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Scientific Article

Targeted Intraoperative Radiation Therapy during Breast-Conserving Surgery for Patients with Early Stage Breast Cancer: A Phase II Single Center Prospective Trial

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Purpose: Patients with early stage breast cancer (ESBC) are conventionally treated with breast-conserving surgery (BCS) followed by whole-breast external beam radiation therapy (EBRT). The emergence of targeted intraoperative radiation therapy (TARGIT) with Intrabeam has been used as a therapeutic alternative for patients with risk-adapted ESBC. Here we present our radiation therapy toxicities (RTT), postoperative complications (PC), and short-term outcomes of the prospective phase II trial at the McGill University Health Center.

Methods and Materials: Patients aged ≥50 years with biopsy-proven hormone receptor-positive, grade 1 or 2, invasive ductal carcinoma of the breast, cT1N0, were eligible for the study. Enrolled patients underwent BCS followed by immediate TARGIT of 20 Gy in 1 fraction. Upon final pathology, patients with low-risk breast cancer (LRBC) received no further EBRT, and those with high-risk breast cancer (HRBC) received further 15 to 16 fractions of whole breast EBRT. HRBC criteria included pathologic tumor size >2 cm, grade 3, positive lympho-vascular invasion, multifocal disease, close margins (<2 mm), or positive nodal disease.

Results: A total of 61 patients with ESBC were enrolled in the study; upon final pathology, 40 (65.6%) had LRBC, and 21 (34.4%) had HRBC. The median follow-up was 3.9 years. The most common HRBC criteria were close margins in 66.6% (n = 14) and lymphovascular invasion in 28.6% (n = 6). No grade 4 RTT were observed in either group. The most common PC were seroma and cellulitis for both groups. The rate of locoregional recurrence was 0% in both groups. The overall survival in LRBC was 97.5% and in HRBC 95.2% with no significant differences. Deaths were nonbreast cancer related.

Conclusions: In patients with ESBC undergoing BCS, the use of TARGIT shows low rates of RTT and PC complications. Moreover, our short-term outcomes show no significant difference at 3.9 years median follow-up for locoregional recurrence or overall survival

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All data generated can be found in the published article. The data analyzed can be provided upon request.

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between groups of patients receiving TARGIT alone or TARGIT followed by EBRT. Of all patients, 34.4% required further EBRT, most commonly due to close margins.

Introduction

Patients who receive diagnoses of early stage breast cancer (ESBC) are conventionally treated with breast-conserving surgery (BCS) followed by whole-breast external beam radiation therapy (EBRT). The addition of postoperative EBRT has been correlated with reduced local recurrence (LR) and increased overall survival (OS) in this patient population.[1] Since most LRs are thought to be due to residual tumor cells at or near the tumor bed,[2,3] the need for large radiation therapy fields encompassing the whole breast in low-risk ESBC was questioned. As a result, accelerated partial breast irradiation (APBI) techniques have emerged,[4-6] gaining attraction because a higher dose per fraction can be delivered to the tumor bed over a reduced treatment time and sparing of normal surrounding tissue.

Targeted intraoperative radiation therapy (TARGIT), a type of APBI, has been used in carefully selected patients undergoing BCS, offering the potential of delivering 1 single dose of radiation straightaway after surgery. The advantages of this technique are the immediate treatment of residual disease in the surgical cavity,[7] decreased risk of geographic miss,[8] fewer hospital visits, and consequently a smaller number of treatments.

TARGIT with Intrabeam has been used as a therapeutic alternative for patients with low-risk ESBC given the results of the TARGIT-A trial.[9] This multicentric noninferiority trial included 3451 women, aged ≥45 years with unifocal invasive ductal carcinoma (IDC), and tumor size <3.5 cm, comparing patients undergoing BCS + TARGIT versus BCS + EBRT. Moreover, this trial included 2 strata of patients: 1 undergoing prepathology (n = 2298) TARGIT concurrent with lumpectomy, and a postpathology (n = 1153) subgroup receiving delayed TARGIT by reopening the wound. Early results in 2010 showed that immediate delivery of TARGIT was much more favorable than delayed delivery of the intraoperative radiation therapy (IORT).[9]

