

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

Intraoperative radiation therapy for early-stage breast cancer: a single-institution experience

Authors: Fantine Giap, Lillie O'steen, I-Chia Liu, Lisa E. Spiguel, Christina M. Shaw, Christopher G. Morris, Raymond B. Mailhot Vega, Judith L. Lightsey, Julie A. Bradley, Nancy P. Mendenhall, Paul G. Okunieff, Natalie A. Lockney

DOI: 10.5603/RPOR.a2022.0075

Article type: Research paper

Published online: 2022-07-05

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited.

Intraoperative radiation therapy for early-stage breast cancer: a single-institution experience

Running title: Intraoperative radiotherapy for breast cancer

10.5603/RPOR.a2022.0075

Fantine Giap¹, Lillie O'steen², I-Chia Liu³, Lisa E. Spiguel⁴, Christiana M. Shaw⁴, Christopher G. Morris¹, Raymond B. Mailhot Vega¹, Judith L. Lightsey⁵, Julie A. Bradley¹, Nancy P. Mendenhall¹, Paul G. Okunieff¹, Natalie A. Lockney⁶

¹*Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL, United States*

²*Department of Radiation Oncology, Baptist MD Anderson Cancer Center, Jacksonville, FL, United States*

³*Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States*

⁴*Department of Surgery, University of Florida College of Medicine, Gainesville, FL, United States*

⁵*Department of Radiation Oncology, Robert Boissoneault Oncology Institute, Ocala, FL, United States*

⁶*Department of Radiation Oncology, Vanderbilt Medical Center, Nashville, TN, United States*

Corresponding author: Fantine Giap, MD, Department of Radiation Oncology, University of Florida College of Medicine; 2000 SW Archer Road, PO Box 100385, Gainesville, FL, USA 32610-0385, tel: (352) 265-0287, fax: (352) 265-7045; e-mail: fantine.giap@shands.ufl.edu

Abstract

Background: To assess outcomes and toxicity after low-energy intraoperative radiotherapy (IORT) for early-stage breast cancer (ESBC).

Materials and methods: We reviewed patients with unilateral ESBC treated with breast-conserving surgery and 50-kV IORT at our institution. Patients were prescribed 20 Gy to the surface of the spherical applicator, fitted to the surgical cavity during surgery. Patients who did not meet institutional guidelines for IORT alone on final pathology were recommended adjuvant

treatment, including additional surgery and/or external-beam radiation therapy (EBRT). We analyzed ipsilateral breast tumor recurrence, overall survival, recurrence-free survival and toxicity.

Results: Among 201 patients (median follow-up, 5.1 years; median age, 67 years), 88% were Her2 negative and ER positive and/or PR positive, 98% had invasive ductal carcinoma, 87% had grade 1 or 2, and 95% had clinical T1 disease. Most had pathological stage T1 (93%) N0 (95%) disease. Mean IORT applicator dose at 1-cm depth was 6.3 Gy. Post-IORT treatment included additional surgery, 10%; EBRT, 11%; adjuvant chemotherapy, 9%; and adjuvant hormonal therapy, 74%. Median total EBRT dose was 42.4 (range, 40.05-63) Gy and median dose per fraction was 2.65 Gy. At 5 years, the cumulative incidence of ipsilateral breast tumor recurrence was 2.7%, the overall survival rate was 95% with no breast cancer-related deaths, and the recurrence-free survival rate was 96%. For patients who were deemed unsuitable for postoperative IORT alone and did not receive recommended risk-adapted EBRT, the IBTR rate was 4.7% versus 1.7% ($p = 0.23$) for patients who were either suitable for IORT alone or unsuitable and received adjuvant EBRT. Cosmetic toxicity data was available for 83%, with 7% experiencing grade 3 breast toxicity and no grade 4–5 toxicity.

Conclusions: IORT for select patients with ESBC results in acceptable outcomes in regard to ipsilateral breast tumor recurrence and toxicity.

Key words: intraoperative radiation; breast cancer; clinical outcomes; radiation toxicity; Intrabeam

Introduction

Breast cancer is the most common cancer diagnosed in women in the United States. General local-regional treatment strategies for early-stage breast cancer include partial or total mastectomy with surgical axillary staging, followed by adjuvant radiotherapy as indicated. Due to the results of randomized clinical trials demonstrating the local-regional benefit of adjuvant radiation following breast-conserving surgery in reducing local-regional recurrence following breast conservation, adjuvant radiation to the whole breast became the standard of care for early-stage breast cancer patients [1, 2]. Hypofractionated whole-breast radiation has become a standard approach following more recent level 1 evidence of equivalent disease control and

toxicity outcomes [3, 4]. Shortened radiotherapy courses are more convenient for patients and less costly to the healthcare system [5–8].

For select patients with favorable early-stage breast cancer, accelerated partial breast irradiation (APBI) has also become a reasonable option after breast-conserving surgery. Not only is the total radiation course shortened to 5–10 days of treatment, but there is the added benefit of reduced radiation exposure to the breast skin and tissue as well as underlying lungs and heart [9]. Over the past 20 years, phase II and III trials evaluating APBI have demonstrated promising local-regional control and cosmetic outcomes with numerous APBI modalities, including brachytherapy and external-beam radiation therapy (EBRT) [10–14]. For example, intraoperative radiation therapy (IORT) strategies using low-energy (50 kV) photons or electrons in a single-fraction treatment were evaluated as modalities in the TARGIT-A and the ELIOT trials [11, 12]. Phase III non-inferiority trials have demonstrated acceptable short-term local-regional control outcomes with APBI, though notably their reported outcomes for APBI did not meet the non-inferiority threshold when compared to outcomes with whole-breast radiation [11]. Utilizing this data, the American Society for Radiation Oncology (ASTRO) has created expert Consensus Guidelines to identify patients suitable for APBI, including low-energy photon IORT specifically [15].

Our institution began an APBI program using low-energy photon IORT with the INTRABEAM device (Carl Zeiss AG, Oberkochen, Germany), prior to the updated 2016 ASTRO Consensus Guidelines [15]. Herein, we report ipsilateral breast tumor recurrence (IBTR), recurrence-free survival (RFS), and overall survival (OS) outcomes, as well as physician-reported toxicity and cosmetic outcomes, to contribute to the body of evidence for IORT in the treatment of select patients with early-stage breast cancer.

Materials and methods

Under institutional review board approval, we retrospectively reviewed the medical records of women with unilateral early-stage breast cancer, clinical stage T1-2N0M0, treated at our institution with breast-conserving surgery followed by 50-kV photon IORT delivered using INTRABEAM. Patients included in this cohort underwent breast IORT between November 10, 2010, and December 31, 2017. All patients underwent mammography and core needle biopsy of the breast; 86% of patients had preoperative breast magnetic resonance imaging. Initial

University of Florida institutional guidelines for INTRABEAM use were adopted from the TARGIT trial selection criteria [11], although updated and current institutional guidelines for INTRABEAM use are more restrictive than TARGIT and have included: age \geq 50 years old, invasive ductal carcinoma (IDC) with or without ductal carcinoma in situ (DCIS), Nottingham grade 1–2 tumors, tumor size $<$ 3 cm, estrogen receptor (ER) and/or progesterone receptor (PR) positivity, human epidermal growth factor receptor 2 (Her2) negative, clinically node negative (N0), and no lymphovascular space invasion (LVSI). Invasive lobular carcinoma was excluded, but IDC with a lobular component was eligible.

