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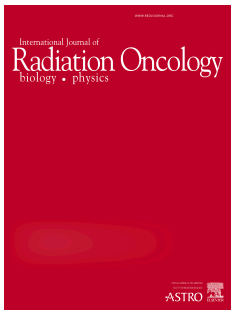

Cosmesis and breast-related quality of life outcomes following intra-operative radiotherapy for early breast cancer - a sub-study of the TARGIT-A trial

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Conflict of interest

DJ received a research grant from Photoelectron Corp in 2001 to support data management. JSV received a research grant from Photoelectron Corp (1996–99) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK) and has subsequently received honoraria. MB was on the scientific advisory board of Carl Zeiss and was paid monthly consultancy fees until 2010. 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 radiotherapy is being made for all authors apart from AN and MT. Carl Zeiss had no involvement in this publication.

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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 sub-study, 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 re-opening the wound (post-pathology).

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Abstract

Purpose:

The international randomized TARGIT-A trial compared risk-adapted single-dose intra-operative radiotherapy (TARGIT-IORT) to 3-7 weeks of daily conventional external beam radiotherapy (EBRT) in women with early breast cancer treatable with breast conserving surgery. TARGIT-A showed TARGIT-IORT to be non-inferior compared to EBRT in terms of reducing the risk of local cancer recurrence and found no difference in breast cancer survival however its effect on patient reported cosmesis and breast-related quality of life (QOL) have not yet been described.

Methods and Materials:

Longitudinal cosmesis and QOL data were collected from a sub-set of TARGIT-A participants who received TARGIT-IORT as a separate procedure (post-pathology). Patients completed a cosmetic assessment before radiotherapy and annually thereafter for at least five years. Patients also completed the combined EORTC core questionnaire (QLQ-C30) and Breast Specific Module (BR23) in addition to the Body Image after Breast Cancer Questionnaire (BIABC) at baseline and annually thereafter. The combined EORTC questionnaires were also collected 3, 6, and 9 months after wide local excision (WLE).

Results:

An Excellent-Good (EG) cosmetic result was scored more often than a Fair-Poor (FP) result for both treatment groups across all time points. 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:

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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.

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Introduction

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

Targeted Intra-Operative Radiotherapy (TARGIT-IORT) allows delivery of radiation directly to tissues at the site of the primary tumour in a single session at the time of wide local excision (WLE) or shortly afterwards. The TARGIT-A trial compared TARGIT-IORT to conventional EBRT. Five year results found TARGIT-IORT to be non-inferior to EBRT in terms of risk of local recurrence when delivered during WLE (pre-pathology) (non-inferiority could not be established for post-pathology, 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 post-operative seromas (2% vs. 0.8%)[12]. Cosmesis analysis utilising digital photographs showed better outcomes with TARGIT-IORT in the first year[13].

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

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Patients and Methods

Patients and Treatment

Between 2000 and 2012 TARGIT-A registered 3451 patients from 33 centres in 11 countries. Patients with early breast cancer suitable for breast conserving surgery were randomized to receive either a single dose of TARGIT-IORT (50kV X-rays with INTRABEAM$^{(TM)}$ Carl Zeiss, Oberkochen Germany) or conventional 3-7 weeks EBRT. TARGIT-IORT patients with unfavourable pathology also received EBRT in ~15% of cases however these were excluded from this analysis.

This sub-study includes 126 patients from three treatment centres in Western Australia. Relevant ethics approvals were obtained and all participants provided written informed consent.

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

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

Instruments and evaluations

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

Cosmesis

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The Global Harris Scoring System of Excellent, Good, Fair or Poor was used[14-16]. Responses are dichotomized into Excellent and Good (EG) or Fair and Poor (FP) categories (Table e1 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 Organisation 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. EORTC questionnaires were also collected 3, 6 and 9 months after WLE. These tools were chosen due to their reliability, validity and ongoing use in several international breast cancer trials[17-21].

The EORTC QLQ-C30 comprises five functional scales (Physical, Role, Emotional, Cognitive, Social), three symptom scales (Fatigue, Nausea/Vomiting, Pain), six single-item scales and a Global QOL scale[18,22]. The validated EORTC QLQ-BR23 has 23 questions grouped into five 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[18,22,23].

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[18]. 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 four-week time frame.

The BIABC is comprised of 6 domains: Vulnerability, Body Stigma, Limitations, Body Concerns, Transparency and Arm Concerns. Scoring was in accordance with the corrected scoring system[24].