The TARGIT-A's risk-adapted 5-year results were published in 2013, with a reported risk of LR in the prepathology strata of 3.3% for TARGIT versus 1.3% for EBRT.[10] The absolute risk difference of LR was 2%, lower than the 2.5% noninferiority margin determined by the group. In the postpathology group, the absolute risk difference was >2.5% (TARGIT 5.4% vs EBRT 1.7%). Overall, supplemental EBRT after TARGIT was used in 21.6% of the prepathology patients and in 3.6% of the postpathology stratum. Recently, long-term results were published,[11] with a median follow-up of 8.6 years for the prepathology group. The study showed no statistically significant difference for local recurrence-free survival (LRFS), mastectomy-free survival, distant metastasis-free survival, OS, and breast cancer mortality. Mortality from nonbreast cancer−related causes was significantly lower for patients receiving TARGIT or TARGIT + EBRT compared with those only receiving EBRT.

In view of the early results of TARGIT-A trial,[9] we developed a phase II prospective single-arm trial using TARGIT to assess the incidence on our center of locoregional recurrence, OS, postoperative complications, and radiation therapy toxicities (RTT) in patients with low-risk ESBC using a risk-adapted strategy. We further analyzed our study results and already published data from larger clinical trials in the context of the recently adopted practice of extreme hypofractionation for breast cancer.

Methods and Materials

Study design

During the period between September 2013 and May 2021, patients aged ≥50 years with biopsy-proven primary breast cancer, estrogen receptor (ER) positive, progesterone receptor (PR) positive, human epidermal growth factor-2 (HER2) negative, grade 1 or 2, IDC, and cT1N0 were eligible to be in the study upon consent. All enrolled patients underwent BCS followed by TARGIT, receiving 20 Gy in 1 fraction immediately after surgery. Upon final surgical pathology, patients with low-risk breast cancer (LRBC) criteria were assigned to receive no further EBRT (arm 1) given a lower risk for LR. Low-risk criteria were defined as IDC histology, grade 1 or 2, tumor size ≤2 cm on pathologic examination, no evidence of invasive lobular carcinoma (ILC), no presence of lymphovascular invasion (LVI), unifocal breast cancer, cN0 and pN0, DCIS component <25%, and margins >2 mm. Until the update of the American Society for Radiation Oncology (ASTRO) guidelines in 2017,[12,13] we only included patients aged >60 years and then updated accordingly, including patients aged >50 years. Further EBRT was indicated for patients with the following high-risk breast cancer (HRBC) criteria: pathologic grade 3, ILC histology, tumor size >2 cm, positive LVI, multifocal disease, close margins ≤2 mm, or positive nodal disease (Fig. 1).

TARGIT dose prescription and delivery

After the tumor resection was completed by the surgeon, the tumor bed was inspected to assure complete

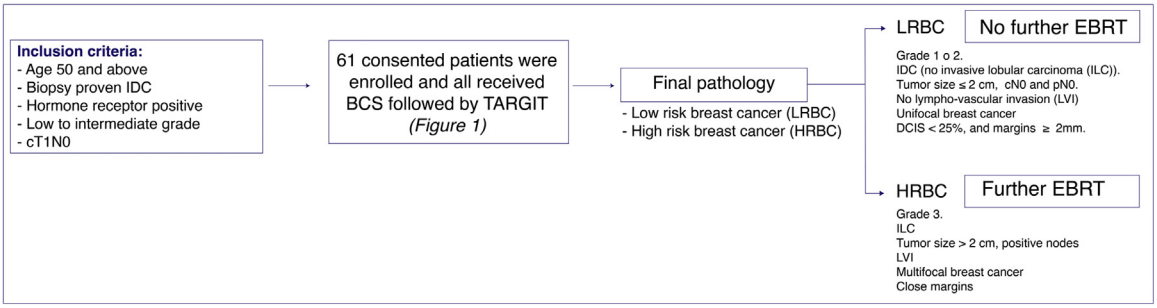

Figure 1 Study design and treatment groups. *Abbreviations:* BCS = breast-conserving surgery; EBRT = external beam radiation therapy; IDC = invasive ductal carcinoma; HRBC = high-risk breast cancer; LRBC = low-risk breast cancer; TARGIT = targeted intraoperative radiation therapy.

hemostasis (Fig. 2a, b). Later, Intrabeam was used with the largest applicator available to ensure the highest dose delivered to the tumor bed tissue at the surface. The applicator to skin distance was verified by the treating physician. The energy used by Intrabeam was 50 kv x-rays. The applicator sphere was inserted into the surgical cavity, and 20 Gy in 1 fraction were delivered to the surface of the surrounding breast tissue (Fig. 2c). EBRT was conventionally given in a total dose of 40 to 42.5 Gy in 15 to 16 fractions.

