International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial

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Received Jan 14, 2016, and in revised form Apr 5, 2016. Accepted for publication Apr 17, 2016.

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This work was supported in Australia 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, and a Cancer Council of Western Australia Project Grant.

Conflict of interest: D.J.J. received a research grant from Photoelectron Corp in 2001 to support data management; M.B. was on the scientific advisory board of Carl Zeiss and was paid monthly consultancy fees until 2010. J.S.V. received a research grant from Photoelectron Corp (1996-1999) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, United Kingdom) and has subsequently received honoraria. Carl Zeiss sponsored most of the travel and accommodation for meetings of the international steering committee and when necessary for conferences where a presentation about targeted intraoperative radiation therapy was being made for all authors apart from A.K.N. and M.T. Carl Zeiss had no involvement in this publication.

Supplementary material for this article can be found at www.redjournal.org.

Acknowledgments—The authors thank all of the TARGIT-A Trial substudy participants, local clinicians and research coordinators for their long-term and ongoing involvement in the study, and the TARGIT-A Steering Committee and Coordinating Centers for their support.

Int J Radiation Oncol Biol Phys, Vol. 96, No. 1, pp. 55–64, 2016

http://dx.doi.org/10.1016/j.ijrobp.2016.04.024

Summary

The TARGIT-A trial found no significant difference between TARGIT-IORT and EBRT in terms of local recurrence of breast cancer or breast cancer survival. In this longitudinal, single-site TARGIT-A substudy, TARGIT-IORT had similar cosmetic outcomes to EBRT but better breast-related quality of life, as reported by patients. This was despite this analysis being limited to patients who had received TARGIT-IORT as a separate procedure by reopening the wound (postpathology).

Purpose: To report the first comprehensive investigation of patient-reported cosmesis and breast-related quality of life (QOL) outcomes comparing patients randomized to risk-adapted single-dose intraoperative radiation therapy (TARGIT-IORT) versus external beam radiation therapy (EBRT) on the TARGIT-A trial.

Methods and Materials: Longitudinal cosmesis and QOL data were collected from a subset of TARGIT-A participants who received TARGIT-IORT as a separate procedure (postpathology). Patients completed a cosmetic assessment before radiation therapy and annually thereafter for at least 5 years. Patients also completed the combined European Organization for Research and Treatment of Cancer (EORTC) core questionnaire and Breast-Specific Module in addition to the Body Image after Breast Cancer Questionnaire at baseline and annually thereafter. The combined EORTC questionnaires were also collected 3, 6, and 9 months after wide local excision.

Results: An Excellent–Good cosmetic result was scored more often than a Fair–Poor result for both treatment groups across all time points. The TARGIT-IORT patients reported better breast-related QOL than EBRT patients. Statistically and clinically significant differences were seen at month 6 and year 1, with EBRT patients having moderately worse breast symptoms (a statistically significant difference of more than 10 in a 100-point scale) than TARGIT-IORT patients at these time points.

Conclusion: Patients treated with TARGIT-IORT on the TARGIT-A trial have similar self-reported cosmetic outcome but better breast-related QOL outcomes than patients treated with EBRT. This important evidence can facilitate the treatment decision-making process for patients who have early breast cancer suitable for breast-conserving surgery and inform their clinicians.

Introduction

Whole-breast external beam radiation therapy (EBRT) delivered in 15 to 35 daily fractions over 3 to 7 weeks is standard adjuvant treatment for women undergoing breast-conserving surgery for early breast cancer (1, 2). External beam radiation therapy may require temporary relocation for women who are geographically isolated or unable to travel daily (3). External beam radiation therapy can have acute toxicities, such as erythema, edema, breast induration, and skin breakdown (4), and long-term toxicities, including local pain, fibrosis, telangiectasia, and cosmetic changes (4, 5). Approximately 1% to 2% may develop pneumonitis, pulmonary fibrosis, cardiotoxicity, osteoradionecrosis, or secondary malignancies (4, 6, 7). Some women choose to forego radiation therapy owing to the inconvenience or potential toxicities, either accepting increased recurrence risks or choosing mastectomy (8-10).

Targeted intraoperative radiation therapy (TARGIT-IORT) allows delivery of radiation directly to tissues at the site of the primary tumor in a single session at the time of wide local excision (WLE) or shortly afterward. The TARGIT-A trial compared TARGIT-IORT with conventional EBRT. Five-year results found TARGIT-IORT to be non-inferior to EBRT in terms of risk of local recurrence overall and when delivered during WLE (prepathology) (non-inferiority could not be established for postpathology, but the difference was not statistically significant), and there was no difference in breast cancer survival (11). Toxicities were low; TARGIT-IORT had significantly fewer skin toxicities (0.5% vs 2%) but higher risk of postoperative seromas (2% vs 0.8%) (12). Cosmesis analysis utilizing digital photographs showed better outcomes with TARGIT-IORT in the first year (13).

