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## Outcomes of selective whole breast irradiation following lumpectomy with intraoperative radiation therapy for hormone receptor positive breast cancer

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### Abstract

**Background:** For low risk breast cancer, the TARGIT-A randomized trial supported lumpectomy with intraoperative radiation therapy (IORT) and selective whole breast radiation (WBXRT). Selection criteria for WBXRT vary.

**Methods:** Women with hormone-receptor positive, clinically node-negative breast cancer were categorized retrospectively as suitable for IORT alone or also needing WBXRT by TARGIT-A or expanded TARGIT criteria (TARGIT-MCC). We evaluated local recurrence (LR) by selection criteria and receipt of WBXRT.

**Results:** Among 194 cases followed a median of 44 months, 54 (27.8%) met TARGIT-MCC criteria for WBXRT (34 met TARGIT-A criteria). Thirty patients were recommended and 21 (10.8%) received WBXRT. Of 13 patients with LR, none received WBXRT. LR was 10.5% in patients meeting TARGIT-MCC criteria who did not receive WBXRT versus 0% after WBXRT ( $p = 0.299$ ).

**Conclusions:** Selective WBXRT may have mitigated LR. Nearly all LR were in patients not recommended WBXRT. Further work should refine criteria for WBXRT after IORT.

**Summary:** Prior work among women with early breast cancer supported lumpectomy with intraoperative radiation therapy and selective adjuvant radiation using a risk-adapted approach. An expanded set of criteria for adjuvant radiation appear to further mitigate local recurrence risk. Local recurrence after lumpectomy with IORT could be further minimized by identification of additional high-risk features, as well as greater adherence to adjuvant endocrine therapy.

### Introduction

For early breast cancer, lumpectomy with adjuvant whole breast radiation therapy (WBXRT) is standard of care, offering equivalent outcomes to mastectomy.<sup>1</sup> The burden of completing adjuvant radiation therapy, which is typically performed five days per week over a three to

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Appendix A. Supplementary data

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seven-week period, can deter some patients from selecting a breast conserving strategy.<sup>2</sup> Given that the majority of local recurrences occur in the same quadrant as the primary breast cancer, some have advocated for a more targeted approach to radiotherapy.<sup>3,4</sup>

Intraoperative radiation therapy (IORT), a type of accelerated partial breast irradiation, was developed as an alternative to whole breast radiation therapy (WBXRT). With IORT, the entirety of adjuvant radiation therapy is delivered to the tumor bed in the operating room immediately following lumpectomy, mitigating a lengthy and potentially morbid series of daily radiation treatments after surgery in most cases. A potential disadvantage of IORT is that radiation is delivered prior to final pathologic assessment of the tumor, and in certain cases might be insufficient if high risk features are present that were not appreciated on preoperative evaluation.

The TARGIT-A trial was an international, multicenter, randomized controlled trial comparing IORT to standard whole breast radiation in women  $\geq 45$  years with clinically node-negative, invasive ductal carcinoma that was suitable for breast conservation surgery. It used a risk-adapted approach, in which patients who were randomized to IORT also received whole breast radiation in select cases if final pathology demonstrated pre-specified high-risk features.<sup>5</sup> Using this approach, 14% of patients in the IORT arm received adjuvant whole breast radiation while the majority (86%) received IORT as their only radiation treatment. The study demonstrated that using a risk-adapted approach, lumpectomy with IORT and selective WBXRT was not inferior to standard lumpectomy with whole breast radiation in terms of local recurrence or overall survival.<sup>6</sup>

The TARGIT-A protocol pre-specified four pathologic features for which whole breast radiation would be recommended in the IORT group: unexpected invasive lobular carcinoma, extensive intraductal component (defined as  $\geq 25\%$ ), positive margins at the first excision, and final margin  $< 1$  mm.<sup>5</sup> Latitude was given to participating centers to develop additional criteria for which they would recommend whole breast radiation. When our institution, Moffitt Cancer Center, initiated IORT with selective whole breast radiation, we adopted the TARGIT-A selection criteria in addition to other institutional factors that were believed by our multidisciplinary team to portend higher local recurrence risk. Given ongoing ambiguity regarding which patients should receive WBXRT after lumpectomy with IORT, we sought to compare local recurrence rates based on suitability for IORT alone versus those meeting TARGIT-A or institutional TARGIT criteria at Moffitt Cancer Center (TARGIT-MCC) for addition of whole breast radiation.

