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ORIGINAL ARTICLE – RADIATION ONCOLOGY

Risk Factors Leading to Complications in Early-Stage Breast Cancer Following Breast-Conserving Surgery and Intraoperative Radiotherapy

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ABSTRACT

Objective. The aim of this study was to evaluate outcomes after breast-conserving surgery (BCS) and intraoperative radiotherapy (IORT), and to identify risk factors associated with complications.

Materials/Methods. We evaluated patients with early-stage breast cancer treated from January 1, 2011 to January 31, 2014 with BCS and IORT at a single institution. The presence of breast cancer recurrences, complications, or fat necrosis were assessed at subsequent follow-up visits using physical examination and breast imaging.

Results. Overall, 113 patients, of whom three were undergoing bilateral treatments, were identified. The median length of time for IORT was 29 min and 36 s (range 15:50–59:00). Fifteen patients received additional external beam radiotherapy (EBRT), and the median follow-up was 40.3 months (range 1.6–58.3) for all patients. To date, one biopsy-proven ipsilateral recurrence has been noted (0.9%), for which the patient elected to undergo a mastectomy. Nine patients were found to have wound complications (7.7%) and two had fat necrosis (1.7%) on follow-up. Of all the evaluated risk factors, only applicator size ($p < 0.01$) had a statistically significant association with an increase in complications.

Conclusions. With a short follow-up, IORT appears to be a safe treatment modality for a select group of patients, leading to a reasonable increase in operating room time and complication rates following BCS. The utilization of larger applicators at the time of IORT was associated with an increase in wound complications and fat necrosis.

With the adoption of screening mammography, the incidence of early-stage breast cancer has increased.[1] Multiple randomized studies have shown the equivalence in survival for patients with early-stage breast carcinoma undergoing mastectomy versus breast-conserving surgery (BCS) followed by fractionated whole-breast radiotherapy;[2,3] however, whole-breast radiotherapy is both costly and time consuming, and, although well-tolerated, it is associated with some unavoidable acute and late toxicity.[4,5]

With data showing that the highest risk of local recurrence occurs near the original site of disease, radiation may be targeted to this area alone.[6] The experimental finding that the majority of recurrences are localized near the lumpectomy bed is the rationale underlying all forms of accelerated partial breast irradiation (APBI). By delivering hypofractionated doses to limited volumes, APBI has the potential to improve sparing of normal tissues and reduce treatment duration. Presently, there are multiple forms of this therapy in use, including multicatheter interstitial brachytherapy, balloon and strut-based brachytherapy, external beam APBI (with 3-D conformal radiotherapy or intensity-modulated radiation therapy) and intraoperative radiotherapy (IORT).[7]

IORT allows for delivery of a single fraction of radiation to the tumor bed at the time of surgery. The device studied

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in this report is manufactured by Carl Zeiss Meditec AG and is brought to the operating room shortly before surgery. The device accelerates electrons down a probe, striking a gold target, which in turn generates low-energy photons and delivers them through a spherical applicator selected to match the surgical cavity size. Initial data from the TARGIT-A trial and other retrospective series[8–10] have shown low ipsilateral breast recurrence rates and good-to-excellent cosmesis.

At our center, IORT has been used in very carefully selected patients with clinical stage I breast cancer. The goal of this study was to evaluate outcomes for patients undergoing BCS followed by IORT and, secondarily, to identify any factors associated with an increase in complication rates.

METHODS/MATERIALS

This study was approved by our Institutional Review Board. All patients treated with IORT from January 1, 2011 to January 31, 2014 were identified and were eligible for inclusion. Eligibility criteria included women aged 50 years or older, clinical stage T1, estrogen receptor-positive, grade 1 or 2, unicentric and unifocal disease, invasive ductal or other favorable subtypes at the time of biopsy, and the ability to undergo BCS. Data including patient demographics, tumor characteristics, treatment details, and outcomes were collected from electronic medical records.

