

## ORIGINAL ARTICLE

# Patient preferences for adjuvant radiotherapy in early breast cancer are strongly influenced by treatment received through random assignment

Tammy Corica<sup>1,2</sup>  | Christobel M. Saunders<sup>3</sup> | Max K. Bulsara<sup>4</sup> | Mandy Taylor<sup>5</sup> | David J. Joseph<sup>3,5</sup> | Anna K. Nowak<sup>2</sup>

<sup>1</sup>School of Medicine, University of Western Australia, Perth, Western Australia, Australia

<sup>2</sup>Radiation Oncology Clinical Trials and Research Unit, Comprehensive Cancer Centre, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

<sup>3</sup>School of Medicine, Division of Surgery, University of Western Australia, Perth, Western Australia, Australia

<sup>4</sup>Institute for Health Research, University of Notre Dame, Fremantle, Western Australia, Australia

<sup>5</sup>Radiation Oncology, Comprehensive Cancer Centre, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

## Correspondence

Tammy Corica, Radiation Oncology Clinical Trials and Research Unit, Comprehensive Cancer Centre, Sir Charles Gairdner Hospital, Nedlands, WA, Australia.  
Email: Tammy.Corica@health.wa.gov.au

## Funding information

This work was supported by a National Health and Medical Research Council Project Grant (393703), a Cancer and Palliative Care Research and Evaluation Unit Small Project Early Investigator Grant (SG12/002) and a Cancer Council of Western Australia Project Grant (APP1021376).

## Abstract

**Objective:** TARGIT-A randomised women with early breast cancer to receive external beam radiotherapy (EBRT) or intraoperative radiotherapy (TARGIT-IORT). This study aimed to identify what extra risk of recurrence patients would accept for perceived benefits and risks of different radiotherapy treatments.

**Methods:** Patient preferences were determined by self-rated trade-off questionnaires in two studies: Stage (1) 209 TARGIT-A participants (TARGIT-IORT  $n = 108$ , EBRT  $n = 101$ ); Stage (2) 123 non-trial patients yet to receive radiotherapy (pre-treatment group), with 85 also surveyed post-radiotherapy. Patients traded-off risks of local recurrence in preference selection between TARGIT-IORT and EBRT.

**Results:** TARGIT-IORT patients were more accepting of IORT than EBRT patients with 60% accepting the highest increased risk presented (4%–6%) compared to 12% of EBRT patients, and 2% not accepting IORT at all compared to 43% of EBRT patients. Pre-treatment patients were more accepting of IORT than post-treatment patients with 23% accepting the highest increased risk presented compared to 15% of post-treatment patients, and 15% not accepting IORT at all compared to 41% of pre-treatment patients.

**Conclusions:** Breast cancer patients yet to receive radiotherapy accept a higher recurrence risk than the actual risk found in TARGIT-A. Measured patient preferences are highly influenced by experience of treatment received. This finding challenges the validity of post-treatment preference studies.

## KEYWORDS

breast cancer, external beam radiotherapy, intraoperative radiotherapy, partial breast irradiation, patient preferences, preference questionnaire

## 1 | INTRODUCTION

Women with early breast cancer must make a number of treatment decisions in conjunction with their treating team. Many of

these decisions need patients to weigh up the advantages and disadvantages of treatment options with which they are not familiar, in the context of their individual circumstances, values and wishes. Patients preferring breast conservation surgery receive adjuvant

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. *European Journal of Cancer Care* Published by John Wiley & Sons Ltd

radiotherapy to reduce local recurrence risk; however, external beam radiotherapy (EBRT) is inconvenient, comprising 3–7 weeks of daily treatments (Early Breast Cancer Trialists' Collaborative Group, 2005; Smith et al., 2011). Patients must also consider the potential toxicities of radiotherapy, and sometimes decide to forego radiotherapy (increasing their risk of recurrence) or choose mastectomy to avoid radiotherapy side effects and inconveniences (Boscoe et al., 2011; Collins et al., 2009; NSW Department of Health, 2011; Pan, Smith, & Shih, 2014; Throckmorton & Esserman, 2009).

The introduction of partial breast irradiation now means that patients having breast conservation surgery may need to decide between two radiotherapy options, trading a possible increased risk of local recurrence for a shorter, and hence more convenient, radiotherapy treatment (Vaidya et al., 2014; Veronesi et al., 2010). Targeted intraoperative radiotherapy (TARGIT-IORT) delivers radiation directly to the primary tumour bed, during a single session at the time of wide local excision (WLE) or shortly afterwards. The TARGIT-A trial randomised women having breast conservation surgery to receive either standard EBRT or intraoperative radiotherapy (TARGIT-IORT). At 5 years after randomisation, more women in the TARGIT-IORT arm (2.1%) than the EBRT arm (1.1%) had experienced a local recurrence when IORT was delivered during WLE (before pathology results were available); this difference was not statistically significant and was within the 2.5% pre-specified non-inferiority margin. However, non-inferiority could not be established when IORT was delivered as a separate procedure, with local recurrence rates of 5.4% vs. 1.7% for post-pathology IORT and EBRT respectively. (Vaidya et al., 2014, 2015). Patients treated with TARGIT-IORT overall had the same breast cancer mortality risk but significantly fewer non-breast cancer deaths than those treated with EBRT (1.4% vs. 3.5%  $p = 0.0086$ ) (Vaidya et al., 2014). This finding was supported by a recent meta-analysis of partial breast irradiation techniques vs. whole breast radiotherapy (Vaidya et al., 2016).

TARGIT-IORT has been shown to have less skin toxicity and better patient-reported outcome measures such as pain and cosmetic outcome when compared to EBRT (Keshtgar et al., 2013; Vaidya et al., 2010; Welzel et al., 2013).

When the TARGIT-A study began recruiting, the risk of local recurrence following IORT was unknown, as was the level of risk that patients might accept in order to have the more convenient single treatment. We hypothesised that even if TARGIT-IORT treatment resulted in a higher risk of local recurrence, a proportion of patients may nevertheless be willing to trade a greater long-term local recurrence risk for increased short-term convenience. We also hypothesised that demographic and social factors including employment status, having dependents, and living further from a treatment centre may influence these patient preferences.

