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BRIEF REPORT

Long-term outcomes among breast cancer patients with extensive regional lymph node involvement: implications for locoregional management

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Abstract Extensive lymph node (LN) involvement portends significant risk for distant metastasis (DM) among breast cancer patients. As a result, local management may be of secondary import to systemic control in this population. We analyzed patients with ≥10 involved LNs (N3) to evaluate the feasibility of breast conserving therapy (BCT) vs modified radical mastectomy (MRM) in this high-risk cohort. Among 98 women with N3 disease 46 (46.9 %) underwent BCT and 52 (53.1 %) received MRM. Nearly all patients (92 %) received comprehensive radiotherapy (RT) including axillary and supraclavicular fields. The Kaplan–Meier method and Cox regression analyses were used to analyze time-to-event outcomes. Median follow-up was 76 months, with a 5-year DFS of 64.9 % and OS of 71.9 % among the cohort. Poorly differentiated ($p = 0.007$), ER-negative tumors ($p = 0.015$) had adverse DFS outcomes. Treatment groups did not differ with regard to 10-year DFS (45.4 % for MRM vs. 57.6 % for BCT; $p = 0.31$), or OS (61.4 vs. 63.7 %; $p = 0.79$). DM-free survival was 48.9 % following MRM and 60.6 % following BCT ($p = 0.19$). Patients with ≥10 involved LNs have similar outcomes following BCT or MRM, suggesting that RT may obviate the need for more-extensive surgery. While local control is comparably favorable regardless of surgical approach, systemic control remains a challenge in this population.

Keywords Breast cancer · Mastectomy · Lumpectomy · Recurrence · Radiotherapy

Introduction

Breast conserving therapy (BCT) and modified radical mastectomy (MRM) have long been mainstays in the surgical management of invasive breast cancer. However, despite numerous landmark trials demonstrating the efficacy of BCT, the optimal approach for certain populations remains unclear. Several prospective randomized trials have validated the overall survival equivalence of BCT and MRM for the majority of patients, although few data exist to guide treatment in those subgroups at highest risk [1–3]. A constellation of factors including extensive lymph node (LN) involvement, nipple/areolar retraction, young age, triple negative subtype, and ratio of tumor to breast volume are all considered in determining the appropriateness of BCT for a particular patient [4–6].

Observations regarding the natural history of breast cancer involving ≥10 LNs (N3 disease) suggest that this presentation is a harbinger of early distant dissemination and systemic disease [7]. Notably, although the overall risk of LN involvement is directly related to the size of the tumor, the *number* of involved LNs appears relatively independent of tumor size and location within the breast [8].

Patients with advanced nodal disease exhibit both reduced overall survival and an increased risk of locoregional recurrence (LRR). For patients with 1–3 positive axillary LNs, LRR has been estimated to be ~9–15 % at 5 years. This risk increases markedly to 25–50 % in patients with 4–9 or >9 involved axillary LNs [9].

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Of note, a number of reports suggest that LRR is not a main determinant of patient longevity because of the competing risk conferred by systemic disease. Consequently, for patients with ≥10 involved LNs with a high risk of early distant recurrence, studies have largely focused on optimizing systemic therapy rather than local treatment [10–13]. However, there does appear to be a direct relationship between locoregional control and breast cancer mortality [1–3]. Therefore, we sought to study outcomes of breast cancer patients with ≥10 involved LNs with a particular focus on BCT in comparison to MRM among this high-risk population.

Methods

Patient population and treatment

Between 1973 and 2011, we treated 98 patients with breast cancer involving ≥10 involved axillary LNs who otherwise had primary breast tumors amenable to conservative surgery. The medical records of these patients were collected and represent the current study cohort. All patients had pathologically confirmed invasive breast carcinoma and were treated with either BCT or MRM including adjuvant radiotherapy. Patients were excluded if they did not complete the prescribed treatment regimen, had inflammatory breast cancer, if they received neoadjuvant chemotherapy, if they were male, if they did not receive adjuvant radiotherapy (RT), or if they presented with distant metastases at the time of diagnosis.