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Higher scores signify worse functioning across all domains. Each domain has a different range of possible scores[20,24,25]. All questions relate to patient experience in the last four weeks.

Panel Review of quality of life domains

To reduce multiple testing and investigate only relevant breast-related domains, we performed a hypothesis-generating panel review of the two breast-specific questionnaires (BR23 and BIABC). The review was exploratory; we wished to hypothesise which domains might show differences between patients having TARGIT-IORT vs. 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: Arm Concerns-as 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 $p<0.01$ to account for multiple comparisons[22,26].

Clinical significance utilizing the Osoba method is discussed according to QOL reporting guidelines[22,27,28]. 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[22,29].

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Sensitivity analyses were performed to investigate robustness of the complete case data. The EORTC scoring system allows domain scores to be calculated in two ways; a) only when all questions in that domain have been answered (complete case analysis) and b) 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)[18]. Multiple imputation of missing data was also applied to both questionnaires[18,30-32]. Given the similarities in outcomes across the three datasets, only the findings from the complete case analysis are reported.

IBM-SPSS V22 (SPSS Inc,.Chicago, IL) was used for: scoring QOL questionnaires; non-parametric analysis (Mann-Whitney-U and Chi^2) of raw unadjusted data and for multiple imputation and single imputation for the sensitivity analyses. Generalized estimating equations (GEE) 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 V9.3 (SAS Institute, Cary, NC).

Results

Of 385 Western Australian TARGIT-A patients, only the first 152 consecutive patients were invited to participate in this sub-study due to resource constraints, with 6 declining participation. A further 20 were excluded due to confounders which would render cosmesis data uninterpretable, including a) received both TARGIT-IORT and EBRT (n=9), b) received TARGIT-IORT during WLE (n=1), c) no radiotherapy given (n=2) or d) history of contralateral disease (n=8). This left 126 evaluable participants, of whom 60 had TARGIT-IORT and 66 had EBRT (Figure 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 www.redjournal.org). Sensitive domains relating to sexual function had the worst compliance with a range of 21% to 81% missing

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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 EG result compared to EBRT patients overall, multivariate longitudinal analysis did not reveal any statistically significant differences between treatment group at any time point (Figure 1). 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[33]. Univariate analysis revealed TARGIT-IORT patients had better cosmetic outcome compared to EBRT patients at Year-5 with 90% and 68.4% scoring EG respectively (p=0.007) (Figure 2).

Quality of life results

Mean baseline scores for the 8 QOL domains selected a-priori did not demonstrate any significant differences at the p<0.01 level between the two treatment groups (Table e3 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=0.007).

Beyond baseline, TARGIT-IORT patients tended to fare better than EBRT patients in terms of breast-related QOL. Non-parametric testing revealed statistically significantly better results consistently favoring the TARGIT-IORT group in the Arm Concerns domain at Year-1 (p<0.0001) (Table e4 www.redjournal.org), and Months 6 and 9 and Years 1, 3 and 4 (p<0.001) 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=0.006) and Arm Concerns (p=0.005) domains, both favouring TARGIT-IORT (Table 3). Age was also found to be a significant factor in the Body Image (p=0.004) and Sexual

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Function ($p<0.001$) 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 ($p=0.008$). The Sexual Enjoyment domain shows mixed results suggesting an interaction between treatment and time ($p<0.001$) with TARGIT-IORT patients scoring worse function from BL to 6 months, then better function from 9 months onwards with clinically significant differences at Years 1, 3 and 4. Age adjusted mean scores for QOL domains are illustrated in Figure 2 with further details shown in Table e5 www.redjournal.org.

Although the core EORTC questionnaire was not used in the a-priori analysis, we explored the Global QOL domain, which contains two questions relating to overall health and overall quality of life respectively. A higher score denotes better global QOL and results revealed 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) (Figure e1 www.redjournal.org).

Sensitivity Analyses

All three approaches to analysis (complete case, single imputation, multiple imputation) produced similar parameter estimates and p-values. Minor disagreement was seen in two domains of the BIABC questionnaire at the $p<0.05$ level, but no differences were seen at the $p<0.001$ level. Specimen size was significant ($p=0.035$) in the complete case analysis of body stigma but insignificant in the MI analysis ($p=0.064$). The treatment vs. time interaction of the arm concerns domain was significant for the complete case analysis ($p=0.006$) but insignificant in the MI analysis ($p=0.112$).

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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.

