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RESEARCH ARTICLE

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Breast conserving surgery with targeted intraoperative radiotherapy for the management of ductal carcinoma in situ

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Background: A prospective randomized controlled trial has established the efficacy of targeted intraoperative radiotherapy (TARGIT) in the management of invasive breast cancer treated with breast-conserving surgery (BCS). The purpose of this analysis is to evaluate the efficacy of TARGIT in the management of ductal carcinoma in situ (DCIS).

Methods: A prospective nonrandomized trial was designed to evaluate the success of TARGIT in the management of DCIS, as measured by a low risk of requiring additional surgery or radiotherapy and an acceptable local recurrence rate (LRR).

Results: Fifty-five patients with DCIS received BCS and TARGIT from November 2007 to March 2017. Median patient age was 57 years (range, 42-83 years) and median histological lesion size was 14.4 mm (range, 2-51 mm). Four patients required either re-excision and/or whole breast irradiation, yielding a rate of additional therapy of 7.3% (4 of 55). Among 46 women administered TARGIT at the time of initial BCS, two local recurrences were observed yielding a 4.3% (2 of 46) LRR at 46 months median follow-up (range, 4-116 months). There were no clinically significant adverse events.

Conclusions: Preliminary evidence indicates TARGIT can be performed with a low risk of requiring additional therapy (7.3%) and an acceptable LRR (4.3%) when administered at the time of BCS.

KEYWORDS
breast cancer, ductal carcinoma in situ, intraoperative radiotherapy, partial breast irradiation, targeted intraoperative radiotherapy

1 | INTRODUCTION

Ductal carcinoma in situ (DCIS) is a nonobligate precursor of invasive breast cancer, which if inadequately treated, may progress to regional and systemic metastasis in a subset of patients.[1] To reduce the risk of disease progression, the current standard of care for the treatment of localized DCIS is breast-conserving surgery (BCS) combined with radiotherapy, with the selective omission of radiotherapy in prognostically favorable cases.[2,3]

Multiple long-term studies have demonstrated a propensity for breast cancers to recur near their site of origin.[4-7] Recognition of this local recurrence pattern laid the foundation for the development of accelerated partial breast irradiation (APBI) as a strategy to target the radiation treatment to the most at-risk region of the breast.

Abbreviations: ABS, American Brachytherapy Society; APBI, accelerated partial breast irradiation; ASBrS, American Society of Breast Surgeon; ASTRO, American Society of Therapeutic Radiation Oncology; BCS, breast conserving surgery; CC, cranial-caudal; CE-MRI, contrast-enhanced magnetic resonance imaging; DCIS, ductal carcinoma in situ; ER, estrogen receptor; GEC-ESTRO, The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology; IORT, intraoperative radiotherapy; LRR, local recurrence rate; MG, mammogram; MLO, mediolateral-oblique; PR, progesterone receptor; TARGIT, targeted intraoperative radiotherapy; WBI, whole breast irradiation.

Growing interest in APBI is further driven by a desire amongst oncologists and patients to reduce treatment time and treatment-related side effects associated with whole breast irradiation (WBI). The call for more limited and less burdensome therapy is also echoed by public health officials who advocate for more selective and judicious management of this frequently indolent lesion.

Evidence supporting the efficacy and safety of APBI is almost entirely derived from the treatment of invasive breast cancer. Multiple long-term patient series evaluating catheter-based brachytherapy show 5- to 10-year local recurrence rates (LRRs) of 2.6% to 5.3% for women presenting with early-stage invasive breast cancer, comparable to women treated with WBI.[8,9] A meta-analysis of 11 published comparative studies of APBI and WBI including four randomized controlled trials demonstrated no significant difference in LRR, disease-free survival, or overall survival among 7097 patients with invasive breast cancer.[10] On the basis of these data, in 2009 the American Society of Therapeutic Radiation Oncology (ASTRO) consensus guideline for early-stage invasive breast cancer defined eligibility criteria for APBI to identify suitable, cautionary, and unsuitable patients based on their risk of local recurrence.[11] By 2012, approximately 15% of Medicare patients received some form of APBI.[12]

Despite the growing acceptance of APBI in the management of invasive breast cancer, the inclusion of DCIS among the indications for APBI had been delayed by the absence of published randomized trials and the paucity of long-term, nonrandomized trials data examining the efficacy of APBI in the management of DCIS. Subsequently, several nonrandomized series of patients with DCIS treated with catheter-based APBI reported LRRs of 0% to 2.4% with 24 to 60 months of median follow-up, which compared favorably to patients treated with WBI.[13] Similarly, a pooled analysis of 300 participants in the William Beaumont Hospital and the American Society of Breast Surgeon's MammoSite registries demonstrated 5-year LRR of 2.6%.[8] Based on these results, the 2016 ASTRO and the 2017 American Brachytherapy Society consensus statements on APBI defined a subgroup of patients with DCIS considered suitable for APBI, but explicitly excluded the use of intraoperative radiotherapy (IORT) outside of a clinical trial due to the absence of data on the treatment of DCIS.[14,15] However, it is noteworthy that both consensus statements were accepted for publication after our initial targeted intraoperative radiotherapy (TARGIT)-DCIS experience was published in 2016.[16] Ironically, the 2017 American Brachytherapy Society guideline includes DCIS but restricts all uses of IORT to treatment on clinical trials.[15] The 2010 GEC-ESTRO guideline assigned DCIS to the "intermediate risk" group but the guideline's anticipated update is yet to be published.[17]

With respect to surgical margins, the ASTRO guideline restricts suitable DCIS to lesions resected with margins ≥3 mm despite the absence of data indicating that 3 mm margins are required to achieve adequate local control. In fact, ASTRO's 3-mm margin requirement is based on the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network E5194 trial, which examined factors associated with local recurrence in subjects treated with lumpectomy for whom all forms of radiation were omitted[11,15,17,18] (Table 1).