Since American Joint Committee on Cancer (AJCC) nodal staging does not distinguish among patients with ≥10 involved axillary LNs [14], for the purposes of analysis we categorized N3 patients into groups with 10–14, 15–19, and ≥20 involved LNs. Adjuvant treatment data were collected regarding the use of RT, chemotherapy, hormonal therapy, and biologic therapy. Furthermore, data were collected for clinical and pathologic parameters to identify predictors of recurrence following BCT or MRM.

All patients underwent surgical resection of the primary tumor via either BCT (46 patients; 47 %) or MRM (52 patients; 53 %), followed by comprehensive adjuvant RT to the whole-breast/chest wall and regional lymph nodes as described below. While all patients underwent axillary lymph node dissection (ALND), 28 (29 %) first underwent a sentinel lymph node biopsy which was positive and prompted completion dissection.

RT was delivered to the chest wall (following MRM) or intact breast (following lumpectomy) using 6 MV opposed-tangent photon beams to a median dose of 50 Gy (range 37–54 Gy) over 6 weeks at 1.8–2.0 Gy per fraction. This was followed by an *en face* electron boost (median 10 Gy) to the chest wall (including mastectomy scar) or lumpectomy cavity in 65 (67 %) cases. Regional nodal irradiation was delivered to the ipsilateral axillary lymph nodes (50 Gy), the supraclavicular fossa (50 Gy) and the internal mammary chain (45–50 Gy) for nearly all patients (92 %). Technical treatment details were unavailable for seven patients.

Follow-up and definition of endpoints

Patients underwent follow-up 4–6 weeks after the completion of radiotherapy and 6 months thereafter, followed by annual mammography. Follow-up time was calculated from the date of diagnosis to the date of an event, or to the last known date of disease-free status.

Endpoints of interest included local recurrence (LR) defined as recurrence within the ipsilateral breast or chest wall, distant metastasis (DM), disease-free survival (DFS), and overall survival (OS). Time to LR was defined as any ipsilateral in-breast or chest wall recurrence (including invasive or in situ histology) without evidence of metastatic disease in the subsequent 4 months [15, 16]. Patients with evidence of distant metastases within 4 months of LR were considered to have synchronous local and distant recurrence.

Statistical analysis

Descriptive statistics were used to enumerate the distribution of clinical characteristics in the study cohort as stratified by the treatment received (BCT versus MRM). Comparisons of continuous covariates were conducted using the Wilcoxon rank-sum test. Comparisons of categorical covariates were made using the Chi squared test. Time to an event was defined as the time from diagnosis to the date of the event in question or last disease assessment.

The method of Kaplan–Meier was used to characterize rates of LR and DM, along with DFS and OS as stratified by treatment arm. The log-rank test and Cox proportional hazards models were used to assess the effect of patient characteristics and disease factors on these outcomes. Variables with p value <0.1 on univariate analysis entered the multivariable model. Multivariable analyses using the Cox model were performed via proportional hazards regression to determine which variables were independent predictors of DFS and OS. All analyses were performed using SAS version 9.3 (SAS Institute, Carey, NC, USA).

Results

Baseline distribution of clinical and pathologic factors as stratified by surgical approach

Among 98 patients in the study cohort who presented with ≥10 involved axillary lymph nodes, 46 (47 %) underwent BCT while 52 (53 %) underwent MRM (Table 1). A median of 20 LNs were retrieved (range 10–60) with a median of 14

Table 1 Baseline patient characteristics

	Breast conservation (*n*)	Mastectomy (*n*)	*p* value
Total	46	52	
Age in years			$p = 0.84$
<50	20	21	
>50	26	31	
T-stage			$p = 0.01$
T1 (<2 cm)	17	18	
T2 (2-5 cm)	28	23	
T3 (>5 cm)	1	11	
Histology			$p = 0.33$
Invasive ductal	38	43	
Invasive lobular	6	9	
Occult	2	0	
Estrogen receptor			$p = 0.48$
Positive	30	39	
Negative	16	13	
Her2 amplification			
Present	7	6	$p = 0.77$
No/not assessed	39	46	
Grade			$p = 0.37$
Well-moderate diff	11	17	
Poorly differentiated	32	31	
Unknown	3	4	
Extracapsular extension			$p = 0.73$
Present	28	25	
Absent	4	5	
Unknown	14	22	
Lymphovascular invasion			$p = 0.80$
Present	29	33	
Absent	17	19	
Number involved LNs			$p = 0.74$
10–14	23	30	
15–19	13	12	
>20	10	10	
Hormonal therapy			$p = 0.91$
Yes	26	30	
No	20	22	
Adjuvant chemotherapy			$p = 0.62$
Yes	36	43	
No	10	9	
Margins			$p < 0.001$
>2 mm	27	48	
<2 mm (close)	11	2	
Positive	8	2	