Trade-off methodology has been validated for determining patient preferences in oncology (Blinman, King, Norman, Viney, & Stockler, 2012; Blinman et al., 2010, 2011; Duric, Fallowfield et al., 2005; Stiggelbout & de Haes, 2001). Respondents are instructed to consider the positive and negative effects of a treatment together with the probabilities of these effects (Duric & Stockler, 2001; Simes

& Coates, 2001). Subjects choose between competing treatment options with differing outcomes (in this case, differing risks of local recurrence), and thus, measure the relative desirability of one treatment option compared with another.

Successful recruitment to TARGIT-A demonstrated that treatment-naïve patients were willing to try a more convenient treatment option with an unknown level of risk. This sub-study was designed to investigate what maximum increase in risk of local recurrence patients would accept to receive TARGIT-IORT in place of EBRT, in order to subsequently contextualise the TARGIT-A clinical results from a patient perspective.

## 2 | PATIENTS AND METHODS

A total of 3,451 patients from 33 centres in 11 countries were recruited into TARGIT-A between 2000 and 2012 (ISRCTN-34086741) (Vaidya et al., 2010, 2014). Patients with early breast cancer suitable for breast-conserving surgery were randomized to receive either a single dose of TARGIT-IORT (50 kV X-rays with INTRABEAM(TM) Carl Zeiss, Oberkochen Germany) or conventional 3–7 weeks EBRT. TARGIT-IORT patients with high-risk pathology as previously described also received EBRT (15%) (Vaidya et al., 2010).

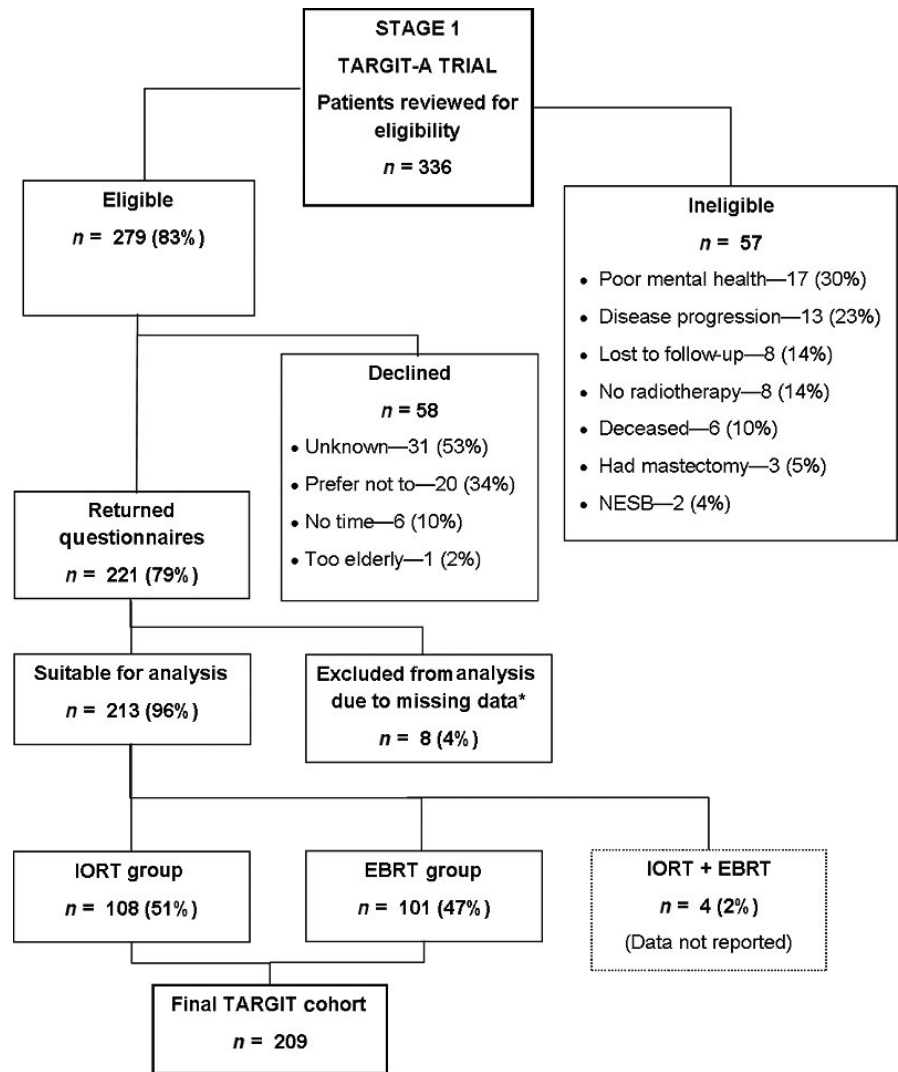
Stage-1 of this patient preference study was prospectively planned as a sub-study of the TARGIT-A Trial. In 2011, treatment preferences were collected from 213 TARGIT-A patients treated at least 3 months previously as per their allocated randomisation. Participants were reviewed by their Radiation Oncologist for suitability for inclusion in the preference sub-study. Patients were ineligible if the study would be considered an unwelcome imposition based on social, psychological or other circumstances (Figure 1).

From 2012 to 2014 preferences were collected from a further 123 usual-care patients recently diagnosed with breast cancer but yet to receive radiotherapy (Stage-2). Stage-2 (pre-treatment group) was developed as a follow-up study to test additional hypotheses informed by Stage-1. In 2015, Stage-2 participants who had initially been surveyed pre-treatment, and who had not declined further contact, were mailed a second "post-treatment" questionnaire. Human research ethics approvals were obtained for all studies and all participants provided written informed consent.

### 2.1 | Instruments and evaluations

#### 2.1.1 | Stage-1, TARGIT-A group

TARGIT-A participants were mailed an invitation letter with an opt-out card. Patient preference, demographics and the Patient Disease And Treatment Assessment (Patient DATA) questionnaires utilised in previous preference studies were adapted for this study and were mailed to patients who did not opt out (Supporting Information Appendices S1–S3) (Blinman et al., 2010; Duric, Stockler, et al., 2005; Simes & Coates, 2001). The questionnaire method of eliciting patient



**FIGURE 1** CONSORT diagram—Stage-1. IORT: intra-operative radiotherapy; EBRT: external beam radiotherapy; NESB: non-English speaking background. \*Missing data: questionnaires were returned with key data missing, and attempts to contact patients to retrieve missing data were unsuccessful

preferences has been validated through prospective comparison to scripted face-to-face methodology (Blinman et al., 2010).