Discussion of results

Intra-operative radiotherapy is a new way to offer adjuvant breast radiotherapy and few studies of cosmesis and QOL have been reported[34-37]. This TARGIT-A sub-study provides comprehensive patient-reported results comparing post-pathology TARGIT-IORT to EBRT. TARGIT-IORT was found to significantly impact breast symptoms, improving quality of life.

TARGIT-IORT patients 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 (EG scores were 68.4%-EBRT and 90%-TARGIT-IORT, p=0.007, 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 70-80% of EBRT patients can expect an EG cosmetic outcome[4].

Clinically and statistically significant findings were seen at Year-1 for Arm Concerns and 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; pre-pathology patients)[35,37] and toxicity results from TARGIT-A[12].

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The increase in self-reported breast symptoms in EBRT patients observed 6-months post-WLE which subsided by the 9th 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. 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 radiotherapy. 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[21,38].

Breast symptoms for both groups continued to reduce over time, showing better results for both groups at 4 years (4.2 for TARGIT-IORT and 9.9 for EBRT) when compared to 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 which assessed both short and long term QOL post EBRT [21,38,39].

In comparison to the 50Gy 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 to 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 to the EBRT group (70.3, p=0.007) who had a

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similar score to the baseline scores for the 50Gy EBRT group in the START trials (69.8)[40]. The administration of the baseline questionnaire in the present study was performed after patients were randomised. We may hypothesise that either patients randomised to the TARGIT-IORT arm were actually experiencing better QOL, or that simply being randomised to the single treatment may have had a positive effect on their sense of wellbeing which improved reported QOL. Anecdotally, patients randomised to TARGIT-IORT were visibly relieved to not have to endure the 6 week burden of EBRT, and patients randomised 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 suggests 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 prior to 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 where 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 (post-pathology). Internationally, TARGIT-IORT during WLE (pre-pathology) is now the preferred approach and we would not anticipate that the concurrent procedure would result in worse cosmetic or QOL outcomes. As it is reasonable to expect that cosmetic outcome and quality of life would be worse in patients who have an additional procedure after

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WLE, this is a factor that would work against finding better outcomes with TARGIT-IORT vs. EBRT in this study. Therefore, our findings of equal or better outcomes in such patients are even more significant.

Limitations and Strengths

This sub-study describes only a sub-set of TARGIT-A patients with a mix of patients from the pre and post-pathology stratifications. Sensitivity analysis showed 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[18,41]. 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 generalisability of the reported findings for this domain despite excellent compliance rates. Furthermore, this study did not distinguish between partnered and non-partnered 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 by these factors.

While the results of this study show 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 post WLE which encompass the radiotherapy treatment time frame is therefore a strength of this study as 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 radiotherapy end date may have been easier to interpret.

Conclusion

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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 (post-pathology). EBRT patients 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. This evidence is important for clinicians and patients as it can facilitate the decision-making process regarding treatment options for early breast cancer treatable with breast conserving surgery, particularly due to the convenience of TARGIT-IORT which may better suit patient preferences for treatment.

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REFERENCES

1. Early Breast Cancer Trialists' Collaborative G. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *The Lancet.* 2011;378(9804):1707-1716.
2. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for Whole Breast Irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. *International Journal of Radiation Oncology*Biology*Physics.* 2011;81(1):59-68.
3. Coombs N CJ, Vaidya U, Singer J, Bulsara M, Tobias J, Wenz, F, Joseph D, Brown D, Rainsbury R, Davidson T, Adamson D, Massarut S, Morgan D, Potyka I, Corica T, Falzon M, Williams N, Baum M, Vaidya J. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open.* 2016 2016;6.
4. Buchholz TA. Radiation Therapy for Early-Stage Breast Cancer after Breast-Conserving Surgery. *New England Journal of Medicine.* 2009;360(1):63-70.
5. Kurtz JM. Impact of radiotherapy on breast cosmesis. *The Breast.* 1995;4(3):163-169.
6. The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *LANONC.* 2008;9(4):331-341.
7. The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *The Lancet.* 2008;371(9618):1098-1107.
8. Boscoe FP, Johnson CJ, Henry KA, et al. Geographic proximity to treatment for early stage breast cancer and likelihood of mastectomy. *The Breast.* 2011;20(4):324-328.
9. Pan I-W, Smith BD, Shih Y-CT. Factors Contributing to Underuse of Radiation Among Younger Women With Breast Cancer. *Journal of the National Cancer Institute.* January 1, 2014 2014;106(1).
10. NSW Department of Health. Factors that impact on referral rates for radiotherapy. In: Health, ed. NSW: NSW Department of Health; 2011:22.
11. Vaidya JS, Wenz F, Bulsara M, et al. 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.* 2014;383(9917):603-613.
12. 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. *The Lancet.* 2010;376(9735):91-102.
13. Keshtgar M, Williams N, 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.
14. Harris JR, Levene MB, Svensson G, et al. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *International Journal of Radiation Oncology*Biology*Physics.* 1979;5(2):257-261.
15. Kramer BA, Arthur DW, Ulin K, et al. Cosmetic Outcome in Patients Receiving an Interstitial Implant as Part of Breast-Conservation Therapy1. *Radiology.* 1999;213(1):61-66.
16. Rose MA, Olivotto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. *Archives of surgery.* 1989;124(2):153-157.
17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *Journal of the National Cancer Institute.* 1993;85(5):365-376.
18. Fayers PA, N. Bjordal, K.Groenvold, M.Curran, D. Bottomley, A., on behalf of the EORTC Quality of LIfe Group. EORTC QLQ-C30 Scoring Manual (3rd Edition). 2001. http://groups.eortc.be/qol/documentation_manuals.htm.
19. Osoba D, Zee B, Pater J, et al. Psychometric properties and responsiveness of the EORTC Quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Quality of Life Research.* 1994/10/01 1994;3(5):353-364.