Patients were evaluated by both the surgeon and radiation oncologist and then discussed preoperatively and postoperatively by a multidisciplinary tumor board. Patients were counseled preoperatively that the final decision to proceed with IORT would be made by the surgeon during surgery based on the following evidence: negative sentinel lymph node(s) upon intraoperative frozen section, spherical applicator distance at least 1 cm from the skin, and tumor bed less than 5 cm in diameter. At the time of breast-conserving surgery, the spherical applicator, which ranged from 3 cm to 5 cm in diameter at 0.5 cm increments, was fitted into the lumpectomy cavity and a purse-string closure of the breast tissue over the applicator was completed by the surgeon. Subsequently, 20 Gy was delivered to the surface of the spherical applicator at a constant rate (dependent on applicator size), which attenuated to approximately 5-7 Gy at a 1-cm depth. The IORT procedure was monitored by the radiation oncologist throughout the duration of the radiation treatment.

At our institution, additional treatment, including further surgery and/or risk-adapted EBRT, is recommended after IORT based on final pathology when institutional guidelines as described above for IORT alone are not met. Amongst our cohort, additional breast surgery was recommended based on margin assessment, and at times additional axillary surgery was indicated. Adjuvant risk-adapted whole-breast EBRT was generally recommended if final surgical pathology demonstrated close margins \leq 2mm, grade 3 disease, tumor size \geq 3cm, presence of LVSI, and/or the positive sentinel lymph nodes. However, patients $>$ 70 years old with pathologic stage T1N0 disease who were planned for adjuvant endocrine therapy may not have been recommended for additional adjuvant EBRT after IORT despite other risk factors, as per NCCN guidelines suggesting these women may consider omission of any radiotherapy based on CALGB 9343 outcomes [16, 17]. Adjuvant EBRT may also have been omitted owing to

significant comorbidities or patient refusal. Adjuvant EBRT was typically delivered to the whole breast via a hypofractionated regimen (40–42.4 Gy over 15–16 fractions); if regional nodal irradiation was indicated, a conventional fractionation was used (50 Gy over 25 fractions). No additional external-beam boost to the tumor bed was delivered since IORT served as the “boost.” Patients received adjuvant chemotherapy and/or endocrine therapy as indicated by standard practice.

The primary endpoints were the actuarial rates of IBTR, RFS, and OS. IBTR was defined as a breast cancer occurring in the ipsilateral breast regardless of quadrant. RFS was defined as freedom from any local, regional, or distant recurrence. Patients were also categorized following final pathology as suitable versus unsuitable for IORT by current University of Florida institutional guidelines and ASTRO 2016 Consensus Guidelines. Outcomes for suitable patients or unsuitable patients who received risk-adapted adjuvant EBRT were compared to unsuitable patients who did not receive risk-adapted adjuvant EBRT. In addition, cosmetic toxicity data was obtained via chart review and graded post hoc using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.

SAS and JMP software were utilized for all statistical analysis (SAS Institute, Cary, NC). The Kaplan-Meier product limit estimator provided estimates of IBTR, RFS, and OS. The log-rank test statistic then assessed whether there were significant impacts on these outcomes after stratifying by selected prognostic factors. The cumulative incidence method that integrates competing risks, such as intercurrent death and regional or distant failure, was included via the CIF macro in SAS as a complement to Kaplan-Meier analysis of IBTR. No post hoc adjustment to p values to control the experiment-wise error rate for this retrospective, correlative analysis was performed; the chance of a type I error is, therefore, higher than the $\alpha=0.05$ cutoff for determining statistical significance.

Results

Patient, tumor, and treatment characteristics

A total of 201 patients were eligible for analysis with a median follow-up of 5.1 years (range, 0.1–9.1 years). Clinical patient and tumor characteristics are summarized in Table 1. The median age was 67 years. On initial biopsy, most patients’ tumors were diagnosed as invasive ductal carcinoma (98%), grade 1 or 2 (87%), clinical stage T1 (95%) with a median clinical tumor size

of 1.1 cm, and Her2 negative and ER-positive and/or PR-positive (88%) status. Most patients (75%; 150/201) in this cohort met our updated, current institutional guidelines for preoperative selection for IORT.

Final pathological tumor characteristics are summarized in Table 1. Upon review of surgical pathology, 69% (103/150) of patients initially judged suitable for IORT preoperatively per current institutional guidelines remained suitable for IORT alone without subsequent risk-adapted EBRT. While most patients had pathological stage T1 (93%) N0 (95%) disease, some patients failed to meet one or more suitability criteria, including pure DCIS (1%), invasive lobular carcinoma (1%), pT2 disease (5%), nodal disease (5%), LVSI (8%), and close (< 2 mm) (25%) or positive (3%) margins. Following review of final surgical pathology, 51% of all patients in the study cohort (103/201) were suitable for IORT alone by our current institutional criteria.

Treatment characteristics are shown in Table 1. The median INTRABEAM applicator size was 4.5 cm with a mean dose at a 1-cm depth of 6.3 Gy delivered over an average time of 37 minutes. Twenty-one patients (10%) underwent additional surgery, either re-excision of the breast (n = 20) and/or completion total mastectomy (n = 5). Four patients underwent more than one additional surgery after initial breast-conserving surgery due to persistently positive margins. Indications for additional surgery included close (n = 16) or positive (n = 6) margins or positive lymph nodes on final pathology (n = 1). Adjuvant chemotherapy was given to 9% of patients and adjuvant hormone therapy to 74%. Adjuvant risk-adapted EBRT was delivered to 11% (n = 22), with indications including close (n = 5) or positive (n = 3) margins, positive lymph nodes (n = 6), LVSI (n = 4), multifocal disease (n = 2), ILC histology (n = 1), grade 3 disease (n = 1), and/or Her2-positive status (n = 1). The median total dose of EBRT was 42.4 Gy (range, 40.05–63 Gy) delivered at a median 2.65 Gy per fraction. Two patients underwent an EBRT boost treatment: 1 patient underwent post-mastectomy radiation with mastectomy scar boost and 1 patient underwent adjuvant hypofractionated whole-breast radiation with a lumpectomy cavity boost to a non-overlapping site of completely excised multicentric disease, discovered postoperatively.

Ipsilateral breast tumor recurrence

With a median follow-up of 5.1 years, the 5-year cumulative IBTR rate was 2.7% [95% confidence interval (CI): 1.1–6.4%] (Fig. 1A) based on both Kaplan-Meier analysis and the

cumulative incidence method. On univariate analysis of eleven selected variables, histology other than IDC (i.e. ILC, DCIS) was the only factor found to be statistically significant in predicting higher IBTR with a 5-year IBTR risk of 14.3% versus 2.3% with IDC ($p = 0.02$) (Tab. 2).

Nine patients developed an IBTR (Supplementary File — Tab. S1); all were ER+, pathologic grade 1-2, and pathologic stage T1 N0. One patient had Her2-positive disease. Eight patients had IDC and one had ILC. Margin re-excision was performed in only 1 of the 3 patients with close surgical margins. One patient had multifocal, microinvasive ductal carcinoma. None of the 9 patients who developed IBTR received adjuvant risk-adapted EBRT following IORT, although, per current institutional guidelines, 6 patients had indications to undergo whole-breast EBRT. None of the 9 patients who developed IBTR underwent chemotherapy, although 1 patient was recommended for chemotherapy based on Oncotype testing and one patient declined both chemotherapy and Oncotype testing. Although all patients who experienced recurrence were ER positive, only 5 patients underwent recommended endocrine therapy.

