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Mastectomy Scar Boost Results in Low Risk of Locoregional Recurrence in the Setting of Close or Involved Surgical Margins

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ABSTRACT

Background: Several Phase III randomized trials have demonstrated improved local control and survival for post-mastectomy radiotherapy in patients with high-risk pathologic features. Close or involved surgical margins were not included as high-risk in these protocols, but have been associated with increased risk of local failure; however, the impact of a boost dose following chestwall radiotherapy in this setting remains to be determined. Methods: Retrospective single-institution outcomes analysis for patients with close or involved surgical margins treated with post-operative radiotherapy is followed by a boost. Results: Between 2003 and 2011, 34 patients were identified for inclusion in the present study. The median chestwall dose was 5040 cGy (range 5000 - 5040) and median boost dose was 1080 cGy (900 - 1620). At a median follow-up of 38.4 months (10.2 - 115.6; with 29% more than 5 years), 28 patients were alive without evidence of recurrence, 3 were alive with recurrent disease (1 chestwall), and 3 had died (none with recurrent disease). The 3-year local control, disease-free survival, and overall survivals were 96.9%, 93.9%, and 93.1%, respectively. Conclusion: Chestwall radiotherapy plus boost results in low risk of early locoregional recurrence for women with close or involved surgical margin(s) at mastectomy. Further investigation of PMRT with or without boost in this setting is warranted.

KEYWORDS

Breast Neoplasms; Mastectomy; Adjuvant Therapy; Radiotherapy

1. Introduction

Randomized trials have demonstrated that post-mastectomy radiation therapy (PMRT) reduces the risk of loco-regional recurrence (LRR) by 50% - 65% for women with high-risk features at mastectomy [1-4]. These high-risk pathologic features included invasion of the skin or pectoralis fascia, tumor size ≥5 cm, and/or lymph node involvement [2-4]. While surgical margin status was not specifically recorded, analysis of patients with skin and/or deep fascia invasion (subsets with anticipated high likelihood of margin involvement) demonstrated significant reduction of LRR at 10 years (40% vs. 7%) [3,4]. These trials employed standardized regimens (48 - 50 Gy over 4 - 5 weeks via electrons or 37.5 Gy over 3 - 4 weeks via tangents in the European and Canadian protocols, respectively), with mandatory comprehensive nodal irradiation (including both axillary and internal mammary nodal targets) [2,4]. No boost was employed in the setting of close or involved surgical margins, and for the overall study populations, the LRR was 5% - 10% for irradiated patients.

Retrospective studies of node-negative patients who did not receive PRMT have demonstrated increased risk of LRR in the setting of close or involved margins (<2 mm) when compared with more widely negative margins [5,6]. While the impact of PMRT in this setting is

unclear [7,8], evidence from breast preservation studies suggests that a "boost" to the tumor bed decreases LRR beyond that of whole-breast irradiation alone [9,10], and this benefit was preserved with elevated doses in the setting of close or involved surgical margins [11]. In the setting of PMRT, registry-based data suggest improved LRR rates with higher-dose radiotherapy [12,13]; however, the impact of boost doses was implied rather than directly studied. The present investigation seeks to supplement the current literature by defining disease control, patterns of failure, and survival rates among women with close or involved margins who received PMRT with boost.

2. Methods & Materials

This retrospective review was approved by the University of North Dakota, Sanford Health, and St. Alexius Medical Center institutional review boards. Eligible patients were identified from electronic medical records of patients diagnosed with breast cancer between 2003 and 2011, who received PMRT plus boost at the Bismarck Cancer Center. PMRT was employed following chemotherapy (if indicated, at the discretion of the medical oncologist and patient), and was accomplished via megavoltage photons (6 - 10 MV) via tangents (with or without subsegmentation) or static intensity modulated radiation therapy. Standard fractionation (1.8 - 2 Gy per once-daily fraction) was employed, with chestwall doses of 50 - 50.4 Gy and boost doses of 9 - 16 Gy, at the discretion of the treating physician. The boost volume included the surgical incision plus 2 - 3 cm margin uniformly, treated with electrons (multifield if necessary owing to size/convexity of the target, with or without bolus based upon target thickness and electron beam energy employed). Regional lymphatics treated as clinically indicated, generally in the setting of pathologically involved lymph nodes at mastectomty. Patients were required to have had histologically confirmed invasive or *in situ* breast carcinoma, with close (≤2 mm) or involved/positive margins at mastectomy. This cutoff value was selected based upon previously published data demonstrating increased risk of LRR [5,6].

Study data were collected from existing quality assurance databases and electronic medical records, and included patient demographics, tumor characteristics (including tumor location, histology, tumor grade, hormone receptor status, HER2 status, surgical margin specifics, and pathologic stage), treatment factors (including radiotherapy and systemic therapy specifics), and outcome variables (including patterns of failure and survival). Pre-operative chemotherapy was permitted for inclusion in the present study, with both pre- and post-chemotherapy staging information recorded.

The outcome variables measured in this study included freedom from locoregional failure (FFLF), overall freedom from failure (FFF), and overall survival (OS). All endpoints were measured from the date of initial tissue diagnosis (biopsy), with events recorded at time of first detection.

SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL) was used to analyze demographic and clinical characteristics of patients. The Kaplan-Meier method was employed to describe estimates of disease control and survival.

3. Results

Between 2003 and 2011, 34 patients met criteria and were included in the present study. Patient demographics and tumor characteristics are shown in **Table 1**. Of note, all patients were white and only one patient had a prior history of cancer. No cases of isolated *in situ* carcinoma were identified; all had invasive carcinoma, and lymphovascular invasion was specifically identified in 23 patients.

Five patients underwent chemotherapy prior to mastectomy; for the remaining 29 patients, the median interval from biopsy to mastectomy was 14 days (range, 0 - 63). All but one patient underwent surgical nodal staging at the time of mastectomy. The median number of lymph nodes removed was 9 (range, 0 - 34), with 9 patients undergoing sentinel lymph node biopsy only. For 24 patients with involved lymph nodes, the median number involved was 5 (range, 1 - 20), with extranodal extension observed in 18 patients.

Pathologic stage breakdown is demonstrated in **Table 2**, and detailed treatment characteristics are summarized in **Table 3**. Of note, 25 patients received radiotherapy to the regional lymphatics in addition to the chestwall (dose range 5000 - 5040 cGy).

At a median follow-up of 38.4 months (10.2 - 115.6; including 29% with >5 years), 28 patients were alive without evidence of recurrence, 3 were alive with recurrent disease (1 LRR at the chestwall), and 3 had died (none with recurrent disease). As demonstrated in **Figure 1**, the 3-year FFLF were 96.9% (95% C.I.; 95.9% - 97.9%), with only one patient having chestwall failure. The overall 3-year FFF was 93.9% (92.5 - 95.3%). Three-year OS was 93.1% (91.5 - 94.7%).

4. Discussion

Following mastectomy, LRR is an unanticipated and concerning site of cancer recurrence. Data suggests that approximately half of patients who experience isolated chestwall failure will subsequently develop distant metastasis within 5 years of LRR, including a 25% risk for the subset of patients with initial pT1-2N0 disease at

Table 1. Demographics and tumor characteristics.

Variable	Median (Range)	N (%)
Ageat Diagnosis		
Median (Range)	59 yrs (27-87)	
≤50 yrs		8 (24)
Method of Detection		
Screening Mammogram		5 (15)
Self breast exam		28 (82)
Clinical breast exam		1 (3)
Histology		
Invasive Ductal		24 (71)
Invasive Lobular		9 (26)
Mixed Ductal/Lobular		1 (3)
Laterality		
Right/Left		19 (56)/15 (44)
Estrogen Receptor		
Positive		26 (76)
Negative		8 (24)
Progesterone Receptor		
Positive		21 (62)
Negative		13 (38)
HER2 Status[a]		
Positive		10 (29)
Negative		23 (68)
Surgical Margin		
Involved/Positive		18 (53)
<1 mm		16 (47)
1 mm		4 (12)
1.5 mm		2 (6)
2 mm		4 (12)

[a]Defined as 3 + by immunohistochemistry, and/or with FISH confirmation; one patient's diagnosis preceded routine HER2 analysis of tumors.

Table 2. Pathologic stage distribution.[a]

		N-Stage				
		pN0	pN1	pN2	pN3	pNx
T-Stage	pT1	2[b]	2[b]	1[c]		
	pT2	3	6	3	1	
	pT3	3	5[b,b]	3	3[b]	1
	pT4				1	

[a]As per AJCC Cancer Staging Manual, version 7; includes 5 patients who received [b]pre-operative chemotherapy and 1 patient who received [c]pre-operative anastrazole.

mastectomy [14]. Thus, optimization of local control following mastectomy is critical. Standard criteria for PMRT include tumor size ≥5 cm, invasion of the pectoralis and/or skin, inflammatory breast cancer, and/or lymph node involvement, as per Phase III randomized trials in Denmark [2,3] and Canada [4]. The use of PMRT in these trials confirmed by LRR benefit as well as improved OS; however, surgical margin status was not reported, and thus the benefit in this setting has not yet been evaluated prospectively.

Table 3. Treatment characteristics.

Variable		N (%)
Chemotherapy		
None		6 (18)
Neoadjuvant		5 (15)
Adjuvant		23 (68)
Hormone Therapy		23 (68)
Radiotherapy		
Median Duration (Range)	48.5 days (41 - 83)	
Chestwall Dose		
5000 cGy/25		25 (74)
5040 cGy/28		9 (26)
Boost Dose		
900 cGy/5		10 (29)
1000 cGy/5		4 (12)
1080 cGy/6		5 (15)
1260 cGy/8		2 (6)
1400 cGy/7		1 (3)
1600 cGy/8		10 (29)
1620 cGy/9		2 (6)