The rationale for utilizing TARGIT in the treatment of DCIS is based on the TARGIT-A trial, a prospective randomized controlled trial comparing TARGIT and WBI in the management of early-stage invasive breast cancer in which 50% of participants were found to have coexisting DCIS in their surgical pathology specimens.[15,17] Despite this high percentage of concurrent DCIS, equivalent 5-year LRRs were observed between patients receiving TARGIT at the time of BCS compared with patients receiving WBI. This proves the principle that IORT is capable of preventing recurrences of both DCIS and invasive breast cancer. Based on the presumption that IORT would be equally efficacious as WBI for selected DCIS lesions, we undertook a prospective nonrandomized clinical trial to evaluate the use of TARGIT in women with DCIS who were candidates for BCS.

2 | MATERIALS AND METHODS

A prospective nonrandomized trial was designed to determine whether or not patients with DCIS could be successfully treated with BCS and TARGIT with a low risk of requiring additional surgery or radiotherapy. Study participants were recruited under an IRB-approved protocol at the University of Southern California's Kenneth Norris Cancer Center (Los Angeles, CA) or treated under a multidisciplinary treatment protocol at the Los Angeles Center for Women's Health (Los Angeles, CA), 90210 Surgery Medical Center (Beverly Hills, CA) or DISC Surgery Center (Santa Monica, CA). All data were tracked prospectively in the American Society of Breast Surgeon's Mastery of Surgery Registry. Preoperatively, all candidates underwent bilateral digital mammography and bilateral breast contrast-enhanced magnetic resonance imaging (CE-MRI) for evaluation of the extent of disease. Imaging studies were interpreted by board-certified radiologists with expertise in breast imaging. Patients with pure DCIS were deemed eligible for TARGIT if the lesion were estimated at less than equal to 4 cm on both digital mammography and CE-MRI and judged to be resectable with clear margins using BCS (see Figure 1 for the study schema). Patients were divided into two treatment cohorts based on time of TARGIT delivery: (1) cohort 1, consisting of patients selected to receive TARGIT at the time of initial DCIS resection [the concurrent group] and (2) cohort 2, comprised of patients selected to receive IORT at a second operation typically at the time of re-excision of positive margins following a previous unsuccessful lumpectomy (the delayed group). All procedures were performed by or under the supervision of a single senior breast surgeon (DRH). Postoperatively, DCIS lesion size determined by imaging was compared with lesion size and surgical margin status obtained from the surgical pathology specimen. This information was used to evaluate the ability of digital mammography combined with CE-MRI to identify suitable candidates for concurrent IORT (the study's primary endpoint) as judged by a low requirement of additional surgery or radiotherapy. The main secondary endpoint was to determine the LRR among women with DCIS treated with BCS and TARGIT who did not require additional treatment (mastectomy or WBI).

To compensate for potential imaging size underestimation, the surgeon aimed to excise the DCIS lesion with gross surgical margins

TABLE 1 Comparison of four consensus recommendations for patients considered suitable for APBI

	ASTRO[11]	GEC-ESTRO[17]	ASBrS[18]	ABS[15]
Patient factors				
Age, y	≥50	>50	≥45	≥45
BRCA ½ mutation	Negative			
Pathological factors				
Tumor size	≤2.0 cm IDC or ≤2.5 cm DCIS	≤3.0 cm	≤3.0 cm	≤3.0 cm
T stage	T1 DCIS[a], if all of the following are present: screen detected-nuclear grade I or II- size ≤2.5 cm, margins ≥3.0 mm	T1-2	T1-2 DCIS	T1-2[a], DCIS[a]
Margins	IDC: ≥2.0 mm, DCIS: ≥3.0 mm	≥2.0 mm	Negative	Ink: no tumor on ink DCIS: ≥2.0 mm
Grade	Any	Any		
LVSI	Absent	Absent		Absent
ER status	ER+	Any		Any
Multicentricity	Unicentric	Unicentric	Unicentric	
Multifocality	Unifocal	Unifocal		
Histology	IDC or other favorable subsets, nuclear grade I or II DCIS[a]	IDC, mucinous, tubular, colloid, and medullary	IDC, DCIS	All invasive subtypes and DCIS
EIC	Absent	Absent		
Associated LCIS	Absent	Allowed		
Nodal factors				
N stage	pN0	pN0	pN0	pN0

Abbreviations: ABS, American Brachytherapy Society; ASBrS, American Society of Breast Surgeon; ASTRO, American Society of Therapeutic Radiation Oncology; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component; ER, estrogen receptor; GEC-ESTRO, The Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma in situ; LVSI, lymphovascular space invasion.
[a]Use of intraoperative radiotherapy excluded outside of clinical trial.

width of 10 mm with the ultimate goal of achieving final histological margins of 2 mm or greater in keeping with DCIS margin requirements for BCS commonly applied at the time the study was initiated. Resection was aided by preoperative placement of one or more bracketing localizing wires to target the imaging abnormality and/or the microclip. Sentinel node biopsy was reserved for individuals whose clinical or imaging findings suggested a higher risk of concurrent invasive malignancy (eg, palpable DCIS or imaging studies suggesting a mass component). Patients with surgical margins of less than 2 mm were initially advised to undergo re-excision. At its inception, the protocol prescribed WBI after margin re-excision if clear margins were achieved, regardless of the histological findings. However, a subsequent protocol modification limited WBI to margin re-excision when residual disease was found in the re-excision specimen. WBI was also advised when the maximal lesion diameter exceeded 5 cm, even if widely excised (Figure 1).