The cohort was stratified into suitable and unsuitable groups based on our current institutional suitability criteria and the ASTRO 2016 APBI Consensus Guidelines. Notably, only 32% of patients considered unsuitable for IORT alone based on our current institutional criteria received additional risk-adapted whole-breast EBRT, and only 36% of patients considered unsuitable for IORT alone based on ASTRO consensus criteria received EBRT. Additional analysis was completed to compare the 134 patients who received radiation therapy as recommended (suitable patients by ASTRO criteria who received IORT alone as well as unsuitable patients who received both IORT and adjuvant EBRT) to the 67 patients who did not (unsuitable patients who underwent IORT but did not receive adjuvant EBRT despite indications). At 5 years, the IBTR rate was 1.7% for the group of combined suitable patients and unsuitable patients who received adjuvant EBRT versus 4.7% for unsuitable patients who did not receive adjuvant EBRT ($p = 0.23$) (Fig. 1B).

Overall survival and relapse-free survival

The 5-year RFS rate was 95.7% (95% CI: 91.2–98.0%). In total, 2 patients developed regional recurrence (both of these patients presented with IBTR at the time of regional recurrence). While 3 total patients developed distant metastasis, 2 of these patients presented with only distant

disease (1 of these patients had simultaneous IBTR and regional disease). On univariate analysis, only histology other than IDC was found to be associated with lower 5-year predicted RFS (85.7% vs. 96.1%; $p=0.004$; **Table 2**).

The 5-year OS rate was 95.3% (95% CI: 90.7% to 97.6%). A total of 9 patients died, and none were breast cancer-related deaths. On univariate analysis, the following criteria were found to be associated with lower OS: tumor size > 2 cm (76.4% vs. 96.4%; $p<0.001$), LVSI (75.2% vs. 97.1%; $p = 0.001$), and EIC (80% vs. 95.7%; $p = 0.03$), while ethnicity, age, histology, tumor grade, margin status, ER/PR status, hormonal therapy, and chemotherapy were not (Tab. 2).

Neither RFS nor OS were significantly different for patients who completed recommended therapy (i.e., suitable for IORT alone or unsuitable for IORT alone with adjuvant EBRT received) compared to patients not receiving recommended radiation therapy (i.e., unsuitable for IORT alone with no adjuvant EBRT received) (96.1% vs. 95.3%, $p = 0.54$; 95.4% vs. 95.0%, $p = 0.28$, respectively).

Toxicity outcomes

Toxicity information was available for 83% ($n = 167$) of the cohort and is summarized in Figure 2. Only the highest graded toxicity for each cosmetic outcome was recorded for each patient. The timing of the toxicity occurrence was not tabulated. The common cosmetic toxicities evaluated include seroma, fibrosis, dermatitis, and infection. Some patients were scored as having more than one toxicity, but the highest CTCAE toxicity grade reported in the 167 patients evaluable for toxicity was grade 1 in 80 (48%), grade 2 in 23 (14%), and grade 3 in 11 (7%). Grade 1 seroma was noted in 32% of patients, grade 2 in 8%, and grade 3 in 4%. Grade 1 fibrosis was documented in 29% of patients, grade 2 in 1%, and grade 3 in < 1%. Grade 1 dermatitis was described in 15% of patients; grade 2 in < 1%; and grade 3 in < 1%. Grade 1 wound infections occurred in 3% of patients, grade 2 in 11%, and grade 3 in 3%. The all-inclusive incidence of grade 3 adverse events was 8.4%. No grade 4 or 5 toxicity was reported.

Discussion

This report updates the outcomes of our institutional experience with INTRABEAM, demonstrating low IBTR rates in women with select early-stage breast cancer. Our 5-year risk of

IBTR was 2.7%, which is comparable to that of the TARGIT-A trial (which was initially reported as 3.3%, but with longer follow-up was recently updated to 2.11%) and ELIOT trial (4.4%) [11, 12, 18]. These IORT trials have reported relatively worse IBTR outcomes than other landmark trials evaluating APBI, including the GEC-ESTRO brachytherapy trial (5-year IBTR, 1.44%) and the NSABP B-39/RTOG 0413 trial allowing both brachytherapy and EBRT modalities (10-year IBTR, 4.6%) [10, 13]. As hypothesized in a recent meta-analysis of APBI randomized trials, poorer IBTR rates, specifically in the IORT subgroup of APBI modalities, could be attributed to (1) the IORT delivery of radiation to a less-generous margin around the tumor resection cavity and (2) the inclusion of higher-risk patients with high-grade tumors and nodal involvement in the IORT trials [11, 12, 19]. Since the publication of the TARGIT and ELIOT trials, no additional randomized clinical trials have been published to evaluate IORT for adjuvant radiation treatment of early-stage breast cancer. However, several retrospective experiences report similar low local recurrence rates. Two larger retrospective studies of INTRABEAM use in France and the U.S. (University of Oklahoma) have reported similar local recurrence rates, with the former study reporting a 1.7% 5-year IBTR rate with a 54-month median follow-up and the latter study reporting a 3.9% 5-year IBTR rate with a 4.6-year median follow-up. At the 2-year follow-up, both the TARGIT-R study and the Cleveland Clinic experience demonstrated an approximately 2% median IBTR rate (2.3% and 2%, respectively) [20, 21]. However, with longer follow-up, a recent 2021 update of TARGIT-R reported a 5-year IBTR rate of 6.6% [20]. A summary of photon IORT trials is shown in Supplementary File — Table S2 [18, 20–25].

On univariate analysis, non-IDC histology (i.e., pure DCIS or ILC) was statistically significant in predicting higher IBTR rate. In a retrospective review evaluating adjuvant IORT for treatment of DCIS at a single institution, the 2-year IBTR rate was 4.9% [26]. Notably, the TARGIT and ELIOT trials excluded DCIS patients from enrollment. While histology appeared to be the only significant IBTR predictor in our cohort, the ELIOT trial also identified the negative prognostic factors of tumor size > 2 cm, nodal positivity (> 4 lymph nodes), high grade, and estrogen-negative (triple-negative) status that almost double the risk of IBTR [12].

Our current institutional inclusion criteria (which has changed from the TARGIT trial inclusion criteria used initially) select favorable patients based on available clinical information from initial imaging, physical examination, and biopsy. While 75% of patients in this cohort met our currently defined suitability criteria, most patients in this series still had favorable clinical tumor

characteristics as previously outlined above. Of note, the TARGIT-A study allowed for patients > 45 years old, any histological grade, tumors < 2.5 cm (T1 and small T2), and clinical N1 disease, which was less restrictive than the suitability criteria from the ASTRO 2009 APBI Consensus Statement limiting suitable candidates to women of at least 60 years of age who were ER+ with T1N0 disease [11, 15]. Additionally, TARGIT-A defined a close margin as within 1 mm, whereas the ASTRO guidelines both in 2009 and in 2016 defined a close margin as within 2 mm. Ultimately, when compared to the current expanded ASTRO 2016 APBI Consensus Guidelines, our institutional guidelines remain more conservative in regard to excluding grade 3 disease and Her2-positive disease.

