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Intraoperative radiation therapy in early-stage breast cancer: Presence of lobular features is not associated with increased rate of requiring additional therapy

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ABSTRACT

Background: There is a paucity of data regarding the application of IORT to the treatment of carcinomas with lobular features.
Methods: This study includes women with invasive breast cancer who underwent breast conservation in combination with IORT from February 2011 to October 2016. Patients whose final pathology did not satisfy inclusion criteria or had inadequate margins were recommended to undergo additional therapy (AT) with WBRT as well as re-excision of inadequate margins.
Results: 243 invasive breast cancers were treated with IORT. The lobular features (LF) group comprised 62 patients and the invasive ductal carcinoma (IDCA) group consisted of 172 patients. Rate of AT was similar between groups (LF 19 patients, 30.6%, vs IDCA 56 patients, 32.6%, $p = 0.87$) groups. Lobular histology was not associated with a need for AT. Local recurrence rate for the cohort was 1.2% with a median follow up of 46 months. There was no difference in recurrence or survival after 46 months of follow-up.
Conclusions: IORT is an effective treatment option for well-selected patients with early breast cancer and can be considered for patients with lobular histology.

Background

Breast conserving therapy (BCT) is a standard treatment option for patients with early-stage breast cancer with similar overall and disease-free survival compared to mastectomy.[1–3] BCT comprises partial mastectomy and axillary staging followed by adjuvant whole breast radiation therapy (WBRT) and systemic therapy. BCT offers many advantages over mastectomy including positive effects on physical appearance and emotional well-being.[4] The advent of oncoplastic BCT has further improved oncologic outcomes while offering optimal aesthetic results by implementing plastic surgery techniques in the resection of breast cancer.[5–7]

The addition of adjuvant radiation therapy to partial mastectomy with adequate surgical margins has reduced the rate of local recurrence to 3.5–6.5% at 10 years, with most recurrences presenting between 2 and 3 years after initial cancer diagnosis.[8] Consequently, radiation therapy is considered an integral component of BCT.[9] The majority of local disease recurrences have been found to be of the same histologic type and in close proximity to the initial cancer, suggesting that local recurrence is a failure of local control.[10,11] This finding provided the basis for directly targeting radiation therapy to the tumor cavity.[11] Intraoperative radiation therapy (IORT) delivers a single dose of radiation therapy directly into the tumor bed at the time of partial mastectomy, minimizing radiation exposure to surrounding structures, including the heart and lungs.[12]

The TARGIT-A trial reported similar rates of local recurrence and breast-cancer related mortality when they compared IORT delivered at the time of initial partial mastectomy to adjuvant WBRT in the treatment of early stage breast cancer.[11] This study found that breast cancer recurrence is lowest when IORT is performed at the time of the index operation; therefore selection of appropriate patients for IORT is critical. Identifying ideal candidates for IORT is a challenge since the true extent of disease and presence of higher

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risk factors such as lymphovascular invasion can only be confirmed on final pathology which is not available until several days after surgery. There has been growing interest in refining selection criteria for IORT to maximize outcomes.[12,13] Although some recent studies have started to include some lobular carcinomas, IORT has not been well-studied in invasive carcinomas with lobular features (LF) due to the insidious and diffuse nature of this histology.[12,13]

Methods

This prospective cohort study includes women with invasive breast cancer treated with oncoplastic breast conserving surgery and IORT from 2011 to 2016 at Virginia Mason Medical Center in Seattle, Washington. The study was approved by the institutional review committee and met the guidelines of the responsible governmental agency. All study data were gathered from a prospective institutional database. All patients diagnosed with invasive breast cancer underwent standard preoperative workup under Virginia Mason Breast Center protocol including mammography, ultrasound, and breast MRI unless contraindicated or not tolerated. Patients with unifocal tumors $\leq$3 cm on imaging, no evidence of nodal disease, and absence of lymphovascular invasion on core needle biopsy were offered IORT at the time of oncoplastic partial mastectomy and were offered symmetry procedures for the contralateral side. Oncoplastic partial mastectomy techniques included radial ellipse tissue transfer, wise pattern reduction mammoplasty, mastopexy, and racquet mammoplasty.