## Methods

We performed a retrospective cohort study of outcomes for lumpectomy plus IORT with selective adjuvant whole breast radiation performed at Moffitt Cancer Center from January 1, 2011 through December 31, 2015. The cohort included adult women with hormone-receptor positive, clinically node negative breast cancer for which breast conservation surgery was technically feasible. Included histologies based on biopsy were invasive ductal carcinoma (including mucinous and papillary), invasive mammary, ductal carcinoma in situ, and mixed types. Patients with invasive lobular carcinoma on diagnostic biopsy were

excluded. Women with prior cancer and/or irradiation of the involved breast were also excluded, as were those with clinically apparent multicentric disease.

Lumpectomy and IORT were performed according to the procedures described in the TARGIT-A trial.<sup>5</sup> Briefly, 20 Gy was delivered to the tumor bed surface using a spherical applicator. The radiation attenuates to 5–7 Gy at a depth of 1 cm beyond the applicator surface. Prior to IORT, margins were evaluated using gross assessment and re-excised per the surgeon's discretion. For select patients, whole breast radiation therapy was delivered in the adjuvant setting per institutional protocol, typically 40–50 Gy with IORT serving as the boost to the tumor bed.<sup>5</sup>

Participants were categorized retrospectively based on final clinicopathologic criteria as suitable for IORT alone or meeting criteria for additional whole breast radiation by either TARGIT-A or TARGIT-MCC criteria (Table 1). TARGIT-A criteria for selective WBXRT included invasive lobular carcinoma on final pathology, extensive intraductal component (>25%), positive margin at the first excision (regardless of whether re-excised post-IORT), and final margin <1 mm. In addition to the TARGIT-A criteria, our institution defined additional factors for which WBXRT was recommended (TARGIT-MCC criteria): tumor size >3 cm, positive lymph node(s), presence of lymphovascular space invasion, final margin <2 mm, or presence of tumor in re-excision specimen, if performed. For cases in 2011–2013, cases with tumor in the re-excision specimen with re-excised margin >2 mm were not recommended WBXRT. In practice, deviations from these selection criteria were made on an individual case basis by our multidisciplinary tumor board recommendations; hence, some patients who met TARGIT-MCC criteria were not recommended whole breast radiation, while additional patients were recommended WBXRT who did not meet TARGIT-A or TARGIT-MCC criteria.

Local recurrence was defined as second breast cancer in the previously treated ipsilateral breast. Patients with concurrent local and distant recurrence were included as local recurrences. We also documented contralateral breast cancer, distant recurrences, and vital status at last follow-up for the study cohort. Local recurrence was compared based on whether patients met criteria for whole breast radiation, had recommendation for WBXRT, and received WBXRT. Additional clinical factors were evaluated for their association with local recurrence, including receipt of adjuvant endocrine therapy.

Patient characteristics were summarized using descriptive statistics including mean, standard deviation, and median for continuous measures and proportions and frequencies for categorical measures. The associations between continuous variables, receipt of whole breast radiation, and local recurrence were assessed using Wilcoxon rank sum tests. Fisher's exact tests were used for categorical variables. The study was approved by the Institutional Review Board of the University of South Florida.

## Results

There were 194 cases of lumpectomy with IORT performed in 192 patients. Two patients had bilateral breast cancer with treatment of each breast considered separately. Details of the

study cohort are listed in Table 2. All cases were completed successfully. Final pathology demonstrated invasive ductal carcinoma (179, 92.3%), invasive lobular carcinoma (3, 1.5%), DCIS (3, 1.5%) and other invasive mammary histologies (9, 4.6%). Five percent were multifocal. Twelve patients (6.3%) had a positive sentinel lymph node biopsy and 12 (6.3%) demonstrated lymphovascular space invasion. Thirty-one patients (16.0%) returned to the operating room for re-excision of at least one margin after final pathology demonstrated at least one close or involved margin.