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20. Baxter NN, Goodwin PJ, McLeod RS, et al. Reliability and Validity of the Body Image after Breast Cancer Questionnaire. *The Breast Journal.* 2006;12(3):221-232.

21. Sundaresan P, Sullivan L, Pendlebury S, et al. Patients' Perceptions of Health-related Quality of Life During and After Adjuvant Radiotherapy for T1N0M0 Breast Cancer. *Clinical Oncology.* 2015;27(1):9-15.

22. Bottomley A, Biganzoli L, Cufer T, et al. 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.* July 1, 2004 2004;22(13):2576-2586.

23. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *Journal of experimental & clinical cancer research : CR.* 2008;27:32.

24. Baxter NN. Final Corrections of the scoring of the Body Image After Breast Cancer Questionnaire. In: Corica T, ed. Corrections to the published scoring system ed2014:3.

25. Baxter NN. *The Body Image After Breast Cancer Questionnaire: the design and testing of a disease-specific measure*. Canada: University of Toronto, University of Toronto; 1998.

26. Bland JM, Altman DG. *Multiple significance tests: the Bonferroni method.* Vol 3101995.

27. Efficace F, Bottomley A, Osoba D, et al. Beyond the Development of Health-Related Quality-of-Life (HRQOL) Measures: A Checklist for Evaluating HRQOL Outcomes in Cancer Clinical Trials—Does HRQOL Evaluation in Prostate Cancer Research Inform Clinical Decision Making? *Journal of Clinical Oncology.* September 15, 2003 2003;21(18):3502-3511.

28. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Quality of Life Research.* 2013/08/01 2013;22(6):1161-1175.

29. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. *Journal of Clinical Oncology.* January 1, 1998 1998;16(1):139-144.

30. Peyre H, Leplege A, Coste J. Missing data methods for dealing with missing items in quality of life questionnaires. A comparison by simulation of personal mean score, full information maximum likelihood, multiple imputation, and hot deck techniques applied to the SF-36 in the French 2003 decennial health survey. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* Mar 2011;20(2):287-300.

31. Lin T. A comparison of multiple imputation with EM algorithm and MCMC method for quality of life missing data. *Qual Quant.* 2010/02/01 2010;44(2):277-287.

32. Spratt M, Carpenter J, Sterne JAC, et al. Strategies for Multiple Imputation in Longitudinal Studies. *American Journal of Epidemiology.* August 15, 2010 2010;172(4):478-487.

33. Australian Government Department of Health. About Overweight and Obesity. Vol http://www.health.gov.au/internet/main/Publishing.nsf/Content/health-pubhlth-strateg-hlthwt-obesity.htm. Canberra, Australia2009.

34. Lemanski C, Azria D, Gourgon-Bourgade S, et al. Intraoperative Radiotherapy in Early-Stage Breast Cancer: Results of the Montpellier Phase II Trial. *International Journal of Radiation Oncology*Biology*Physics.* 3/1/ 2010;76(3):698-703.

35. Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiation oncology (London, England).* 2013;8:9.