involved LNs per patient (range 10–50). Lymph node ratios (LNR) were calculated as involved LNs divided by resected LNs, yielding the majority of patients (74 %) with a high-risk LNR >0.65 and an overall median LNR of 0.8 [17]. A comparison between the groups revealed that higher T-stage was significantly associated with receipt of MRM ($p = 0.01$); of 12 T3 patients overall, 11 received MRM and only one underwent BCT ($p = 0.001$). Otherwise, there were no significant baseline differences in the distribution of age ($p = 0.84$), histologic subtype (invasive ductal versus lobular carcinoma; $p = 0.33$), estrogen receptor positivity ($p = 0.48$), pathologic grade ($p = 0.37$), presence of nodal extracapsular extension ($p = 0.73$), presence of lymphovascular invasion ($p = 0.80$), or number of involved lymph nodes ($p = 0.74$) (Table 1).

Treatment characteristics

Overall, 56 patients (57 %) received adjuvant endocrine therapy and 15 (15 %) received trastuzumab. Chemotherapy was administered in 79 cases (81 %) with varying regimens given over the time period of study: 41 patients received doxorubicin and cyclophosphamide followed by a taxane, ten patients received 5-fluorouracil, doxorubicin and cyclophosphamide, and 28 received other variations of adjuvant systemic therapy. Given the wide time interval across which patients were accrued (1973–2011), we analyzed treatment variables as dichotomized before and after the year 2000 and noted no significant differences between BCT and MRM arms for either time interval ($p = 1.000$). Of note, adjuvant chemotherapy was not administered in 19 cases (Table 2).

Patterns of recurrence as stratified by surgical approach

In total, eight local recurrences were observed: two were diagnosed after undergoing MRM and six after BCT (Fig. 1a). In the mastectomy group, one of the local recurrences was diagnosed 7 months after the diagnosis of distant recurrence; the other occurred at the surgical scar 9.25 years after surgery, with a distant recurrence observed 5.25 years thereafter. For the six local recurrences diagnosed after BCT, three were discovered synchronously with a distant recurrence. Overall, the BCT group demonstrated a 10-year local control rate of 89.5 % (95 % CI 74.0–96.0 %) in comparison to 92.5 % (95 % CI 70.9–98.3 %) for the mastectomy group ($p = 0.32$).

Forty-seven patients (48 %) developed distant metastatic disease: 28 after MRM and 17 after BCT (Fig. 1b). 10-year distant-metastasis-free survival was 48.9 ± 7.9 % for MRM versus 60.6 ± 8.3 % for BCT ($p = 0.44$). Notably, 87 % of patients with distant metastatic disease did not manifest any evidence of local or regional recurrence.

Survival outcomes by surgical approach

At a median follow-up of 76 months, 5-year overall survival for the entire cohort was 71.9 % and 10-year

Table 2 Univariate and multivariate analyses of distant recurrence and overall survival

