; Konstantin J. Dedes, MD; Marcus Niewald, MD, PhD; Jens Blohmer, MD, PhD; David McCready, MD; Richard Hoefer, MD; Pond Kelemen, MD; Gloria Petralia, MD; Mary Falzon, MD; Michael Baum, MD; David Joseph, MD

IMPORTANCE Conventional adjuvant radiotherapy for breast cancer given daily for several weeks is onerous and expensive. Some patients may be obliged to choose a mastectomy instead, and some may forgo radiotherapy altogether. We proposed a clinical trial to test whether radiotherapy could be safely limited to the tumor bed.

OBJECTIVE To determine whether delayed second-procedure targeted intraoperative radiotherapy (TARGIT-IORT) is noninferior to whole-breast external beam radiotherapy (EBRT) in terms of local control.

DESIGN, SETTING, AND PARTICIPANTS In this prospective, randomized (1:1 ratio) noninferiority trial, 1153 patients aged 45 years or older with invasive ductal breast carcinoma smaller than 3.5 cm treated with breast conservation were enrolled from 28 centers in 9 countries. Data were locked in on July 3, 2019.

INTERVENTIONS The TARGIT-A trial was started in March 2000; patients were randomized after needle biopsy to receive TARGIT-IORT immediately after lumpectomy under the same anesthetic vs EBRT and results have been shown to be noninferior. A parallel study, described in this article, was initiated in 2004; patients who had their cancer excised were randomly allocated using separate randomization tables to receive EBRT or delayed TARGIT-IORT given as a second procedure by reopening the lumpectomy wound.

MAIN OUTCOMES AND MEASURES A noninferiority margin for local recurrence rate of 2.5% at 5 years, and long-term survival outcomes.

RESULTS Overall, 581 women (mean [SD] age, 63 [7] years) were randomized to delayed TARGIT-IORT and 572 patients (mean [SD] age, 63 [8] years) were randomized to EBRT. Sixty patients (5%) had tumors larger than 2 cm, or had positive nodes and only 32 (2.7%) were younger than 50 years. Delayed TARGIT-IORT was not noninferior to EBRT. The local recurrence rates at 5-year complete follow-up were: delayed TARGIT-IORT vs EBRT (23/581 [3.96%] vs 6/572 [1.05%], respectively; difference, 2.91%; upper 90% CI, 4.4%). With long-term follow-up (median [IQR], 9.0 [7.5-10.5] years), there was no statistically significant difference in local recurrence-free survival (HR, 0.75; 95% CI, 0.57-1.003; $P = .052$), mastectomy-free survival (HR, 0.88; 95% CI, 0.65-1.18; $P = .38$), distant disease-free survival (HR, 1.00; 95% CI, 0.72-1.39; $P = .98$), or overall survival (HR, 0.96; 95% CI, 0.68-1.35; $P = .80$).

CONCLUSIONS AND RELEVANCE These long-term data show that despite an increase in the number of local recurrences with delayed TARGIT-IORT, there was no statistically significant decrease in mastectomy-free survival, distant disease-free survival, or overall survival.

TRIAL REGISTRATION ISRCTN34086741, ClinicalTrials.gov Identifier: NCT00983684

JAMA Oncol. 2020;6(7):e200249. doi:10.1001/jamaoncol.2020.0249
Published online April 2, 2020. Corrected on May 21, 2020.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jayant S. Vaidya, MBBS, MS, DNB, PhD, Division of Surgery and Interventional Science, University College London, 43-45 Foley St, London W1W 7JN, United Kingdom (jayantvaidya@gmail.com).

In 2018, there were 2 million new cases of breast cancer diagnosed worldwide and 626 000 deaths.[1] Most patients are suitable for treatment with breast-conserving surgery and adjuvant radiotherapy, rather than total mastectomy. The TARGIT-A randomized clinical trial (accrual from 2000-2012) compared risk-adapted TARGeted intraoperative radiotherapy (TARGIT-IORT) during the initial surgical excision of the cancer[2-5] with conventional whole-breast external beam radiotherapy (EBRT) over several weeks.[2,6,7] The results of this trial demonstrated noninferiority particularly when TARGIT-IORT was delivered at the time of initial excision of cancer.

In 2004, 4 years after accrual began in the main TARGIT-A trial, and at the request of potentially high-volume centers, we sought and received additional ethics approval and opened a parallel study. This was previously referred to as "postpathology stratum" and recruited 1153 patients using a separate randomization table. Patients were randomized after their initial surgery to have either conventional fractionated whole-breast radiotherapy (n = 572), or to undergo a further operation to deliver delayed radiotherapy to the wound (n = 581) by reopening the original incision. This trial was initiated mainly because of the convenience of easier scheduling of delayed TARGIT-IORT in the operation theater. A potential benefit was that the inclusion criteria could be made more selective, choosing the patients with better prognosis based on the full histopathologic results that would be available after tumor excision. For example, the knowledge of the