Targeted IORT is now considered an acceptable treatment option in several countries, with delivery during WLE (prepathology) being the preferred approach. Awareness of cosmesis and quality of life (QOL) outcomes is paramount when clinicians are discussing treatment options with patients, in particular when comparing treatments with similar efficacy and survival. This substudy is the first comprehensive investigation of patient-reported cosmesis and breast-related QOL outcomes comparing patients randomized to TARGIT-IORT versus EBRT on the TARGIT-A trial.

Methods and Materials

Patients and treatment

Between 2000 and 2012, TARGIT-A registered 3451 patients from 33 centers in 11 countries. Patients with early breast cancer suitable for breast-conserving surgery were

Table 1 Baseline patient characteristics by treatment

Patient, treatment, and tumor characteristics	TARGIT-IORT	EBRT
N (%)	60 (48)	66 (52)
Age (y)		
Mean ± SD	63 ± 8.2	62 ± 7.4
Range	50-83	50-80
Baseline assessments before any surgery, n (%)	1 (2)	12 (18)
Baseline BMI (kg/m^2), mean ± SD	29 ± 5.5	30 ± 5.9
Baseline BMI group* (BMI range in kg/m^2) (%)		
1, Underweight (<18.5)	0	0
2, Normal (18.5-24.99)	30	16
3, Overweight (25-29.99)	30	50
4, Obese (30+)	40	34
Tumor size (mm), mean ± SD	10 ± 4.2	11 ± 5.0
<11 (%)	62	52
11-20 (%)	38	46
>21† (%)	-	1.5
Tumor grade, n (%)		
1	37 (62)	38 (57)
2	23 (38)	27 (41)
3†	0	1 (1.5)
Tumor type, n (%)		
IDC	59 (98)	64 (97)
Mixed IDC/ILC†	1 (1.7)	2 (3)
Lesions, n (%)		
1	60 (100)	65 (98)
2†	0	1 (1.5)
Extensive DCIS (>25% of tumor + inside and out of tumor),† n (%)	0	4 (6.3)
ER$^+$	60 (100)	64 (97)
PR$^+$	44 (73)	52 (79)
ER$^-$ and PR$^-$†	0	2 (3)
Positive nodes†	0	1 (1.5) (1 node)
Largest specimen length (mm), mean ± SD	89 ± 37.2	89 ± 38.4
Range (mm)	25-205	40-267
Extent of axillary surgery, n (%)		
Nil	3 (5)	2 (3)
SLNBx	49 (82)	55 (83)
Clearance	8 (13)	9 (14)
Further surgery required, n (%)		
SLNBx	2 (3.3)	2 (3)
Margins	2 (3.3)	7 (11)
Revision of scar	2 (3.3)	0
Radiation therapy dose (Gy), range	16-33‡	45-50.4
Fractions (range)	1	25 (25-28)
Boost given (20 Gy in 10 fractions), n (%)	N/A	11 (17)
Supraclavicular treatment, n (%)	N/A	1 (1.5)
Chemotherapy,† n (%)	0	1 (1.5)
Baseline patient Harris score (% excellent–good), mean ± SD	85 ± 0.36	82 ± 0.39
Baseline BR23 QOL scores (range of possible scores), mean ± SD		
Body Image (0-100)§	93 ± 15.6	93 ± 9.6
Breast Symptoms (0-100)§	20 ± 17.4	21 ± 18.4
Sexual Function (0-100)‖	22 ± 21.1	19 ± 20.1
Sexual Enjoyment (0-100)‖	49 ± 34.3	52 ± 19.7
Baseline BIABC QOL scores (range of possible scores), mean ± SD		
Arm Concerns (5-25)§	9 ± 2.5	9 ± 2.9
Body Concerns (6-30)§	16 ± 4.3	16 ± 4.4
Body Stigma (15-75)§	30 ± 8.4	33 ± 7.6
Transparency (5-25)§	6 ± 2.7	7 ± 2.2

Abbreviations: BIABC = Body Image After Breast Cancer Questionnaire; BMI = body mass index; BR23 = Breast-Specific Module; DCIS = ductal carcinoma in situ; EBRT = external beam radiation therapy; ER = estrogen receptor; IDC = Invasive Ductal Carcinoma; ILC = Invasive Lobular Carcinoma; PR = progesterone receptor; QOL = quality of life; SD = standard deviation; SLNBx = sentinal lymph node biopsy; TARGIT-IORT = targeted intraoperative radiation therapy.