36. Belkacémi Y, Chauvet M-P, Giard S, et al. Partial breast irradiation as sole therapy for low risk breast carcinoma: Early toxicity, cosmesis and quality of life results of a MammoSite brachytherapy phase II study. *Radiotherapy and Oncology.* 2009;90(1):23-29.

37. Welzel G, Hofmann F, Blank E, et al. Health-Related Quality of Life After Breast-Conserving Surgery and Intraoperative Radiotherapy for Breast Cancer Using Low-Kilovoltage X-rays. *Ann Surg Oncol.* 2010/10/01 2010;17(3):359-367.

ACCEPTED MANUSCRIPT

38. Whelan TJ, Levine M, Julian J, et al. The effects of radiation therapy on quality of life of women with breast carcinoma. *Cancer.* 2000;88(10):2260-2266.

39. Hopwood P, Haviland JS, Sumo G, et al. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *The Lancet Oncology.* 2010;11(3):231-240.

40. Hopwood P, Haviland J, Mills J, et al. The impact of age and clinical factors on quality of life in early breast cancer: An analysis of 2208 women recruited to the UK START Trial (Standardisation of Breast Radiotherapy Trial). *The Breast.* 2007;16(3):241-251.

41. Osborne JW. Best Practices in Data Cleaning: A complete guide to everything you need to do before and after collecting your data. *Six: Dealing with missing or incomplete data: Debunking the Myth of Emptiness*: SAGE Research Methods; 2013. Accessed 18/06/2014.

Figure 1: CONSORT Diagram

Figure 2: Proportion of patients self-reporting Excellent-Good Cosmesis

Figure 3: Age-Adjusted Mean QOL Scores

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Table 1: Baseline patient characteristics by treatment

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Patient, treatment and tumour	**TARGIT-IORT**	**EBRT**
N (%)	60 (48%)	66 (52%)
Age (mean years +/- SD)	63 (+/- 8.2)	62 (+/- 7.4)
Range	50-83	50-80
Baseline assessments prior to any surgery	1 (2%)	12 (18%)
Baseline BMI (mean score +/- SD)	29 (+/- 5.5)	30 (+/- 5.9)
Baseline BMI Group* (BMI Range)		
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%
Mean Tumour Size (mm)	10 (+/- 4.2)	11 (+/- 5.0)
<11(mm)	62%	52%
11-20 (mm)	38%	46%
>21(mm) * **	-	1.5%
Tumour Grade		
1	37 (62%)	38 (57%)
2	23 (38%)	27 (41%)
3***	0	1 (1.5%)
Tumour Type		
IDC	59 (98%)	64 (97%)
Mixed IDC/ILC***	1 (1.7%)	2 (3%)
Lesions		
1	60 (100%)	65 (98%)
2***	0	1 (1.5%)
Extensive DCIS ***(>25% of tumour + inside and out of tumour)*****	0	4 (6.3%)
ER+ve	60 (100%)	64 (97%)
PR+ve	44 (73%)	52 (79%)
ER and PR –ve***	0	2 (3%)
Positive Nodes***	0	1 (1.5%) (1 node)
Largest Specimen Length (mean -mm +/- SD)	89 (+/- 37.2)	89 (+/- 38.4)
Range	25-205	40-267
Extent of Axillary Surgery		
Nil	3 (5%)	2 (3%)

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SLNBx	49 (82%)	55 (83%)
Clearance	8 (13%)	9 (14%)
Further Surgery Required		
SLNBx	2 (3.3%)	2 (3%)
Margins	2 (3.3%)	7 (11%)
Revision of Scar	2 (3.3%)	0
Radiotherapy Dose Range (Gy)	16-33**	45-50.4
Fractions (range)	1	25 (25-28)
Boost Given (20Gy in 10 fractions)	N/A	11 (17%)
Supraclavicular Treatment	N/A	1 (1.5%)
Chemotherapy* **	0	1 (1.5%)
Baseline Patient Harris *(% Excellent-Good)*	85 (+/- 0.36)	82 (+/- 0.39)
Baseline BR-23 QoL Scores (Range of possible scores) (+/-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) (+/-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)

SD: Standard Deviation.* BMI: Body Mass Index. Australian Government Department of Health. About Overweight and Obesity. Canberra, Australia 2009.**Dose to surface of applicator. ***Factors relevant only to the pre-pathology stratification. † Higher score denotes worse symptoms. †† Higher score denotes better functioning. SLNBx: Sentinal Lymph Node Biopsy

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Table 2: Statistically and Clinically Significant Differences in long term QOL between TARGIT-IORT and EBRT

