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PATTERNS AND RISK FACTORS OF LOCOREGIONAL RECURRENCE IN T1-T2 NODE NEGATIVE BREAST CANCER PATIENTS TREATED WITH MASTECTOMY: IMPLICATIONS FOR POSTMASTECTOMY RADIOTHERAPY

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Abstract

Purpose—Postmastectomy radiation therapy (PMRT) can reduce locoregional recurrences (LRR) in high-risk patients, but its role in the treatment of lymph node negative (LN–) breast cancer remains unclear. The aim of this study was to identify a subgroup of T1-T2 breast cancer patients with LN– who might benefit from PMRT.

Methods and Materials: We retrospectively reviewed 1,136 node-negative T1-T2 breast cancer cases treated with mastectomy without PMRT at the Massachusetts General Hospital between 1980 and 2004. We estimated cumulative incidence rates for LRR overall and in specific subgroups, and used Cox proportional hazards models to identify potential risk factors.

Results: Median follow-up was 9 years. The 10-year cumulative incidence of LRR was 5.2% (95% CI: 3.9–6.7%). Chest wall was the most common (73%) site of LRR. Tumor size, margin, patient age, systemic therapy, and lymphovascular invasion (LVI) were significantly associated with LRR on multivariate analysis. These five variables were subsequently used as risk factors for stratified analysis. The 10-year cumulative incidence of LRR for patients with no risk factors was 2.0% (95% CI: 0.5–5.2%), whereas the incidence for patients with three or more risk factors was 19.7% (95% CI: 12.2–28.6%).

Conclusion: It has been suggested that patients with T1-T2N0 breast cancer who undergo mastectomy represent a favorable group for which PMRT renders little benefit. However, this study suggests that select patients with multiple risk factors including LVI, tumor size ≥ 2 cm, close or positive margin, age ≥ 50, and no systemic therapy are at higher risk of LRR and may benefit from PMRT.

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Keywords

Breast cancer; Mastectomy; Postmastectomy radiation; Risk factors; Locoregional recurrence

INTRODUCTION

Radiation therapy plays an important role in the management of locally advanced breast cancer. Several trials have demonstrated substantial improvement in disease control and, in some trials, benefit in overall survival from the addition of postmastectomy radiation therapy (PMRT) for patients with Stage II and III breast cancer (1–6). Despite an abundance of data supporting the benefit of radiation for more advanced cases of breast cancer, uncertainty exists regarding the appropriate selection of patients with less advanced disease (7). There is a general consensus to advise PMRT for patients with more than four positive lymph nodes and for patients with large local primaries (T3) in the setting of any nodal involvement (8, 9). However, the issue of whether or not patients with less advanced disease, such as those with Stage II disease and one to three positive lymph nodes (LN+1–3) or those with T1–T2 disease and poor prognostic factors, should receive PMRT is debated. In the past, radiation after mastectomy was only considered for patients with T1–T2N0 cancers if surgical margins were positive. However, multiple recent studies have questioned whether early-stage disease with aggressive biological markers in fact confers a higher risk of local recurrence than previously recognized. Concern has been raised that pathological characteristics such as lymphovascular invasion (LVI), grade, receptor status and patient characteristics such as young age should impact the decision for PMRT in otherwise early stage disease (8–11).

The importance of local control is underscored by data showing that improvement in locoregional control will lead to improvement in overall survival from breast cancer (2, 3, 12). These findings were demonstrated in randomized trials and later supported by a report from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which demonstrated a survival benefit with avoidance of one breast cancer death for every four locoregional recurrences (LRR) avoided (12).

Although potential benefits exist for delivery of radiation, treatment is not devoid of complications and therefore identifying the population with a favorable risk/benefit ratio for receiving radiotherapy is the goal of several studies. Whether a subgroup of T1–T2N0 breast cancer patients could benefit from PMRT remains unclear, but recent data demonstrate that a select subset of this population have a higher risk of LRR than would have been perceived in the past (13, 14).

Patients with T1–T2N0 breast cancer are considered to be at low risk for LRR and are typically spared PMRT. We have already shown that tumor size, LVI, margins, and menopausal status are important predictors of LRR after mastectomy in node-negative (LN –) patients (13). The purpose of this study was to update and expand the previous series to include 1,097 patients in an attempt to identify a subgroup of T1–T2N0 patients who might benefit from PMRT.