IORT to the surgical cavity was administered at the time of surgical resection of the tumor using the ©Carl Zeiss Meditec AG INTRABEAM system. This device provided a point source of 50 kV energy X-rays at the center of a spherical applicator. Once the appropriate sized applicator was selected, 20 Gy of radiation was prescribed to the surface of the applicator.[8] After surgery, pathological review of each specimen was performed. If adverse pathologic features were identified (typically, high grade; lobular component; lymphovascular invasion; positive axillary node; positive margin; extensive intraductal component of ductal carcinoma in situ [DCIS]), patients then received a recommendation to undergo external beam radiotherapy (EBRT) to the whole breast without a boost.

Patient demographics included age at the time of surgery and date of last follow-up. Tumor characteristics included tumor histology, tumor size, estrogen/progesterone receptor status, presence of lymphovascular invasion, axillary nodal status, tumor grade, and margin status. Treatment details included length of time for IORT, applicator diameter used for IORT (range 3.0–5.0 cm), and the need for additional radiation or surgery. Follow-up notes and imaging reports were used to assess local recurrence in the ipsilaterally-treated breast. Toxicities included findings of wound complications and fat necrosis. Wound complications were diagnosed on physical examination if findings were consistent with infection or dehiscence, with infection being defined as requiring antibiotics. Fat necrosis was only diagnosed radiographically. The Wilcoxon rank-sum test was used to evaluate multiple risk factors that could have led to an increase in complication rates.

RESULTS

Overall, 113 eligible patients with a median age of 68 years (range 52–90) were identified, of whom three underwent bilateral treatment. Tumor details are outlined in Table 1. The median length of time for radiotherapy was 29 min and 36 s (range 15:50–59:00). Two patients were treated using a 3 cm applicator, 34 patients with 3.5 cm applicator, 51 patients with 4 cm applicator, 9 patients with a 4.5 cm applicator, and 20 patients with a 5.0 cm applicator. From the date of treatment, median follow up was 40.3 months (range 1.6–58.3).

Following BCS and IORT, 15 patients received additional whole-breast EBRT. The reasons for this recommendation included three patients with EIC, seven patients with a positive axillary lymph node, one patient with invasive lobular carcinoma, one patient with high-grade disease with a close positive margin, and two patients with lymphovascular invasion (one of these also had a positive micrometastatic lymph node foci and the other had EIC). One patient who was found to have multiple positive sentinel lymph nodes received a recommendation to undergo both chemotherapy and radiotherapy, but refused any additional treatment. External beam regimens included nine patients receiving 45 Gy in 1.8 fractions, two receiving 50.4 Gy in 1.8 fractions, and three receiving 40.05 Gy in 2.67 fractions to the whole breast only. One patient underwent treatment to the breast to 45 Gy, and 50.4 Gy to a supraclavicular field.

From all subsequent follow-up visits and imaging, one patient (0.9%) was found to have an image-detected lesion that was biopsied and found to be positive for malignancy. The original tumor was located in the left breast in the upper outer quadrant, while the recurrence was found in the periareolar region. This patient elected to undergo mastectomy. Nine patients were found to have wound complications (7.7%) and two (1.7%) were found to have fat necrosis. Multiple factors were then assessed using the Wilcoxon rank-sum test, with only applicator size ($p < 0.01$) statistically positive for association with an increase in wound complications and/or fat necrosis (Table 2).

TABLE 1 Tumor characteristics

Histology	
IDCA	98
ILCA	6
DCIS	9
Other	3
Tumor size, mm	
>1 to ≤5	22
>5 to ≤10	36
>10 to ≤20	50
>20 to ≤50	6
Estrogen receptor status	
Positive	114
Negative	2
Progesterone receptor status	
Positive	97
Negative	18
Unknown	1
Lymphovascular invasion	
Positive	6
Negative	109
Unknown	1
Grade	
1	63
2	43
3	7
Unknown	3
Nodal status	
Positive	10
Negative	94
No nodal assessment	12

IDCA infiltrating ductal carcinoma, *ILCS* infiltrating lobular carcinoma, *DCIS* ductal carcinoma in situ

TABLE 2 Wilcoxon rank-sum test assessing factors associated with wound complications and fat necrosis

Risk factors	*P* value
Duration of radiation	0.21
Tumor size	0.85
Age at last follow-up	0.21
Additional EBRT	0.09
Applicator size	<0.01

EBRT external beam radiotherapy

DISCUSSION

IORT appears to be a safe and effective treatment modality for a very select group of early-stage breast cancer patients. From our cohort, the recurrence rate observed were low. Additionally, both wound complications and fat necrosis rates were also low, but greater in patients treated with larger applicator sizes.