Data collection and statistical analysis

The patients' demographic and clinical information was obtained from electronic medical records. The surgical complications and radiation therapy side effects were based on a complete clinical history and physical examination and retrieved from electronic medical records. The toxicity assessment for radiation therapy side effects was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02. Treatment outcomes included LR, distant metastasis-free survival, cause-specific mortality, and OS. Statistical analyses were done using SPSS. Figure making was done with Prism 7 (GraphPad). We performed binary logistic regression analyses to compare the treatment arms associated toxicities. Kaplan-Meier survival curves and the log-rank (Mantel-Cox) test were used for illustrating outcomes. The data represents the mean ±SD. A P value < .05 was considered significant.

Results

Between September 2013 and May 2021, 65 patients with ESBC were enrolled in the study. From these, 4 patients withdrew (2 withdrew before receiving TARGIT, 1 was off protocol due to technical issues with the machine, and 1 refused further EBRT). Of all 61 patients in the study, 40 (65.6%) had LRBC criteria, and 21 (34.4%) had HRBC criteria. The mean age for the LRBC group was 71.27 years (±7.27) and for the HRBC group was 68 years (±7.44). The median follow-up for all patients was 3.9 years (3.5 ± 2.08 years for LRBC and 4.53 ± 1.81 years for HRBC). The average tumor size for the LRBC group was 1.08 ± 0.75 cm and for the HRBC group was 1.3 ± 0.46 cm.

The clinical T stages for the LRBC and HRBC groups were, respectively, T1a (12.5% and 9.5%), T1b (52.5% and

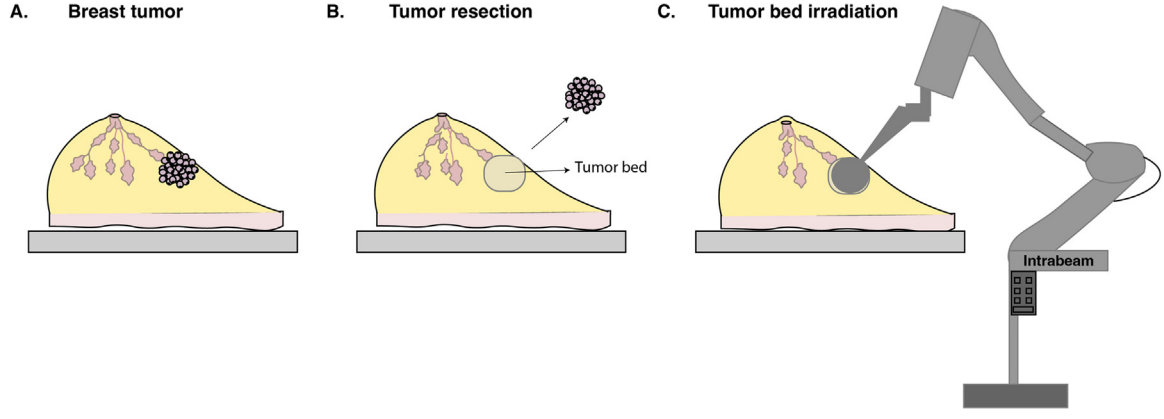

Figure 2 Intraoperative radiation therapy using Intrabeam. (A) Breast tumor. (B) Tumor resection. (C) Tumor bed irradiation.

14.3%), and T1c (35% and 76.2%). The tumor histologies for the LRBC and HRBC groups were, respectively, IDC (87.5% and 85.7%), mucinous (7.5% and 0%), ILC (0% and 4.8%), and mixed (5% and 4.8%). Tumors grade 1 in the LRBC group were 37.5% and for the HRBC group were 14.3%. Tumors grade 2 in the LRBC were 62.5% and for the HRBC group were 85.7%. LVI was present in 2.5% (1 patient) in the LRBC group and 19% (4 patients) in the HRBC group. All patients in both groups were ER and PR positive. The HER2 status was equivocal in 1 patient in the LRBC group and 2 patients in the HRBC group. All other patients were HER2 negative in both groups (Table 1). Chemotherapy was not used. Hormonal therapy (HT) was used in 25 of 40 patients (62.5%) for the LRBC group and in 16 of 21 patients (76.1%) in the HRBC group (Table 1).