Margins were evaluated with intraoperative specimen radiograph by the operating surgeon as well as with gross evaluation and sectioning with additional specimen radiographs by the on-call pathologist. Nodal evaluation comprised gross evaluation and frozen section performed intraoperatively by the on-call pathologist. During the pathologic evaluation of the breast and axillary specimens, the tumor cavity was prepared to accommodate the radiation-delivery applicator of the Xoft Axxent Electronic Brachytherapy System. The balloon was inflated with saline (30–75 cc) and a series of sutures was placed to conform tumor bed tissue to applicator surface to ensure accurate delivery of the prescribed 20 Gy radiation dose. Ultrasound was used to confirm presence of at least 7 mm between the balloon and skin surface to minimize skin toxicity. IORT was delivered over 15–45 min directly into the tumor bed once margins and nodes were determined to be negative by intraoperative evaluation.

Patients with final pathology showing unifocal cancer, negative sentinel nodes, margins $\geq$2 mm and no evidence of lymphovascular invasion, were treated with IORT only. Those who did not meet all inclusion criteria were counseled to undergo additional therapy (AT) including an additional 50 Gy dose of whole breast radiation without boost. Sentinel nodes were sent for frozen section evaluation intraoperatively; if carcinoma was found, IORT was not delivered and whole breast radiation was recommended. Patients with inadequate margins were recommended to undergo re-excision or mastectomy followed by WBRT. Systemic therapy was administered at the treating clinician's discretion per standard of care. All patients were seen in post-operative follow-up within two weeks of their operation, then at 1, 3, 6, 9, 12 months and then biannually for the first 5 years and then annually thereafter along with annual screening imaging.

Rates of recommendation for AT, recurrence, and survival were compared between patients with LF and patients with IDCA. Continuous variables were compared using t-tests and categorical data were compared using Fisher's exact tests. Multivariable-adjusted odds ratios were estimated with logistic regression. P-values of <0.05 were considered statistically significant.

Results

A total of 234 patients were treated with IORT. Of those, 159 (67.9%) patients met the criteria for single-dose IORT and 75 (32.1%) patients were recommended to undergo AT (Table 1). The LF group comprised 62 (26.5%) patients including 13 (5.6%) with pure invasive lobular carcinoma. The other 49 patients had mixed carcinoma with ductal and lobular features. The IDCA group consisted of 172 patients.

There was no difference in patient age (LF 63.6 ± 8.9 years *vs* IDCA 63.3 ± 8.6 years, p = 0.35). Patients with LF had larger tumor sizes on both mammogram and ultrasound (1.55 ± 0.63 cm vs 1.24 ± 0.63 cm, p < 0.001 and 1.55 ± 0.64 cm vs 1.21 ± 0.63 cm, p < 0.001, respectively) but similar tumor sizes on MRI (1.54 ± 0.63 cm vs 1.53 ± 0.69 cm, p = 0.99). Tumor sizes, receptor profiles, and nodal status on final pathology were similar between groups.

Rate of recommendation for AT was similar between groups (LF 19 patients, 30.6% vs IDCA 56 patients, 32.6%, p = 0.87) (Table 2). The indications for AT were similar with inadequate margins comprising the most common single indication. Rates of inadequate margins were also similar between groups (LF 11 patients, 17.7% vs IDCA 31 patients, 18.0%, p > 0.99) (Table 2). Forty (95.2%) of the 42 patients with inadequate margins obtained clear margins with re-excision. The mastectomy rate for cohort was low, 0.9%, with 1 patient in each group electing mastectomy to achieve adequate margins (Table 3). Rates of receipt of AT and endocrine therapy were similar between groups.