The use of APBI continues to increase in the treatment of early-stage breast cancer and is now listed as an option as per the National Comprehensive Cancer Network guidelines.[11] Currently, multiple forms are in use, including multicatheter interstitial brachytherapy, balloon- or strut-based brachytherapy, hybrid-based brachytherapy, external beam, and IORT. Relatively few randomized trials are available comparing the various forms of APBI with whole-breast radiotherapy. A recent 5-year update by the GEC-ESTRO group also showed that the use of multicatheter brachytherapy was non-inferior to adjuvant whole-breast radiotherapy following surgery for early-stage disease for local recurrence and rates of toxicity.[12] A meta-analysis reviewed numerous studies of varying trial designs comparing multiple forms of APBI versus whole-breast radiotherapy. No statistical difference between nodal recurrence, systemic recurrence, or overall survival was found. A higher rate of in-breast failures was observed in patients treated with APBI; however, the absolute relapse rates were still low. Selection biases and heterogeneity of treatment make these comparisons tenuous.[13]

IORT following BCS for early-stage disease has been studied in large multi-institution randomized trials. The TARGIT-A trial randomized patients to an initial strategy of IORT (with additional whole-breast radiation only in the event of high-risk features on final pathology) versus EBRT to the whole breast.[8] The 5-year rate for local recurrence was 1.3% for EBRT versus 3.3% for the IORT arm. Wound complications were similar between both groups but grade 3–4 skin complications were significantly less in the IORT group (4 of 1720 vs. 13 of 1731). IORT yielded both good oncologic and cosmetic outcomes, although these were based on short-term follow-up and inclusion of a relatively low-risk population. Our results reinforce this finding and present a longer median follow-up than seen in the TARGIT-A trial.

Similar to our review, there have been multiple retrospective series demonstrating good outcomes with IORT. Abbot et al. reported the use of IORT following BCS, showing a low rate of in-breast recurrences and would complications.[10] Additionally, a recent study (TARGIT-R), which reported on outcomes on over 935 patients treated with IORT following BCS, not only showed an increase in the use of this form of therapy, but also low rates of complications and recurrences. Again, with these various series, it shows that IORT is a well-tolerated form of therapy, with good outcomes in well-selected patients, just as in our study.[9]

Even with the growing use of APBI, there are still studies showing mixed outcomes. Interim results from the

RAPID trial, comparing partial breast irradiation with the use of EBRT therapy versus standard whole-breast irradiation, show a higher rate of adverse cosmesis at 3 years with APBI (29% vs. 17%; $p < 0.001$). Results from this study led the authors to caution against the use of external beam APBI outside of a clinical trial.[14]

A recurring theme with all various studies in regard to APBI is that the follow-up is still short compared with other randomized trials assessing EBRT to the intact whole breast following BCS. Additional data will need to be collected, with longer follow-up from larger data sets or registries, in order to see if this form of therapy still shows good treatment outcomes. Nonetheless, from our study and studies previously mentioned, acute toxicity rates are low with IORT. Larger size of applicator was associated with an increase in breast complications; however, it is unclear whether this effect is simply due to the toxicity associated with larger surgical excision or to the dose distribution associated with a larger applicator.

CONCLUSIONS

IORT performed at the time of BCS for a very select group of early-stage breast cancer patients appears to be a safe and effective modality. Rates of in-breast recurrences, wound complications, and fat necrosis were low in this cohort. Caution may be warranted when larger applicators are used, especially when using 5 cm applicators, as they were associated with a higher rate of complications.

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