Based on final pathologic assessment, 34 patients (17.5%) met at least one of the criteria established in TARGIT-A for adjuvant whole breast radiation therapy. An additional 20 (10.3%) met at least one of the additional criteria established by Moffitt Cancer Center (TARGIT-MCC) for whole breast radiation. Thus 54/194 (27.8%) of the total cohort met our institutional criteria for whole breast radiation. WBXRT was recommended in 30 cases, 24 of whom met TARGIT-MCC criteria and 6 for reasons outside established criteria (reasons provided were multifocal disease (2), lack of hormone receptor expression on final pathology (2), age <65 years (1), and margin re-excision outside standard criteria for close/involved margin (1)).

There were 30 patients who met criteria for adjuvant whole breast radiation therapy but for whom it was not recommended. In the majority of cases, the criteria for WBXRT were an initial positive margin or close final margin, for which some providers' recommendations deviated from the protocol. In half of the cases in which margin management resulted in WBXRT not being recommended, the patient had undergone a re-excision that contained no tumor or what was felt by the treating providers to be an adequate margin. Despite the institutional protocol recommending WBXRT in these cases, providers elected not to recommend WBXRT.

Twenty-one (10.8%) patients received whole breast radiation. All patients received a recommendation for adjuvant endocrine therapy, but 41 patients (21.1%) declined. Among patients with at least five years of follow-up data (N = 67), 54 (80.6%) received some endocrine therapy and 41 (61.2%) completed at least five years of endocrine therapy.

At a median follow-up of 44.3 (range 0.49–91.2) months, thirteen patients (6.7%) had a local recurrence. Of these, 11 patients had local recurrence only. One patient had concurrent local and distant recurrences. Another had concurrent local recurrence and a new diagnosis of contralateral breast cancer. In addition to these thirteen patients, another 4 had contralateral breast cancer and 2 had distant metastases during the follow-up period.

Patients with local recurrence had older mean age (73.9 versus 69.7 years,  $p = 0.039$ ) and longer follow-up (63.1 versus 44.6 months,  $p = 0.010$ ) (Table 3). No pathologic features (histologic type or grade, tumor size, nodal status, lymphovascular invasion, extensive intraductal component) were associated with local recurrence. An initial positive or close margin (within 1 mm or 2 mm) prior to IORT was not associated with local recurrence (Table 3). Among patients with local recurrence, all had estrogen receptor positivity 80%.

Of the 13 patients who recurred locally, four met TARGIT-MCC criteria but were not recommended radiation. One was in a patient who was recommended WBXRT though she

did not meet TARGIT-MCC criteria, but who declined. The other eight patients who recurred locally did not meet criteria for and were not recommended adjuvant whole breast radiation (Table 4). In patients who met criteria for whole breast radiation but did not receive it, local recurrence occurred in 10.8% (4/38) versus 0% (0/17) who met criteria and did receive it ( $p = 0.299$ ). Receipt of whole breast radiation was not significantly associated with local recurrence (0% (0/21) with WBXRT versus 7.5% (13/173) without WBXRT,  $p = 0.368$ ). The sole factor that was significantly associated with decreased likelihood of local recurrence was receipt of adjuvant endocrine therapy (3.9% (6/153) with endocrine therapy versus 17.1% (7/41) without endocrine therapy,  $p = 0.007$ ).

In a secondary analysis, 30 patients who met TARGIT-MCC criteria (inclusive of TARGIT-A criteria) but were not recommended WBXRT were excluded because their care deviated from the pre-established protocol. In this “per protocol” analysis of 164 patients, 17 met at least one TARGIT-A criteria for WBXRT and an additional 7 met TARGIT-MCC criteria. Of those who met criteria and were recommended whole breast radiation, 66.7% received it, while the remainder declined. The rate of local recurrence was 5.5% (9/164), with all recurrences occurring in patients who did not meet selection criteria for addition of whole breast radiation and did not receive it. Again, the association between whole breast radiation and local recurrence did not achieve significance (0% with radiation, 6.3% without radiation,  $p = 0.250$ ).

