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Toxicities and Locoregional Control After External Beam Chest Wall and/or Regional Lymph Node Re-irradiation for Recurrent Breast Cancer

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Abstract. *Background/Aim: To evaluate toxicities and clinical outcomes in breast cancer (BC) patients who underwent external beam chest wall (CW) and/or regional lymph node (LN) re-irradiation (re-RT) for locoregional recurrence (LRR). Patients and Methods: We performed a retrospective review of our institutional database to identify BC patients diagnosed with an isolated ipsilateral CW or nodal recurrence after prior whole breast/CW irradiation. Results: Fifteen patients met the study criteria. Median time between completion of RT courses was 68.3 months (range=7.8-245.4 months). Median CW re-RT dose was 45 Gy (range=42.3-50.4 Gy). The majority of patients (80%) received proton beam re-RT. Grade 2-3 dermatitis occurred in 87% patients. Grade 2-3 pain was reported by 33% of patients. At a median follow-up of 14 months (range=1.0-90.5 months), the rate of isolated LRR was 13%. Conclusion: Re-RT of the CW and/or regional LNs is feasible with acceptable rates of toxicity and low rates of isolated LRR.*

The standard local therapy for early-stage breast cancer (BC) is breast conserving surgery (BCS) followed by adjuvant radiation treatment (RT) and mastectomy with or without RT for advanced stage BC (1-3). Although local-regional recurrence (LRR) rates have improved with therapeutic and technical advances in recent years, it remains as the most common form of relapse (4, 5). Standard therapy for LRR has historically been surgical resection with or without systemic therapy. More recently, with improved radiotherapeutic techniques and the increasingly early detection of small volume recurrences, there has been growing interest in salvage gross total resection with adjuvant re-irradiation (re-RT). However, selection of patients for re-RT is challenging due to concerns regarding normal tissue toxicity (6). More data are necessary to characterize outcomes with re-RT to guide the evolving management of recurrent BC.

Several strategies have been proposed for re-RT including partial breast irradiation, electrons, twice-daily treatment, proton-based RT, brachytherapy, concurrent systemic therapy, and hyperthermia (6-11). Recently published RTOG 1014 trial reported 5% recurrence rate in ipsilateral breast and 7% late grade 3 toxicity following partial breast re-RT after a second lumpectomy for recurrence of BC (7). Although result of this study suggests that this treatment approach is an effective alternative to mastectomy, many patients are not eligible to this protocol, including those with isolated axillary or chest wall (CW) recurrence. Therefore, the specific role for re-RT in LRR of BC remains a challenging and clinically relevant question. In this study, we report toxicities and clinical outcomes in patients who underwent external beam CW and/or regional lymph node re-RT for LRR.

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Table I. *Baseline characteristics*.

Patient, n	15
Age, median, years (range)	
At initial diagnosis	46 (32-72)
At recurrent diagnosis	55 (38-75)
Breast laterality, n (%)	
Left	5 (33)
Right	10 (66)
Histology, n (%)	
Invasive ductal carcinoma	15 (100)
AJCC clinical T stage, n (%)	
T0	1 (7)
T1	8 (52)
T2	1 (7)
T3	1 (7)
T4	4 (27)
AJCC clinical N stage, n (%)	
N0	10 (66)
N1	4 (27)
N2	1 (7)
Receptor status, n (%)	
Estrogen receptor-positive	6 (40)
Progesterone receptor-positive	4 (27)
HER2/neu-amplified	4 (27)
History of smoking, n (%)	8 (52)
Diabetes, n (%)	3 (20)
Median BMI, (range)	30 (18-44)
Follow-up	
Median, months (range)	14 (1-91)

BMI: Body mass index; AJCC: American Joint Committee on Cancer.

Patients and Methods

We performed a retrospective review of our institutional database to identify breast cancer patients treated with re-RT from 2015 to 2020. Patients were eligible for this study if they had an isolated ipsilateral breast/CW or nodal recurrence after prior whole breast/CW irradiation. Locoregional management of recurrent disease included surgical resection and external beam re-RT.

Baseline clinical characteristics were collected and included patient age, race, body mass index (BMI), and history of breast cancer and treatment. Disease-related characteristics included histology, grade, hormone receptor status, American Joint Committee on Cancer (AJCC) T stage, and AJCC N stage. Treatment-related factors included receipt of chemotherapy, receipt of hormonal therapy, and type of surgical resection.

Early toxicity outcomes were graded by the treating physician during the treatment course using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. For patients with an intact breast or reconstruction, patient-reported cosmetic outcomes were graded as excellent, good, fair, or poor during their last follow-up visit. Follow-up was calculated from the completion of the second course of RT. Statistical analyses were performed using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

Table II. *Treatment-related characteristics*.

Initial radiation therapy parameters	
Median dose, Gy (range)	50 (33.5-50.4)
Boost, n (%)	11 (73)
Median dose, Gy (range)	10 (10-16)
Radiation Field Design	
3-4 fields[a]	5 (33)
Re-radiation therapy parameters	
Median dose, Gy (range)	45 (42.3-50.4)
Boost, n (%)	7 (47)
Median dose, Gy (range)	12.5 (6-20)
Radiation Field Design	
3-4 fields[a]	14 (93)
Systemic therapy (initial)	
Chemotherapy, n (%)	11 (73)
Systemic therapy (recurrent)	
Chemotherapy, n (%)	14 (93)
Concurrent chemoradiation, n (%)	4 (27)
Endocrine therapy, n (%)	7 (47)
Number of lymph node removed	
Median (range)	9 (1-31)

[a]Supraclavicular field with or without a posterior axillary boost.