Lobular histology, tumor size on imaging, tumor grade, and receptor status were not associated with need for AT on both univariate and multivariate analyses. After 46 months of follow-up, there were 3 (1.3%) local recurrences, all in the IDCA group treated with IORT alone. All three recurrences were in patients with estrogen receptor (ER)/progesterone receptor (PR) positive Her2 negative tumors. Two of these 3 patients had high risk features on final pathology and met institutional criteria for AT but declined it. Both of them had inadequate margins and one of them had an additional indication with the finding of multifocality. The local recurrence rate for patients treated with IORT alone was 1.9%. There

Table 1
Clinicopathologic features of patients treated with oncoplastic breast conserving surgery and IORT.

	LF (n = 62)	IDCA (n = 172)	p-value
Patient Characteristics			
Age, years	63.6 ± 8.9	63.3 ± 8.6	0.35
BMI, kg/m^2	28.8 ± 7.3	28.6 ± 6.9	0.83
Smoking history, n	22 (35.4%)	67 (39.0%)	0.65
Tumor Characteristics			
Imaging size, cm			
Largest on any imaging	1.55 ± 0.64	1.54 ± 0.69	0.72
MRI*	1.54 ± 0.63	1.53 ± 0.69	0.99
Mammogram	1.55 ± 0.63	1.24 ± 0.63	<0.001
Ultrasound	1.55 ± 0.64	1.21 ± 0.63	<0.001
Final pathology size, cm	1.52 ± 1.06	1.36 ± 0.77	0.15
Grade, n			
Grade 1	9 (14.5%)	68 (39.5%)	<0.001
Grade 2	48 (77.4%)	62 (36.0%)	
Grade 3	5 (8.1%)	42 (24.4%)	
Receptor Status, n			
ER positive	61 (98.4%)	158 (91.9%)	0.13
PR positive	55 (88.7%)	142 (82.6%)	0.31
Her2 positive	2 (3.2%)	10 (5.8%)	0.73
Triple negative	1 (1.6%)	9 (5.2%)	0.46
Nodal Status			
Positive	2 (3.2%)	12 (7.0%)	0.36
Negative	60 (96.8%)	160 (93.0%)	

Table 2
Reasons for needing AT.

Reason for needing AT	LH (n = 62)	IDCA (n = 172)	p-value
Multiple[a]	6 (9.7%)	11 (6.4%)	0.40
Margins	5 (8.1%)	20 (11.6%)	0.63
Multifocal	2 (3.2%)	8 (4.7%)	>0.99
Positive lymph nodes	2 (3.2%)	12 (7.0%)	0.36
Size >3 cm	3 (4.8%)	4 (2.3%)	0.39
Lymphovascular invasion	1 (1.6%)	1 (0.6%)	0.46
Total	19 (30.6%)	56 (32.6%)	0.87

[a] All patients with "multiple" reasons for needing AT had inadequate margins in addition to one or more additional indications.

Table 3
Adjuvant therapy use and recurrence rates in patients treated with IORT.

Outcome	LH (n = 62)	IDCA (n = 172)	p-value
Recommendation for AT, n	19 (30.6%)	56 (32.6%)	0.87
Inadequate margins, n	11 (17.7%)	31 (18.0%)	>0.99
Received AT, n	12 (19.4%)	42 (24.4%)	0.48
Received Endocrine Therapy, n	47 (75.8%)	146 (84.9%)	0.12
Mastectomy, n	1 (1.6%)	1 (0.6%)	0.46
Locoregional recurrence, n	0	3 (1.7%)	0.56
Distant recurrence, n	0	0	>0.99
Survival, n	62 (100%)	171 (99.4%)	>0.99

were no distant recurrences. One (0.4%) patient in the IDCA group died of an unrelated cancer.