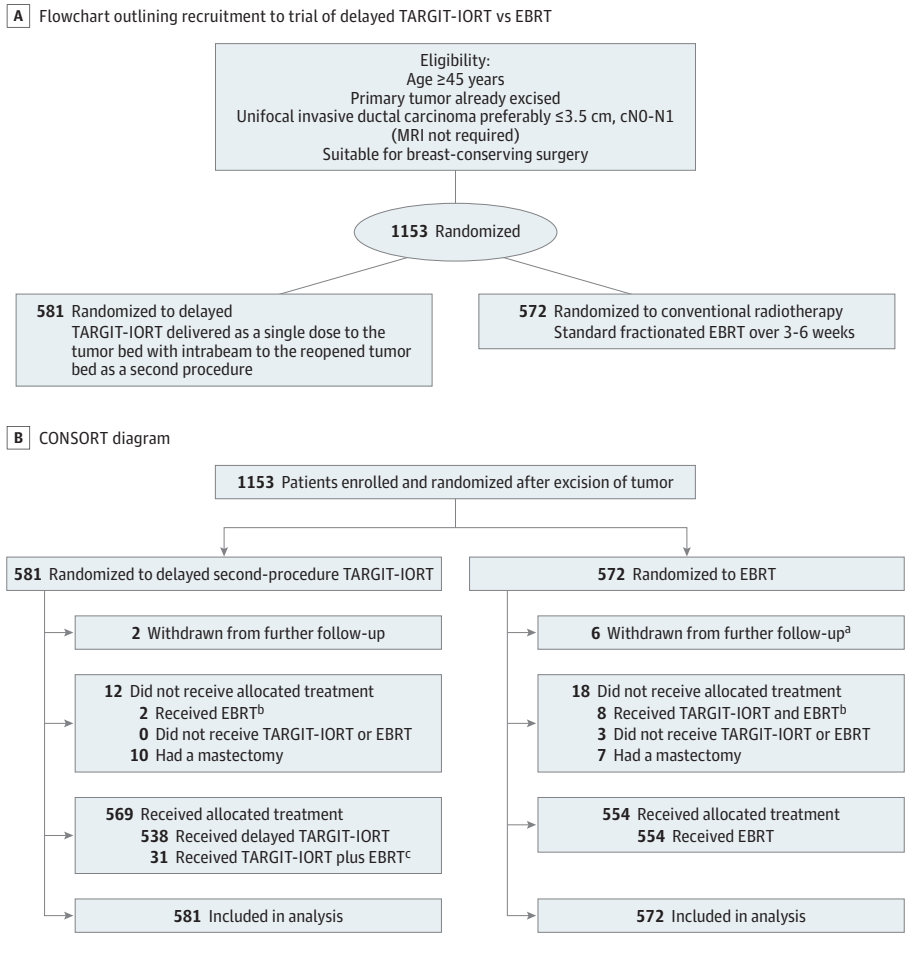
Key Points

Question For early breast cancer, is 5-year local control with delayed second-procedure targeted intraoperative radiotherapy (TARGIT-IORT) noninferior to whole-breast postoperative external beam radiotherapy (EBRT), and how do long-term outcomes compare?

Findings In this randomized clinical trial including 1153 participants, delayed second-procedure TARGIT-IORT was not noninferior to EBRT at 5-year complete follow-up; however, long-term (median 9 years) mastectomy-free survival, distant disease-free survival, and overall survival were not different.

Meaning For early breast cancer, delayed second-procedure single-dose TARGIT-IORT given by reopening the lumpectomy wound had similar long-term mastectomy-free and overall survival compared with EBRT despite higher local recurrence.

Figure 1. Flowchart and CONSORT Diagram



EBRT indicates whole-breast external beam radiotherapy; MRI, magnetic resonance imaging; TARGIT-IORT, targeted intraoperative radiotherapy. A, Flowchart outlining recruitment to trial of delayed TARGIT-IORT vs EBRT. B, CONSORT diagram of participant randomization.

[a] The difference in number withdrawn was not statistically significant ($P = .15$).

[b] As per protocol, 31 of 581 patients (5.3 %) allocated to delayed TARGIT-IORT received EBRT after TARGIT-IORT.

[c] Two of 581 patients (0.3%) allocated to delayed TARGIT-IORT received EBRT and 8 of 572 (1.4%) allocated EBRT received TARGIT-IORT as well.

Table 1. Patient and Tumor Characteristics

Characteristic	No. (%)[a] Delayed TARGIT-IORT (n = 581)	EBRT (n = 572)	*P* value[b]
Age, y			
≤50	30 (5.2)	23 (4.02)	.54
51-60	166 (28.6)	171 (29.9)	
61-70	302 (52.0)	284 (49.7)	
>70	83 (14.3)	94 (16.4)	
Pathologic tumor size, mm			
≤10	294 (51.0)	290 (51.8)	.79
11-20	249 (43.2)	243 (43.4)	
>20	33 (5.7)	27 (4.8)	
Unknown	5 (0.9)	12 (2.1)	
Grade			
1	305 (56.5)	339 (63.8)	.06
2	204 (37.8)	159 (29.9)	
3	31 (5.7)	33 (6.2)	
Unknown	41 (7.1)	41 (7.2)	
Margin			
Free	539 (92.9)	520 (92.4)	.46
DCIS only	16 (2.8)	18 (3.2)	
Invasive	25 (4.3)	25 (4.5)	
Unknown	1 (0.2)	9 (1.6)	
Lymphovascular invasion			
Absent	536 (94.7)	533 (96.6)	.13
Present	30 (5.3)	19 (3.4)	
Unknown	15 (2.6)	20 (3.5)	
Lymph nodes involved			
0	543 (93.6)	537 (95.2)	.39
1-3	34 (5.9)	26 (4.6)	
>3	3 (0.5)	1 (0.2)	
Unknown	1 (0.2)	8 (1.4)	
ER status			
Positive	569 (98.3)	550 (97.9)	.62
Negative	10 (1.7)	12 (2.1)	
Unknown	2 (0.3)	10 (1.7)	
PgR status			
Positive	440 (81.8)	423 (82.0)	.94
Negative	98 (18.2)	93 (18.0)	
Unknown	43 (7.4)	56 (9.8)	
ERBB2 status			
Positive	30 (5.4)	33 (6.0)	.65
Negative	526 (94.6)	515 (94.0)	
Unknown	25 (4.3)	24 (4.2)	
Method of presentation			
Screen detected	420 (73.6)	395 (70.5)	.26
Symptomatic	151 (26.4)	165 (29.5)	
Unknown	10 (1.7)	12 (2.1)	
Endocrine therapy			
Received	336 (58.0)	334 (59.4)	.63
Did not receive	243 (42.0)	228 (40.6)	
Unknown	2 (0.3)	10 (1.8)	
Chemotherapy			
Received	26 (4.5)	14 (2.5)	.07
Did not receive	553 (95.5)	546 (97.5)	
Unknown	2 (0.3)	12 (2.1)	

Abbreviations: DCIS, ductal carcinoma in situ; EBRT, whole-breast external beam radiotherapy; ER, estrogen receptor; PgR, progesterone receptor; TARGIT-IORT, targeted intraoperative radiotherapy.

[a] For percentage calculation, the denominator for unknown percentages is the total number randomized (581 and 572) and the denominator for each category is the total number of known cases.