RTT grade 1 (25% and 23.8%), grade 2 (5% and 14.3%), and grade 3 (2.5% and 4.8%) were observed for the LRBC and HRBC groups, respectively. No grade 4 RTT were observed in either group. The postoperative complications observed were seroma (17.5% and 33.3%), cellulitis (5% and 4.8%), fat necrosis (2.5% and 9.5%), and hematoma (2.5% and 0%) for the LRBC and HRBC groups, respectively (Table 2). There were no statistically significant differences when comparing treatment arms with both RT and postoperative complications (Table E1).

The most common HRBC criteria were close margins <2 mm in 66.6% (n = 14), LVI in 28.6% (n = 6), and N1mic disease in 4.8% (n = 1). For the patients who presented close margins, 11 patients (78.6%) had margins <1 mm, and 3 patients (21.4%) had margins ≥1 mm and <2 mm.

The rate of LR was 0% in both groups with a LRFS of 100% (Fig. 3). The OS in the LRBC group was 97.5% and in the HRBC group was 95.2% (Fig. 4). The deaths reported in the LRBC and in the HRBC were nonbreast cancer related.

Discussion

In risk-adapted ESBC, TARGIT with Intrabeam can be used as a therapeutic alternative to conventional EBRT. Our data shows that when all patients are initially selected to get TARGIT and then assigned to receive further EBRT based on final pathology HRBC criteria, there were no differences in LR or OS between both groups.

The long-term results of the TARGIT-A published in 2020[11] showed no significant difference in LRFS, mastectomy-free survival, OS, and breast cancer mortality between BCS + TARGIT versus BCS + EBRT. Moreover, the ELIOT trial[14] used IORT with electrons and studied 1305 women

Table 1 Clinical demographics baseline characteristics

Patient baseline characteristics		TARGIT alone (n, %)	TARGIT + EBRT (n, %)
Clinical variables Mean ±SD	Age (years)	71.27 (±7.27)	68 (±7.44)
	Median follow-up (years)	3.50 (±2.08)	4.6 (±1.81)
	Tumor size (cm)	1.08 (±0.75)	1.3 (±0.46)
Clinical T stage	T1a	5 (12.5)	2 (9.5)
	T1b	21 (52.5)	3 (14.3)
	T1c	14 (35)	16 (76.2)
Histology	Ductal	35 (87.5)	18 (85.7)
	Mucinous	3 (7.5)	0
	Lobular	0	1 (4.8)
	Mixed	2 (5.0)	2 (9.5)
Tumor grade	Grade 1	15 (37.5)	3 (14.3)
	Grade 2	25 (62.5)	18 (85.7)
Lympho-vascular invasion	Absent	39 (97.5)	17 (81)
	Present	1 (2.5)	4 (19)
Estrogen receptor Progesterone receptor	Positive	40 (100)	21 (100)
	Positive	40 (100)	21 (100)
HER2 status	Negative	39 (97.5)	19 (90.5)
	Equivocal	1 (2.5)	2 (9.5)
Hormonal therapy use	Yes	25 (62.5)	14 (66.6)
	No	15 (37.5)	7 (33.4)

Abbreviations: EBRT = external beam radiation therapy; TARGIT = targeted intraoperative radiation therapy.

Table 2 Radiation therapy toxicities and postoperative complications

Treatment	TARGIT alone	TARGIT + EBRT
Radiation therapy toxicities	n (%)	n (%)
Grade 1	10 (25)	5 (23.8)
Grade 2	2 (5)	3 (14.3)
Grade 3	1 (2.5)	1 (4.8)
None	27 (67.5)	12 (57.1)
Surgical complications	n (%)	n (%)
Seroma	7 (17.5)	7 (33.3)
Cellulitis	2 (5)	1 (4.8)
Fat necrosis	1 (2.5)	2 (9.5)
Hematoma	1 (2.5)	0
None	29 (72.5)	11 (52.3)

for a median follow-up time of 12.4 years. The group showed that the IORT group compared with EBRT had an absolute increase of ≥54 ipsilateral breast tumor recurrences, without differences in OS. A recent Surveillance, Epidemiology, and End Results study analysis in ESBC treated with BCS (n = 8614) followed by EBRT (97,164; 98.5%) and IORT (1450; 1.5%) showed no significant difference in OS. Other studies, such as TARGIT-R,[15] showed results that differed from the previous, with IBRTs ≥6.6% at 5 years with the use of IORT. However, this was a retrospective study, it included fewer patients, and there was non-compliance to HT reported by the group. Our results with a median follow-up of 3.9 years are more concordant with those found in TARGIT-A for locoregional recurrence and OS between both groups.