The TARGIT-A trial study design anticipated that 15% of TARGIT recipients would require additional surgery (eg, margin re-excision or mastectomy) and/or WBI due to unfavorable surgical pathology findings.[16] Therefore, we adopted the less than equal to 15% threshold as a desired goal for additional therapy following TARGIT but considered an additional therapy rate of greater than 25% to be unacceptable. Although DCIS re-excision rates of 20% to 40% are commonly accepted, we intentionally selected a more conservative re-excision rate goal of less than equal to 15% to minimize personnel and resource utilization for TARGIT recipients who would ultimately require re-excision, WBI or mastectomy due to incomplete lesion resection. By protocol design, an additional therapy rate between 16% to 25% would permit protocol modifications (eg, reducing maximum lesion size) to maintain the additional therapy rate less than equal to 15%. Management of local recurrences was not included in the additional therapy calculation because the management of local recurrences was not considered a component of the initial cancer therapy.

2.1 | MAMMOGRAPHY

Standard two-view (mediolateral-oblique and cranial-caudal views) digital mammograms were obtained as well as any additional diagnostic mammograms requested by the interpreting radiologist. Mammograms of insufficient quality or mammograms performed more than 60 days before determination of eligibility was repeated. Mammographic lesion size was measured in three perpendicular dimensions using a centimeter ruler encompassing the entire span of suspicious or indeterminate microcalcifications, asymmetry, distortion, and/or spiculations. The interpreting radiologists documented lesion dimensions, multicentricity, multifocality, and/or evidence of invasive disease.