[b] *P* values are given for differences between TARGIT-IORT and EBRT, calculated using a χ^2 test for known values.

microscopically measured tumor size, grade, and nodal status could be used to select a much lower-risk patient population before randomization.

This delayed procedure was performed at a median (IQR) of 37 (29-51) days after the initial excision as a second surgical procedure in the operation theater, rather than immediate intraoperative radiotherapy given during the initial cancer operation. This article describes the long-term outcomes of this parallel study.

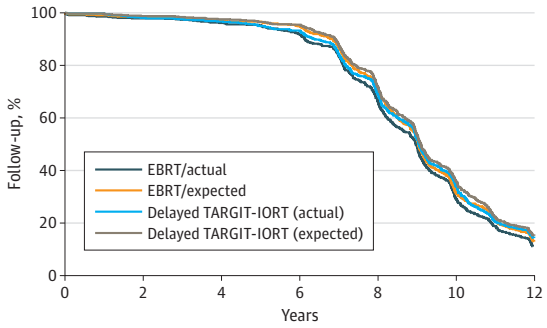
Methods

The TARGIT-A trial was a pragmatic, prospective, international, multicenter, open label, randomized, phase 3 trial that compared the policy of risk-adapted TARGIT-IORT vs the conventional policy of whole-breast EBRT. The trial protocol (https://njl-admin.nihr.ac.uk/document/download/2006598) and the details of sample size calculations, the process of random allocation, have been previously described.[6,7] The trial protocol is available in Supplement 1. The study received ethics approval from the joint University College London and University College London Hospital committees of ethics of human research.

Participants

Women were eligible to participate in the delayed TARGIT-IORT trial if their breast cancer was already excised. They needed to be aged 45 years or older with unifocal breast cancer on examination and conventional imaging. Pragmatically, we permitted individual centers to prespecify the final postoperative histopathologic criteria that would make patients eligible for randomization and these were prespecified in the center's treatment policy document. Because most centers specified criteria for eligibility: aged 50 years or older, grade 1 or 2 disease, and uninvolved nodes, only 5% of patients in the trial had any adverse prognostic criteria. All patients gave informed written consent and needed to be available for regular follow-up for at least 10 years. Follow-up clinical examination was at least every 6 months for the first 5 years and annually thereafter, including a mammogram once per year.

Figure 2. Actual Follow-up and Expected Follow-up for the Trial of Delayed Second-Procedure TARGIT-IORT vs EBRT



No. at risk							
EBRT/actual	572	560	550	526	379	167	63
EBRT/expected	572	563	555	543	406	180	74
Delayed TARGIT-IORT (actual)	581	570	562	542	402	197	83
Delayed TARGIT-IORT (expected)	581	574	567	555	417	208	88

EBRT indicates whole-breast external beam radiotherapy; TARGIT-IORT, targeted intraoperative radiotherapy.

Random allocation was in a 1:1 ratio, to receive either single-dose delayed TARGIT-IORT or EBRT as per standard schedules over several weeks, with randomization blocks stratified by center. The flow diagram and CONSORT diagram are given in **Figure 1**A and B.

The concept and the delayed TARGIT-IORT technique have been described previously[3-5,8-11] and enabled these patients to have their radiotherapy in 1 sitting, albeit by undergoing a second procedure, usually under a general anesthetic.[12] Radiation was given over 20 to 50 minutes delivering 20 Gy to the surface of the tumor bed attenuating to 5 to 7 Gy at 1-cm depth.

The patients in the conventional arm underwent standard EBRT, which always included fractionated whole-breast radiotherapy for 3 to 6 weeks, with or without an EBRT tumor bed boost, as determined by local criteria prespecified by the collaborating center.

Statistical Analysis

The statistical analysis plan (Supplement 1) was signed off on 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. It specified the primary outcome as local recurrence-free survival. This outcome, consistent with the DATECAN[13] and STEEP[14] guidelines, estimates the chance of a patient being alive without local recurrence and therefore included local recurrence or death as events, ie, patients who had died were not censored. The other outcomes included mastectomy-free survival, distant disease-free survival, overall survival, breast cancer mortality and non-breast cancer mortality. Statistical analysis was performed using established methods, using STATA statistical software (versions 15.0 and 16.0, STATA Corp) for data compilation, validation, and analysis.[13-15] Data analysis took place between September 11, 2019 to January 15, 2020.

In the original protocol, noninferiority was specified as being achieved if the difference in 5-year local recurrence rate did not cross a stringent margin of 2.5%. However, we have applied an even more rigorous criterion since 2013: that the upper 90% CI of the absolute difference in the binomial proportions of local recurrence rate at 5-year complete follow up should not cross 2.5% in absolute terms.

Kaplan-Meier graphs were displayed as recommended by Pocock et al,[16] who recommend that the x-axis of these graphs should be extended until 10% to 20% of patients are at risk of an event. The log-rank test was used to compare the difference between survival functions and to obtain *P* values.

Main Outcomes and Measures

The cause of death was specified by the center. If the cause 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 center 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.

Figure 1B shows the CONSORT diagram, which describes the treatment received in each of the randomized arms. The reference date for completeness was May 2, 2018, 8 years after the first data lock. A patient was considered as having complete follow-up if they were seen for the specified duration of follow-up, had died, or had withdrawn from the trial. As the last patient was randomized in 2012, the statistical analysis plan specified that the 5-year follow-up would be considered complete if 95% of patients had complete follow-up. It also specified that 10-year follow-up would be considered complete if the patient had at least 10 years of follow-up, had been seen within 1 year of the reference date, or had died or withdrawn; the 10-year follow-up would be considered complete if this was achieved by 90% of patients. Because there was no specific trial funding for individual centers, return of follow-up relied on individual investigators and their teams' efforts, enthused by the trial-center team. The trial statistician and the chief investigator produced reports of completeness of follow up using blinded databases on a regular basis. As recommended by the independent steering committee, the database was unblinded for analysis once the prespecified goals for completeness of follow up were achieved. The reference date for analy-

Table 2. Twelve-Year Kaplan-Meier Estimates of Outcomes Measures for TARGIT-IORT vs EBRT