* See reference 14.

† Factors relevant only to the prepathology stratification.

‡ Dose to surface of applicator.

§ Higher score denotes worse symptoms.

‖ Higher score denotes better functioning.

randomized to receive either a single dose of TARGIT-IORT (50-kV X rays with INTRABEAM [Carl Zeiss, Oberkochen Germany]) or conventional 3 to 7 weeks' EBRT. The TARGIT-IORT patients with unfavorable pathology also received EBRT in approximately 15% of cases; however, these were excluded from this analysis.

This substudy includes 126 patients from 3 treatment centers in Western Australia. Relevant ethics approvals were obtained, and all participants provided written, informed consent.

The TARGIT-IORT dose to 1 cm was 5 to 6 Gy (16-33 Gy at applicator surface), and EBRT was conventional 3-dimensional conformal radiation therapy (45-50.4 Gy in 25-28 fractions).

Eligibility for Australian patients randomized to the postpathology stratification was stricter than for the main trial: unifocal invasive ductal (not lobular) <2-cm tumors, node negative, hormone positive, limited ductal carcinoma in situ, and lymphovascular negative disease. Fourteen EBRT and 4 IORT patients in this analysis were randomized prepathology where these criteria did not apply, hence some deviations are shown in Table 1.

Instruments and evaluations

Patients were routinely assessed at baseline, that is, after initial surgery but before receiving either TARGIT-IORT (as a separate procedure) or EBRT, and annually thereafter for 5 years using the instruments given below.

Cosmesis

The Global Harris Scoring System of Excellent, Good, Fair, or Poor was used (15-17). Responses are dichotomized into Excellent and Good (EG) or Fair and Poor (FP) categories (Table E1; available online at www.redjournal.org). Harris Scores were also completed by a radiation oncologist, nurse, and an objective photographic measurement system (BCCT.core); however, these data will be reported separately.

Quality of life

The European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), Breast-Specific Module (BR23), and the Body Image after Breast Cancer Questionnaire (BIABC) were used. The EORTC questionnaires were also collected 3, 6, and 9 months after WLE. These tools were chosen because of their reliability, validity, and ongoing use in several international breast cancer trials (18-22).

The EORTC QLQ-C30 comprises 5 functional scales (Physical, Role, Emotional, Cognitive, Social), 3 symptom scales (Fatigue, Nausea/Vomiting, Pain), 6 single-item scales, and a Global QOL scale (19, 23). The validated EORTC QLQ-BR23 has 23 questions grouped into 5 domains (Systemic Treatment Side Effects, Arm Symptoms, Breast Symptoms, Body Image, Sexual Functioning) and 3 single-item domains for Sexual Enjoyment, Hair Loss, and Future Perspectives (19, 23, 24).

The EORTC questionnaires were scored according to guidelines, resulting in scores ranging from 0 to 100. A high score signifies better functioning for functional domains but poorer scores for symptom domains (19). The focus of this analysis is on the BR23 module. Most questions relate to patient experience in the last week, except for sexual functioning, which has a 4-week time frame.

The BIABC is composed of 6 domains: Vulnerability, Body Stigma, Limitations, Body Concerns, Transparency, and Arm Concerns. Scoring was in accordance with the corrected scoring system (25). Higher scores signify worse functioning across all domains. Each domain has a different range of possible scores (21, 25, 26). All questions relate to patient experience in the last 4 weeks.

Panel review of QOL domains

To reduce multiple testing and investigate only relevant breast-related domains, we performed a hypothesis-generating panel review of the 2 breast-specific questionnaires (BR23 and BIABC). The review was exploratory; we wished to hypothesize which domains might show differences between patients having TARGIT-IORT versus EBRT.

Ten health professionals from radiation and medical oncology, surgery, nursing, and clinical trials who were familiar with TARGIT-IORT and EBRT participated. A domain was included in the analysis if it was scored as relevant by at least 3 responders. Four domains were identified from the BIABC questionnaire, and the range of possible scores were as follows: Arm Concerns, because it includes a question about breast pain (5-25), Body Concerns (6-30), Body Stigma (15-75), and Transparency (obviousness of cancer to others and concern about cancer-related appearance) (5-25). Four domains were identified from the BR23 questionnaire: Body Image, Breast Symptoms, Sexual Function, and Sexual Enjoyment.

Analysis and interpretation

Despite the panel review reducing the number of evaluable QOL domains from 26 to 8, a large number of tests were still required for the primary analysis. Statistical significance was therefore set at $P<.01$ to account for multiple comparisons (23, 27).