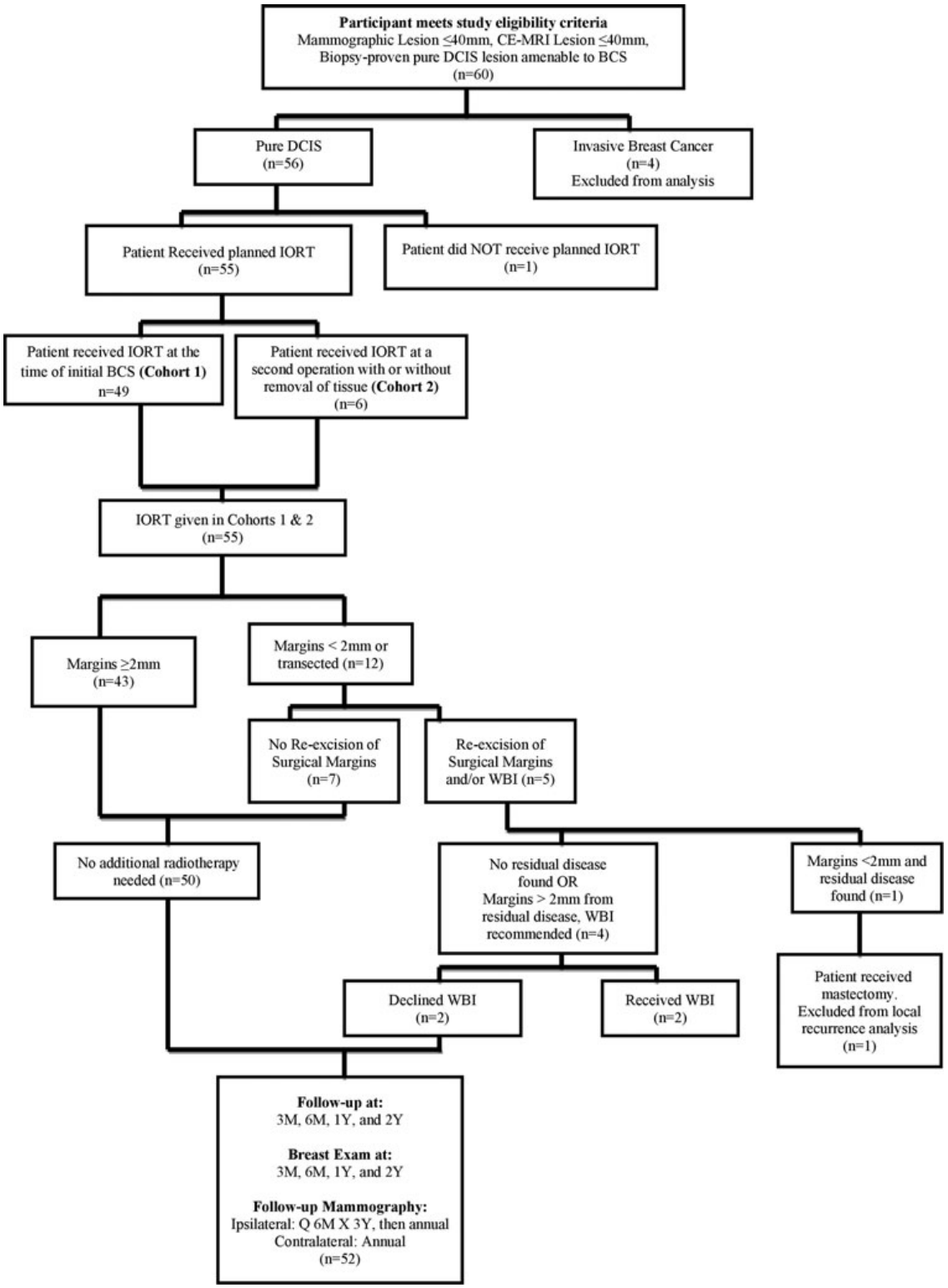

FIGURE 1 Study schema: the schema represents the treatment algorithm for patients determined eligible for BCS and IORT. Fifty-two patients subsequently were identified for local recurrence analysis and required to receive follow-up. BCS, breast-conserving surgery; CE-MRI, contrast-enhanced magnetic resonance imaging; IORT, intraoperative radiotherapy; DCIS, ductal carcinoma in situ; n, sample size; WBI, whole breast irradiation

2.2 | Contrast-enhanced magnetic resonance imaging

CE-MRI of the breast was required for all patients before determination of eligibility for IORT. CE-MRI deemed of insufficient quality or those that were performed more than 60 days before eligibility assessment was repeated. Patients underwent bilateral CE-MRI using a 1.5- or 3.0-T MRI unit using a dedicated double breast coil. Images were acquired in the prone position using the following or similar sequences: (1) localizer/scout T1 FLASH coronal/sagittal/axial images, (2) STIR or T2 weighted FSE axial images, (3) T1 weighted FSE axial images, (4) dynamic T1 weighted gradient-echo contrast-enhanced axial images utilizing standard rates and volumes of a Food and Drug Administration approved gadolinium-based agent. Fat saturated and/or subtraction images were obtained of the dynamic sequences, and three-dimensional (3D) subtracted maximum intensity projections were reviewed on a dedicated MRI CAD workstation. Using the axial and 3D dynamic subtraction images, the area of maximal enhancement was outlined and measured in three dimensions using a centimeter ruler. All studies were interpreted by fellowship-trained breast radiologists with expertize in breast CE-MRI. Morphologic and kinetic analysis for suspicious enhancing lesions was performed using the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) lexicon. Kinetic analyses were performed for the lesion(s) of interest in early enhancement (1-2 minutes after injection) and late enhancement (5-6 minutes after injection). Morphological analyses of lesions (masses, foci, and regions) were made by assessing the size, borders, and homogeneity of enhancement. In general, irregular or heterogeneous lesions were considered suspicious. Masses (>5 mm in size by definition) were considered suspicious if they exhibited at least a 50% increase in early signal intensity with late washout kinetics unless they possessed characteristic features of an intramammary lymph node. Segmental, linear, or clumped enhancement was considered suspicious for DCIS regardless of kinetics. Lesions not meeting ACR BI-RADS criteria for suspicion were considered benign or probably benign.

2.3 | Second look ultrasound

All discrete, suspicious, and indeterminate lesions were seen on the CE-MRI were evaluated with "second look" or correlative ultrasound to determine if the lesions were amenable to ultrasound-guided needle biopsy, if the results of the biopsy would significantly alter the surgical plan (eg, conversion from BCS to mastectomy or performance of a significantly wider local excision), or if they would in some way affect eligibility for TARGIT. The MRI-guided biopsy was performed on suspicious lesions not amenable to ultrasound-guided biopsy.

2.4 | Minimally invasive biopsies

Minimally invasive breast biopsies were performed on all additional suspicious lesions seen on mammogram, ultrasound, or CE-MRI to obtain definitive information about the presence or absence of malignancy. Biopsies were performed either using an 8- or 11-G vacuum-assisted needle, a 14-G core biopsy needle, or similar devices guided by the imaging study that best depicted the abnormality. DCIS histology was determined using the Philadelphia Consensus Guidelines and assessed in the minimally invasive biopsy specimen before the administration of IORT.

2.5 | Surgery and pathology

Patients underwent planned BCS with IORT if they met protocol criteria. Following single or bracketed wire localization, patients generally underwent standard lumpectomy with the goal of excising a 10 mm gross parenchymal margin surrounding the imaging abnormality. Oncoplastic surgical techniques were commonly used, include glandular advancement flaps, dissection of surgical margins from the subcutaneous layer to the muscular fascia, and full thickness parenchymal closure. Intraoperative ultrasound was commonly used to assess wire trajectory, document the location of biopsy site markers, and localize ultrasound visible lesions in a few cases. Two-view specimen radiographs were obtained at the time of surgery to assess gross surgical margins followed immediately by directed excision of close margins. Surgical specimens underwent a routine histological evaluation to determine DCIS histology, lesion dimensions, surgical margin width, prognostic markers (if not previously performed on the core specimen), and the presence or absence of invasive carcinoma. Surgical margin width was measured as the distance of the tumor cells to the nearest inked margin. Anterior and posterior margins were considered widely clear if the skin (anterior) or muscular fascia (posterior) were resected with the surgical specimen.