	Delayed TARGIT-IORT (n = 581)		EBRT (n = 572)		Significance test for the full follow-up	
Outcomes	Events	Kaplan-Meier estimates (95% CI)	Events	Kaplan-Meier estimates (95% CI)	HR (95% CI)	*P* value for log rank
Local recurrence-free survival[a]						
Estimate					0.75 (0.57-1.003)	.052
5-y	41	92.87 (90.44-94.70)	19	96.63 (94.77-97.84)		
10-y	98	80.16 (76.19-83.54)	72	84.36 (80.51-87.51)		
12-y	106	75.30 (70.13-79.72)	79	78.38 (72.32-83.27)		
Invasive local recurrence-free survival[a]						
Estimate					0.75 (0.56-1.002)	.051
5-y	38	93.39 (91.03-95.15)	17	96.99 (95.20-98.12)		
10-y	95	80.68 (76.73-84.02)	68	85.15 (81.35-88.23)		
12-y	103	75.87 (70.72-80.24)	75	79.23 (73.23-84.04)		
Mastectomy-free survival[a]						
Estimate					0.88 (0.65-1.18)	.38
5-y	39	93.24 (90.87-95.02)	23	95.93 (93.93-97.27)		
10-y	82	83.79 (80.14-86.83)	75	83.82 (79.94-87.01)		
12-y	92	77.80 (72.57-82.16)	79	80.44 (75.16-84.71)		
Distant disease-free survival[a]						
Estimate					1.00 (0.72-1.39)	.98
5-y	26	95.49 (93.44-96.90)	18	96.80 (94.97-97.97)		
10-y	62	87.50 (84.13-90.19)	62	86.91 (83.37 89.74)		
12-y	71	81.98 (76.91-86.04)	67	82.18 (76.44-86.65)		
Overall survival						
Estimate					0.96 (0.68-1.35)	.80
5-y	19	96.70 (94.87-97.88)	13	97.69 (96.06-98.65)		
10-y	56	88.62 (85.35-91.19)	56	87.77 (84.22-90.56)		
12-y	65	83.13 (78.11-87.10)	59	84.72 (79.52-88.70)		
Breast cancer mortality						
Estimate					0.81 (0.43-1.52)	.50
5-y	9	1.58 (0.82-3.01)	4	0.72 (0.27-1.90)		
10-y	20	3.79 (2.45-5.83)	16	3.50 (2.11-5.77)		
12-y	21	4.39 (2.77-6.93)	17	4.63 (2.52-8.43)		
Mortality from other causes						
Estimate					1.02 (0.68-1.55)	.89
5-y	10	1.75 (0.95-3.23)	9	1.60 (0.84-3.06)		
10-y	36	7.90 (5.69-10.90)	40	9.05 (6.62-12.31)		
12-y	44	13.05 (9.35-18.05)	42	11.17 (7.78-15.88)		

Abbreviations: EBRT, whole-breast external beam radiotherapy; HR, hazard ratio; TARGIT-IORT, targeted intraoperative radiotherapy.

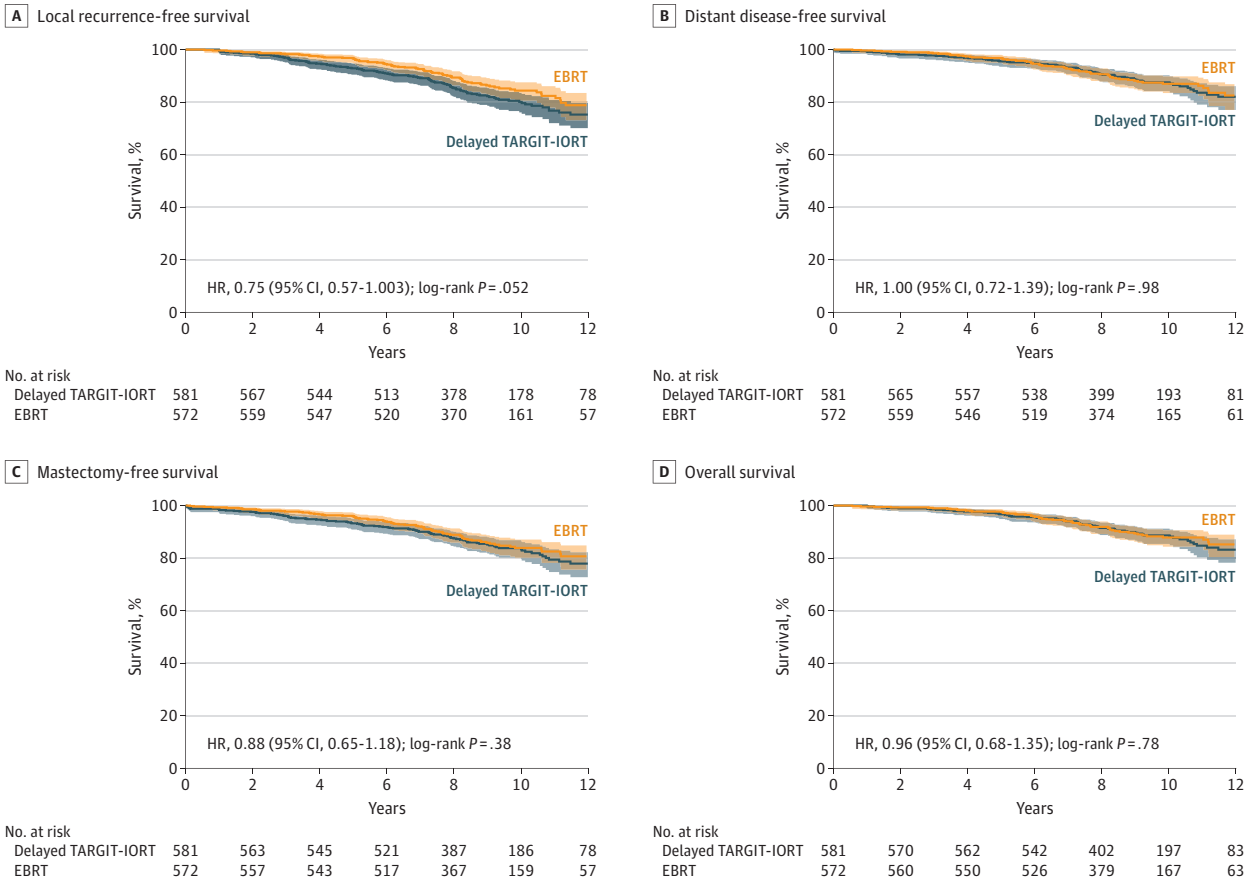
[a] Each of these survival measures include death as an event.

sis was 3 July 2019, so that all events up until 2 July 2019 were included for analysis. The chief investigator/corresponding author and the trial statistician (J.S.V. and Ma.B.) had access to all data sent by the trial center for analysis; all authors were responsible for the decision to submit the article. Since the last analysis, the trial oversight has been provided by an independent steering committee, appointed by the Health Technology Assessment program of the National Institute of Health Research, Department of Health, United Kingdom.