The preference questionnaire was used to determine the largest 5-years recurrence risk that women considered acceptable in return for the shorter duration and altered toxicity profile of TARGIT-IORT. Participants were asked to imagine they knew what their risk of local recurrence would be with conventional EBRT. They were then asked to determine the maximum increased risk of local recurrence they would accept in order to receive TARGIT-IORT. Risk of recurrence of EBRT was represented as 3% in Question 1, 6% in Question 2, then as 3/100 in Question 3 and 6/100 in Question 4 (Supporting Information Appendix S1).

Acknowledging that an event such as treatment for breast cancer may alter some variable patient characteristics, such as work status, where appropriate the demographics questionnaire was answered for three separate time points: “before breast cancer,” “during breast cancer treatment” and “now” (being the time of questionnaire completion) (Supporting Information Appendix S2).

The patient DATA form consists of 22 questions which are scored from 0 (no trouble at all) to 10 (Worst Imaginable) by participants

to indicate the extent to which different aspects of their treatment troubled them. Participants were instructed to recall symptoms during radiotherapy treatment. The scores are grouped as shown in Supporting Information Appendix S3.

### 2.1.2 | Stage-2, pre-treatment group

Potential participants were identified during multidisciplinary team meetings, and the study was discussed by the attending surgeon. Interested patients were telephoned by the study coordinator who then mailed out questionnaires to those who agreed to participate. The preference questionnaire was modified slightly for the pre-treatment setting (Supporting Information Appendix S4). Stage-1 participants had demonstrated a preference for risk presented as a proportion; hence, the questions represented as percentages were removed. This allowed an alternative preference scenario to be examined: TARGIT-IORT being delivered either during WLE, or as a second procedure. Demographics were also collected. Participants who agreed to further contact were mailed a second questionnaire 1 year later, to capture preferences “post-treatment.”

## 2.2 | Analysis and interpretation

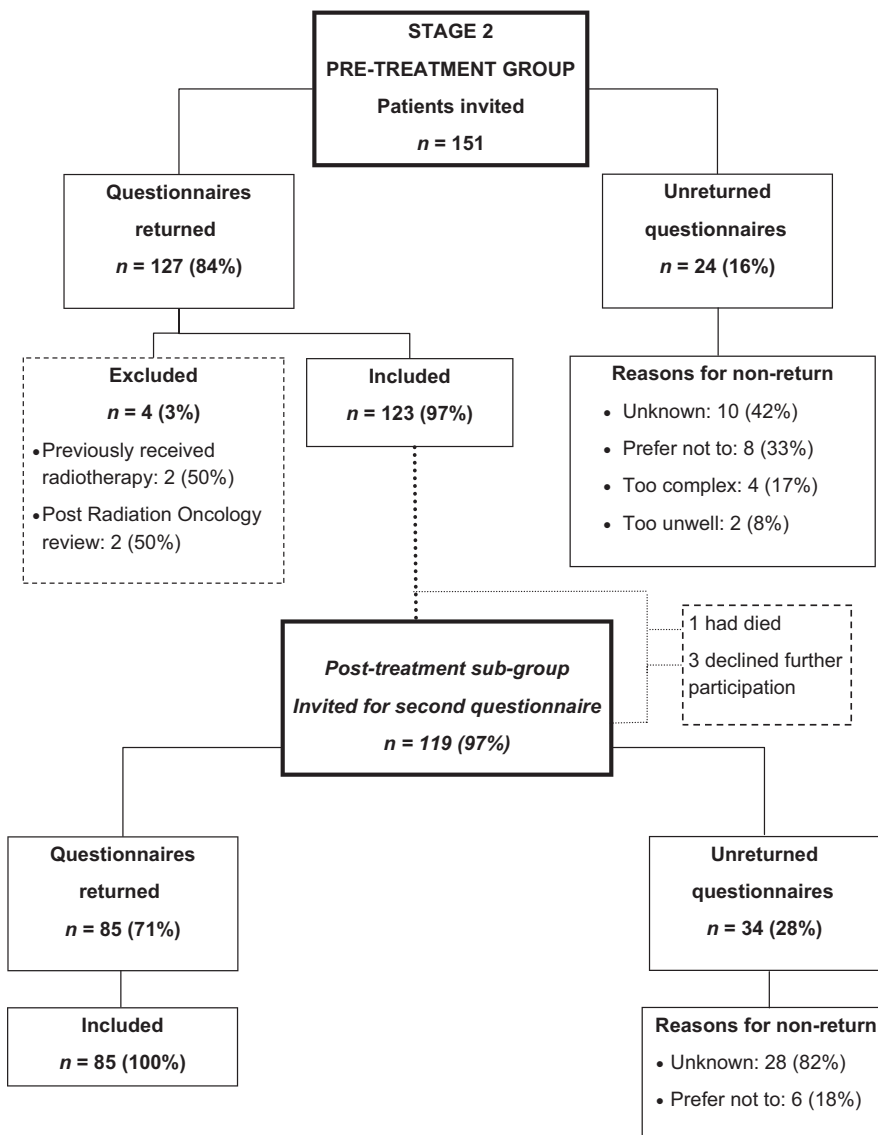
Statistical significance was set at  $p < 0.01$  to account for multiple comparisons (Bland & Altman, 1995; Bottomley et al., 2004). IBM-SPSS-V23 (SPSS Inc., Chicago, IL, USA) was used for all analyses. The Kappa statistic was used to determine reliability between percentage and proportion based questions and between the two baseline levels of recurrence risk presented. Kappa scores were interpreted based on levels of agreement described by Landis and Koch;  $<0$  Poor,  $0.0-0.20$  Slight,  $0.21-0.40$  Fair,  $0.41-0.60$  Moderate,  $0.61-0.80$  Substantial,  $0.81-1.00$  Almost perfect (Landis & Koch, 1977). Non-parametric Wilcoxon Signed-Rank (paired) tests were used to test differences between responses for TARGIT-IORT as a separate procedure vs. TARGIT-IORT delivered during WLE, and between the pre-treatment vs. post-treatment preference setting. Multivariate and univariate Poisson regression was utilised to test potential predictors of patient preference.