2.6 | Radiation therapy

Patients were treated in accordance with the TARGIT-A trial's radiation protocol. Preoperatively, all patients were evaluated by a radiation oncologist. IORT was administered using the Intrabeam device (Carl Zeiss Meditec, Oberkochen, Germany), which delivers a point source of radiation in the form of 50 kV X-rays at the center of a 1.5 to 5 cm diameter spherical applicator. The applicator best matching the cavity was positioned within the tumor bed, and one or more purse-string sutures were used to confirm the surgical margins to the applicator surface. In addition, sutures and skin retractors were applied in some cases to pull the skin edges away from the radiation source to minimize skin radiation exposure. Radiation therapy was administered at a dose of 20 Gy to the surface of the lumpectomy cavity and 5 to 7 Gy at a depth of 1 cm. Treatment time varied 17 to 45 minutes depending on the diameter of the selected applicator.[19]

2.7 | Follow-up

Patients were evaluated at the 3, 6, 12, and 24 months post-IORT to assess adverse events. Follow-up mammograms of the treated breast were performed semiannually for the first 3 years after IORT, before returning to routine annual mammography. CE-MRI was not routinely

performed after IORT but was used selectively to evaluate clinical or mammographic findings or for follow-up of previous MRI findings.

2.8 | Statistical considerations

The study design was selected based on the primary aim to evaluate the ability of CE-MRI and mammography to identify patients with DCIS for whom BCS and concurrent TARGIT could be offered at the time of initial BCS with a low probability of requiring additional surgery or WBI. If 15% or fewer patients required additional surgery and/or radiotherapy, we would consider concurrent TARGIT an acceptable treatment option for selected patients with DCIS. Conversely, if additional surgery and/or WBI were required in greater than 25% of subjects, we would consider concurrent TARGIT an unacceptable treatment option for patients with DCIS. On the other hand, additional therapy rates of 16% to 25% would permit protocol modifications to achieve the desired rate.

3 | RESULTS

Table 2 provides a summary of the patient and tumor characteristics. A total of 60 patients were screened and considered for BCS and TARGIT between November 2007 and March 2017. Median patient age was 57 years (range, 42-83 years) and median histological lesion size was 14.4 mm (range, 2-51 mm). Four patients were excluded from the primary endpoint and local recurrence analyses due to detection of invasive carcinoma in the surgical pathology results (Table 5). One patient did not receive TARGIT due to a software problem with the IORT system (Table 2).

The majority of participants received TARGIT concurrent with BCS (n = 49) whereas six patients received TARGIT at the time of re-excision of positive margins. Among 55 patients completing TARGIT for pure DCIS, 43 patients met criteria for negative margins (ie, margins ≥2 mm) whereas 12 patients had nontransected but positive margins initially defined by the protocol as margin width less than 2 mm. Five of the patients with margins less than 2 mm were advised to undergo margin re-excision and/or receive WBI. No additional radiation or surgery was recommended for the remaining seven patients with nontransected margins based on a treatment policy modification that eliminated the requirement for margin re-excision in patients with nontransected margins, ie, "no tumor on ink." Altogether, 21.8% (12 of 55) of patients met the criteria for additional therapy (ie, re-excision and/or WBI) before this protocol modification. Following the protocol modification, only 7.3% (4 of 55) met criteria for additional therapy. Table 3 summarizes the post-operative data for the cohort of 55 patients with pure DCIS (Table 3).

Among 55 patients receiving BCS and TARGIT for pure DCIS, 50 had no indication for additional surgery or WBI whereas two patients underwent margin re-excision but declined recommended WBI. One patient with a persistent positive margin necessitating mastectomy and two patients that received WBI were excluded from the local recurrence analysis. This yielded 52 patients with pure DCIS who were evaluable for the local recurrence analysis.

TABLE 2 Summary of preoperative patient data (n=55)

	n	%
Age on study, y		
Mean	57	
Range	42-83	
40-50	19	35
51-60	17	31
61-70	14	25
>70	5	9
Time of TARGIT		
Initial BCS (concurrent, cohort 1)	49	89
Re-excision (delayed, cohort 2)	6	11
Maximum dimension by mammography, mm		
Mean	14.04	
Range	2.2-39.0	
0-10	30	55
11-20	14	25
21-30	9	16
31-40	2	4
Grade		
I	7	13
II	27	49
III	21	38
Receptor status		
ER+PR+	38	69
ER+PR−	5	9
ER−PR−	12	22

Abbreviations: BCS, breast-conserving surgery; ER, estrogen receptor; PR, progesterone receptor; TARGIT, targeted intraoperative radiotherapy.

With a median follow-up of 49 months (range, of 4-116 months), four patients experienced an ipsilateral breast recurrence yielding an LRR of 7.7% (4 of 52). When stratified by the timing of TARGIT delivery, local recurrences were observed in two patients that received TARGIT concurrent with BCS for an LRR of 4.3% (2 of 46) at the median follow-up of 46 months (range, 4-116 months). One of these recurrences was invasive and the other was DCIS. Among the six patients that received TARGIT at the time of re-excision, two experienced local recurrences of DCIS at a median follow-up of 68 months (range, 7-112 months) for an LRR of 33.3% (2 of 6). No regional recurrence, distant recurrence or deaths were observed among TARGIT recipients. No local recurrences occurred among the four patients upstaged to invasive breast cancer (median follow-up 15.5 months).

Table 4 summarizes the outcome of the patients that required additional surgery and/or WBI for positive margins or recurrent disease (Table 4).