Results

Overall, 581 women were randomized to delayed TARGIT-IORT and 572 to EBRT. The patient and tumor characteristics are given in **Table 1** and were well matched between the randomization arms. Most patients were estrogen receptor positive (1119 [98%]), *ERBB2* negative (1041 [94%]); 670 patients (58%) received endocrine therapy, and 40 (3.5%) received che-

Figure 3. Twelve-Year Kaplan-Meier Curves Comparing Delayed Second-Procedure TARGIT-IORT vs EBRT



EBRT indicates whole-breast external beam radiotherapy; TARGIT-IORT, targeted intraoperative radiotherapy. In each of these Kaplan-Meier graphs, the blue lines represent delayed TARGIT-IORT with light blue shading indicating the 95% confidence intervals. The orange lines represent EBRT with light orange shading indicating the 95% confidence intervals.

motherapy. The completeness of follow-up is demonstrated in **Figure 2**.

At 5-year complete follow-up, the local recurrence rates were TARGIT-IORT, 23 (including 3 DCIS) of 581 (3.96%) vs EBRT, 6 (including 2 DCIS) of 572 (1.05%), giving a difference of 2.9% with its upper 90% CI of 4.4, which crossed the noninferiority margin of 2.5%.

Kaplan-Meier estimates and log-rank *P* values for delayed TARGIT-IORT vs EBRT are given in **Table 2** and **Figure 3**. The median follow-up was 9 years and the differences between delayed TARGIT-IORT and EBRT were not statistically significant for local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, distant disease-free survival, breast cancer mortality, non-breast cancer mortality, and overall survival. No patients had uncontrolled local recurrence at the time of death.

Discussion

The TARGIT-A trial was originally conceived because of the clinicopathologic observation that local recurrence after breast-conserving surgery occurs predominantly in the index quadrant,[17,18] despite the fact that more than 60% of patients suitable for breast conserving surgery are known to have microscopic foci of the disease outside the index quadrant.[17-19]

The delayed TARGIT-IORT approach was proposed mainly for logistical reasons. It allowed better planning of operation theaters as well as theoretically stricter selection of patients with low-risk disease based on final histopathologic analysis results. It also allowed using TARGIT-IORT in patients coming to a cancer center after having had their cancer excised in a smaller or remote hospital. Concordant with the results of our 2013 analysis, with mature follow-up (5 years complete follow-up with a median of 9 years) delayed TARGIT-IORT was found not to be noninferior to EBRT in terms of local control, with the upper 90% confidence limit of the 2.9% absolute difference in the 5-year local recurrence rate being 4.4%, which is above our stringent 2.5% noninferiority margin.

This noninferiority margin of 2.5% was decided after considerable thought,[6] and is much more stringent than the 7% margin set in the in the ELIOT trial, the only other trial to our knowledge of intraoperative radiotherapy.[20] We believe that it is important to consider how much the absolute differ-

ences seen in the trial matter to the patient. When considering treatments for patients with early breast cancer, local recurrence has been given great importance because of the perceived risk of consequent mastectomy, the danger of distant disease, and the potentially lower survival. The long-term data show that there was no impairment of mastectomy-free survival, distant disease-free survival, or overall survival, up to 12 years from randomization (Figure 3). Moreover, quality of life studies have shown that despite having a second procedure, the quality of life and patient-reported outcomes, such as cosmesis, breast-related quality of life, and breast pain, have been demonstrated to be superior with TARGIT-IORT,[21,22] and this approach is preferred by patients even in the face of a hypothetically higher local recurrence risk.[23,24] These findings may mitigate some of the patient concerns, and results of further patient preference research would help these discussions.

Limitations

The reasons for higher local recurrence with delayed second-procedure TARGIT-IORT may be multifactorial. First, the propensity of tumor recurrence in the index quadrant could be owing to a tumor promoting effect of the microenvironment of the surgical wound,[25-27] a risk that has been shown to be beneficially manipulated by TARGIT-IORT to the fresh tumor bed,[25,27,28] but perhaps not when TARGIT-IORT is given as a delayed second procedure. Second, the surgical procedure of lumpectomy has changed. Early on in the trial, the tissues around the tumor bed were often not approximated after lumpectomy, and the tumor bed remained easily identifiable as a fluid-filled cavity at the time of the second procedure, although some healing had already occurred and fibrosis was setting in by the time the delayed TARGIT-IORT was delivered (median, 37 days later). A limitation of the study was that we did not anticipate a change in surgical practice in later years, such that the tumor bed was approximated after tumor excision rather than leaving a cavity. The resultant scarring could have made it difficult to accurately locate the primary tumor bed. Given the rapid attenuation of dose, with distance from the applicator surface, adequate dose may not have reached the original tumor bed. Finally, one can also speculate that the additional surgical trauma owing to the necessary second procedure in every case of delayed TARGIT-IORT could stimulate residual cancer cells. Notwithstanding these theoretical reasons, the final judgments must be based on the long-term outcomes data.