Clinical significance utilizing the Osoba method is discussed according to QOL reporting guidelines (23, 28, 29). A difference of at least 10 points on a 100-point scale is considered a minimal clinically meaningful change; a difference between 10 and 20 points is considered a moderate effect; and differences over 20 are considered a large effect (23, 30).

Sensitivity analyses were performed to investigate robustness of the complete case data. The EORTC scoring system allows domain scores to be calculated in 2 ways: (*1*) only when all questions in that domain have been answered (complete case analysis); and (*2*) when at least half of the questions in the domain have been answered, allowing the calculation of an average score for the domain (single imputation with mean substitution) (19). Multiple imputation of missing data was also applied to both questionnaires (19, 31-33). Given the similarities in outcomes across the 3 datasets, only the findings from the complete case analysis are reported.

IBM-SPSS version 22 (SPSS, Chicago, IL) was used for the following: scoring QOL questionnaires; nonparametric analysis (Mann-Whitney U and χ^2) of raw unadjusted data; and for multiple imputation and single imputation for the sensitivity analyses. Generalized estimating equations with a variable covariance structure were used for the longitudinal dichotomized cosmesis endpoint, and linear mixed models were used for the continuous longitudinal QOL endpoints using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of 385 Western Australian TARGIT-A patients, only the first 152 consecutive patients were invited to participate in this substudy owing to resource constraints, with 6 declining participation. A further 20 were excluded because of confounders that would render cosmesis data

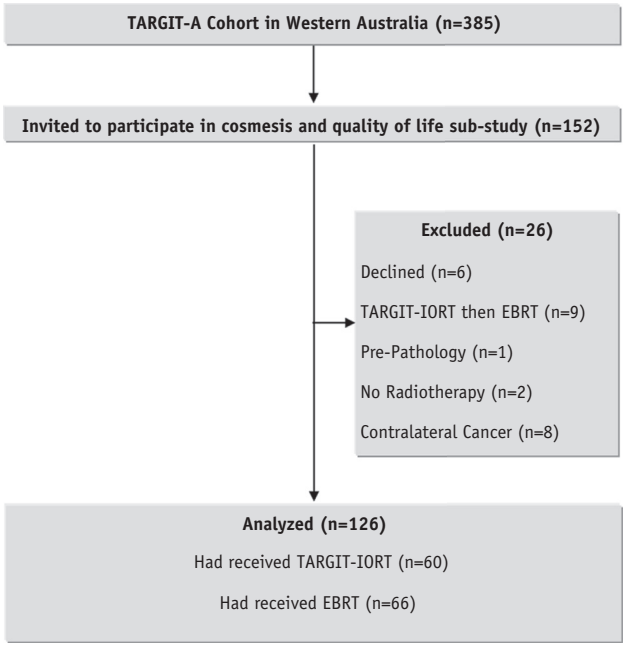

Fig. 1. CONSORT diagram. *Abbreviations:* EBRT = external beam radiation therapy; TARGIT-IORT = targeted intraoperative radiation therapy.

uninterpretable, including (*1*) received both TARGIT-IORT and EBRT (n=9); (*2*) received TARGIT-IORT during WLE (n=1); (*3*) no radiation therapy given (n=2); or (*4*) history of contralateral disease (n=8). This left 126 evaluable participants, of whom 60 had TARGIT-IORT and 66 had EBRT (Fig. 1).

Participants and compliance

Compliance was very good and nearly identical across both treatment groups; however, as expected in a longitudinal study, compliance decreased over time (Table E2; available online at www.redjournal.org). Sensitive domains relating to sexual function had the worst compliance, with a range of 21% to 81% missing data across time points. There were no significant differences in baseline patient characteristics between treatment groups (Table 1).

Cosmesis

Despite a trend for greater proportions of TARGIT-IORT patients self-reporting an Excellent-Good result compared with EBRT patients overall, multivariate longitudinal analysis did not reveal any statistically significant differences between treatment group at any time point (Fig. 2). Models to test whether other factors (such as age, body mass index, specimen size, EBRT boost, and additional surgery) may have an impact revealed no other drivers of self-reported cosmetic outcome (14). Univariate analysis revealed that TARGIT-IORT patients had better cosmetic