Receipt of adjuvant endocrine therapy remained protective against local recurrence in the per-protocol analysis (2.3% (3/129) with endocrine therapy versus 17.1% (6/35) without endocrine therapy,  $p = 0.001$ ). However, among those patients who met criteria for whole breast radiation but did not receive it ( $N = 30$ ), adherence to endocrine therapy was better (80%, 6/24), but did not appear to mitigate local recurrence (12.5% (3/21) with endocrine therapy versus 16.7% (1/5) without endocrine therapy,  $p = 0.788$ ).

## Discussion

In this cohort of women with hormone receptor positive early breast cancer managed by lumpectomy with IORT and selective whole breast radiation using the expanded TARGIT-MCC criteria, the majority of local recurrences were in patients who did not meet criteria for selective whole breast radiation. Among those meeting criteria, there appeared to be a clinically important difference in local recurrence based on receipt of adjuvant whole breast radiation therapy, though statistical significance was not achieved. This suggests that more uniform application of expanded criteria for selective whole breast radiation could decrease local recurrence rates after lumpectomy with IORT; however, these additional criteria capture the minority of high-risk patients, with most local recurrences happening in patients who are not currently identified as being at high risk of local failure. As such, further work is needed to understand which additional factors predict local recurrence to refine current management of patients undergoing lumpectomy with IORT.

In this study with median follow-up of 44 months, the local recurrence rate was 6.7%. This is on par with historic local recurrence rates after breast-conserving surgery with lumpectomy and adjuvant whole breast radiation. In the original randomized controlled trial

that established the equivalence of breast conservation surgery to total mastectomy with respect to disease-free, distant disease-free, and overall survival, local recurrence at 5 years was 7.7% with lumpectomy and radiation versus 27.9% with segmental mastectomy and no radiation.<sup>7</sup>

At the same time, the rate of local recurrence in this study was somewhat higher than other more contemporary studies evaluating IORT with selective whole breast radiation. In TARGIT-A, the landmark randomized study comparing lumpectomy with IORT and selective WBXRT to standard lumpectomy with WBXRT, the local recurrence rate at five years was 2.1% in the group of patients that received IORT prior to final pathology, as in our study cohort.<sup>6</sup> The ELIOT trial randomized women with early breast cancer to electron intraoperative radiotherapy with selective WBXRT if four or more involved axillary lymph nodes were present. Compared to conventional lumpectomy and WBXRT, the local recurrence rate was 4.4% in the experimental arm (versus 0.4% in the control arm).<sup>8</sup>

In this study, there were no local recurrences among patients who met criteria for WBXRT and received it, while 4 local recurrences occurred in patients who met criteria but did not receive it. This suggests that a risk-adapted strategy, potentially including our additional selection criteria, mitigates risk of local recurrence. Unfortunately, there was significant variation in application of the pre-specified selection criteria in the study population, and lack of adherence to the expanded criteria for WBXRT may have contributed to the higher observed local recurrence rate. Specifically, while nearly 30% of women in this study met pre-specified expanded criteria for selective WBXRT after IORT, only 47% of these women were recommended WBXRT and 35% received WBXRT. This amounted to selective WBXRT being performed in 10% of cases managed with lumpectomy and IORT. While this rate of selective WBXRT is comparable to that of the TARGIT-A trial, in which 15% received selective WBXRT, the broader TARGIT-MCC criteria, if applied uniformly, should have resulted in a higher proportion of patients receiving WBXRT and might have reduced the rate of local recurrence.

Further, the majority of patients with local recurrence in this study did not meet either TARGIT-A or TARGIT-MCC criteria for selective whole breast radiation. This suggests that additional factors contribute to risk of local recurrence after lumpectomy with WBXRT. Other studies have examined alternate criteria for WBXRT, including patient age, tumor size 2–3 cm, histologic grade, and lack of estrogen receptor expression. While inclusion of any one of these criteria would result in a much larger patient population being recommended WBXRT, these could also be used in a more refined fashion by which the presence of a pre-designated number of high risk features could prompt a recommendation for WBXRT.<sup>9</sup>

Beyond clinical and pathologic factors that are currently measured on a routine basis, other unmeasured factors might be useful in selecting high risk patients for WBXRT after IORT. For example, molecular subtype has been found to impact risk of locoregional recurrence.<sup>10,11</sup> A minority of patients in this study underwent molecular tumor analysis, so we are unable to compare local recurrence rates between molecular subtypes, or by risk categories or scores on available gene assays. This could potentially be used to refine criteria for selective WBXRT after IORT in the future.