Adverse events were low overall and commensurate with the rate of adverse events reported in the TARGIT-A trial. Among 55 patients that received TARGIT for pure DCIS, one patient (1.8%) developed a hematoma that was managed expectantly; one patient (1.8%) developed an infected seroma that was managed with

TABLE 3 Summary of postoperative and outcome data (n = 55)

	n	%
DCIS size on final pathology, mm		
Mean	14.4	
Range	2-51	
0-10	27	49.1
11-20	14	25.5
21-30	10	18.2
31-40	2	3.6
40-50	1	1.8
>51	1	1.8
Final margin status		
Negative	50	90.9
Positive	5	9.1
Adjuvant tamoxifen/aromatase inhibitor		
Yes	30	54.6
No	21	38.2
Declined	2	3.6
Unknown	2	3.6
Local recurrence: cohorts 1 and 2, n = 52, mo		
Median FU (Range)	49 (4-116)	
No	48	92.3
Yes	4	7.7
Local recurrence: concurrent group: cohort 1, n = 46[a]		
Median FU (Range)	46 (4-116)	
No	44	95.7
Yes	2	4.3
Local recurrence: delayed group: cohort 2, n = 6		
Median FU (Range)	68 (7-112)	
No	4	66.7
Yes	2	33.3
Regional recurrence		
No	55	100
Yes	0	0
Distant recurrence		
No	55	100
Yes	0	0

Abbreviation: DCIS, ductal carcinoma in situ, FU, follow-up.
[a]Local recurrence analysis excluding a single patient treated with initial mastectomy and two patients treated with WBI.

aspiration and oral antibiotics; and two patients (3.6%) developed noninfected symptomatic seromas that required more than three aspirations. There were no instances of grade 3 or 4 fibrosis or wound breakdown.

4 | DISCUSSION

Approximately 250 000 women were diagnosed with breast cancer in the year spanning 2017 to 2018, 25% (63 410) of which were DCIS and over two-thirds of which were candidates for BCS and WBI.[20] However, a desire among many patients to avoid a protracted course of WBI combined with a national resurgence of mastectomy has led to a growing call for more reasonable and selective approaches for the management of DCIS in an effort to reduce the treatment burden and morbidity of a condition that is often indolent and rarely life threatening.[21]

There are currently no randomized controlled trials directly comparing mastectomy to breast-conserving therapy for the management of DCIS. Instead, traditional management of DCIS has been largely extrapolated from randomized trials of invasive breast cancer that established equivalence between breast-conserving therapy and mastectomy in terms of local control and overall survival.[21,22] Consequently, the preferred management of localized DCIS has been BCS plus WBI or BCS alone in selected patients.[3]

APBI has emerged as an alternative strategy to WBI that minimizes the duration and extent of breast irradiation following BCS. Several recent DCIS studies of MammoSite balloon catheter-based intracavitary brachytherapy (delivered in 10 fractions) demonstrated LRR of 0 to 3.4% among nearly 600 patients with 9.5 to 60 months median follow-up (level of evidence: III).[23-28] Level Ib evidence regarding the efficacy of APBI will be provided by the anticipated publication of the NSABP B-39/RTOG 0413 randomized controlled trial comparing WBI to APBI (specifically 3D-CRT, intracavitary and interstitial brachytherapy) in the management of invasive breast cancer and DCIS. Over 4200 women were enrolled in the study, one-fourth (1024) of which had pure DCIS. Although NSABP B-39 will provide an important milestone in defining a role for ABPI in the management of DCIS, the omission of IORT from the randomized trial will leave many questions unanswered regarding the efficacy of IORT compared with WBI and other APBI modalities in the management of DCIS.

IORT offers several key advantages over WBI that balance the goal of optimizing local cancer control with the desire to minimize treatment burden. IORT permits breast surgery and radiotherapy to be completed in one session while the patient is still under anesthesia, thereby ensuring radiotherapy compliance and eliminating temporal miss. Focused administration of radiation to the exposed surgical margins eliminates geographical miss while also reducing radiation side effects on the remaining breast, skin, and adjacent organs.[29] Placement of a radiation barrier or beam stopper along the chest wall before IORT enables greater reduction in cardiac and pulmonary morbidity—uncommon but unacceptable treatment consequences of a malignancy that is rarely life threatening. Though generally not required for low energy IORT (eg, Intrabeam), radiation barrier placement is mandatory for high-energy IORT (eg, Novac7 or Mobetron), which is minimally attenuated by natural chest wall structures.[30]

Despite its obvious advantages, a major obstacle to the use of IORT in the management of DCIS is the paucity of direct clinical data demonstrating its efficacy in the treatment of DCIS. Indirect data supporting the use of IORT for DCIS may be derived from the TARGIT-A trial in which 50% of study participants in the TARGIT and WBI treatment arms had invasive breast cancer and coexisting DCIS.[19] Nonetheless, equivalent LRR between TARGIT and WBI treatment arms points to the ability of both radiotherapy strategies to prevent recurrences of the DCIS component. TARGIT-A has also been criticized for relatively short median follow-up of 5 years

TABLE 4 Patients requiring additional surgery and/or WBI for positive margins or recurrent disease