Discussion

Intraoperative radiation therapy offers an effective form of radiation therapy for the treatment of early stage breast cancer. In our study, at a median follow up of 46 months, the local disease recurrence rate was 1.3% for the overall study cohort and 1.9% for patients treated with IORT alone, similar to rates reported in the TARGIT-A study and by Silverstein et al. in their 1000 patient series.[11,12]

The majority of tumors in this trial were biologically favorable with 90% of them ER positive and 81% PR positive. Only 5% were Her2 positive and 4% were triple negative. Silverstein et al. showed local recurrence rates were lower in luminal A tumors compared to those in non-luminal A tumors and suggested that biologic subtyping may help to refine criteria for patient selection for IORT. Although our overall numbers are small, all 3 of the local recurrences we observed were in patients with ER positive tumors and none of them had lobular histology. None of the patients with Her2 of triple negative tumors had local recurrences suggesting that these receptor profiles should not be an absolute contraindication to IORT in the setting of other favorable features.

Additionally, 2 of the 3 recurrences we observed were in patients that were recommended to undergo AT. No patients who completed WBRT based on findings on final pathology experienced local recurrence. This finding parallels findings by Broman et al. and supports their argument that the risk-adapted strategy in IORT studies may help to mitigate the risk of local recurrence from pathologic factors that are not known prior to IORT administration.[13] Additionally, they found that the only factor associated with decreased rate of local recurrence was receipt of endocrine therapy which underscores the importance of adherence to adjuvant systemic therapy recommendations.[13]

Overall, 67.9% of patients completed all of their local treatment in a single surgical procedure. The other 32.1% of patients met institutional criteria for WBRT, a rate similar to that found in other recent large institutional series.[12,13] Like Silverstein et al. and Broman et al., we found variable rates of patient adherence to WBRT recommendations. In combination, these findings highlight the importance of ongoing work to improve our ability to identify appropriate patients for IORT preoperatively.

Despite some of the challenges with preoperative identification of appropriate candidates for IORT, the majority of patients in the study were able to complete their radiation therapy with single-dose IORT. Some of the observed advantages to single-dose IORT include lower incidence of grade 3 and grade 4 radiotherapy-related toxicity as well as a reduced rate of non-breast cancer death in the IORT group.[11] Subsequent studies have also demonstrated advantages such as improved cosmesis, skin toxicity, and improved quality of life.[14–16] Additionally, radiation therapy at the time of partial mastectomy is also thought to alter the microenvironment and growth factors in the tumor bed thereby inhibiting tumor proliferation during the interval between surgery and initiation of WBRT.[17,18]

One of the disadvantages of BCT is a protracted treatment course due to daily WBRT over a 3–6 week period. Travel distance to a radiation therapy center as well as the frequency and duration of treatments can pose logistical impediments, unnecessary stress, and inconvenience, which can lead to noncompliance and ultimately result in suboptimal oncologic outcomes.[19] The increased risk of ischemic heart disease and radiation-associated malignancies as well as the challenges associated with a prolonged course of daily WBRT may also drive some patients' decision to pursue mastectomy despite being appropriate candidates for BCT.[20,21]

With its unpredictable and infiltrative growth pattern, lobular histology has been associated with an increased rate of inadequate margins.[22–25] The concern for inability to achieve clear margins in a single excision has played a role in the limited study of IORT in patients with LF. In this study, LF was not associated with an increased rate of inadequate margins or high-risk features necessitating AT. In line with the findings of Mukhtar et al., application of oncoplastic techniques may reduce inadequate margin rates in patients with LF and therefore maximize their chances of successfully completing single-dose IORT.[22] Additionally, we observed no local recurrences in patients with LF.

IORT is an effective treatment option for well-selected patients with early-stage breast cancer, and can be considered for patients with LF. Further studies are warranted to assess long-term oncologic outcomes and to ascertain additional patient and tumor factors that can identify suitable candidates for IORT.

Declaration of competing interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.11.017.

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