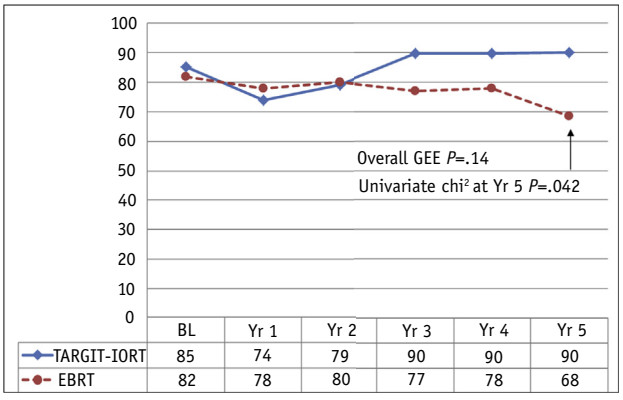

Fig. 2. Proportion of patients self-reporting excellent–good cosmesis. *Abbreviations:* EBRT = external beam radiation therapy; GEE = generalized estimating equation; TARGIT-IORT = targeted intraoperative radiation therapy.

outcome compared with EBRT patients at year 5, with 90% and 68.4% scoring EG, respectively, (P=.042) (Fig. 2).

QOL results

Mean baseline scores for the 8 QOL domains selected a priori did not demonstrate any significant differences at the P<.01 level between the 2 treatment groups (Table E3; available online at www.redjournal.org). Exploratory analysis of Global QOL scores showed significantly better scores for TARGIT-IORT patients at baseline (79.5 TARGIT-IORT, 70.3 EBRT, P=.007).

Beyond baseline, TARGIT-IORT patients tended to fare better than EBRT patients in terms of breast-related QOL. Nonparametric testing revealed statistically significantly better results consistently favoring the TARGIT-IORT group in the Arm Concerns domain at year 1 (P<.0001) (Table E4; available online at www.redjournal.org), and months 6 and 9 and years 1, 3, and 4 (P<.001) of the Breast Symptoms domain. A number of differences were also considered clinically significant (Table 2).

Treatment (and its interaction with time) had a statistically and clinically significant impact on the Breast Symptoms (P=.006) and Arm Concerns (P=.005) domains, both favoring TARGIT-IORT (Table 3). Age was also found to be a significant factor in the Body Image (P=.004) and Sexual Function (P<.001) domains, where an increase in age was associated with worse body image and sexual function. Time since treatment was found to impact the Sexual Function domain, with lower scores seen at the year 5 time point for both treatment groups (P=.008). The Sexual Enjoyment domain shows mixed results suggesting an interaction between treatment and time (P<.001), with TARGIT-IORT patients scoring worse function from baseline to 6 months, then better function from 9 months onward, with clinically significant differences at years 1, 3, and 4. Age-adjusted mean scores for

Table 2 Statistically and clinically significant differences in long-term QOL between TARGIT-IORT and EBRT

Domain	Baseline	3 mo	6 mo	9 mo	1 y	2 y	3 y	4 y	5 y
Body Image	.2	.5	.2	.4	.3	.3	.1	.8	.5
Breast Symptoms	.6	.2	.000* (12)	.001* (7.9)	.000* (10.4)	.010† (5.8)	.000* (8.5)	.001* (5.7)	.014† (6.2)
Sexual Function	.5	.2	.9	.9	.5 (18.8)	.3 (15.8)	.4 (15.7)	.1 (22.1)	.035* (11.3)
Sexual Enjoyment	.7	.7	.3	.4	.013† (18.8)	.091† (15.8)	.036† (15.7)	.028† (22.1)	.6
Arm Concerns	.5	n/a	n/a	n/a	.000* (12.7)	.2	.031† (7.5)	.2	.4
Body Concerns	1	n/a	n/a	n/a	.9	.7	.9	.4	.9
Body Stigma	.05	n/a	n/a	n/a	.5	.2	.2	.3	.2
Transparency	.5	n/a	n/a	n/a	.3	1	.1	.6	.1

Abbreviations as in Table 1.

Values in parentheses are the Osoba clinical significance score. Note that Osoba clinical significance is reached with a difference >10 on a 100-point scale. All clinically and statistically significant differences favored TARGIT-IORT.

* Significant at the .01 *P* level (Mann-Whitney *U* test).

† Significant at the .05 *P* level.

QOL domains are illustrated in Figure 3, with further details shown in Table E5 (available online at www.redjournal.org).

Although the core EORTC questionnaire was not used in the a priori analysis, we explored the Global QOL domain, which contains 2 questions relating to overall health and overall QOL, respectively. A higher score denotes better Global QOL, and results revealed that TARGIT-IORT patients consistently scored higher scores than EBRT patients, with statistically significant differences found at baseline, 3 and 6 months, and 1 year. Clinically significant differences were seen at 3 and 6 months (moderate and minimal clinical significance, respectively) (Fig. E1; available online at www.redjournal.org).