## 3 | RESULTS

A total of 336 consecutive TARGIT-A participants were reviewed for suitability, and exclusions are shown in Figure 1. Two hundred and thirteen evaluable responses were received; 108 had received TARGIT-IORT, 101 had received EBRT and four had received both TARGIT-IORT and EBRT.

A total of 151 standard care patients were invited to participate in Stage-2 (pre-treatment preference study), with 123 evaluable questionnaires received. The "post-treatment" questionnaire was mailed to 119 of the 123 initial participants with 85 returned (Figure 2).

Demographics were similar across all groups, although Stage-2 patients were slightly younger, had more child dependents, and higher levels of education and employment than Stage-1 participants (Table 1). These factors were considered in single and multivariate analysis of patient preference (Supporting Information Appendix S5).



**FIGURE 2** CONSORT diagram—Stage-2

TABLE 1 Demographics

	Stage-1: TARGIT-A GROUP						Stage-2: PRE-Rx GROUP																	
	Overall n = 213			Overall n = 209			IORT group n = 108			EBRT group n = 101			IORT+EBRT group n = 4			Pre-Rx Q n = 123			Post-Rx Q n = 85					
	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%	Median	Range	%
Age (years)	67	53-85		67	53-85		66	53-85		68	53-84		77	69-82		61	47-80		61	47-80		61	47-80	
Travel time from home (minutes)	108	10-1,440		55	10-1,440		55	10-720		55	10-1,140		35	10-60		66	10-480		66	10-480		45	10-480	
Time since radiotherapy (months)	34	4-85		34	4-85		34	4-85		35	4-85		77.5	68-84		n/a	n/a		n/a	n/a		Not collected	Not collected	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Has a partner	152	71	150	72	77	71	73	72	73	72	72	2	50	86	70	65	76							
Demographics																								
Lives alone	45	21	43	21	20	18	23	23	23	23	23	2	50	26	21	13	15							
Has dependents	97	46	96	46	45	42	51	50	51	50	50	1	25	59	48	45	53							
Has children	194	91	191	91	100	93	91	90	91	90	90	3	75	112	91	77	91							
Has children ≤ 15 years	1	0.5	1	0.5	1	1	0	0	0	0	0	0	0	6	5	5	6							
Has children >15 years	191	90	188	90	98	91	90	90	90	90	90	3	75	109	89	75	88							
Has child dependents	16	8	16	8	8	7	8	8	8	8	8	0	0	40	23	32	38							
Where stayed	a		a		a		a		a		a		a		b		b							
Home	161	76	157	75	88	82	69	68	69	68	68	4	100	108	88	74	87							
Relatives/Friends	18	8	18	9	11	10	7	7	7	7	7	0	0	11	9	8	9							
Hospital lodge	24	11	24	11	4	4	20	20	20	20	20	0	0	2	2	2	2							
Hospital inpatient	1	<1	1	<1	1	1	0	0	0	0	0	0	0	1	<1	1	1							
Motel	9	4	9	4	4	4	5	5	5	5	5	0	0	1	<1	0	0							
Education level																								
Primary	12	6	12	6	4	4	8	8	8	8	8	0	0	2	2	1	1							
Lower high school	70	33	67	32	38	35	29	29	29	29	29	3	75	37	30	24	28							
Intermediate high school	61	29	61	29	30	28	31	31	31	31	31	0	0	33	27	21	25							
Trade	35	16	34	16	15	14	19	19	19	19	19	1	25	18	15	14	16							
Tertiary	35	16	35	17	21	19	14	14	14	14	14	0	0	33	27	25	29							
Employment																								
Full time	15	7	15	7	9	8	6	6	6	6	6	0	0	26	21	18	21							

(Continues)

TABLE 1 (Continued)

	Stage-1: TARGIT-A GROUP						Stage-2: PRE-Rx GROUP							
	Overall n = 213		Overall n = 209		IORT group n = 108		EBRT group n = 101		IORT+EBRT group n = 4		Pre-Rx Q n = 123		Post-Rx Q n = 85	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
Part time/Casual	35	16	35	17	21	19	14	14	0	0	25	20	17	20
Unemployed	4	2	4	2	1	1	3	3	0	0	1	1	1	1
Student	1	<1	1	<1	1	1	0	0	0	0	1	1	1	1
Retired	116	54	113	54	55	51	57	58	3	75	50	41	37	44
Unable to work	2	1	2	1	0	0	2	2	0	0	1	1	1	1
Home duties	29	14	29	14	16	15	13	13	0	0	16	13	10	12
Other	11	5	10	5	5	5	5	5	1	25	3	2	0	0

Notes. EBRT: external beam radiotherapy; IORT: intraoperative radiotherapy; Pre-Rx: Pre-treatment (pre-radiotherapy).

<sup>a</sup>Where stayed during radiotherapy. <sup>b</sup>Where stayed during surgery.

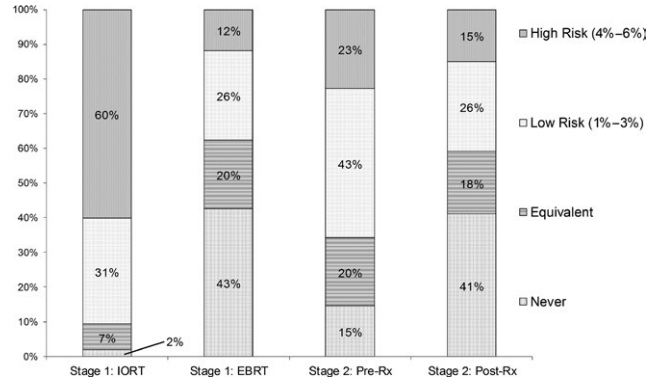


FIGURE 3 Averaged maximum acceptable increased risk. IORT: Patients received TARGIT-IORT on the TARGIT-A Trial (Stage-1); EBRT: Patients received EBRT on the TARGIT-A Trial (Stage-1); Pre-Rx: Patients completed preference questionnaire prior to any radiotherapy (Stage-2); Post-Rx: Patients completed the preference questionnaire after radiotherapy (Stage-2); High Risk: Would accept IORT if local recurrence was 4%–6% higher than EBRT; Low Risk: Would accept IORT if local recurrence was 1%–3% higher than EBRT; Equivalent: Would only accept IORT if local recurrence was equivalent to EBRT; Never: Would never accept IORT

TARGIT-IORT patients recalled fewer symptom concerns during treatment than EBRT patients across all Patient DATA form questions. Significant ( $p \leq 0.01$ ) differences were found in seven of 22 questions, with TARGIT-IORT patients recalling fewer problems with fatigue, energy levels, skin problems, breast sensitivity, treatment convenience, coping with treatment and being able to do the things they wanted (Supporting Information Appendix S6). These factors were considered in single and multivariate analysis of patient preference (Supporting Information Appendix S5).