The sole factor that was statistically associated with local recurrence in this population was receipt of adjuvant endocrine therapy. The NSABP B-14 randomized trial established the benefit of adjuvant endocrine therapy in prolonging disease-free survival among patients with estrogen-receptor positive, node negative breast cancer.<sup>12</sup> NSABP B-21 subsequently established that for patients with hormone-receptor positive tumors <1 cm like the average patient in the present study, the combination of adjuvant radiation and endocrine therapy provided the greatest reduction in in-breast tumor recurrence. When only one adjuvant modality was used, radiation therapy alone was more effective in reducing local recurrence risk than endocrine therapy alone.<sup>13</sup> In the present study, 21% of patients declined endocrine therapy, and in those who recurred locally, significantly more women (54% versus 19%) received no adjuvant endocrine therapy. Interestingly, in patients who met criteria for adjuvant whole breast radiation but for whom it was not recommended, receipt of adjuvant endocrine therapy did not decrease local recurrence rate. This reinforces the importance of additional local treatment (i.e. radiation) for patients at high risk of local failure.

A strength of this study is the follow-up duration of more than 7 years for some patients, with a median follow-up of almost four years. Lengthy follow-up is needed to detect recurrences of localized breast cancer, as evidenced by the fact that follow-up was longer in those patients with documented recurrence in this cohort. Limitations of this study include its single-institution, retrospective nature. There was variable adherence to the pre-established criteria for selective WBXRT after IORT, which could result in selection bias. Further, though there was a marked difference in LR for those patients meeting TARGIT-MCC criteria who actually received adjuvant WBXRT, the low overall event rate and relatively small sample size limited statistical power to confirm a true difference.

## Conclusions

This retrospective cohort of women with hormone receptor positive breast cancer confirmed the therapeutic value of lumpectomy and intraoperative radiation therapy, which can eliminate the burden of adjuvant radiation therapy in most patients. Compared to the foundational TARGIT-A criteria for selective whole breast radiation in this population, expanded selection criteria may further mitigate local recurrence risk. As the majority of recurrences were in patients who did not meet either TARGIT-A or TARGIT-MCC pre-established criteria and recognizing the important role of endocrine therapy, further work is needed to understand which additional factors predict local recurrence and to improve adherence to adjuvant endocrine therapy. This could enable refinement of existing criteria for selective whole breast radiation and improve local control in women who elect intraoperative radiation therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1** Selection criteria for whole breast radiation therapy after lumpectomy with intraoperative radiation therapy per TARGIT-A and TARGIT-MCC protocols.

Characteristic	TARGIT-A	TARGIT-MCC
Initial margin	Initial margin positive (regardless of re-excision)	Initial margin positive (regardless of re-excision)
Final margin *	<1 mm (regardless of re-excision)	≤2 mm (or presence of tumor in re-excision specimen)
Final histology	Invasive lobular carcinoma	Invasive lobular carcinoma
Extensive intraductal component *	If present	If present
Lymphovascular space invasion	Per institution	If present
Positive sentinel lymph node	Per institution	If present
Tumor Size	Not specified <sup>d</sup>	>3 cm

\* Including re-excised margin, if performed.

\* Greater than or equal to 25% intraductal component on final pathology.

<sup>d</sup>TARGIT-A protocol excluded women with tumors >3.5 cm.

**Table 2**

Study cohort. IQR=Interquartile range (25–75th percentile range).