Sensitivity analyses

All 3 approaches to analysis (complete case, single imputation, multiple imputation) produced similar parameter estimates and *P* values. Minor disagreement was seen in 2 domains of the BIABC questionnaire at the $P<.05$ level, but no differences were seen at the $P<.001$ level. Specimen size was significant ($P=.035$) in the complete case analysis of body stigma but insignificant in the multiple imputation analysis ($P=.064$). The treatment × time interaction of the Arm Concerns domain was significant for the complete case analysis ($P=.006$) but insignificant in the multiple imputation analysis ($P=.112$).

The effect of missing data on the year-5 cosmesis scores was tested by carrying forward the previous years' result. This increased the proportion of an EG score from 68.4% to 69% for the EBRT group and decreased the proportion from 90% to 88% in the TARGIT-IORT group.

Discussion

Intraoperative radiation therapy is a new way to offer adjuvant breast radiation therapy, and few studies of cosmesis and QOL have been reported (34-37). This TARGIT-A substudy provides comprehensive patient-reported results comparing postpathology TARGIT-IORT

Table 3 Longitudinal mixed model regression *P* values, adjusted for age and time

Domain	Age	Treatment	Time	Treatment × time	BMI	Specimen size (mm)
Body Image	.004* (0.28)	.8	.9	.7	n/a	n/a
Breast Symptoms	.2	<.001* (−1.48)	<.001*	.006*	n/a	n/a
Sexual Function	<.001* (−1.15)	.3	.008*	.9	.027† (−3.05)	n/a
Sexual Enjoyment	.05	.5	.3	<.001*	n/a	n/a
Arm Concerns	.6	.021† (−0.43)	.002*	.005*	n/a	n/a
Body Concerns	.6	.6	.4	.8	n/a	n/a
Body Stigma	.3	.2	.5	.6	n/a	.019† (0.038)
Transparency	.016† (−0.05)	.6	.4	.4	n/a	n/a

Abbreviations as in Table 1.

Values in parentheses are the parameter estimates of TARGIT-IORT versus EBRT: for every 1 unit of the variable, the QOL domain increases or decreases by this value. All significant findings favored the TARGIT-IORT group.

* Significant at the <.01 level.

† Significant at the <.05 level.