### 3.1 | Preference results

Figure 3 illustrates averaged preference scores in four ordinal categories for each patient group. In Stage-1, patients who had received TARGIT-IORT through random assignment were less risk-averse than those who had received EBRT with 60% vs. 12% accepting IORT at the 4%–6% increased risk level, 31% vs. 26% at the 1%–3% increased level, 7% vs. 20% if equivalent to EBRT and 2% vs. 43% not finding it acceptable at all (“never”). In Stage-2, pre-treatment patients were less risk-averse than post-treatment patients with 23% vs. 15% accepting IORT at the 4%–6% increased risk level, 43% vs. 26% at the 1%–3% increased level, 20% vs. 18% if equivalent to EBRT and 15% vs. 41% not finding it acceptable at all (“never”) (Figure 3).

With 23% of the Stage-2 pre-treatment respondents accepting TARGIT-IORT at the 4%–6% increased risk, they were more risk-averse than Stage-1 TARGIT-IORT patients (60%) but less risk-averse than the Stage-1 patients who had completed EBRT following random assignment (12%).

However, after Stage-2 participants had completed treatment, their responses changed to more closely approximate Stage-1 post-EBRT responses (15% and 12% accepting 4%–6% increased risk

respectively). Overall acceptance (those not selecting “never”) of TARGIT-IORT was 98% for the Stage-1 post-TARGIT-IORT group, 58% for the Stage-1 post-EBRT group, 86% for the Stage-2 pre-treatment group and 59% for the Stage-2 post-treatment group.

The only significant characteristic impacting preference in Stage-1 was the treatment patients had received on the TARGIT-A Trial (TARGIT-IORT or EBRT;  $p = <0.001$ , mean difference 2.5). This remained unchanged when controlling for other potential drivers of treatment preference.

In the pre-treatment Stage-2 participants, no significant relationship was observed between preference outcomes and demographics. Post-treatment, having child dependents was a weak predictor for greater acceptance of TARGIT-IORT as a separate procedure ( $p = 0.006$ ) in multivariate analysis, but this was not significant for IORT during WLE ( $p = 0.019$ ). Stage-2 patients were more accepting of TARGIT-IORT pre-treatment than they were post-treatment (Wilcoxon signed-rank test  $p < 0.001$ ).

### 3.2 | Analyses specific to the TARGIT-A group (Stage-1)

Twenty-six percentage of participants preferred risk represented as a percentage, 56% preferred a proportion out of 100% and 15% had no preference.

Multivariate and univariate analysis revealed no significant differences in patient characteristics over the different time points used in the demographics questionnaire (“before breast cancer,” “during treatment” and “now”), hence only the “now” data were used in the final analysis.

### 3.3 | Analyses specific to the pre-treatment group (Stage 2)

Table 2 shows patient, tumour and treatment characteristics of Stage 2 participants with 60% meeting the “low risk” criteria used for TARGIT-A in Australia (<2 cm tumours, Grade 1–2, clear margins, hormone receptor positive, node negative, ductal (not lobular), negative for extensive intraductal component or lymphovascular invasion) (Vaidya et al., 2010). 82% of Stage-2 participants subsequently received conventional 6-week EBRT, 15% received hypofractionated (3–4 week) EBRT and 2% received TARGIT-IORT. If all treatment modalities offered equivalent outcomes, 13% of pre-treatment patients chose EBRT, 25% chose TARGIT-IORT as a separate procedure and 62% chose TARGIT-IORT during WLE as their preferred option (Figure 4). After the patients had completed treatment, acceptability of EBRT increased to 29% but decreased for the TARGIT-IORT options to 15% for TARGIT-IORT separate to WLE and 55% for TARGIT-IORT during WLE (paired  $t$  test  $p = 0.013$ , mean difference 0.24). Overall, 87% of patients who had not yet had radiotherapy accepted TARGIT-IORT over EBRT, and this proportion decreased to 70% after patients had received treatment.

There was no difference in preferences when patients were presented with alternative scenarios of IORT as a separate procedure

**TABLE 2** Tumour and treatment characteristics of pre-treatment group

	Pre-treatment questionnaire		Post-treatment questionnaire	
	n	%	n	%
TARGIT-A eligible <sup>a</sup>				
Yes	74	60	50	59
No	49	40	35	41
Pathology				
Grade 1 or 2	111	90	75	88
Unifocal	120	98	82	96
≥ 50 years	114	93	78	92
≤2 cm	108	88	75	88
No extensive intraductal component (EIC-ve)	109	89	77	91
No lymphovascular invasion (LVI-ve)	116	94	82	96
Hormone receptor positive	116	94	81	95
Radiotherapy received <sup>b</sup>				
EBRT (6 weeks)	–	–	70	82
EBRT (3–4 weeks)	–	–	13	15
IORT	–	–	2	2

Notes. EBRT: external beam radiotherapy; IORT: intraoperative radiotherapy.

<sup>a</sup>Patient and tumour characteristics were within the eligibility criteria for TARGIT-A in Australia (<20 cm tumours, Grade 1–2, clear margins, hormone receptor positive, node negative, ductal (not lobular), negative for extensive intraductal component or lymphovascular invasion). <sup>b</sup>Radiotherapy details were only collected from patients providing a post-treatment questionnaire.

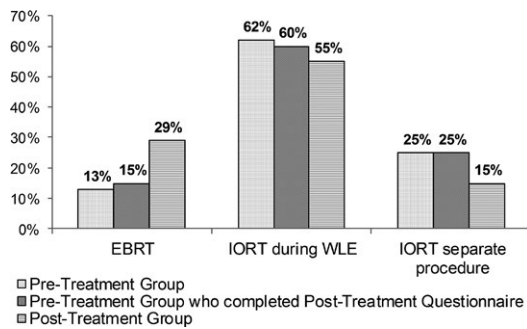
or during WLE at either level of baseline recurrence risk (Wilcoxon signed-rank test  $p = 0.338$  and  $0.335$  respectively) for pre-treatment or post-treatment groups ( $p = 0.216$  and  $0.624$  respectively).