It is also notable that, in our experience, 69% of patients initially considered suitable by preoperative clinical criteria remained suitable on final pathological criteria. A disadvantage of INTRABEAM and other forms of IORT is that final pathological details, such as final margin status and final tumor grade, are not known at the time of radiotherapy. Therefore, our results are useful for informing counseling of future patients eligible for breast-conserving surgery with IORT. This result confirms the prior institutional experience at Moffitt Cancer Center, which demonstrated that adjuvant whole-breast radiotherapy may be recommended in 30 to 33% of cases after lumpectomy and IORT [27].

Per the TARGIT trial design, adjuvant whole-breast radiation was planned for patients who did not meet trial suitability criteria and, thus, IORT was treated as a lumpectomy bed boost [11, 18]. Currently, a similar risk-adapted regimen is used at our institution to determine when whole-breast EBRT is recommended following IORT based on final pathological details. As our current institutional guidelines were not defined until later in this study, only 32–36% of patients who were considered unsuitable by either our current institutional criteria or the ASTRO consensus criteria on final pathology underwent indicated EBRT, which is similar to another institutional experience reporting that, while 46% of their patients treated with IORT had indications to receive whole-breast EBRT, 19% did not [28]. Reasons why EBRT may have been omitted include additional surgery, such as undergoing completion mastectomy, meeting CALGB 9343 or PRIME II eligibility criteria for omission of radiotherapy without meeting IORT suitability criteria [16, 29], and patient refusal. For future studies examining only patients treated in the era of our current institutional guidelines, it will be useful to document how many patients refuse additional EBRT when indicated after IORT. Regardless, no significant difference in IBTR, OS,

or RFS was observed for patients who received all recommended radiation therapy versus those who did not (ie, unsuitable patients who did not receive additional EBRT).

In regard to toxicity outcomes, our experience is congruent to the published TARGIT experience, which reported only 4 of 1721 patients with grade 3 or 4 skin complications [11], with only 0.6% of patients (n = 1) experiencing grade 3 radiation dermatitis. The 1 patient who experienced grade 3 fibrosis also had a preceding grade 3 seroma managed by two re-excisions; this patient also received adjuvant whole-breast radiation. Our findings are comparable to those of the GEC-ESTRO trial, which reported grade 3 fibrosis with whole-breast radiation whereas patients who underwent APBI alone exhibited no grade 3 fibrosis [10]. Our incidence of wound infection and seroma requiring intervention was similar to that of a recently published phase II study evaluating acute toxicities after breast IORT delivered as a boost before EBRT [30]. In this study, 2.0% of patients experienced infection and 13.6% experienced seroma needing aspiration. In another study evaluating 120 patients, 3.9% of patients who received IORT alone and 20% who received both IORT and WBRT underwent seroma evacuation [31]. Similarly, analyzing 102 patients with a median follow up of 29.2 months, Tejera Hernandez et al. reported similar rates of fibrosis (17%), seroma (11%), and infection (5.8%) (23). Of the 167 evaluable patients in our cohort, the highest CTCAE toxicity grade reported was grade 1 in 80 patients (48%), grade 2 in 23 patients (14%), and grade 3 in 11 patients (7%). These rates are comparable to those of the NSABP-B39 experience, which reported the following highest toxicity grades after APBI: grade 1 in 845 (40%), grade 2 in 921 (44%), and grade 3 in 201 (10%) patients.

Our study has its limitations. First, there were few recurrence events, limiting the study of prognostic factors for IBTR on our univariate analyses, and there were too few events for multivariate analyses. Additionally, owing to the retrospective nature of our study, our conclusions regarding toxicity may be limited by a lack of data regarding the timing of the adverse events, and interpretation biases due to post hoc toxicity grading. Nevertheless, our institutional experience provides more granular toxicity outcomes than other published photon IORT studies. Our study is also strengthened by a median follow-up of 5.1 years.

Conclusions

IORT for select patients with early-stage breast cancer followed by risk-adapted therapy has led to acceptable outcomes in regard to IBTR and toxicity in our single-institution series with long-term follow-up.

Conflict of interest

The authors declare that there is no conflict of interests.

Funding

This publication was prepared without any external source of funding.

Data availability statement

The authors agree to share anonymized data upon reasonable request by researchers.

References

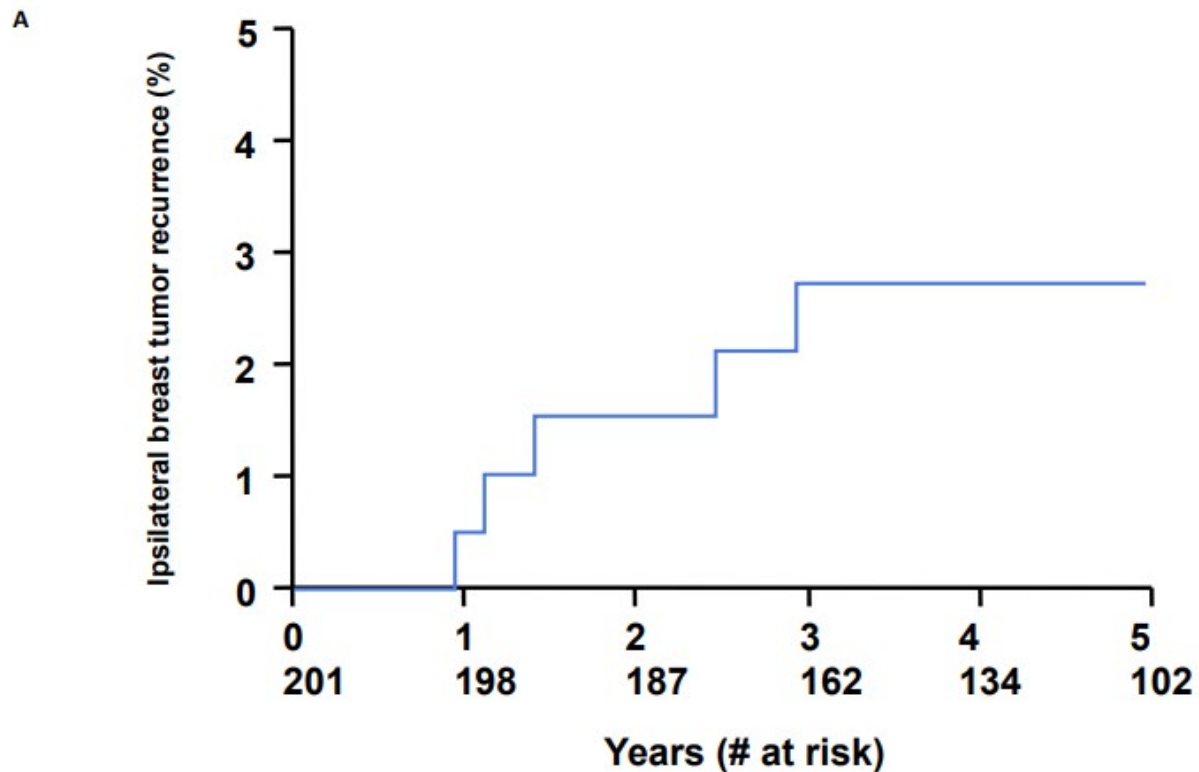
1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002; 347(16): 1233-1241, doi: [10.1056/NEJMoa022152](https://doi.org/10.1056/NEJMoa022152), indexed in Pubmed: [12393820](https://pubmed.ncbi.nlm.nih.gov/12393820/).
2. Darby S, McGale P, Correa C, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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. *Lancet.* 2011; 378(9804): 1707-1716, doi: [10.1016/S0140-6736\(11\)61629-2](https://doi.org/10.1016/S0140-6736(11)61629-2), indexed in Pubmed: [22019144](https://pubmed.ncbi.nlm.nih.gov/22019144/).
3. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010; 362(6): 513-520, doi: [10.1056/NEJMoa0906260](https://doi.org/10.1056/NEJMoa0906260), indexed in Pubmed: [20147717](https://pubmed.ncbi.nlm.nih.gov/20147717/).
4. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol.* 2008; 9(4): 331-341, doi: [10.1016/S1470-2045\(08\)70077-9](https://doi.org/10.1016/S1470-2045(08)70077-9), indexed in Pubmed: [18356109](https://pubmed.ncbi.nlm.nih.gov/18356109/).
5. Ojerholm E, Freedman GM, Bekelman JE. The Dollars and Sense of Hypofractionated Breast Radiation. *J Natl Cancer Inst.* 2017; 109(11), doi: [10.1093/jnci/djx090](https://doi.org/10.1093/jnci/djx090), indexed in Pubmed: [29059429](https://pubmed.ncbi.nlm.nih.gov/29059429/).
6. Bekelman JE, Sylwestrzak G, Barron J, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. *JAMA.* 2014; 312(23): 2542-2550, doi: [10.1001/jama.2014.16616](https://doi.org/10.1001/jama.2014.16616), indexed in Pubmed: [25494006](https://pubmed.ncbi.nlm.nih.gov/25494006/).
7. Alvarado MD, Mohan AJ, Esserman LJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol.* 2013; 20(9): 2873-2880, doi: [10.1245/s10434-013-2997-3](https://doi.org/10.1245/s10434-013-2997-3), indexed in Pubmed: [23812769](https://pubmed.ncbi.nlm.nih.gov/23812769/).