	Age	MG lesion size, mm	MRI lesion size, mm	Pathology size, mm	Receptors	Nuclear grade	Timing of IORT	Initial margins width, mm	Intervention	Findings	Tam/AI	LR	WBI
Patients requiring additional therapy for recurrent disease													
A	58	40	20	29	ER+, PR+	2	Concurrent	5	Lumpectomy	0.7 cm, ER+ (98%), PR+ (80%), HER2/neu negative, sentinel node negative, surgical margins negative (closest 2 mm), high nuclear grade, invasive ductal carcinoma	Yes	Yes	Yes
B	47	10	10	5	ER+, PR−	2	Concurrent	5	Mastectomy	No residual disease; history of mantle radiation	Yes	Yes	No
C	49	30	25-30 next to seroma	12	ER+, PR+	2	Delayed	<1	Mastectomy	3 mm residual DCIS	No	Yes	No
D	67	10	0	45	ER+, PR−	3	Delayed	1-2	Mastectomy (after recurrence)	No residual disease	Yes	Yes	No
Patients meeting criteria for additional therapy (before protocol modifications to permit nontransected margins)													
D	67	10	0	45	ER+, PR−	3	Delayed	1-2	Refused recommended re-excision and WBI	n/a	Yes	Yes	No
E	55	10	0	3	ER+, PR+	2	Concurrent	0.1	Re-excision	No residual disease	No	No	No
F	57	30	0	2.4	ER+, PR+	3	Concurrent	0.5	Re-excision	No residual disease	Yes	No	No
G	55	8	17	15	ER+, PR+	2	Concurrent	0	Re-excision, WBI	No residual disease	Yes	No	Yes
H	48	10	0	25	ER−, PR−	3	Concurrent	<1	Re-excision, mastectomy	3.0 cm at re-excision, 2 cm at mastectomy	No	No	No
I	49	20	30	51	ER+, PR+	2	Concurrent	<1 focal	WBI	Focal DCIS	No	No	Yes

Abbreviations: ER, estrogen receptor; IORT, intraoperative radiotherapy; MG, mammogram; MRI, magnetic resonance imaging; PR, progesterone receptor; Tam/AI, tamoxifen/aromatase inhibitor; WBI, whole breast irradiation.

TABLE 5 Intent to treat patients with invasive cancer on final pathology

Age	MG lesion size, mm	MRI lesion size, mm	Invasive pathology size, mm	Receptors	Nuclear grade	Timing of IORT	Initial margin width, mm	Intervention	DCIS component size, mm	TAM/AI	SNLB	LR	WBI/chemotherapy
55	18	22	6	ER+, PR−, HER2 3+, Ki-67 75%	High	Concurrent	8	Lumpectomy	19	Yes	Yes (−)	No	Yes, chemotherapy
48	17	0	1	ER+, PR−, HER2 3+, Ki-67 60%	Intermediate	Concurrent	10	Lumpectomy	18	Yes	Yes (−)	No	No
40	18	18	12	ER+, PR+, HER2 3+, Ki-67 30%	High	Concurrent	1	Lumpectomy	6	Yes	Yes (−)	No	Yes, chemotherapy
50	10	0	4.5	ER−, PR−, HER2 1+, Ki-67 40%	High	Concurrent	11	Lumpectomy	Not identified	No	No	No	No

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; IORT, intraoperative radiotherapy; MG, mammogram; MRI, magnetic resonance imaging; PR, progesterone receptor; Tam/AI, tamoxifen/aromatase inhibitor; WBI, whole breast irradiation.

compared with over two decades of WBI randomized controlled data. However, this criticism must be examined in light of a preponderance of clinical trial data indicating that the highest risk of recurrence following BCS occurs within the initial 5 years of follow-up. The best example of this is the Oxford overview analysis of 3700 participants in five randomized controlled trials comparing DCIS treated with BCS plus WBI versus BCS alone.[31] Patients receiving WBI had a 7.6% 5-year LRR versus a 12.9% 10-year LRR of either invasive cancer or DCIS. Among those treated with BCS alone, the LRR at 5 years was 18.1% compared with 28.1% at 10 years. Thus, with or without radiotherapy, approximately half of the local recurrences observed over the 10-year period had already been documented by the fifth year of follow-up. When stratified by type of local recurrence at 5 or 10 years, the overview analysis observed that nearly two-thirds of the DCIS recurrences had occurred within 5 years of therapy whether or not radiotherapy was administered (BCS with WBI group: 4.7% 5-year LRR versus 6.5% 10-year LRR) or omitted (BCS alone: 10.5% 5-year versus 14.9% 10-year LRR). Thus, the initial 5 years of follow-up provide valuable insights into the expected trend of local recurrence that is likely to be observed over 10 years.[32]

In the present study, we observed local recurrences in four patients (4 of 52), yielding an LRR of 7.7% at 49 months (range, 4-116) median follow-up of the total cohort. However, when stratified by the timing of radiotherapy, only two of the four recurrences occurred in the concurrent group (2 of 46), yielding a 4.3% LRR at 46 months median follow-up (range, 4-116), which approximates the 3.4% 5-year LRR reported among 194 patients with pure DCIS included in the American Society of Breast Surgeon (ASBrS) MammoSite Registry. The concurrent TARGIT LRR is also similar to the 4% 5-year LRR observed among 240 women treated with multicatheter interstitial APBI in the pooled registry of multicatheter interstitial sites study and as well in the 3.0% 4-year LRR reported in a series of 214 patients treated with X-ray IORT using the Xoft Axxent Electronic Brachytherapy System (Xoft, San Jose, CA).[33,34] The pooled analysis of 300 participants in the William Beaumont Hospital and the ASBrS MammoSite registries demonstrated a 5-year LRR of 2.6%, which is modestly lower than the rate observed herein.[13] However, it is also important to recognize that the TARGIT cohort represented a higher risk population compared with the MammoSite cohort. For example, subjects in the TARGIT study were of younger median age (58 years [TARGIT] vs 62 years [MammoSite]), had larger median DCIS lesions (10 mm [TARGIT] vs 7 mm [MammoSite]), were more frequently estrogen-receptor receptor negative (22.2% [TARGIT] vs 14.3% [MammoSite]) and more often high grade (38.9% [TARGIT] vs 21.6% [MammoSite]).