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Domain	BL	3 month	6 month	9 month	1 Year	2 Year	3 Year	4 Year	5 Year
Body Image	0.2	0.5	0.2	0.4	0.3	0.3	0.1	0.8	0.5
Breast Symptoms	0.6	0.2	**0.000** (12)**	**0.001** (7.9)**	**0.000** (10.4)**	0.010* (5.8)	**0.000** (8.5)**	**0.001** (5.7)**	0.014* (6.2)
Sexual Function	0.5	0.2	0.9	0.9	0.5 (18.8)	0.3 (15.8)	0.4 (15.7)	0.1 (22.1)	0.035* (11.3)
Sexual Enjoyment	0.7	0.7	0.3	0.4	0.013* (18.8)	0.091* (15.8)	0.036* (15.7)	0.028* (22.1)	0.6
Arm Concerns	0.5	n/a	n/a	n/a	**0.000** (12.7)**	0.2	0.031* (7.5)	0.2	0.4
Body Concerns	1	n/a	n/a	n/a	0.9	0.7	0.9	0.4	0.9
Body Stigma	0.05	n/a	n/a	n/a	0.5	0.2	0.2	0.3	0.2
Transparency	0.5	n/a	n/a	n/a	0.3	1	0.1	0.6	0.1

BL: Baseline.*significant at the 0.05 p-level, ****significant at the 0.01 p-level (Mann-Whitney-U-Test)**. 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 favoured 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	**0.004** (0.28)**	0.8	0.9	0.7	n/a	n/a
Breast Symptoms	0.2	**<0.001** (-1.48)**	**<0.001****	**0.006****	n/a	n/a
Sexual Function	**< 0.001** (-1.15)**	0.3	**0.008****	0.9	0.027* (-3.05)	n/a
Sexual Enjoyment	0.05	0.5	0.3	**<0.001****	n/a	n/a
Arm Concerns	0.6	0.021* (-0.43)	**0.002****	**0.005****	n/a	n/a
Body Concerns	0.6	0.6	0.4	0.8	n/a	n/a
Body Stigma	0.3	0.2	0.5	0.6	n/a	0.019* (0.038)
Transparency	0.016* (-0.05)	0.6	0.4	0.4	n/a	n/a

BMI: Body Mass Index.*significant at the <0.05 level; ****significant at the <0.01 level**; values in parentheses are the parameter estimates of TARGIT-IORT vs. EBRT: for every one unit of the variable, the QOL domain increases or decreases by this value. All significant findings favoured the TARGIT-IORT group.

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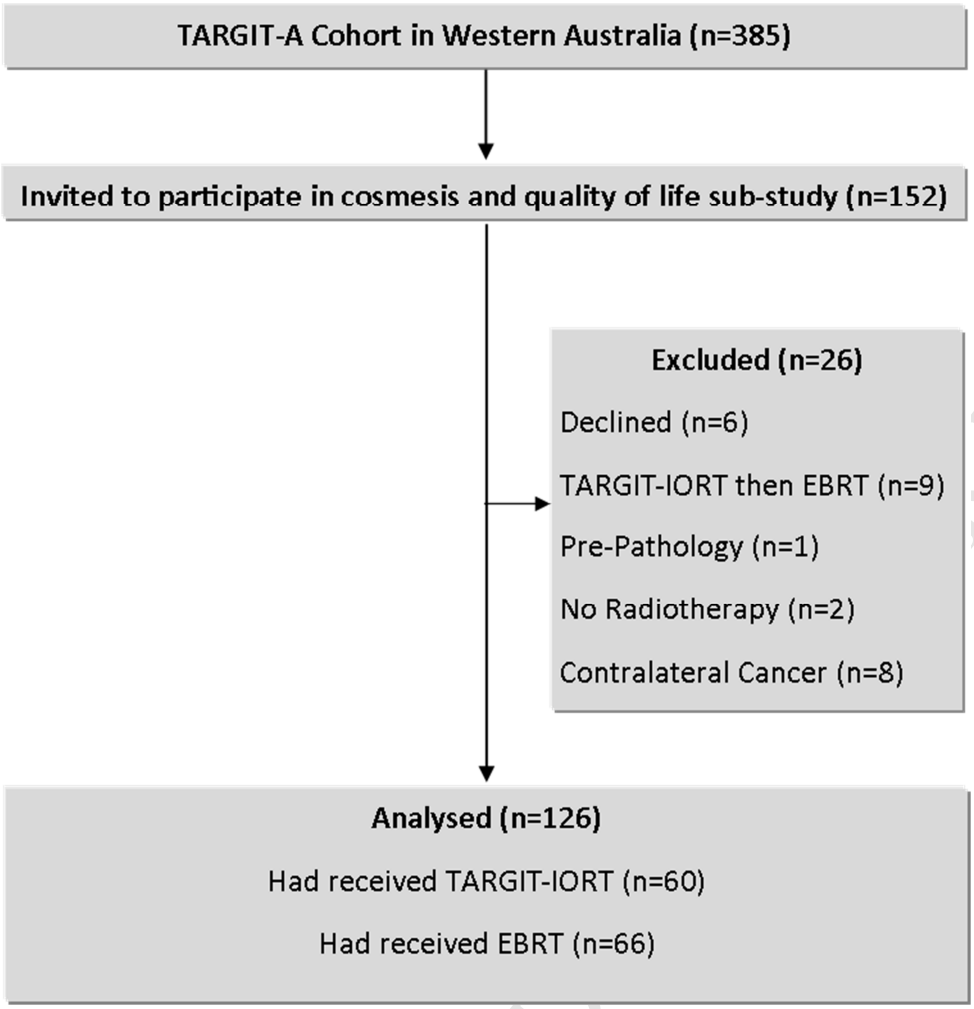