8. Grobmyer SR, Lightsey JL, Bryant CM, et al. Low-kilovoltage, single-dose intraoperative radiation therapy for breast cancer: results and impact on a multidisciplinary breast cancer program. *J Am Coll Surg.* 2013; 216(4): 617-23; discussion 623, doi: [10.1016/j.jamcollsurg.2012.12.038](https://doi.org/10.1016/j.jamcollsurg.2012.12.038), indexed in Pubmed: [23415885](https://pubmed.ncbi.nlm.nih.gov/23415885/).
9. Lettmaier S, Kreppner S, Lotter M, et al. Radiation exposure of the heart, lung and skin by radiation therapy for breast cancer: a dosimetric comparison between partial breast irradiation using multicatheter brachytherapy and whole breast teletherapy. *Radiother Oncol.* 2011; 100(2): 189-194, doi: [10.1016/j.radonc.2010.07.011](https://doi.org/10.1016/j.radonc.2010.07.011), indexed in Pubmed: [20673690](https://pubmed.ncbi.nlm.nih.gov/20673690/).
10. Strnad V, Ott OJ, Hildebrandt G, et al. Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet.* 2016; 387(10015): 229-238, doi: [10.1016/S0140-6736\(15\)00471-7](https://doi.org/10.1016/S0140-6736(15)00471-7), indexed in Pubmed: [26494415](https://pubmed.ncbi.nlm.nih.gov/26494415/).
11. Vaidya JS, Wenz F, Bulsara M, et al. TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* 2014; 383(9917): 603-613, doi: [10.1016/S0140-6736\(13\)61950-9](https://doi.org/10.1016/S0140-6736(13)61950-9), indexed in Pubmed: [24224997](https://pubmed.ncbi.nlm.nih.gov/24224997/).
12. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013; 14(13): 1269-1277, doi: [10.1016/S1470-2045\(13\)70497-2](https://doi.org/10.1016/S1470-2045(13)70497-2), indexed in Pubmed: [24225155](https://pubmed.ncbi.nlm.nih.gov/24225155/).
13. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet.* 2019; 394(10215): 2155-2164, doi: [10.1016/S0140-6736\(19\)32514-0](https://doi.org/10.1016/S0140-6736(19)32514-0), indexed in Pubmed: [31813636](https://pubmed.ncbi.nlm.nih.gov/31813636/).
14. Whelan TJ, Julian JA, Berrang TS, et al. RAPID Trial Investigators. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet.* 2019; 394(10215): 2165-2172, doi: [10.1016/S0140-6736\(19\)32515-2](https://doi.org/10.1016/S0140-6736(19)32515-2), indexed in Pubmed: [31813635](https://pubmed.ncbi.nlm.nih.gov/31813635/).
15. Correa C, Harris EE, Leonardi MC, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol.* 2017; 7(2): 73-79, doi: [10.1016/j.prro.2016.09.007](https://doi.org/10.1016/j.prro.2016.09.007), indexed in Pubmed: [27866865](https://pubmed.ncbi.nlm.nih.gov/27866865/).
16. Hughes KS, Schnaper LA, Bellon JR, et al. Cancer and Leukemia Group B, Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med.* 2004; 351(10): 971-977, doi: [10.1056/NEJMoa040587](https://doi.org/10.1056/NEJMoa040587), indexed in Pubmed: [15342805](https://pubmed.ncbi.nlm.nih.gov/15342805/).
17. National Comprehensive Cancer Network. Breast Cancer (Version 2.2022). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (May 9, 2022).
18. Vaidya JS, Bulsara M, Baum M, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ.* 2020; 370: m2836, doi: [10.1136/bmj.m2836](https://doi.org/10.1136/bmj.m2836), indexed in Pubmed: [32816842](https://pubmed.ncbi.nlm.nih.gov/32816842/).