Results

We identified 15 patients who met the study criteria. Baseline patient characteristics are shown in Table I. Median age was 46 (range=32-72 years) at initial diagnosis and 55 (range=38-75 years) at recurrent diagnosis. Nine patients (60%) had T1-2 recurrent tumors, and 2 (13%) presented with an inflammatory recurrence. Median time between completion of RT courses was 68 months (range=7.8-245.4 months). Median body mass index was 26 (range=18-44). Three patients (20%) had a history of diabetes and eight patients (52%) had a history of smoking.

Median initial whole breast/CW dose was 50 Gy (range=33.5-50.4 Gy) (Table II). Boost was delivered in 11 (73%) patients, and 5 (33%) received nodal RT. Fourteen patients (93%) received chemotherapy for recurrence, including 4 (27%) who received concurrent chemoradiation. Thirteen patients (80%) underwent mastectomy, two patients (13%) wide local excision, and one patient (7%) with axillary lymph node dissection alone. Five patients (33%) underwent LN evaluation for recurrence. Median total number of LNs removed from all surgeries was 9 (range=1-31). Median CW re-RT dose was 45 Gy (range=42.3-50.4 Gy), and 7 patients (47%) received a boost. The axilla was targeted in 87% of patients and the supraclavicular fossa in 73%. The majority of patients (80%) received proton beam re-RT.

Grade 2-3 dermatitis occurred in 87% patients (Table III). Grade 2-3 pain was reported by 33% of patients and grade 3 fatigue by 40%. There were no acute grade 4 toxicities.

Table III. *Treatment related toxicities and patient-reported cosmetic outcomes.*

Dermatitis, n (%)	
Grade 2	12 (80)
Grade 3	1 (7)
Pain, n (%)	
Grade 2	3 (20)
Grade 3	2 (13)
Fatigue, n (%)	
Grade 2	6 (40)
Clinical lymphedema, n (%)	2 (13)
Cosmetic outcome[a]	
Poor	0
Fair	3 (38)
Good	5 (62)
Excellent	0

[a]Eight patients with an intact breast/reconstruction completed cosmetic evaluation.

Among 8 patients with an intact breast/reconstruction, 5 reported good and 3 reported fair cosmetic outcomes. Two patients (13%) developed clinical lymphedema. There were no reports of brachial plexopathy. At a median follow-up of 14 months (range=1.0-90.5 months), the rate of isolated LRR was 13%, overall LRR 27%, and distant metastases 33%.

Discussion

Within a cohort of breast cancer patients with recurrence treated with re-RT of the CW and/or regional LNs, we noted acceptable rates of acute and long-term toxicity and low rates of isolated LRR.

Improvements in systemic therapy have led to increased importance of local control. Curative treatment of LRR may be beneficial both in terms of survival and in symptom control. RTOG 1014 is the only available prospective study on partial breast re-RT following re-BCS that included patients with unicentric tumors ≤3 cm, no skin involvement, and >1 year following prior RT (7). Five-year cumulative incident of ipsilateral recurrence was 5% with grade 3 toxicity of 7%. Although the RTOG 1014 indicated that re-RT is an effective treatment option with acceptable normal tissue toxicity, the result of the trial is limited to patients with in-breast recurrence who underwent re-BCS. Based on limited retrospective data, re-RT of LRR provides a good local control in the setting of gross total resection of the recurrent disease. Fattahi *et al*. recently reported local-regional control of 93% with 13% grade 3 toxicity following re-RT for LRR (12). In this setting, the treatment was directed to recurred regional side alone, such as axilla and breasts were not treated. Our study demonstrates that 13% of patients experience isolated LRR; however, development of distant metastasis remains as a significant concern. Rate of distant metastases was 33% in this study, suggesting that continued effort to optimize systemic therapy for LRR is warranted.

The clinical application of proton-based RT has increased in recent years. The dosimetric benefits of proton-based RT, including a low to medium entrance dose, homogeneous dose distribution in the target area, and a steep fall-off to zero dose distally to the target, result in a significantly reduced whole-body integral dose (13). Re-RT with proton-based RT has been reported in multiple disease sites, including central nervous system, head and neck, gynecologic, gastrointestinal, and lung tumors (14-18). However, there are limited data in the setting of breast re-RT. In our study, the majority of patients (80%) were treated with proton beam re-RT, which may have caused the reduced normal tissue toxicity. LaRiviere *et al*. recently reported favorable outcomes in twenty-seven patients with BC treated with proton-based re-RT for LRR at a median follow-up of 17 months. Rate of local-regional control was >95%, with only 7% of patients experiencing grade 3 toxicity at any point (8). Thorpe *et al*. also reported 16% grade 3 toxicity at any point following proton beam re-RT for BC recurrence (19). We observed similarly low rates of grade 3 toxicity at any point (13%).

Limitations of our study include its small sample size, retrospective design, and inherent confounding factors that cannot be completely accounted for in a non-randomized study. In addition, longer follow-up is needed to further assess local control, late toxicity, and cosmetic outcome.

In conclusion, in a cohort of BC patients treated with re-RT of the CW and/or regional LNs, acute and late toxicity rates were acceptable and isolated LRR rate was low. The majority of patients were treated with proton beam re-RT, which may have contributed to low treatment toxicity.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

MS, BH, and NO designed the study. MS, IR, and IJ collected the data. IR performed data analysis. MS and NO drafted the manuscript. SK, NC, and BH edited the article. All Authors approved the final content for journal submission and publication.

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