Conclusions

Partial breast irradiation was heralded as a new standard[29] at the time of the first publication of the TARGIT-A trial[6] and several other supporting clinical trials have since been published: including the ELIOT trial,[20] interstitial wire-brachytherapy,[30] and partial breast EBRT.[31,32] Based on the randomized evidence of immediate TARGIT-IORT, which has been shown to be an effective alternative to EBRT,[6,7,33] it is clear that the preferred timing of using TARGIT-IORT is immediately—during the initial surgical excision of breast cancer. However, when immediate TARGIT-IORT has not been possible, the long-term data presented in this article may help inform discussions by clinicians and patients who wish to avoid a prolonged postoperative course of EBRT.

ARTICLE INFORMATION

Accepted for Publication: January 16, 2020.

Published Online: April 2, 2020. doi:10.1001/jamaoncol.2020.0249

Correction: This article was corrected on May 21, 2020, to change the liscensing type to open access CC-BY type and to correct an error in Figure 1B.

Author Affiliations: Division of Surgery and Interventional Science, University College London, London, United Kingdom (Vaidya, Bulsara, Brew-Graves, Williams, Potyka, Roberts, Baum); Department of Biostatistics, University of Notre Dame, Fremantle, West Australia, Australia (Bulsara); University of Western Australia School of Surgery, West Australia, Australia (Saunders); Department of Breast Surgery, University of Copenhagen, Copenhagen, Denmark (Flyger); Department of Clinical Oncology, University College London Hospitals, London, United Kingdom (Tobias); Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, West Australia, Australia (Corica, Joseph); Department of Surgery, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy (Massarut); University Medical Center Mannheim, Department of Radiation Oncology, Medical Faculty Mannheim, Heidelberg University, Germany (Wenz, Sperk); Red Cross Hospital, Department of Gynecology and Obstetrics, Technical University of Munich, Munich, Germany (Pigorsch, Eiermann); Department of Surgery, University of California, San Francisco (Alvarado); Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom (Douek); Patient Advocate and Writer, London, United Kingdom (Bernstein); Department of Surgery, Ninewells Hospital, Dundee, United Kingdom (Brown); Department of Surgery, Royal Hampshire County Hospital, Winchester, United Kingdom (Laws); University Medical Center Mannheim, Department of Gynecology and Obstetrics, Medical Faculty Mannheim, Heidelberg University, Germany (Sütterlin); Department of Oncology, St Olav's University Hospital, Trondheim, Norway (Lundgren); Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway (Lundgren); Helen Rey Breast Cancer Foundation, John Wayne Cancer Institute, University of Southern California, Los Angeles (Holmes); Department of Radiation Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy (Vinante); Instituto Oncologico Veneto, Padoa, Italy (Bozza); University Hospital, Department of Radiation Oncology, Ludwig Maximilians Universitat, Munich, Germany (Pazos); Oncologue radiothérapeute, Institut de Cancérologie de l'Ouest, Nantes, France (Le Blanc-Onfroy); Brust Zentrum Seefeld, Zurich, Zurich, Switzerland (Gruber); Department of Surgical Oncology, Medical University of Lublin, Lublin, Poland (Polkowski); Breast Center, Universitätsspital Zürich, Zurich, Switzerland (Dedes); Saarland University Medical Center, Homberg, Germany (Niewald); Sankt Gertrauden-Krankenhaus, and The Charité – Universitätsmedizin Berlin, Berlin, Germany (Blohmer); Princess Margaret Cancer Centre Toronto, Toronto, Ontario, Canada (McCready); Sentara Surgery Specialists, Hampton, Virginia (Hoefer); Ashikari Breast Center, New York Medical College, New York, New York (Kelemen); Department of Surgery, University College London Hospitals, London, United Kingdom (Petralia); Department of Pathology, University College London Hospitals, London, United Kingdom (Falzon).

Author Contributions: Professors Vaidya and Bulsara had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Vaidya, Saunders, Tobias, Corica, Wenz, Douek, Eiermann, Blohmer, Baum, Joseph.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Vaidya, Bulsara, Saunders, Tobias, Douek, Roberts, Holmes,

Baum, Joseph.
Critical revision of the manuscript for important intellectual content: Vaidya, Saunders, Flyger, Tobias, Corica, Massarut, Wenz, Pigorsch, Alvarado, Douek, Eiermann, Brew-Graves, Williams, Potyka, Roberts, Bernstein, Brown, Sperk, Laws, Sutterlin, Lundgren, Holmes, Vinante, Bozza, Pazos, Le-Blanc-Onfroy, Gruber, Polkowski, Dedes, Niewald, Blohmer, McCready, Hoefer, Falzon, Kelemen, Petralia, Baum, Joseph.
Statistical analysis: Vaidya, Bulsara, Douek, Williams.
Obtained funding: Vaidya, Wenz, Williams, Baum.
Administrative, technical, or material support: Vaidya, Corica, Wenz, Pigorsch, Douek, Brew-Graves, Williams, Potyka, Roberts, Brown, Polkowski, Dedes, Niewald, Blohmer, Hoefer, Baum.
Study supervision: Vaidya, Bulsara, Saunders, Flyger, Tobias, Wenz, Williams, Brown, Pazos, Blohmer, Kelemen, Baum, Joseph.

Conflict of Interest Disclosures: Dr Vaidya has received a research grant from Photoelectron Corp (1996-1999) and from Carl Zeiss for supporting data management at the University of Dundee (2004-2008) and has subsequently received honoraria. Drs Vaidya, Tobias, Williams, Potyka, Ms Brew-Graves, and Mr Roberts receive funding from Health Technology Assessment Programme, National Institute for Health Research (NIHR), Department of Health for some activities related to the TARGIT trials. Dr Baum was on the scientific advisory board of Carl Zeiss and was paid monthly consultancy fees briefly before 2010. Dr Wenz 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 Dr Eiermann who declares that he has no conflicts of interest. No other conflicts are reported.

Funding/Support: The study was sponsored by University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre. Funding was provided by UCLH Charities, NIHR Health Technology Assessment Programme, Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research (FKZ 01ZP0508). The infrastructure of the trial operations office in London, United Kingdom, was supported by core funding from Cancer Research Campaign (now Cancer Research UK) when the trial was initiated.