19. Korzets Y, Fyles A, Shepshelovich D, et al. Toxicity and clinical outcomes of partial breast irradiation compared to whole breast irradiation for early-stage breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2019; 175(3): 531-545, doi: [10.1007/s10549-019-05209-9](https://doi.org/10.1007/s10549-019-05209-9), indexed in Pubmed: [30929116](https://pubmed.ncbi.nlm.nih.gov/30929116/).
20. Valente SA, Tendulkar RD, Cherian S, et al. TARGIT-R (Retrospective): 5-Year Follow-Up Evaluation of Intraoperative Radiation Therapy (IORT) for Breast Cancer Performed in North America. *Ann Surg Oncol.* 2021; 28(5): 2512-2521, doi: [10.1245/s10434-020-09432-3](https://doi.org/10.1245/s10434-020-09432-3), indexed in Pubmed: [33433786](https://pubmed.ncbi.nlm.nih.gov/33433786/).
21. Obi E, Tom MC, Manyam BV, et al. Outcomes with intraoperative radiation therapy for early-stage breast cancer. *Breast J.* 2020; 26(3): 454-457, doi: [10.1111/tbj.13574](https://doi.org/10.1111/tbj.13574), indexed in Pubmed: [31562688](https://pubmed.ncbi.nlm.nih.gov/31562688/).
22. Silverstein MJ, Epstein M, Kim B, et al. Intraoperative Radiation Therapy (IORT): A Series of 1000 Tumors. *Ann Surg Oncol.* 2018; 25(10): 2987-2993, doi: [10.1245/s10434-018-6614-3](https://doi.org/10.1245/s10434-018-6614-3), indexed in Pubmed: [29968030](https://pubmed.ncbi.nlm.nih.gov/29968030/).
23. Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC, et al. Complications and local relapse after intraoperative low-voltage X-ray radiotherapy in breast cancer. *Ann Surg Treat Res.* 2020; 98(6): 299-306, doi: [10.4174/astr.2020.98.6.299](https://doi.org/10.4174/astr.2020.98.6.299), indexed in Pubmed: [32528909](https://pubmed.ncbi.nlm.nih.gov/32528909/).
24. Nguyen ML, Pius P, Dooley W, et al. A prospective single-institution study of intraoperative radiotherapy (IORT) for early-stage breast cancer. *Breast J.* 2021; 27(3): 231-236, doi: [10.1111/tbj.14128](https://doi.org/10.1111/tbj.14128), indexed in Pubmed: [33274553](https://pubmed.ncbi.nlm.nih.gov/33274553/).
25. Tallet A, Racadot S, Boher JM, et al. The actual benefit of intraoperative radiation therapy using 50 kV x-rays in early breast cancer: A retrospective study of 676 patients. *Breast J.* 2020; 26(11): 2145-2150, doi: [10.1111/tbj.13827](https://doi.org/10.1111/tbj.13827), indexed in Pubmed: [32233012](https://pubmed.ncbi.nlm.nih.gov/32233012/).
26. Chin C, Hirji S, Onishi M, et al. A Single-Institution Experience in the Preoperative Selection of DCIS Patients for IORT using the ASTRO Consensus Guidelines. *Adv Radiat Oncol.* 2019; 4(2): 253-260, doi: [10.1016/j.adro.2018.11.004](https://doi.org/10.1016/j.adro.2018.11.004), indexed in Pubmed: [31011670](https://pubmed.ncbi.nlm.nih.gov/31011670/).
27. Mellon EA, Orman A, Joya LE, et al. Frequency of whole breast radiation therapy after intraoperative radiation therapy due to criteria identified by lumpectomy. *Brachytherapy.* 2017; 16(1): 174-180, doi: [10.1016/j.brachy.2016.09.012](https://doi.org/10.1016/j.brachy.2016.09.012), indexed in Pubmed: [27816540](https://pubmed.ncbi.nlm.nih.gov/27816540/).
28. Falco M, Masojć B, Milchert-Leszczynska M, et al. Frequency of whole breast irradiation (WBRT) after intraoperative radiotherapy (IORT) is strongly influenced by institutional protocol qualification criteria. *Rep Pract Oncol Radiother.* 2018; 23(1): 34-38, doi: [10.1016/j.rpor.2017.11.003](https://doi.org/10.1016/j.rpor.2017.11.003), indexed in Pubmed: [29270082](https://pubmed.ncbi.nlm.nih.gov/29270082/).
29. Kunkler IH, Williams LJ, Jack WJL, et al. PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol.* 2015; 16(3): 266-273, doi: [10.1016/S1470-2045\(14\)71221-5](https://doi.org/10.1016/S1470-2045(14)71221-5), indexed in Pubmed: [25637340](https://pubmed.ncbi.nlm.nih.gov/25637340/).
30. Ahn SG, Bae SJ, Lee HW, et al. A phase II study investigating the acute toxicity of targeted intraoperative radiotherapy as tumor-bed boost plus whole breast irradiation after breast-conserving surgery in Korean patients. *Breast Cancer Res Treat.* 2019; 174(1): 157-163, doi: [10.1007/s10549-018-5038-x](https://doi.org/10.1007/s10549-018-5038-x), indexed in Pubmed: [30467660](https://pubmed.ncbi.nlm.nih.gov/30467660/).

31. Falco M, Masojć B, Rolla M, et al. Risk factors for seroma evacuation in breast cancer patients treated with intraoperative radiotherapy. *Rep Pract Oncol Radiother.* 2016; 21(3): 225-231, doi: [10.1016/j.rpor.2016.03.003](https://doi.org/10.1016/j.rpor.2016.03.003), indexed in Pubmed: [27601955](https://pubmed.ncbi.nlm.nih.gov/27601955/).

Figure 1. Kaplan-Meier curves. **A.** 5-year ipsilateral breast tumor recurrence; the 5-year rate was 2.7%. **B.** Ipsilateral breast tumor recurrence rates by radiation received and suitability group; the 5-year ipsilateral breast tumor recurrence for patients who completed recommended radiation therapy (i.e., patients who were suitable for intraoperative radiotherapy (IORT) alone according to 2016 ASTRO Consensus Criteria or patients who were unsuitable and also received adjuvant external-beam radiation therapy (EBRT) was 1.7% versus 4.7% for patients who did not meet suitability criteria post-operatively and did not receive adjuvant EBRT ($p = 0.23$)



B

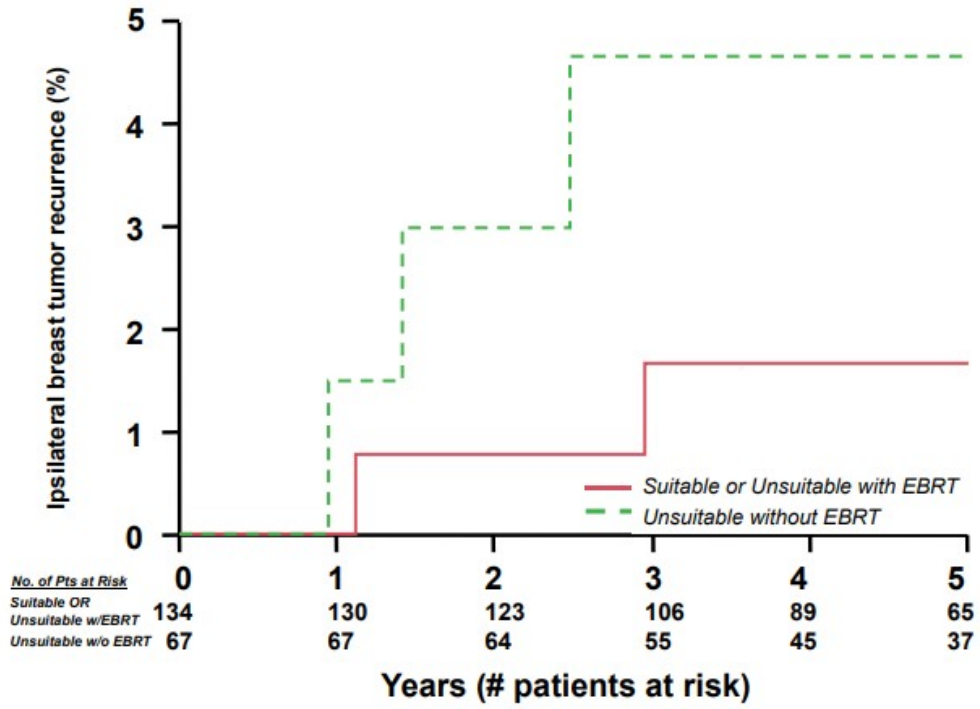


Figure 2. Incidence of adverse events (n = 167); only the highest-grade toxicity for each adverse event was counted for each patient