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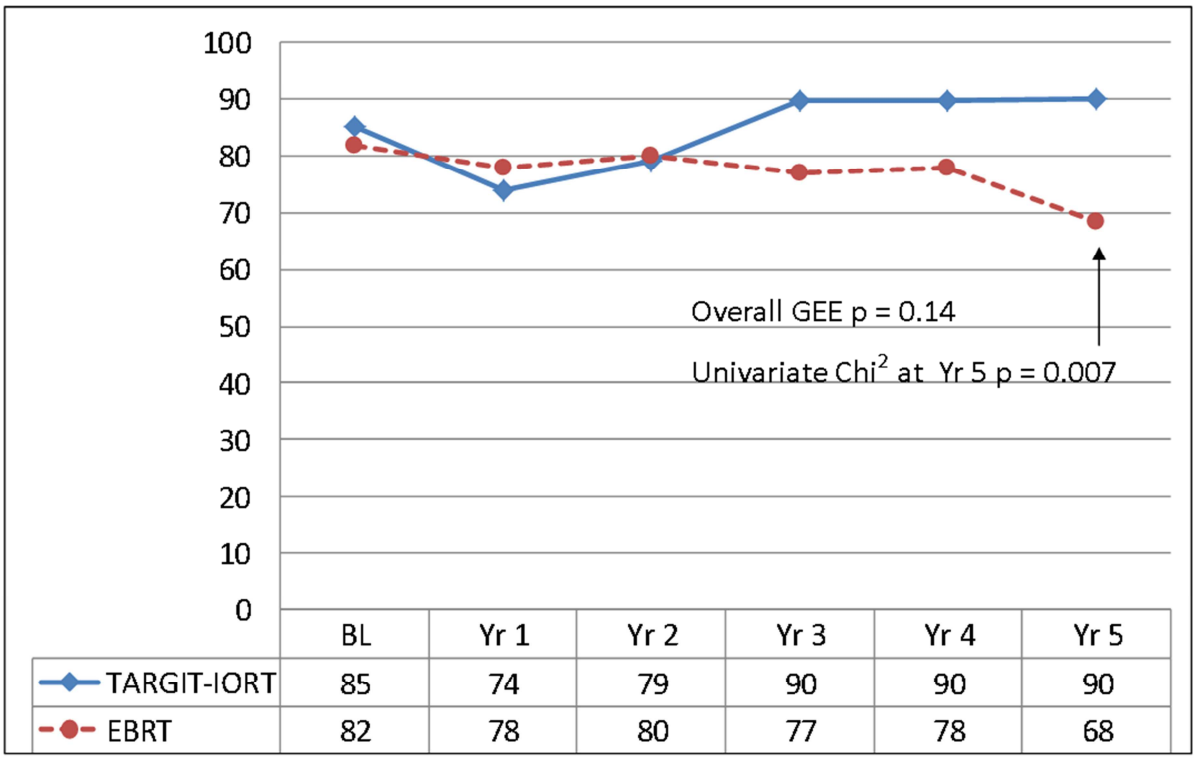

	BL	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
TARGIT-IORT	85	74	79	90	90	90
EBRT	82	78	80	77	78	68