Role of the Funder/Sponsor: The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: We thank the individuals from each center whose help has been invaluable. In addition, we thank those who no longer work in the respective departments and those who may not have been named herein (in order of the date of randomization of the first patient): 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, Mortez Ali, Cindy Li, Alex Shirley, Joanna Hadley, Fatima Akbar, Muhammad Hammed, Daryl Hagan, Olive Murphy, Tina Lennon, Joan Houghton; Surgical Interventional Trials Unit, Division of Surgery and Interventional Science, University College London. Jayant S Vaidya, Jeffrey S Tobias, Michael Baum, Mohammed Keshtgar, Glen Blackman, Chris Brew-Graves, Michael Douek, Mary Falzon, Gloria Petralia, Norman R Williams: University College London Hospital, London, United Kingdom; 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: Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany; Christobel Saunders, David J Joseph, Tammy Corica, Elizabeth Kernutt, Mandy Taylor, Eva Vosikova, Claire Haworth: Sir Charles Gairdner Hospital, Perth, WA, Australia; 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: Centro di Riferimento Oncologico, Aviano, Italy; 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: Ninewells Hospital, Dundee, United Kingdom; 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: University of California, San Francisco Medical Center, San Francisco; 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: Frauenklinik vom Roten Kreuz, Munich in cooperation with Technical University of Munich, Dept. of RadioOncology, Germany; 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: University of Southern California, Los Angeles; 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: Ospedale San Giuseppe di Empoli, Empoli, Italy; Jens-Uwe Blohmer, Petra Feyer, J Gross, G Jautzke, K Luebbert, Michaela Platzer, Joerg Preussler, D Puppe, Esther Wiedemann: Sankt Gertrauden-Krankenhaus, Berlin, Germany; 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: Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; 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: Ludwig Maximilians Universität, Munich, Germany; M Kaufmann, H Boettcher, J Moog, Achim Rody, Claus Rödel, S Schopohl, Christian Weiss, Inge Fraunholz, Ulla Ramm, Martin-Leo Hansmann, R Strohmeier: Universität Frankfurt am Main, Frankfurt, Germany; 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: Herlev/Rigs Hospitals, Copenhagen, Denmark; Wojciech P Polkowski, Malgorzata Jankiewicz, Andrzej Kurylcio, Jerzy Mielko, Magdalena Skorzewska, Bogumila Cisel, Monika Lewicka, Edyta Matejek, Jaroslaw Romanek, Andrzej Stanislawek, Jadwiga Sierocinska-Sawa, Zofia Siezieniewska, Rafal Smyk, Andrzej Bedonski: Medical University of Lublin, Lublin, Poland; Mohammed Keshtgar, Katharine 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: Royal Free Hospital, London, United Kingdom; 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 Stasinos, Melissa Hickson, Alison Jones, Mulyati Mohamed, Tim Crook, Vivienne Maidens, Sylvia Grieve, Elizabeth Tamufor, Lucy Mavriano, Lotta Jonsson, Ciara McNulty: Whittington Hospital, London, United Kingdom; Thomas L Summer, Mario Contreras, Paul M DesRosiers, Irene Gordon, Kazumi Chino, Bedatri Sinha, Cindy McDowell, Mike Ringer, Tammy Spurlock, Lisa Ramsey: Lafayette Surgical Clinic, Lafayette, Indiana; Richard A Hoefer, Mary Berry, Michael Miller, Song Kang: Sentara Surgery Specialists, Hampton, Virginia; 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 and J.Friedmann, Markus Promnik, Christian Ruebe, W Schmidt: Uniklinikum des Saarlandes, Homburg, Germany; David McCready, Akbar Beiki-Ardakani, John Cho, Susan Done, Jamie Escallon, Anthony W Fyles, Wilfred Levin, Alex Vitkin, Marie Vranic: Princess Margaret Cancer Centre, Toronto, Ontario, Canada; Siobhan Laws, Dick Rainsbury, Claire Birch, Lyn Booth, Caroline Cross, Alan Gately, Virginia Hall, Kevin Harris, Sanjay Raj, Balvinder Shoker, Virginia Straker, Jennifer Wilson: Royal Hampshire County Hospital, Winchester, United Kingdom; Christopher Rageth, Uwe Gneveckow, Elisabeth Grob, Guenther Gruber, Baerbel Papassotiropoulos, Barbara Tausch, C Tausch, Zsuszanna Varga, Iris Vergin: Brust Zentrum Seefeld, 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: Breast Centre, Universitätspital Zurich, Zurich, Switzerland; Steinar Lundgren, Anne Beate Marthinsen Langeland, Marianne Brekke, Hans E Fjosne, Jomar Frengen, Kristen Helset, Jarle Karlsen: St Olav's University Hospital, Trondheim, Norway; James Edney, Aaron Sasson, Debra

Spence, Robert Thompson, William W West, Sumin Zhou: University of Nebraska Medical Center, Omaha, Nebraska; 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: Guy's and St Thomas' Hospital, London, United Kingdom; 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: Vassar Brothers Medical Center, Poughkeepsie, New York; P Kelemen, Andrew Ashikari, Ulrich Hermato, Helen Li, Demetrious Makrides, Mike Malamed, Wanda Rivera, Yadita Samnarain, Alfred Tinger, Raphael Yankelevich, Yasmin Yusuf: Ashikari Breast Center, New York Medical College, New York; Tjoung-Won Park-Simon, Peter Hillemans, Ursula Hille, Michael Bremer, Frank Bruns, Frank Rudolf, Hans Grudtke, Jorg Fruhauf, H. H. Kreipe, Florian Laenger, Adelheid Klein: Medizinische Hochschule Hannover, Germany; Magali Le Blanc-Onfroy, Maud Aumont, Francois Dravet, Magali Dejode, Albert Lisbona, Delphine Loussouarn, Christine Sagan, Nicolas Rougé, Stephanie Gaudaine-Josset: Centre Rene Gauducheau, Nantes, France; Michele Pignataro, Fernando Bozza, Raffaello Grigoletto, Silvia Michieletto, Stefano Valente, Tania Saibene, Franco Berti, Ornella Lora, Marta Paiusco, Sonia Reccanello, Davide Canonico, Enrico Orvieto, Marcello Lo Mele, Liliana Spangaro: Instituto Oncologico Veneto; Katharine Pigott, Punita Vyas, Catherine O'Connor, Donna Gibbs, Simon Stevens, Ashley Richmond, Tabasom Ghaus, Thomas Ashford, Deborah Waters, Mohammed Keshtgar: Hospital of St John and St Elizabeth, London, United Kingdom; Marion Fournier, Christine Tunon De Lara, Christelle Breton-Callu, Philippe Lagarde, Sarah Belhomme, Gaetan MacGrogan, Beatrice Gonzalves, Mickael Antoine: Institut Bergonie, Bordeaux, France.