	N	Distant recurrence model						Overall survival model					
		Univariable			Multivariable ($p = 0.02$)			Univariable			Multivariable ($p = 0.23$)		
		HR	95 % CI	*p*	HR	95 % CI	*p*	HR	95 % CI	*p*	HR	95 % CI	*p*
Surgery													
Breast conservation	46	0.70	0.39–1.25	0.22	0.38	0.14–1.08	0.07	1.12	0.61–2.05	0.71	0.94	0.36–2.45	0.9
Mastectomy	52	Ref											
Age at diagnosis													
<50	41	Ref											
≥50	57	0.91	0.51–1.63	0.76	0.86	0.37–2.01	0.73	0.83	0.45–1.54	0.56	0.52	0.20–1.31	0.16
Tumor stage													
T1	33	Ref			Ref			Ref			Ref		
T2	51	1.58	0.81–3.06	0.18	2.12	0.79–5.65	0.14	1.02	0.52–1.96	0.96	0.94	0.33–2.67	0.91
T3	13	1.94	0.80–4.71	0.14	2.09	0.56–7.75	0.27	1.05	0.38–2.91	0.92	1.23	0.22–6.71	0.81
Histology													
Invasive ductal	81	0.78	0.39–1.57	0.48	1.09	0.37–3.23	0.87	1.26	0.53–2.99	0.6	3.12	0.86–11.3	0.08
Invasive lobular	25	1.47	0.80–2.70	0.21				1.19	0.61–2.34	0.61			
Occult	2												
Estrogen receptor													
Positive	71	0.78	0.39–1.56	0.48	0.55	0.21–1.42	0.21	0.98	0.44–2.18	0.96	0.88	0.30–2.60	0.81
Negative	19	Ref						Ref					
Her2 amplified	13	0.49	0.15–1.59	0.24	0.85	0.27–3.15	0.8	0.43	0.10–1.80	0.25	0.38	0.08–1.85	0.22
Grade													
Well-moderate diff	28	2.12	1.10–4.07	0.02	2.78	1.19–6.50	0.02	1.93	0.92–4.06	0.08	3.65	1.41–9.42	0.01
Poorly differentiated	63	Ref						Ref					
Extracapsular extension													
Present	53	1.28	0.72–2.27	0.40	1.33	0.61–2.88	0.48	1.04	0.57–1.92	0.89	0.85	0.38–1.90	0.69
Absent	9	Ref						Ref					
Lymphovascular invasion													
Present	62	0.74	0.42–1.31	0.3	0.64	0.26–1.56	0.32	0.58	0.32–1.07	0.08	0.27	0.10–0.72	0.01
Absent	36	Ref						Ref					
Number involved LNs													
10–14	53	Ref			Ref			Ref			Ref		
15–19	25	2.60	1.36–4.95	0.004	3.5	1.43–8.55	0.01	1.90	0.95–3.95	0.07	1.83	0.67–5.00	0.24
≥20	20	1.52	0.72–3.13	0.27	1.62	0.58–4.57	0.36	1.19	0.53–2.63	0.67	1.17	0.37–0.67	0.79
Hormonal therapy													
Yes	42	0.57	0.32–1.01	0.05	0.77	0.33–1.76	0.53	0.56	0.30–1.04	0.006	0.68	0.27–1.69	0.39
No	56	Ref											
Adjuvant chemotherapy													
Yes	19	1.78	0.72–3.21	0.19	0.76	0.24–2.46	0.65	1.07	0.49–2.32	0.87	0.39	0.11–1.37	0.14
No	79	Ref						Ref					
Margins													
≥2 mm	75	Ref			Ref			Ref			Ref		
<2 mm	13	0.83	0.35–1.98	0.68	2.06	0.54–7.81	0.29	0.95	0.39–2.27	0.9	1.66	0.49–5.59	0.41
Positive	10	0.93	0.72–3.21	0.68	0.14	0.02–1.27	0.08	1.04	0.04–2.63	0.93	0.1	0.01–1.14	0.06

OS was 62.5 %. Of note, both treatment approaches yielded similar 10-year DFS (Fig. 2a) with rates of 48.2 % (95 % CI 32.7–62.1) for MRM and 58.0 % (95 % CI 40.0–72.4) for BCT ($p = 0.47$). With regard to OS, no significant difference was noted at 10 years between patients receiving BCT (63.7; 95 % CI