Participants could opt to leave free text comments on the final page. This data are described in Supporting Information Appendix S7.

## 4 | DISCUSSION AND CONCLUSION

Patient preference studies are increasingly recognised as an important secondary, and in some cases primary, outcome in health care research. This preference study utilised validated questionnaire methodology in two sequential studies, each with two patient cohorts; Stage-1 included patients who had already received either TARGIT-IORT or EBRT on the TARGIT-A trial and Stage-2 included breast cancer patients yet to receive radiotherapy, most of whom were surveyed again post-treatment.

The most striking finding of this research was the discovery that preferences elicited in the post-treatment setting yield very different results to those elicited in the pre-treatment setting. This



**FIGURE 4** Preferred treatment option—Stage-2. EBRT: external beam radiotherapy; IORT: intraoperative radiotherapy; WLE: wide local excision

study, in which preferences were first elicited from patients who had completed treatment with one of two radiotherapy modalities to which they had been randomly assigned, demonstrated that the most important determinant of treatment preference was the treatment already experienced by that patient. Despite patients having entered the trial accepting a 50% chance of randomisation to either radiotherapy technique, those who had been randomised to TARGIT-IORT strongly favoured the treatment they had received, even at a hypothetical increased risk of recurrence compared to the EBRT group. Furthermore, 43% of patients who had been randomised to and received EBRT indicated they would not accept TARGIT-IORT at all. The only plausible explanation for this, in patients with similar characteristics who had provided informed consent to randomisation to either treatment, is that patients were justifying the treatment they had received, therefore indirectly justifying their decision to participate in the randomised trial, thus potentially avoiding decisional regret. Optional comments made by Stage-1 participants demonstrated that as their experience with the treatment they had received on the randomised study was acceptable to them, they were biased towards that treatment when completing the preference questionnaire. There were very few comments suggesting that the recalled toxicities of treatment impacted treatment preferences. Analysis of the Patient DATA form confirmed this; despite TARGIT-IORT patients reporting significantly fewer treatment side effects, none of these factors were determinants of preferences after treatment. Time since treatment did not impact preference results in Stage-1; however, treatment had been completed 4–85 months prior to completion of the Patient DATA form which is likely to have introduced some level of recall bias.

This preference study originally set out to identify what hypothetical level of increased risk of local recurrence patients would accept in order to choose a new, more convenient treatment option (TARGIT-IORT) over conventional EBRT. Preferences varied across all four patient groups, with the least risk-averse group being those who had received TARGIT-IORT on the TARGIT-A study (98% overall acceptance of IORT, and 60% accepting it at the highest increased risk presented which was 4%–6%), and the most risk-averse groups being the TARGIT-A EBRT group and the post-treatment

Stage-2 participants (27%–29% overall acceptance of IORT, with 12%–15% accepting it at the highest risk presented—4%–6%). The Stage-2 pre-treatment group demonstrated intermediate preferences, with 85% overall acceptance of IORT and 23% accepting it at the highest risk presented, 4%–6% increase in local recurrence. These preference results showed that around a third of patients were willing to accept TARGIT-IORT at a higher risk than that which was observed in the TARGIT-A trial, which found non-significant absolute increases in risk of recurrence of 1% in the group having IORT during WLE and 3.7% in the group having IORT as second separate procedure. Although IORT during WLE is the recommended approach, it is not always feasible. These results suggest that some women, at least before they have experienced treatment, may accept a risk of recurrence in keeping with the results of TARGIT-A in order to receive IORT as a separate procedure, if immediate IORT is not possible. The results of this study therefore provide a further discussion point for providers when considering obstacles to radiotherapy access, especially for patients in rural and remote areas. If health professionals and informed patients accept the small additional risk of local recurrence for a more convenient treatment schedule, then it may be considered an option for suitable patients, and would be preferable to forgoing radiotherapy due to the inconvenience of EBRT.

That treatment experience would be the only important determinant of retrospective patient preference in a randomised population was not anticipated when this research began. The only previous preference study of adjuvant radiotherapy following breast-conserving surgery, and indeed most previous preferences research, had been conducted following more homogeneous treatment (Duric, Stockler, et al., 2005; Hayman, Fairclough, Harris, & Weeks, 1997). The methodology and timing of administration of Stage 1 of this study was therefore based on these prior validated studies; furthermore, the validity of the paper-based questionnaire methodology had also been established (Blinman et al., 2010). Our results from Stage 1 of the study are the first to question the validity of eliciting preferences post-treatment and to identify the potential role of avoidance of decisional regret. There was no indication that other aspects of the discrete choice methodology, or the use of a paper-based questionnaire, were less valid in this population than in prior studies. A concurrent study of patient preferences for TARGIT-IORT in the USA reported that 91% of patients found TARGIT-IORT acceptable, with a median increase in acceptable risk of 2.3% (Alvarado et al., 2014). This is comparable to the “low increased risk” category (a 1%–3% increase) in the present study which was acceptable to 91% of the TARGIT-IORT group, 38% of the TARGIT-EBRT group, 66% of the pre-treatment group and 41% of the post-treatment group. However, in that study, combined results were reported from 21 pre-treatment and 60 post-treatment patients. Results from our larger study question the appropriateness of combining these groups.

Another study investigating preferences for adjuvant chemotherapy (ACT) after early breast cancer showed stability of preferences before and after treatment; however importantly, these



patients had selected their treatment, rather than being randomised (Jansen et al., 2001).