The TARGIT-A trial also showed an increased rate of seroma in the TARGIT group compared with the EBRT group.[9-11] The presence of major toxicities (grade 3 or 4) was higher in the EBRT group (3.9%) than in the TARGIT group (3.3%). In our study, both groups had 7 patients who developed seroma. Regarding major RTT, grade 3 RTT were present in 1 patient in each group, and there were no grade 4 toxicities observed in either group. For all toxicities, there were no statistically significant differences when comparing treatment arms.

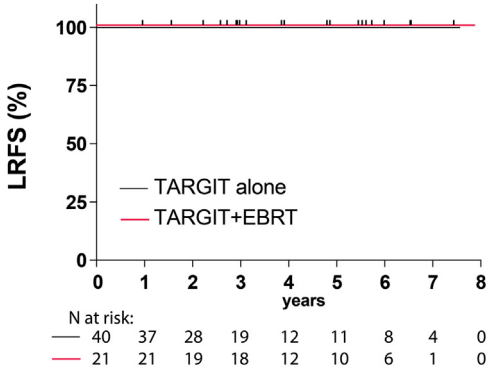

Figure 3 Locoregional-free survival in low-risk breast cancer (LRBC) for targeted intraoperative radiation therapy (TARGIT) alone and high-risk breast cancer (HRBC) (TARGIT + external beam radiation therapy [EBRT]).

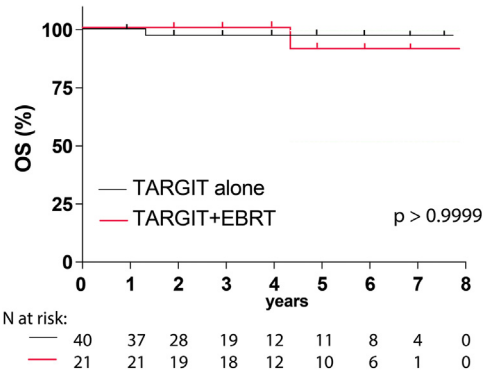

Figure 4 Overall survival in low-risk breast cancer (LRBC) for targeted intraoperative radiation therapy (TARGIT) alone and high-risk breast cancer (HRBC) (TARGIT + external beam radiation therapy [EBRT]).

The TARGIT-A trial showed that there was a statistically significant reduction in nonbreast cancer mortality benefit in patients receiving TARGIT, even when followed by EBRT, compared with patients only having EBRT. In our study, there were no breast cancer–associated deaths at 3.9 years median follow-up.

Regarding indications for further EBRT, we observed that 34.4% of patients had HRBC criteria. The most common indication was close margins (<2 mm). As per the latest ASTRO guidelines update,[16] a cautionary group would have margins <2 mm, which in most of our patients was treated as an absolute indication for further EBRT. Nevertheless, if we were to be less strict allowing margins between ≥1 mm to <2 mm, we would still have 11 of 14 patients with margins at <1 mm that would still need further EBRT. In the TARGIT-A trial, patients were assigned as per protocol to receive further EBRT when margins were <1 mm, which is not comparable to our cohort. A study by Sarria et al[17] assessing the effectivity of upfront kilovoltage IORT as a boost in high-risk ESBC for 653 patients from 4 different centers only showed significant association with age <50 years. In this study close margins (<2 mm) were not associated with increased LR. Therefore, close margins should be analyzed together with other clinical variables to determine whether EBRT is needed rather than as an isolated criterion to decide on further treatment.