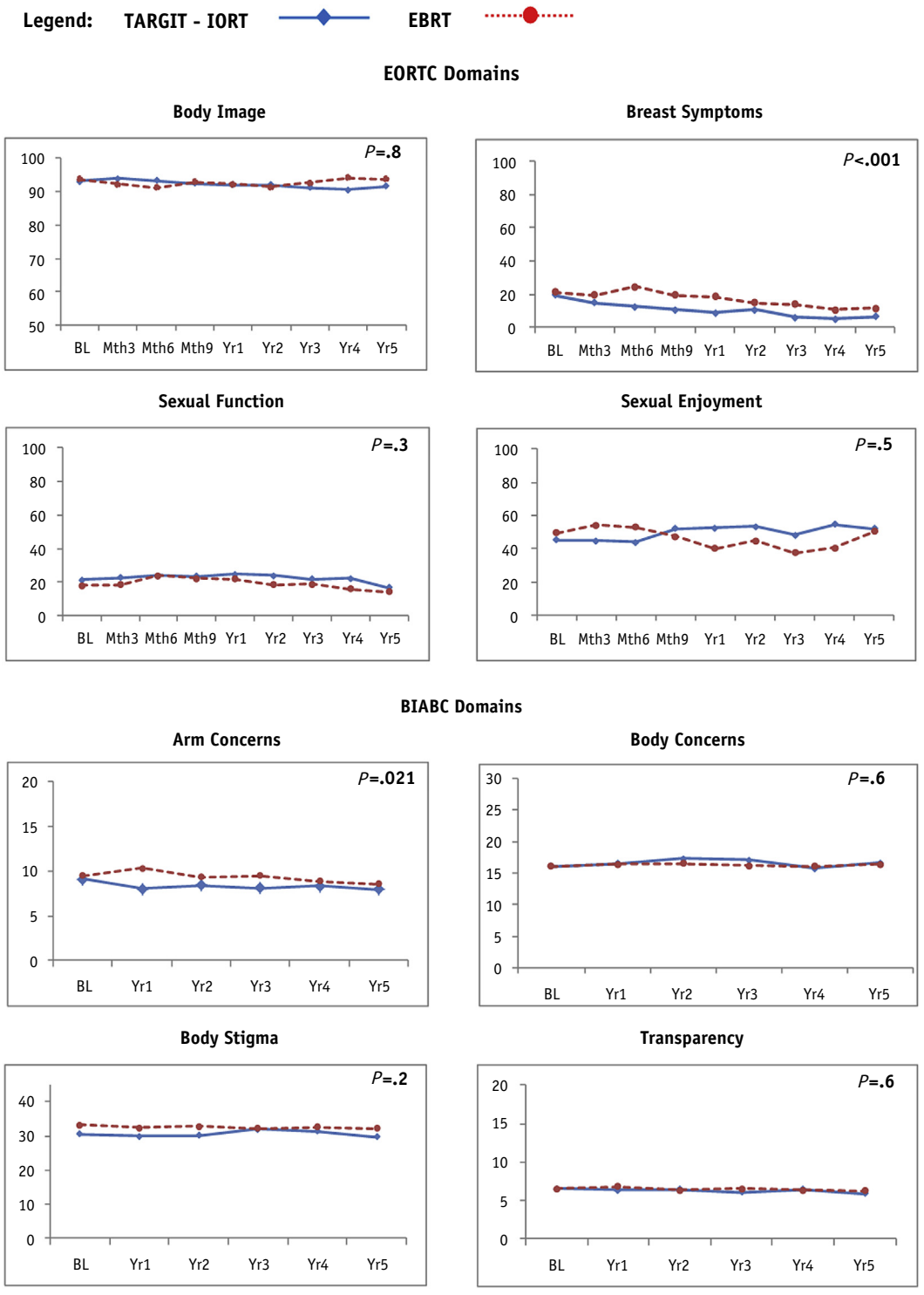

Fig. 3. Age-adjusted mean quality of life scores. *Abbreviations:* BIABC = Body Image After Breast Cancer Questionnaire; EBRT = external beam radiation therapy; EORTC = European Organization for Research and Treatment of Cancer; TARGIT-IORT = targeted intraoperative radiation therapy.

with EBRT. Targeted IORT was found to significantly impact breast symptoms, improving QOL.

Patients receiving TARGIT-IORT tended to self-report better outcomes for both cosmesis and QOL, such that a higher number scored an EG cosmetic result across all time points, and they experienced fewer symptoms and better functioning in breast-related QOL.

The only significant difference in cosmesis was at year 5 (Excellent-Good scores were 68.4% for EBRT and 90% for TARGIT-IORT [$P = .007$], which coincidentally were the

lowest and highest scores reported by patients across all time points). Study attrition as a potential cause of this difference was ruled out by sensitivity analysis. Overall, the proportion of patients scoring themselves as EG was high and compares well to previous research, which has shown that 70% to 80% of EBRT patients can expect an EG cosmetic outcome (4).

Clinically and statistically significant findings were seen at year 1 for Arm Concerns and at month 6 for Breast Symptoms. At these time points, EBRT patients experienced moderately higher levels of treatment-related symptoms, including breast and arm pain, swelling, oversensitivity, and skin problems. These findings are in keeping with the results obtained from cross-sectional studies of QOL in TARGIT-A patients in Germany (median follow-up 47 months; prepathology patients) (35, 37) and toxicity results from TARGIT-A (12).

The increase in self-reported breast symptoms in EBRT patients observed 6 months after WLE, which subsided by the ninth month, was most likely because patients had only just finished their EBRT around this time, when waiting times were on average 4.5 months (2.3-7.9 months) for completion of EBRT. The TARGIT-IORT patients had completed their treatment between 4 days and 4 months after WLE, with the average completion time of 1.6 months. Given the lack of significant difference between breast symptoms reported at 3 months, TARGIT-IORT patients had presumably recovered from their procedure by the time the 3-month questionnaire was administered, when EBRT patients were just starting radiation therapy. By 6 months, TARGIT-IORT patients had improved further in terms of breast side effects, but EBRT patients who had recently ceased or were still receiving treatment were experiencing the peak of treatment-related side effects. By 9 months both treatment groups scored better than baseline scores, which is in keeping with other longitudinal international QOL studies of EBRT (22, 38).

Breast symptoms for both groups continued to decrease over time, showing better results for both groups at 4 years (4.2 for TARGIT-IORT and 9.9 for EBRT) when compared with the German cohort (8.6 for TARGIT-IORT and 19.2 for EBRT) (37). A similar reduction in breast symptoms over time was also seen in the START-A and -B trials, which assessed breast symptoms for different regimens of EBRT from baseline to year 5, and also QOL studies performed in Australia/New Zealand and Canada that assessed both short- and long-term QOL after EBRT (22, 38, 39).

In comparison with the 50-Gy EBRT arm of the START trials, patients treated with TARGIT-IORT in the present study reported fewer breast symptoms at months 6 and years 1 and 5; however, the patients treated with EBRT in the present study showed worse breast symptoms across all follow-up time points compared with TARGIT-IORT (39, 40).