Two local recurrences were detected among the six patients treated in the delayed TARGIT setting among patients receiving TARGIT 31 and 150 days after their initial lumpectomy. However, at the time these patients were invited to receive TARGIT, it had yet to emerge from the TARGIT-A trial that the delayed or postpathology setting was associated with an increased risk of local recurrence. Upon learning of the risk, we subsequently restricted administration

of TARGIT to patients receiving IORT in the concurrent (prepathology) setting and no longer offered IORT at the postpathology setting. It is hypothesized that treatment in the delayed setting predisposed patients to imprecise targeting of the tumor bed (geographic miss) and promotion of residual tumor growth by wound-healing growth factors generated during the interval between surgery and radiation (temporal miss). However even, more pertinent to the two recurrences observed in the delayed setting in this study is that both occurred in patients with persistent close or positive margins after undergoing TARGIT at the time of re-excision of previously positive margins. Unfortunately, both of the patients declined recommendations for WBI or mastectomy until each presented with a local recurrence within 1 year of TARGIT.

The two patients that experienced local recurrences in the concurrent setting had initial surgical margins of 5 mm or greater. One patient had no recognized predisposing factors for local recurrence whereas the second patient had left breast DCIS a history of mantle irradiation at age 16 for Hodgkin's lymphoma, which increased her lifetime risk of breast cancer and potentially that of a recurrence. The latter patient's history of mantle radiation obviated the use of WBI, and 7 years after undergoing lumpectomy and TARGIT, at the age of 53, she presented with newly diagnosed right breast atypical ductal hyperplasia and recurrent left breast DCIS. She also developed cardiomyopathy, which was attributed to receipt of mantle radiotherapy during her teens.

The challenge of estimating lesion size and achieving complete lesion resection underscore one initial concern in the design of our DCIS-TARGIT treatment protocol, that administration of TARGIT at the time of DCIS resection, before definitive margin assessment, might result in unacceptably high rates of positive margins and excessive cost and morbidity related to margin re-excisions, WBI, or mastectomy. Consequently, the primary aim of the current study was to determine whether or not mammography combined with CE-MRI would allow us to reliably select individuals with DCIS who could undergo BCS and TARGIT with a low risk of requiring re-excision, WBI, or mastectomy for positive margins. An "acceptable" rate was defined as the need for additional procedures in less than equal to 15% of patients, with allowance for protocol modifications if additional procedures were required in 16% to 25% of patients. Over the entire period of enrollment, additional procedures were required in 12 out of 55 patients (21.8%), exceeding the 15% "acceptable" threshold. However, after three patients with initial margins less than equal to 2 mm were found to have no additional disease on re-excision, we reduced the margin width requirement to "nontransection" or "no tumor on ink" and eliminated the requirement for WBI if margin re-excision yielded no residual disease. Utilizing these new criteria, the proportion of patients requiring additional therapy was reduced to 7.3% (4 of 55), well below the 15% threshold. Although a fundamental goal of our protocol design was to minimize the need for additional therapy, including additional radiotherapy, a key advantage of the TARGIT approach is that it permits the extent of radiotherapy to be adapted to the extent of disease such that WBI could be added based on tumor histology, margins, or nodal status without increasing treatment morbidity.[35] Ultimately, 98.2% (54 of 55) of patients were initially successfully treated with breast conserving therapy.

We made no effort in this study to conform to ASTRO APBI consensus guideline, which has yet to embrace the use of IORT in the management of DCIS outside of a clinical trial and which we feel is too restrictive for APBI in general. It is a paradox that the ASTRO guideline requires wider margins for ABPI, which administers a higher effective dose of radiotherapy to the surgical margins than WBI alone. Our DCIS-TARGIT treatment policy inclusion criteria included patients with high-grade DCIS and clinical DCIS lesion size measuring up to 4 cm. Furthermore, we rejected the greater than equal to 3 mm APBI margin requirement and continued to apply a "nontransection" or "no tumor on ink" standard to the resection of DCIS. Despite that, we have been able to achieve a 4.3% LRR with 46 months median follow-up in the concurrent setting while applying the same margin standard that ASTRO has promulgated for invasive breast cancer treated with WBI. The overall event rate was too low to identify a relationship between local recurrence and margin width. Therefore, we continue to apply the "no tumor on ink" principle to the management of these patients.

Although our publication provides the longest median follow-up of any population of DCIS patients treated with IORT, its small sample size and nonrandomized design limit the generalizability of our findings. Nonetheless, this experience makes an important contribution to the body of literature supporting the use of APBI in general, and in IORT in particular, in the selective management of DCIS. Ideally, widespread integration of IORT into the management of DCIS would be preceded by a randomized controlled trial comparing IORT to WBI. However, the overall low recurrence rate reported by recent DCIS ABPI studies makes it unlikely that a randomized trial would be conducted given the large sample size that would be required.

Another factor limiting the generalizability of this study is the fact that all surgical procedures were performed by a single breast surgeon with an established track record of successful BCS and a low baseline reoperation rate for DCIS. This enabled adoption of a relatively low threshold for requiring additional therapy (<15%), well below commonly reported re-excision rates for DCIS. A low re-excision track record should be documented by surgeons interested in performing IORT for DCIS to minimize the need of additional therapy due to positive margins, which would be facilitated by the adoption of less stringent margin criteria.

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