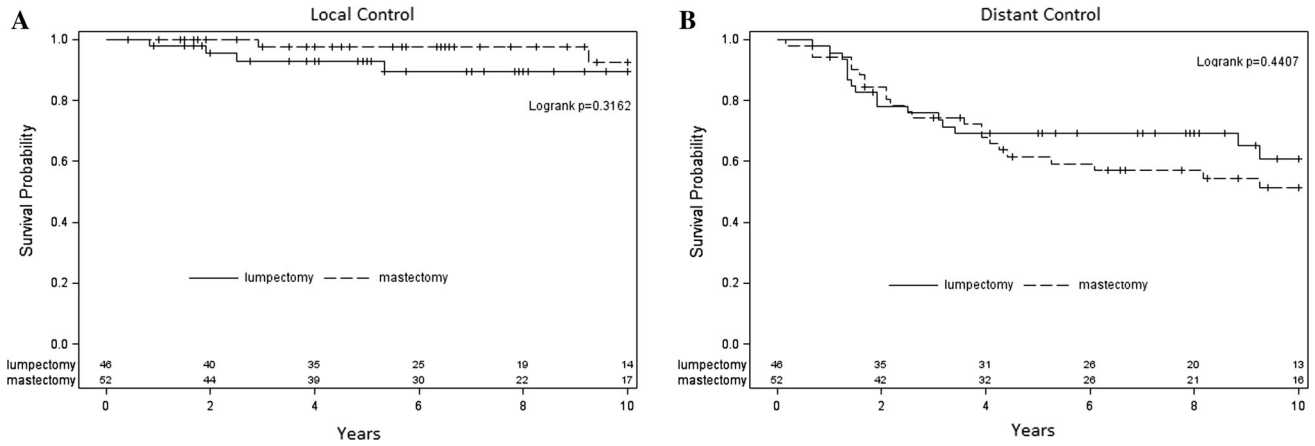

Fig. 1 Kaplan–Meier estimates of local control (**a**) and distant control (**b**) following either breast conserving surgery (*solid line*) or mastectomy (*dashed line*)

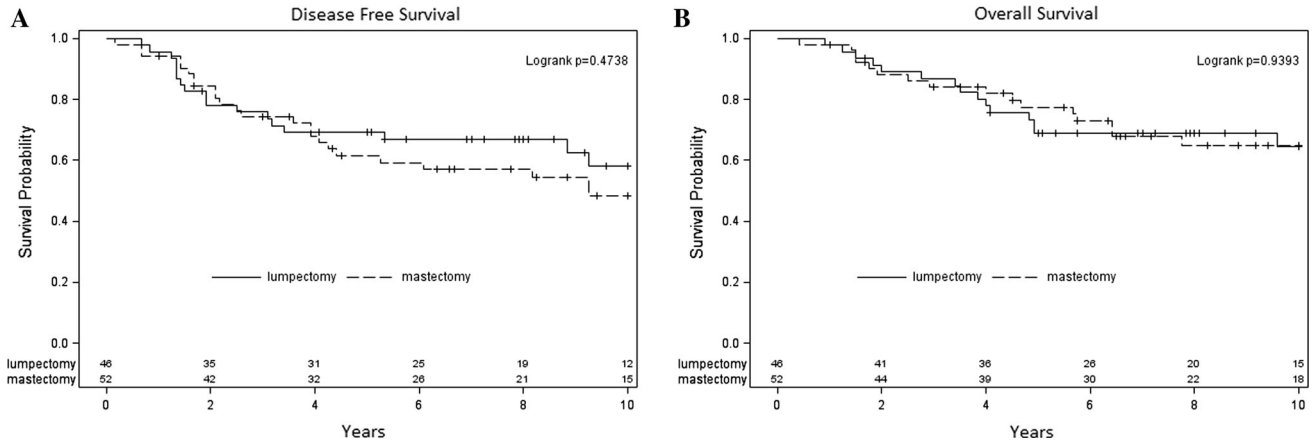

Fig. 2 Kaplan–Meier estimates of disease-free survival (**a**) and overall survival (**b**) following breast conserving surgery (*solid line*) versus mastectomy (*dashed line*)

55.9–71.5) versus those receiving MRM (61.4; 95 % CI 53.6–69.2) ($p = 0.94$; Fig. 2b).

Over the study period, 34 patients succumbed to breast cancer yielding a 5-year disease-specific survival (DSS) of 74.0 % and a 10-year DSS of 68.9 %. Of historical interest, patients treated after the year 2000 showed a trend towards improved 5-year OS when compared to patients treated prior to 2000 (79.0 versus 65.3 %; $p = 0.088$).