Disclaimer: The authors take full responsibility for the manuscript. The trial was initiated by an academic insight and collaboration with the industry was solely for the development of the device.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank the Independent Steering Committee for providing trial oversight. The members were appointed by the Health Technology Assessment Programme of the National Institute for Health Research, Department of Health, United Kingdom: independent members: Freddie Hamdy, MD, Nuffield Department of Surgical Sciences, University of Oxford; Ian Fentiman, MD, DSc, Guys and St Thomas Hospital, London; Mangesh Thorat, PhD, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London; Carolyn Murphy, MSc, King's Clinical Trials Unit, Kings College London; Anne Millman (patient representative), Oxford; Martin Bland, PhD, Department of Health Sciences, University of York; David Dommett, MSc, Consultant Clinical Scientist, Radiotherapy Physics, Southend University Hospital NHS Foundation Trust, Southend, David Morgan, MD, Radiation Oncologist, Nottingham. Drs Vaidya and Bulsara were appointed as nonindependent members of this committee and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank Michael D O'Shea, PhD, Woodward Informatics, Oxfordshire, United Kingdom, for database development, Julie Lindsay, BSc, Ninewells Hospital, Dundee, United Kingdom, for help in data collection, Uma J. Vaidya for help with the figures, tables, and editing of the manuscript, 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.

REFERENCES

1. 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(8):1941-1953. doi:10.1002/ijc.31937

2. Vaidya JS, Baum M, Tobias JS, Houghton J. Targeted Intraoperative Radiothearpy (TARGIT)-trial protocol. Lancet. 1999; https://www.thelancet.com/protocol-reviews/99PRT-47.

3. 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(8):1075-1080. doi:10.1023/A:1011609401132

4. 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(4):447-454. doi:10.1053/ejso.2002.1275

5. 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. Accessed November 9, 2019.

6. 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(9735):91-102. doi:10.1016/S0140-6736(10)60837-9

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(9917):603-613. doi:10.1016/S0140-6736(13)61950-9

8. Tobias JS, Vaidya JS, Keshtgar M, D'Souza DP, Baum M. Reducing radiotherapy dose in early breast cancer: the concept of conformal intraoperative brachytherapy. *Br J Radiol*. 2004;77(916):279-284. doi:10.1259/bjr/17186381

9. 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(2):208-215. doi:10.1667/RR3292

10. Enderling H, Chaplain MA, Anderson AR, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. *J Theor Biol*. 2007;246(2):245-259. doi:10.1016/j.jtbi.2006.12.010

11. Herskind C, Wenz F. Radiobiological comparison of hypofractionated accelerated partial-breast irradiation (APBI) and single-dose intraoperative radiotherapy (IORT) with 50-kV X-rays. *Strahlenther Onkol*. 2010;186(8):444-451. et al. doi:10.1007/s00066-010-2147-9

12. Vaidya JS, Walton L, Dewar J. Single dose targeted intraoperative radiotherapy (TARGIT) for breast cancer can be delivered as a second procedure under local anaesthetic. *World J Surg Oncol*. 2006;4:2. doi:10.1186/1477-7819-4-2

13. Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and noninferiority testing. *Biol Blood Marrow Transplant*. 2009;15(1)(suppl):120-127. doi:10.1016/j.bbmt.2008.10.004

14. Smits PC, Hofma S, Togni M, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet*. 2013;381(9867):651-660. doi:10.1016/S0140-6736(12)61852-2

15. Laster LL, Johnson MF, Kotler ML. Non-inferiority trials: the 'at least as good as' criterion with dichotomous data. *Stat Med*. 2006;25(7):1115-1130. doi:10.1002/sim.2476

16. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359(9318):1686-1689. doi:10.1016/S0140-6736(02)08594-X

17. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer*. 1996;74(5):820-824. doi:10.1038/bjc.1996.442

18. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. [letter; comment]. *Lancet*. 1997;349(9046):208-208. doi:10.1016/S0140-6736(05)60950-6

19. Vaidya JS, Baum M. Clinical and biological implications of the Milan breast conservation trials. *Eur J Cancer*. 1998;34(8):1143-1144.

20. 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(13):1269-1277. doi:10.1016/S1470-2045(13)70497-2

21. Keshtgar 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(3):519-525. doi:10.1007/s10549-013-2641-8

22. 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(1):55-64. doi:10.1016/j.ijrobp.2016.04.024

23. 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(1):135-140. doi:10.1007/s10549-013-2782-9

24. 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

25. 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(5):1325-1332. doi:10.1158/1078-0432.CCR-07-4453

26. Segatto I, Berton S, Sonego M, et al. Surgery-induced wound response promotes stem-like and tumor-initiating features of breast cancer cells, via STAT3 signaling. *Oncotarget*. 2014; 5(15):6267-6279. doi:10.18632/oncotarget.2195

27. Segatto I, Berton S, Sonego M, et al. p70S6 kinase mediates breast cancer cell survival in response to surgical wound fluid stimulation. *Mol Oncol*. 2014;8(3):766-780. doi:10.1016/j.molonc.2014.02.006

28. 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(37):4914-4926. doi:10.1038/onc.2016.23

29. Azria D, Bourgier C. Partial breast irradiation: new standard for selected patients. *Lancet*. 2010; 376(9735):71-72. doi:10.1016/S0140-6736(10)60898-7

30. 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(10015):229-238. doi:10.1016/S0140-6736(15)00471-7

31. 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(4):451-463. doi:10.1016/j.ejca.2014.12.013

32. 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(10099): 1048-1060. doi:10.1016/S0140-6736(17)31145-5

33. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technol Assess*. 2016;20 (73):1-188. doi:10.3310/hta20730