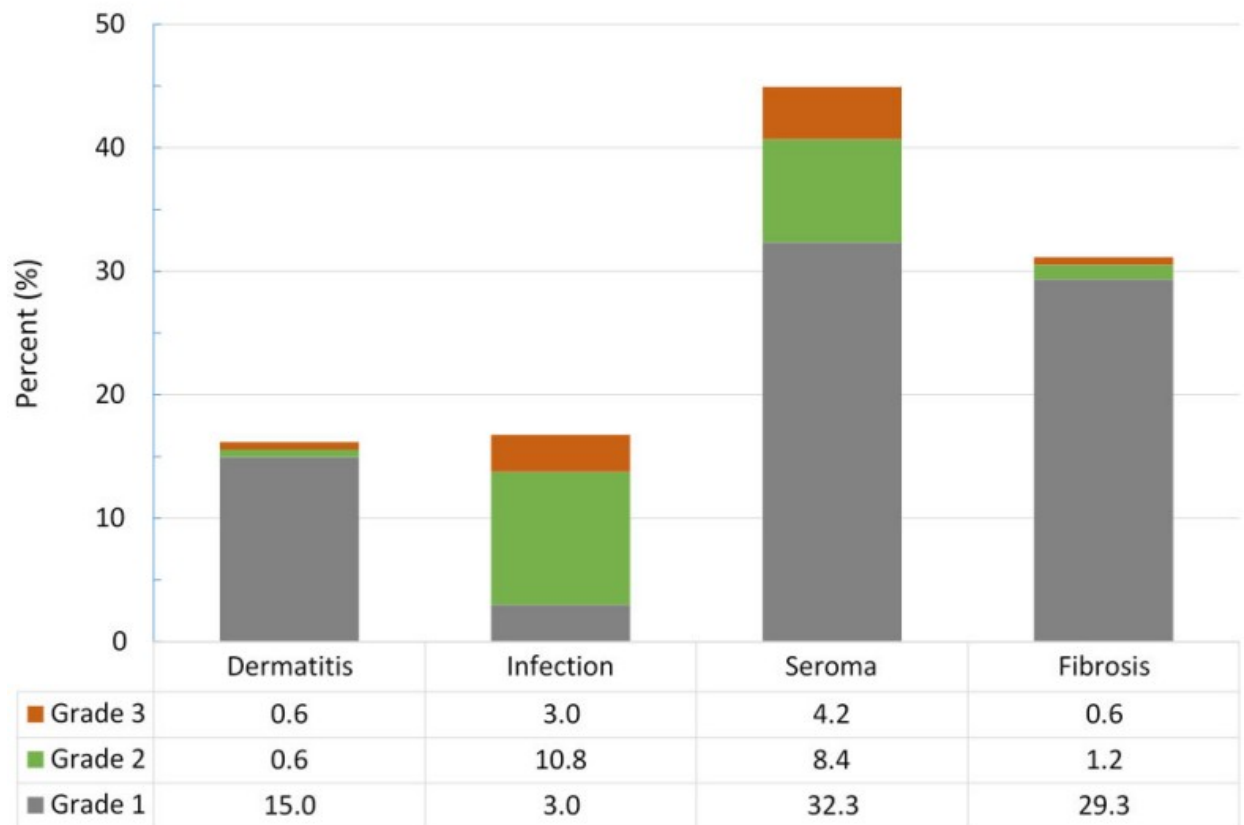


Table 1. Patient, tumor, and treatment characteristics (n = 201)

Characteristic	Number of patients (%) or other value
Patient characteristics	
Median age (range)	67 (48 – 86) years
Race/ethnicity	
White	167 (83%)
Black	13 (6%)
Latinx	6 (3%)
Other	15 (7%)
Tumor (clinical and pathological) characteristics	
Tumor laterality	
Right	96 (48%)
Left	105 (52%)
Hormone receptor status	
ER+ and/or PR+, Her2–	176 (88%)

ER+ and/or PR+, Her2+	14 (7%)
ER-, PR-, Her2-	11 (5%)
Clinical histology	
IDC	196 (98%)
Pure DCIS	2 (1%)
ILC	2 (1%)
Clinical grade	
1	87 (43%)
2	89 (44%)
3	20 (10%)
Unknown	5 (2%)
Clinical tumor (T) stage	
Tis	2 (1%)
T1	191 (95%)
T2	8 (4%)
Median clinical tumor size (range)	1.0 (0.04–4.4) cm
Clinical node positivity	1 (< 1%)
LVSI present in biopsy	9 (4%)
Pathologic histology	
IDC	194 (97%)
Pure DCIS	4 (2%)
ILC	3 (1%)
Pathologic grade	
1	84 (42%)
2	89 (44%)
3	28 (14%)
Pathologic tumor (T) stage	
Tis	3 (1%)
T1	187 (93%)
T2	11 (5%)
Median pathologic tumor size (range)	1.1 (0.08–4.5) cm
Pathological nodal (N) stage	
NX	1 (< 1%)
N0	191 (95%)
N1	8 (4%)
N3	1 (< 1%)

LVSI present upon final pathology	17 (8%)
EIC present upon final pathology	5 (2%)
Margin status¹	
Negative (≥ 2 mm)	144 (72%)
Close (< 2 mm)	51 (25%)
Positive	6 (3%)
Treatment characteristics	
INTRABEAM	
Median applicator size (range)	4.5 (3.5-5) cm
Mean dose at 1 cm depth (range)	6.3 (5.08-7.24) Gy
Mean treatment time (range)	36.9 (18.7-54.7) min
Additional surgery²	21 (10%)
Re-excision/lumpectomy	20 (10%)
Mastectomy	5 (2.5%)
Additional EBRT	22 (11%)
Median total dose EBRT (range)	42.4 (40.05–63) Gy
Median dose per fraction (range)	2.65 (1.8–2.67) Gy
Additional tumor bed boost delivered ³	1 ($< 1\%$)
Regional nodal irradiation ⁴	1 ($< 1\%$)
Adjuvant chemotherapy	18 (9%)
Hormonal therapy	148 (74%)

Note: 75% (n = 150) of all patients met institutional suitability criteria upon clinical examination.

¹Margin status refers to initial breast-conservation surgery; ²Four patients underwent more than one additional surgery after initial breast-conservation surgery. Thus, there were 25 total additional surgeries for 21 patients; ³One patient was found to have multifocal disease after surgery and underwent adjuvant external whole-breast radiation with a tumor bed boost to the second focus of disease at an outside institution; ⁴One patient had pN3 disease and underwent directed regional nodal irradiation; DCIS — ductal carcinoma in situ; EBRT — external-beam radiation therapy; EIC — extensive intraductal component; ER — estrogen receptor; Gy — Gray; Her2 — human epidermal growth factor receptor; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; LVSI — lymphovascular space invasion; min — minute; PR — progesterone receptor