Regression analysis of survival outcomes

Univariate Cox regression analysis revealed a number of factors that were adversely prognostic of distant recurrence including omission of endocrine therapy (HR 1.78; $p = 0.05$), histologic grade (HR 2.12; $p = 0.02$) and increasing number of involved lymph nodes (HR 2.60; $p = 0.004$). With regard to overall survival, omission of endocrine therapy ($p = 0.06$) and increasing number of involved lymph nodes ($p = 0.07$) showed a trend towards significance.

Multivariate Cox regression demonstrated that increasing number of lymph nodes was prognostic for distant recurrence (HR 3.5, $p = 0.01$), but not for overall survival ($p = 0.24$). While histologic grade was prognostic for both distance recurrence ($p = 0.02$) and overall survival ($p = 0.01$), the presence of lymphovascular invasion appeared to herald improved overall survival (HR 0.27, $p = 0.01$).

Of note, the type of surgery (MRM versus BCT) did not appear to influence either distant recurrence or overall survival on univariate analysis despite significant baseline differences between the treatment groups. In addition, multivariate analysis showed similar outcomes between treatment groups while adjusting for all noted baseline differences.

Discussion

Modern oncologic practice is increasingly focused on optimizing functional outcomes via organ preservation. In an evolution from Halstedian *en bloc* resection, advances in surgical technique, radiation delivery and systemic therapies have allowed for radical surgical approaches to be avoided in many cases without compromising oncologic efficacy. Indeed, organ-sparing therapies are now the standard of care in malignancies of the head and neck, prostate and bladder among others. Mature analyses now demonstrate that breast conserving therapy is a safe and effective alternative to radical mastectomy. Although this conclusion arose from decades of rigorous prospective investigation, a small proportion of patients present with extensive axillary nodal disease for which little guidance exists.

The results of this study suggest that among women with extensive regional lymph node involvement, BCT yields long-term outcomes that are comparable to those of MRM. While BCT, in this analysis, yielded slightly increased rates of LRR, this was potentially due to the breadth of practice over the course of the study period, with early patients undergoing now-outdated approaches with regard to local therapy (e.g., lower-quality imaging, lower rates of adherence to system therapy, less-meticulous attention to surgical margins, two-dimensional radiotherapy planning, etc.). This is illustrated by the finding that 10-year local control for all patients treated prior to the year 2000 was 87.3 % (95 % CI 71.5–94.6 %) versus 92.5 % (95 % CI 70.9–98.3 %) for those treated after the year 2000. Moreover, our analysis reveals that recurrences among patients with N3 disease are largely driven by distant metastasis—a finding which is unlikely to be strongly influenced by aggressive local/regional management. Therefore, while MRM may be the approach of choice for extensive local disease, it appears that breast conservation is a viable option for the management of extensive regional disease.

These data must be interpreted in the context of the study design. The retrospective nature of this report carries the risk of confounding among several of our findings. Specifically, the observation that well- and moderately differentiated tumors carried a worse prognosis than their poorly differentiated counterparts is somewhat at odds with both the current literature [18] and breast cancer biology [19]. It should be noted that among seven patients with unknown grade, 85.7 % exhibited a distant recurrence, potentially suggesting they were not evenly distributed between grade levels. On the other hand, it is similarly unusual for well-differentiated tumors to present with extensive regional lymph node involvement, perhaps suggesting that this cohort merits further analysis from a biological standpoint. In addition, the broad time period over which the study population was treated necessarily introduced significant heterogeneity with regard to therapeutic approaches. While significant advances in both BCT and MRM have improved all outcomes over recent decades [20], so too has our understanding of breast cancer which is now known to be a heterogeneous disease consisting of at least five intrinsic subtypes, each with its out prognostic and predictive profile [18]. Since many of our patients were treated prior to this observation, disease subtypes in this analysis are largely indeterminate beyond estrogen receptor status and tumor grade.

Thus, our study demonstrates that among breast cancer patients with extensive axillary LN involvement ($\geq$10 positive LNs), MRM, and BCT yield similar outcomes with regard to distant recurrence and survival. As a result, the data suggest that more aggressive surgery via MRM in this setting does not confer an appreciable benefit, perhaps obviated by the near-universal use of adjuvant radiotherapy in this population. And while local control is achievable with either treatment approach, distant recurrence appears to be the main determinant of outcome in this cohort.

Compliance with ethical standards

Conflicts of interest None.

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