In view that our cohort of patients had a median age of 71.27 years for the LRBC group and 68 years for the HRBC group, one could include as a therapeutic alternative the omission of radiation therapy for carefully selected patients

with LRBC. The LUMINA trial[18] is a prospective multicenter study that selected patients aged ≥55 years with luminal A molecular subtype (ER ≥ 1%, PR > 20%, HER2 negative, and Ki67 ≤ 13.25%) undergoing BCS with T1N0 tumors, grade 1 or 2, and margins ≥1 mm and treated solely with hormone therapy. The group of Whelan et al observed that the 5-year risk of LR was 2.3%, and that the contralateral risk of breast cancer was 1.9% with the omission of radiation therapy.[18] Because our LRBC group aligns with most of the criteria of the LUMINA trial, the omission of radiation therapy and treatment with hormone therapy alone could be considered once the surgical pathologic findings are available. Moreover, the ongoing phase III-BR007 (DEBRA) trial[19] will shed light about safety to deescalate treatment for stage I, hormone-sensitive, HER2-negative breast cancer with oncotype Dx ≤ 18 with only BCS and hormone therapy. Nevertheless, for our HRBC group, this might not be a feasible option given age, close margins (<1 mm), and the presence of LVI or other adverse features in the final pathology.

In terms of health expenses, a United Kingdom cost analysis demonstrated that TARGIT for ESBC is a cost-effective therapeutic alternative to EBRT.[20] The use of TARGIT showed to be less costly and to offer increased quality-adjusted life years (QALY) of 0.18 compared with TARGIT followed by EBRT. Other studies have validated the cost-saving use of IORT over EBRT.[21,22] A study from Patel et al compared the costs and QALYs of IORT versus EBRT for 6 weeks of treatment, showing that IORT had a lower cost per QALY compared with EBRT.[23] However, these studies used 3 to 6 weeks of EBRT, which is different from the recently adopted practice of extreme hypofractionated radiation therapy.[24]

Most trials using Intrabeam and our study were done before the use of extreme weekly hypofractionation. The Fast-Forward trial[24] has changed practice in the last 2 years. This trial proved that 26 Gy in 5 fractions was not inferior to 40 Gy in 15 fractions. In this context, if we were to analyze if Intrabeam is still worth it in terms of a total number of fractions and associated health care costs we would interpret the following: for BCS followed by TARGIT, with a rate of 34.4% of patients receiving further EBRT, 100 patients would receive 1 fraction (100 fractions) and 34 patients (34.4%) would receive further EBRT (34 in 15 fractions = 510 fractions), so in all, a total of 610 fractions would be delivered for this group. If we were to apply the same rationale using EBRT in 5 fractions, 100 patients would receive 5 fractions (500 fractions), and 34 patients (34.4%) with HRBC criteria would receive a boost of 4 fractions (34 in 10 fractions = 136 fractions), so in all, a total of 636 fractions.

Hypothetically, when comparing how our results would translate in the era of extreme weekly hypofractionation, we observed that the final number of treatments between both groups would be similar. Nevertheless, in the Intrabeam group, we would need to consider the costs of increased operating room time, increased health care resources, and the radiation oncologist and radiation therapist time destinated to assist in the delivery of TARGIT. In all, the use of Intrabeam for a selected group of patients still proved of value for those patients in the desire to reduce hospital visits. Therefore, this should be further addressed in future trials comparing TARGIT versus EBRT using weekly extreme hypofractionation.

The limitations of our study are the low number of patients and the median follow-up time under 5 years. These 2 limitations make our study hard to compare to other larger clinical trials. We lacked data on cosmetic outcomes and quality of life, which would prove relevant for comparing patients' treatment selection. Moreover, the length of recruitment in our study was 5 years, during which time several large clinical trials were published and ASTRO APBI guidelines we updated. Most published trials using Intrabeam as well as our study were done before the use of weekly extreme hypofractionation, where the actual benefits of using TARGIT versus conventional EBRT are hard to extrapolate.

Conclusions

In patients with ESBC undergoing BCS, the use of TARGIT using Intrabeam alone shows no significant differences in radiation therapy or postoperative complications between patients who received TARGIT and further EBRT upon HRBC criteria. The short-term follow-up also showed no significant difference in locoregional recurrence or OS. Altogether, these results highlight that TARGIT is a clinically safe treatment for carefully selected patients with ESBC with no pathologic high-risk features. The rate of patients receiving further EBRT was 34.4% patients, mostly indicated because of close margins. This indication as 1 isolated criterion for EBRT must be discussed and considered on an individual patient basis. Further studies are needed to better characterize the systemic biological effects of TARGIT and its concomitant use with weekly extreme hypofractionation. These studies are essential for de-escalation of treatment with the final objective of reducing time toxicity for our patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101236.

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