Overall, patients treated with TARGIT-IORT reported better Global QOL scores at every time point. Despite not reaching clinical significance, it is worth noting that TARGIT-IORT patients scored better Global QOL at baseline (79.5) compared with the EBRT group (70.3, $P = .007$), who had a score similar to the baseline scores for the 50-Gy EBRT group in the START trials (69.8) (40). The administration of the baseline questionnaire in the present study was performed after patients were randomized. We may hypothesize that either patients randomized to the TARGIT-IORT arm were actually experiencing better QOL, or that simply being randomized to the single treatment may have had a positive effect on their sense of well-being, which improved reported QOL. Anecdotally, patients randomized to TARGIT-IORT were visibly relieved to not have to endure the 6-week burden of EBRT, and patients randomized to EBRT would often become visibly upset when informed they drew the conventional arm (particularly those who would need to relocate to the city for the duration of their treatment, leaving behind dependents, animals, or other responsibilities). Statistically and clinically significant differences seen between TARGIT-IORT and EBRT at 3 and 6 months suggest that the impact of undergoing extended treatment was reflected in Global QOL scores of EBRT patients. The administration of the 3-month BR23 generally coincided with the start of EBRT (the median time to start EBRT was 7.5 days before 3-month BR23). This may have contributed to the poorer Global QOL scores in the EBRT group. Patients who received TARGIT-IORT completed the 3-month BR23 a median of 47 days after treatment, hence they may have returned to their usual routine by that time.

Sensitivity analyses comparing complete case, single imputation, and multiple imputation datasets produced similar outcomes. This similarity can be explained by excellent completion rates and generally good health exhibited by participants, which led to few occasions for which imputation was required. Multiple imputation is complex and time consuming and is not necessary with the amount, type, and pattern of missingness experienced by this dataset.

This analysis reports the experience of patients who received TARGIT-IORT as a separate procedure after WLE (postpathology). Internationally, TARGIT-IORT during WLE (prepathology) is now the preferred approach, and we would not anticipate that the concurrent procedure would result in worse cosmetic or QOL outcomes. Because it is reasonable to expect that cosmetic outcome and QOL would be worse in patients who have an additional procedure after WLE, this is a factor that would work against finding better outcomes with TARGIT-IORT versus EBRT in this study. Therefore, our findings of equal or better outcomes in such patients are even more significant.

Limitations and strengths

This substudy describes only a subset of TARGIT-A patients, with a mix of patients from the pre- and postpathology stratifications. Sensitivity analysis showed that

missing data did not affect study outcomes, with the exception of sensitive questions relating to sexual function and intimacy, in which missing data are universal (19, 41). On average, across each time point, 53% and 45% of TARGIT-IORT and EBRT patients, respectively, were sexually active, hence only half of the surveyed population could offer a score for the Sexual Enjoyment domain (on average 19 patients per group per time point). Such small numbers may reduce the generalizability of the reported findings for this domain, despite excellent compliance rates. Furthermore, this study did not distinguish between partnered and nonpartnered women, and information on adjuvant hormonal therapy was not reviewed, hence making it impossible to interpret whether a reduction in sexual function was potentially related to these factors.

Although the results of this study show that TARGIT-IORT and EBRT patients have similar long-term outcomes, the main clinically significant differences were seen within the first year. Collection of data at months 3, 6, and 9 after WLE, which encompass the radiation therapy treatment time frame, is therefore a strength of this study because other studies using a cross-sectional approach miss out on this valuable information. Consideration must be given to the timing of assessment to facilitate interpretation. In this study the significant date was WLE; however, radiation therapy end date may have been easier to interpret.

Conclusion

Patients treated with TARGIT-IORT in the TARGIT-A trial have better breast-related QOL outcomes than patients treated with EBRT, despite receiving TARGIT-IORT as a separate procedure (postpathology). Patients receiving EBRT experience worse breast-specific symptoms such as pain, swelling, oversensitivity, and skin problems during or shortly after treatment. Cosmetic outcomes were similar overall, but TARGIT-IORT patients had better cosmetic outcomes than EBRT patients at 5 years. Recently published meta-analysis data shows that partial breast irradiation such as TARGIT-IORT leads to a reduction in mortality, thus TARGIT-IORT would benefit patients both in terms of quality and quantity of life (42). This evidence is important for clinicians and patients because it can facilitate the decision-making process regarding treatment options for early breast cancer treatable with breast-conserving surgery, particularly owing to the convenience of TARGIT-IORT, which may better suit patient preferences for treatment.

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