Our results challenge the utility of eliciting patient preferences post-treatment in a randomised controlled trial. This population does not represent the knowledge base of treatment-naïve patients, and results may be significantly biased by the avoidance of decision regret, albeit an unconscious bias, in patients who have completed treatment. This interpretation is supported by a recent preference study in patients with endometrial cancer who were randomised to receive ACT vs. no ACT. Preferences were elicited both after randomisation but before treatment, and 9 months later (after treatment) (Blinman et al., 2016). Findings were similar to our study, with patients who had received ACT requiring smaller benefits to accept ACT than those who did not receive it, and less benefit required post-treatment than pre-treatment. These results suggest that the actual experience of ACT treatment may have been better than anticipated, or that preferences justified participation in the randomised trial and avoided decision regret. These results also explain the surprising finding that some women will accept almost zero benefit for ACT for early breast cancer when preferences are elicited after treatment (Duric & Stockler, 2001; Duric, Stockler, et al., 2005; Vaz-Luis et al., 2017).

#### 4.1 | CONCLUSION

In terms of the primary goal of this research, we found that women who had yet to receive radiotherapy for early breast cancer indicated that TARGIT-IORT was an acceptable treatment option, with the majority of patients also willing to accept a higher risk of recurrence in order to have the more convenient treatment option. The most striking finding of this research was however the incidental discovery that preferences elicited post-treatment are significantly biased by the experience of treatment received. Preferences elicited post-treatment appear instead to be an indirect method of eliciting patient satisfaction of treatment already received, and therefore offer a biased account of preference, rather than a consumer perspective of all potential treatments on offer. The results of our study strongly challenge the use and interpretation (and thus the validity) of post-treatment preference studies. We recommend that both qualitative (Duric, Fallowfield, et al., 2005; Jansen et al., 2001) and quantitative pre-treatment patient preference studies are utilised in future research, together with post-treatment preferences and measurements of treatment satisfaction and/or decision regret.

#### ACKNOWLEDGEMENTS

The investigators would like to thank all TARGIT-A Sub-Study participants, as well as local clinicians and research coordinators for their involvement in the study. The early support and guidance from Dr Vlatka Duric, Professor Martin Stockler, and Dr Prunella Blinman from the NHMRC Cancer Trials Centre is also greatly appreciated.

#### CONFLICT OF INTEREST

Carl Zeiss sponsored some of the travel for meetings of the international steering committee and when necessary for conferences where a presentation about TARGIT-A was being made. Carl Zeiss had no involvement in this publication.

#### ORCID

Tammy Corica  <https://orcid.org/0000-0002-1197-0120>

#### REFERENCES

- Alvarado, M., Conolly, J., Park, C., Sakata, T., Mohan, A., Harrison, B., ... Ozanne, E. (2014). Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. *Breast Cancer Research and Treatment*, 143(1), 135–140. <https://doi.org/10.1007/s10549-013-2782-9>
- Bland, J. M., & Altman, D. G. (1995). Multiple significance tests: The Bonferroni method. *BMJ*, 310(6973), 170. <https://doi.org/10.1136/bmj.310.6973.170>
- Blinman, P., Duric, V., Nowak, A., Beale, P., Clarke, S., Briscoe, K., ... Stockler, M. (2010). Adjuvant chemotherapy for early colon cancer: What survival benefits make it worthwhile? *European Journal of Cancer*, 46, 1800–1807. <https://doi.org/10.1016/j.ejca.2009.12.032>
- Blinman, P., King, M., Norman, R., Viney, R., & Stockler, M. R. (2012). Preferences for cancer treatments: An overview of methods and applications in oncology. *Annals of Oncology*, 23(5), 1104–1110. <https://doi.org/10.1093/annonc/mdr559>
- Blinman, P., McLachlan, S. A., Nowak, A. K., Duric, V. M., Brown, C., Wright, G., ... Stockler, M. R. (2011). Lung cancer clinicians' preferences for adjuvant chemotherapy in non-small-cell lung cancer: What makes it worthwhile? *Lung Cancer*, 72(2), 213–218. <https://doi.org/10.1016/j.lungcan.2010.08.007>
- Blinman, P., Mileschkin, L., Khaw, P., Goss, G., Johnson, C., Capp, A., ... Stockler, M. R. (2016). Patients' and clinicians' preferences for adjuvant chemotherapy in endometrial cancer: An ANZGOG substudy of the PORTEC-3 intergroup randomised trial. *British Journal of Cancer*, 115(10), 1179–1185. <https://doi.org/10.1038/bjc.2016.323>
- Boscoe, F. P., Johnson, C. J., Henry, K. A., Goldberg, D. W., Shahabi, K., Elkin, E. B., ... Cockburn, M. (2011). Geographic proximity to treatment for early stage breast cancer and likelihood of mastectomy. *The Breast*, 20(4), 324–328. <https://doi.org/10.1016/j.breast.2011.02.020>
- Bottomley, A., Biganzoli, L., Cufer, T., Coleman, R. E., Coens, C., Efficace, F., ... Piccart, M. (2004). Randomized, Controlled Trial Investigating Short-Term Health-Related Quality of Life With Doxorubicin and Paclitaxel Versus Doxorubicin and Cyclophosphamide As First-Line Chemotherapy in Patients With Metastatic Breast Cancer: European Organization for Research and Treatment of Cancer Breast Cancer Group, Investigational Drug Branch for Breast Cancer and the New Drug Development Group Study. *Journal of Clinical Oncology*, 22(13), 2576–2586. <https://doi.org/10.1200/jco.2004.02.037>
- Collins, E. D., Moore, C. P., Clay, K. F., Kearing, S. A., O'Connor, A. M., Llewellyn-Thomas, H. A., ... Sepucha, K. R. (2009). Can women with early-stage breast cancer make an informed decision for mastectomy? *Journal of Clinical Oncology*, 27(4), 519–525. <https://doi.org/10.1200/JCO.2008.16.6215>
- Duric, V. M., Fallowfield, L. J., Saunders, C., Houghton, J., Coates, A. S., & Stockler, M. R. (2005). Patients' preferences for adjuvant endocrine therapy in early breast cancer: What makes it worthwhile? *British*