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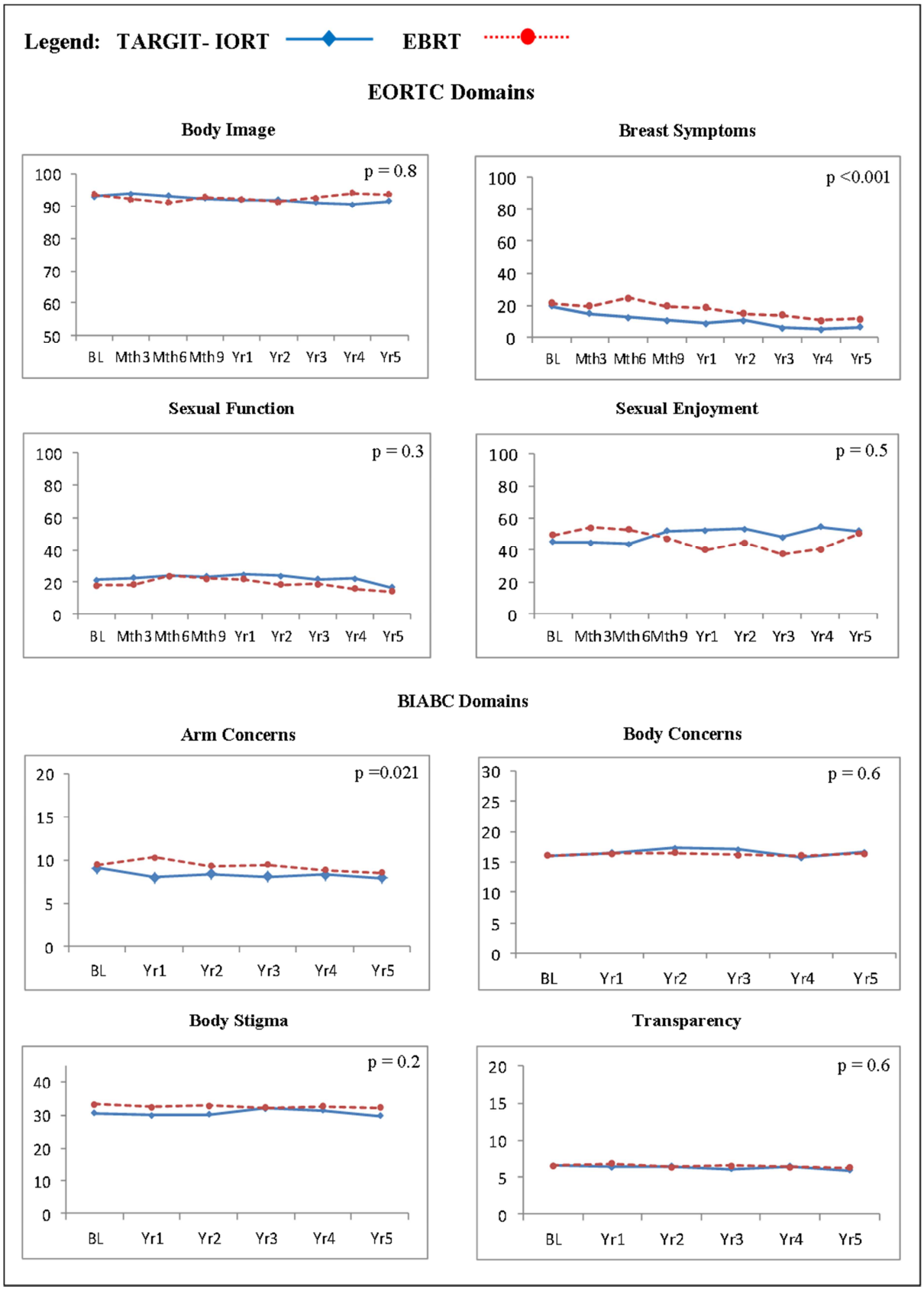
Legend: TARGIT- IORT
EBRT
EORTC Domains
Body Image
p = 0.8
Breast Symptoms
p <0.001
Sexual Function
p = 0.3
Sexual Enjoyment
p = 0.5
BIABC Domains
Arm Concerns
p =0.021
Body Concerns
p = 0.6
Body Stigma
p = 0.2
Transparency
p = 0.6
BL Mth3 Mth6 Mth9 Yr1 Yr2 Yr3 Yr4 Yr5
BL Yr1 Yr2 Yr3 Yr4 Yr5