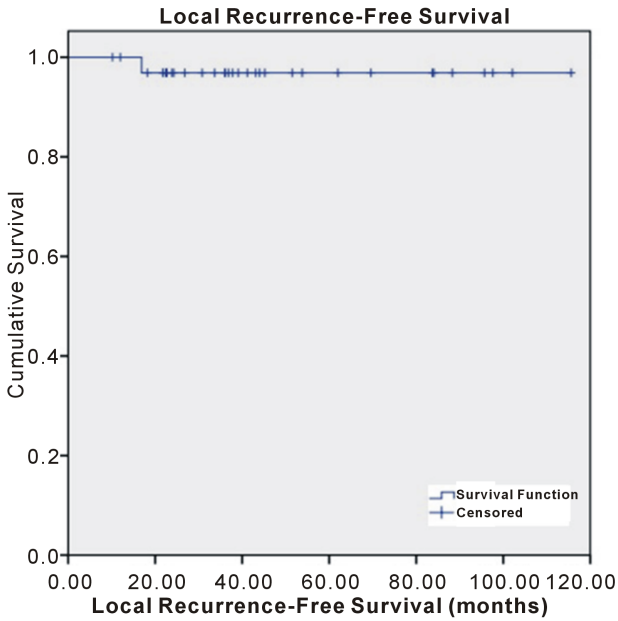

Figure 1. Freedom from locoregional failure.

Close or involved surgical margins have been associated with increased risk of LRR, particularly in the setting of additional high-risk features [5-8]. Jagsi and colleages at Massachusetts General Hospital described a series of 64 node-negative, unirradiated patients with close (≤2 mm) or involved margins at mastectomy whose 10-year LRR was 21%, as compared with 5% for 662 patients with margins >2 mm ($p < 0.001$) [5]. Investigators at the Fox Chase Cancer Center similarly described elevated LRR, employing the same close/involved margin definition (estimated 8-year LRR 24% versus 7%), though this population included patients with 1 - 3 lymph

nodes involved [6]. Thus, margin of ≤2 mm appears to confer a high risk of LRR, and a good population for study for the benefit and optimal dosing of PMRT.

With respect to PMRT and boost doses, retrospective evidence suggests LRR benefit for general populations of high risk patients. Feigenberg *et al.* of the University of Florida described detailed outcomes for PMRT in a general population of 323 patients treated with electrons to the chestwall [12]. A subset of 49 patients with involved margins were described, and at a median follow-up of 8 years, the LRR for patients with and without chestwall boost were 2% (1/41) and 25% (2/8), respectively. Similarly, investigators from the University of Miami performed a retrospective analysis of 582 patients who received PMRT, and evaluated LRR by dose [13]. As standard chestwall doses are 4500 - 5040 cGy, their investigation evaluated the relationship of total radiotherapy dose ≤/>5040 cGy. At a median follow-up of 45 months, the estimated 5-year LRR was 5.7% versus 12.7% in patients who did or did not complete dose >5040 cGy, with benefit extending into FFF and OS as well. Additionally, the boost population had superior outcomes in several high-risk subset populations, including stage III-IVC (inflammatory) disease and triple negative receptor (hormone-insensitive, HER2-negative) status. Our findings agree with these, with similar low rate of LRR in the close/involved margin population, suggesting an advantage of RT boost overall as well in the context of established high-risk features.

Within the present study population, all patients had invasive disease, though one had only DCIS at the surgical margin. The role of radiotherapy in this setting is uncertain; following mastectomy for DCIS, the risk of LRR is minimal, though certain factors such as multi-quadrant involvement, close/involved margins, high-grade DCIS, and/or younger age may increase this risk [15-17]. Several investigations have described disease control for patients treated with mastectomy for DCIS alone, with close or involved margins. Rashtian *et al.* described a retrospective series of 80 patients who had undergone mastectomy for DCIS [15]. In comparing subsets by margin width, LRR developed in 5/31 (16%) with margin ≤2 mm as compared with 1/49 with margin 2.1 - 10 mm. In addition, all LRR occurred in patients aged <60 years, a finding consistent with other investigations [16]. Thus, PMRT would be expected to confer benefit in this setting, as demonstrated by Eulau and colleagues at the Swedish Cancer Institute in Seattle, who described 100% LRR at 5 years for 15 patients who underwent PRMT for DCIS within 2 mm of the mastectomy margin [16]. However, not all studies have determined that close margins are sufficiently high-risk to warrant PMRT. Investigators at the University of California-San Francisco described a heterogeneous population of 59 patients with surgical margin ≤5 mm, of whom only one had. They concluded that PMRT in women with DCIS and close margins is unnecessary, though recommending that further investigation is required in the setting of involved margins [17].

Within the present investigation, all patients with close/involved margins received PMRT plus boost, with favorable early LRR. Going forward, we hope to compare our study population with a matched group of patients who received PMRT without boost, so as to determine whether the supplemental dose is justified in this setting. Additional follow-up will be important so as to ensure that this benefit is preserved over time.

5. Conclusion

This study demonstrates favorable local control with PMRT plus boost in the setting of close or involved margins after MRM. Further investigation is warranted in order to determine whether these benefits are superior to those of PMRT without boost.

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All three lead authors are presently 4th year medical students at the University of North Dakota School of Medicine and Health Sciences, and contributed equally to the design, data extraction, and manuscript development process of this study.

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