<b>Patient Characteristics</b>	<b>N=192</b>
Age, mean $\pm$ SD	70.0 $\pm$ 7.6
Body mass index, mean $\pm$ SD	29.0 $\pm$ 5.6
Smoking status, N (%)	
Current	12 (6.2)
Former	65 (33.9)
Non-smoker	109 (56.8)
Unknown	6 (3.1)
Diabetes, N (%)	
Yes	29 (15.1)
No	159 (82.8)
Unknown	4 (2.1)
<b>Tumor Characteristics</b>	<b>N=194</b>
Biopsy histologic type, N (%)	
Invasive ductal	185 (95.4)
Invasive mammary	5 (2.6)
Invasive mucinous	2 (1.0)
DCIS	1 (0.5)
Papillary carcinoma	1 (0.5)
Biology histologic grade, N (%)	
1	85 (43.8)
2	94 (48.5)
3	15 (7.7)
Hormone receptor status, N (%)	
Estrogen receptor	194 (100.0)
Progesterone receptor	176 (90.7)
Degree of hormone receptor expression (%), median (IQR)	
Estrogen receptor	99 (95–100)
Progesterone receptor	88 (46–95)
Her2_neu (by IHC), N (%)	
0+	74 (38.1)
1+	94 (48.5)
2+	24 (12.4)
3+	2 (1.0)

Table 3

Association of final clinicopathologic features with local recurrence.

Final Clinical and Pathologic Features	Local Recurrence N = 13	No Local Recurrence N = 181	P-Value
Age, mean ± SD	73.9 ± 5.5	69.7 ± 7.6	0.039
Tumor size (cm), mean ± SD	0.99 ± 0.54	1.04 ± 0.58	0.684
Follow-up time (months), mean ± SD	63.1 ± 23.3	44.6 ± 23.4	0.010
Histologic type			0.206
Invasive ductal	12 (6.7)	167 (93.3)	
DCIS	0 (0)	3 (100)	
Invasive lobular	0 (0)	3 (100)	
Invasive mammary	0 (0)	3 (100)	
Invasive mucinous	0 (0)	5 (100)	
Papillary carcinoma	1 (100)	0 (0)	
Histologic grade			0.103
1	3 (3.9)	74 (96.1)	
2	7 (7.4)	88 (92.6)	
3	3 (18.8)	13 (81.3)	
Nodal stage			1.000
N0	13 (7.3)	166 (92.7)	
N1	0 (0)	12 (100)	
Lymphovascular space invasion			0.191
Absent	11 (6.1)	168 (93.9)	
Present	2 (16.7)	10 (83.3)	
Extensive intraductal component <sup>a</sup>			1.000
No	13 (6.8)	178 (93.2)	
Yes	0 (0)	3 (100)	
Tumor size >3 cm			1.000
No	13 (6.8)	178 (93.2)	
Yes	0 (0)	3 (100)	
Initial positive margin			1.000
No	12 (6.7)	167 (93.3)	

Final Clinical and Pathologic Features	Local Recurrence N = 13	No Local Recurrence N = 181	P-Value
Yes	1 (6.7)	14 (93.3)	1.000
Margin <1 mm <sup>b</sup>			
No	12 (6.7)	167 (93.3)	
Yes	1 (6.7)	14 (93.3)	
Margin <2 mm			
No	12 (6.9)	161 (93.1)	1.000
Yes	1 (4.8)	20 (95.2)	

<sup>a</sup> Greater than or equal to 25% DCIS.

<sup>b</sup> Includes positive margin.

Local recurrence based on current criteria for addition of whole breast radiation therapy after lumpectomy with intraoperative radiation therapy.

**Table 4**

<b>Study Cohort</b>	<b>No Local Recurrence N = 181</b>	<b>Local Recurrence N = 13</b>
Suitable for IORT alone (n = 140)		
No recommendation for WBXRT	126	8
WBXRT recommended but not completed	1	1
WBXRT completed	4	0
Met criteria for WBXRT (n = 54)*		
TARGET-A	32	2
TARGET-MCC	18	2
<b>*Patients meeting criteria for WBXRT (n = 54) No Local Recurrence N = 50 Local Recurrence N = 4</b>		
Met criteria and WBXRT recommended (n = 24)		
TARGET-A	17	0
TARGET-MCC	7	0
Met criteria and WBXRT not recommended (n = 30)		
TARGET-A	15	2
TARGET-MCC	11	2
Met criteria and WBXRT received (n = 17)		
TARGET-A	13	0
TARGET-MCC	4	0

IORT=Intraoperative radiation therapy; WBXRT = whole breast radiation therapy; TARGET-A = criteria for selective whole breast radiation therapy in TARGET-A trial; TARGET-MCC = extended criteria for selective whole breast radiation therapy in current study, inclusive of all TARGET-A criteria.