Table 2. Univariate analysis

Variable	5-year IBTR				5-year Relapse-free Survival				5-year Overall Survival			
	%	95% L	95% U	P value	%	95% L	95% U	P value	%	95% L	95% U	P value
Age				0.3345				0.4608				0.476
< 60 years	4.8%	1.2%	17.4%		92.3%	78.5%	97.5%		97.7%	85.6%	99.7%	
≥ 60 years	2.1%	0.7%	6.3%		97.1%	92.5%	98.9%		94.4%	88.5%	97.3%	
Ethnicity				0.3005				0.1511				0.256
White	1.9%	0.6%	5.9%		96.2%	90.9%	98.4%		95.8%	90.9%	98.1%	
Non-white	7.4%	1.9%	25.3%		92.6%	74.7%	98.1%		91.3%	71.0%	97.8%	
Hormone receptor status				0.2978				0.342				0.324
ER+ and/or PR+	2.9%	1.2%	6.8%		95.4%	90.6%	97.9%		95.0%	90.1%	97.5%	
ER-/PR-	0.0%				100.0%				100.0%			
Pathologic tumor size				0.4163				0.4629				<0.0001
0–2 cm	2.9%	1.2%	6.8%		95.4%	90.6%	97.9%		96.4%	92.2%	98.4%	
> 2 cm	0.0%				100.0%				76.4%	37.6%	94.5%	
Pathologic grade				0.6171				0.2289				0.3532
I	1.2%	0.2%	8.1%		97.3%	89.8%	99.3%		97.6%	90.9%	99.4%	
II	5.2%	2.0%	13.2%		94.8%	86.8%	98.0%		95.3%	86.0%	98.5%	
III	0.0%				95.0%	71.8%	99.3%		88.9%	70.6%	96.4%	
Tumor histology				0.0167				0.0044				0.4447
DCIS or ILC	14.3%	2.0%	58.1%		85.7%	41.9%	98.0%		100.0%			
IDC	2.3%	0.9%	6.0%		96.1%	91.3%	98.3%		95.0%	90.3%	97.5%	
LVSI				0.9331				0.7716				0.0014
No	3.0%	1.2%	7.0%		95.4%	90.4%	97.8%		97.1%	93.2%	98.8%	
Yes	0.0%				100.0%				75.2%	44.8%	91.9%	
EIC				0.7086				0.7393				0.0271
No	2.8%	1.2%	6.5%		95.7%	91.0%	98.0%		95.7%	91.1%	98.0%	
Yes	0.0%				100.0%				80.0%	30.9%	97.3%	
Margin status				0.8094				0.8553				0.7739
Close or positive	3.8%	1.0%	14.1%		96.2%	85.9%	99.0%		93.2%	80.6%	97.8%	
Negative	2.3%	0.7%	6.9%		95.5%	89.5%	98.2%		96.1%	91.0%	98.4%	
Receipt of risk-adapted radiation				0.2342				0.5366				0.276
No	4.7%	1.2%	11.9%		95.3%	88.1%	98.8%		95.0%	85.5%	98.4%	
Yes	0.7%	0.3%	5.4%		96.1%	90.7%	98.8%		95.4%	89.2%	98.1%	
Receipt of hormone therapy				0.3525				0.1592				0.2104

No	6.6%	2.1%	18.8%		93.4%	81.2%	97.9%		93.8%	82.4%	98.0%	
Yes	1.5%	0.4%	5.7%		96.5%	90.8%	98.7%		95.8%	90.1%	98.3%	
Receipt of adjuvant chemotherapy				0.1725				0.2168				0.7025
No	3.0%	1.3%	7.0%		95.2%	90.1%	97.8%		95.3%	90.3%	97.8%	
Yes	0.0%				100.0%				94.4%	69.3%	99.2%	

IBTR — ipsilateral breast tumor recurrence; 95% —, lower 95 confidence limit; 95% U — upper 95 confidence limit; ER — estrogen receptor; PR — progesterone receptor; cm — centimeter; DCIS — ductal carcinoma in situ; ILC — invasive lobular carcinoma; IDC — invasive ductal carcinoma; LVSI — lymphovascular space invasion; EIC — extensive intraductal component

Supplementary File

Table S1. Disease and treatment details of patients who experienced a recurrence (n = 9)

Pt. no.	Post-lumpectomy tumor characteristics	Adjuvant therapy	Time to recurrence [yr]	Therapy completed for recurrence	Current disease status
1	ER+Her2- pT1N0 Grade 2 IDC; close margins, LVSI (-)	AI x 0.3 yr (Oncotype RS 30, declined chemotherapy)	0.9	Bilateral mastectomy	NED
2	ER+Her2- pT1N0 Grade 1 ILC; close margins; LVSI (-)	None	5.8	Mastectomy then AI	NED
3	ER+ pTisN0 Grade 2 DCIS; negative margins; LVSI (-)	None	1.4	Partial mastectomy	NED
4	ER+Her2- pT1N0 Grade 1 IDC; negative margins; LVSI (+)	AI x 5 yr	8.1	Fulvestrant/palbociclib due to simultaneous regional and distance metastatic disease	Alive with disease
5	ER+Her2- pT1N0 Grade 2 IDC; negative margins; LVSI (-)	AI x 5 yr	6.8	rmpT1N1a after MRM then Tam (Oncotype 5)	NED
6	ER+Her2- pT1N0 Grade 2 IDC; close margins; LVSI (-)	None	2.5	pT1NX at breast scar after excisional biopsy	NED
7	ER+Her2+ pT1N0 Grade 2 IDC;	AI x 5 yr	6.7	Mastectomy	NED

	negative margins; LVSI (-)				
8	ER+Her2- pT1N0 Grade 2 IDC; negative margins; LVSI (-)	Tam x 2.5 yr	2.9	pT1N0 after partial mastectomy with SLNB	NED
9	ER+Her2- pT1N0 Grade 1 IDC; negative margins; LVSI (-)	None	1.1	pT1N0 in different quadrant of ipsilateral breast after partial mastectomy with SLNB and INTRABEAM	NED

AI — aromatase inhibitor; ER — estrogen receptor; Her2 — human epidermal growth factor receptor; IDC — invasive ductal carcinoma; invasive lobular carcinoma; IDC — invasive ductal carcinoma; invasive lobular carcinoma; LVSI — lymphovascular space invasion; Tam — tamoxifen; MRM — modified radical mastectomy; SLNB — sentinel lymph node biopsy; NED — no evidence of disease; no. — number; yr — year; RS — recurrent score

Table S2. Summary of the literature on photon-based intraoperative radiotherapy

Author/Trial, Year Published	Center and/or Country	Time Period of Inclusion	Multi- or Single Institutional	Number of Patients	Technique Used	Median Follow-up (yr)	Five-year IBTR rate
Silverstein et al, 2018 [22]	Hoag Memorial Hospital Presbyterian, US	2010–2017	Single	984	Photon (50 kV)	3	3.9%*
Tejera Hernández et al, 2020 [23]	Hospital Universitario Insular de Gran Canaria, Spain	2015–2017	Single	102	Photon (50 kV)	2.2	No rate reported. Local relapse in 1 patient
Vaidya/ TARGIT-A, 2020 [18]	UK, Europe, US, Australia, Canada	2000–2012	Multi	1140	Photon (50 kV)	8.6	2.11%
Obi et al, 2020 [21]	Cleveland Clinic, US	2011–2019	Single	201	Photon (50 kV)	1.9	2.0% ¹
Nguyen et al, 2020 [24]	University of Oklahoma, US	2013–2017	Single	77	Photon (50 kV)	4.6	3.9% [‡]
Tallet et al, 2020 [25]	France	2011–2015	Multi	676	Photon (50 kV)	4.5	1.7%
Valente/TARGIT-R, 2021 [20]	US, Canada	2007–2013	Multi	667	Photon (50 kV)	5.1	6.6%
Giap et al. (present series)	University of Florida, US	2010–2017	Single	201	Photon (50 kV)	5.1	2.7%

*4-year rate; ¹1.9-year rate; [‡]4.6-year rate; Yr — year; IBTR — ipsilateral breast tumor recurrence