- Journal of Cancer*, 93(12), 1319–1323. <https://doi.org/10.1038/sj.bjc.6602874>
- Duric, V., & Stockler, M. (2001). Patients' preferences for adjuvant chemotherapy in early breast cancer: A review of what makes it worthwhile? *The Lancet Oncology*, 2(11), 691–697. [https://doi.org/10.1016/S1470-2045\(01\)00559-9](https://doi.org/10.1016/S1470-2045(01)00559-9)
- Duric, V. M., Stockler, M. R., Heritier, S., Boyle, F., Beith, J., Sullivan, A., ... Simes, R. J. (2005). Patients' preferences for adjuvant chemotherapy in early breast cancer: What makes AC and CMF worthwhile now? *Annals of Oncology*, 16(11), 1786–1794. <https://doi.org/10.1093/annonc/mdi370>
- Early Breast Cancer Trialists' Collaborative Group (2005). 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*, 366, 2087–2106. [https://doi.org/10.1016/S0140-6736\(05\)67887-7](https://doi.org/10.1016/S0140-6736(05)67887-7)
- Hayman, J., Fairclough, D., Harris, J., & Weeks, J. (1997). Patient preferences concerning the trade-off between the risks and benefits of routine radiation therapy after conservative surgery for early-stage breast cancer. *Journal of Clinical Oncology*, 15, 1252–1260. <https://doi.org/10.1200/JCO.1997.15.3.1252>
- Jansen, S. J. T., Kievit, J., Nooij, M. A., Haes, J. C. J. M. d., Overpelt, I. M. E., Slooten, H. V., ... Stiggelbout, A. M. (2001). Patients' preferences for adjuvant chemotherapy in early-stage breast cancer: Is treatment worthwhile? *The British Journal of Cancer*, 84(12), 1577–1585. <https://doi.org/10.1054/bjoc.2001.1836>
- Keshtgar, M., Williams, N., Bulsara, M., Saunders, C., Flyger, H., Cardoso, J., ... Joseph, D. (2013). Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: Results from a randomised controlled trial. *Breast Cancer Research and Treatment*, 140(3), 519–525. <https://doi.org/10.1007/s10549-013-2641-8>
- Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, 33, 159–174. <https://doi.org/10.2307/2529310>
- NSW Department of Health. (2011). Factors that impact on referral rates for radiotherapy. NSW: NSW Department of Health. Retrieved from [http://www0.health.nsw.gov.au/resources/pdf/factors\\_impact\\_referral\\_r.pdf](http://www0.health.nsw.gov.au/resources/pdf/factors_impact_referral_r.pdf)
- Pan, I.-W., Smith, B. D., & Shih, Y.-C. T. (2014). Factors contributing to underuse of radiation among younger women with breast cancer. *Journal of the National Cancer Institute*, 106(1), djt340. <https://doi.org/10.1093/jnci/djt340>
- Simes, R. J., & Coates, A. S. (2001). Patient preferences for adjuvant chemotherapy of early breast cancer: How much benefit is needed? *Journal of the National Cancer Institute. Monographs*, 30, 146–152. <https://doi.org/10.1093/oxfordjournals.jncimonographs.a003453>
- Smith, B. D., Bentzen, S. M., Correa, C. R., Hahn, C. A., Hardenbergh, P. H., Ibbott, G. S., ... Haffty, B. G. (2011). Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. *International Journal of Radiation Oncology, Biology, Physics*, 81(1), 59–68. <https://doi.org/10.1016/j.ijrobp.2010.04.042>
- Stiggelbout, A. M., & de Haes, J. C. J. M. (2001). Patient preference for cancer therapy: An overview of measurement approaches. *Journal of Clinical Oncology*, 19(1), 220–230. <https://doi.org/10.1200/JCO.2001.19.1.220>
- Throckmorton, A. D., & Esserman, L. J. (2009). When informed, all women do not prefer breast conservation. *Journal of Clinical Oncology*, 27(4), 484–486. <https://doi.org/10.1200/JCO.2008.19.5057>
- Vaidya, J. S., Bulsara, M., Wenz, F., Coombs, N., Singer, J., Ebbs, S., ... Baum, M. (2016). Reduced mortality with partial-breast irradiation for early breast cancer: A meta-analysis of randomized trials. *International Journal of Radiation Oncology\*Biophysics*, 96(2), 259–265. <https://doi.org/10.1016/j.ijrobp.2016.05.008>
- Vaidya, J. S., Bulsara, M., Wenz, F., Joseph, D., Saunders, C., Massarut, S., ... group, T. t. (2015). Pride, prejudice, or science: Attitudes towards the results of the TARGIT-A trial of targeted intraoperative radiation therapy for breast cancer. *International Journal of Radiation Oncology, Biology, Physics*, 92(3), 491–497. <https://doi.org/10.1016/j.ijrobp.2015.03.022>
- Vaidya, J. S., Joseph, D. J., Tobias, J. S., Bulsara, M., Wenz, F., Saunders, C., ... Baum, M. (2010). Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. *The Lancet*, 376(9735), 91–102. [https://doi.org/10.1016/S0140-6736\(10\)60837-9](https://doi.org/10.1016/S0140-6736(10)60837-9)
- Vaidya, J., Wenz, F., Bulsara, M., Tobias, J. S., Joseph, D. J., Keshtgar, M., ... Baum, M. (2014). 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. *The Lancet*, 383(9917), 603–613. [https://doi.org/10.1016/S0140-6736\(13\)61950-9](https://doi.org/10.1016/S0140-6736(13)61950-9)
- Vaz-Luis, I., O'Neill, A., Sepucha, K., Miller, K. D., Baker, E., Dang, C. T., ... Partridge, A. H. (2017). Survival benefit needed to undergo chemotherapy: Patient and physician preferences. *Cancer*, 123, 2821–2828. <https://doi.org/10.1002/cncr.30671>
- Veronesi, U., Orecchia, R., Luini, A., Galimberti, V., Zurrada, S., Intra, M., ... Maisonneuve, P. (2010). Intraoperative radiotherapy during breast conserving surgery: A study on 1822 cases treated with electrons. *Breast Cancer Research and Treatment*, 124(1), 141–151. <https://doi.org/10.1007/s10549-010-1115-5>
- Welzel, G., Boch, A., Sperk, E., Hofmann, F., Kraus-Tiefenbacher, U., Gerhardt, A., ... Wenz, F. (2013). 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. *Radiation Oncology*, 8, 9. <https://doi.org/10.1186/1748-717x-8-9>

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Corica T, Saunders CM, Bulsara MK, Taylor M, Joseph DJ, Nowak AK. Patient preferences for adjuvant radiotherapy in early breast cancer are strongly influenced by treatment received through random assignment. *Eur J Cancer Care*. 2019;28:e12985. <https://doi.org/10.1111/ecc.12985>