METHODS AND MATERIALS

Between January 1, 1980, and December 31, 2004, 1,188 cases of LN– invasive breast carcinoma treated by mastectomy with axillary dissection or sentinel node biopsy without adjuvant radiation at the Massachusetts General Hospital were identified through the hospital cancer registry and the breast cancer database. Hospital records and pathology

reports were reviewed. Institutional review board approval was obtained prior to review of medical records. Complete anonymity of names and medical record numbers was maintained. Patients with Tx ($n = 15$), T3 ($n = 25$), T4 ($n = 3$) tumors, and neo-adjuvant chemotherapy ($n = 9$) were excluded from this analysis, as were 26 cases with positive or close final surgical margins treated with PMRT. The cohort for this study includes 1,136 cases of LN- breast cancer in 1,097 patients. Sixty-seven and 168 patients had simultaneous (defined as tumor occurring in the contralateral breast within 6 months after the detection of the first cancer) (15) and metachronous (defined as tumor occurring in the contralateral breast more than 6 months after the detection of the first cancer) (16) bilateral disease, respectively. Those cases were included in the analysis as per the inclusion/exclusion criteria described previously.

Recurrence in the chest wall or regional lymph nodes was considered LRR. Local failure is defined as any recurrence of tumor in the ipsilateral chest wall. Regional failure is defined as any recurrence of tumor in the ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes. Simultaneous distant failure (DF) was defined as any subsequent DF that occurred within 4 months after the diagnosis of the LRR (17). Isolated LRR was defined as the first event occurring without evidence of simultaneous DF, and total LRR as the first event occurring with or without simultaneous distant metastasis. LRR occurring after distant metastasis were not included in the analysis of LRR. For patients with bilateral disease, LRR was included if attributed to the same side being evaluated in this study. LVI that did not meet all the pathologic criteria for positivity were reported as “suspicious” and these were considered negative in our analysis. The extent of LVI was only reported in few cases; therefore, no distinction between focal and extensive LVI was made.

Statistical analysis

Because LVI was not always reported in the early years of the study, cases in which LVI was not reported were analyzed in two different ways. In the first analysis, cases where LVI was not reported were considered negative, because the common practice in the early years was to report the presence of LVI and not to document its absence (13). In the second analysis, 392 cases in which LVI was not reported were excluded and the analysis was conducted on cases where LVI was reported as positive, negative, or suspicious.

We calculated the point and 95% confidence interval estimates for the cumulative incidence rates of “isolated” LRR and “total” LRR. We performed univariate analyses and multivariate analyses using Cox proportional hazards models to assess the association between the cause-specific hazards for isolated or total LRR and various factors (age, menopausal status, margin status, tumor stage, tumor size, tumor grade, presence or absence of LVI, number of nodes examined, ER status, HER2 status, and systemic treatment). We then used the variables included in the multivariate model to form risk subgroups and assess potential heterogeneity in LRR incidence rates across different subgroups. We used R version 2.10.1 (The R Project for Statistical Computing, Vienna, Austria) for cumulative incidence analyses and SAS version 9.2 (SAS, Cary, NC) for the remaining analyses. All p values are two-sided and not adjusted for multiple testing.

RESULTS

Patient and tumor characteristics

A total of 1,136 cases of patients who underwent mastectomy for T1-T2N0 invasive breast cancer and did not receive radiation were identified. The median follow-up was 9 years from the date of diagnosis (range, 0.03–27.7). The median age at diagnosis was 62 years (range, 25–92). Median tumor size was 1.5 cm (range, 0.1–5) and median number of lymph nodes

excised for patients who underwent LN dissection ($n = 1,023$) was 15 (range, 1–63). Ninety-eight patients underwent sentinel LN biopsy with median number of LN removed of 2 (range, 1–8). A total of 293 patients had 10 or fewer LN removed at axillary dissection. The patient, tumor, and treatment characteristics are listed in Table 1.

Locoregional failure rate

The proportion of isolated LRR was 39 of 1,136, and the proportion of total LRR was 58 of 1,136 during the entire follow-up period. The cumulative incidence of isolated LRR at 10 years was 3.5% (95% CI: 2.5–4.8%) and the cumulative incidence of total LRR at 10 years was 5.2% (95% CI: 3.9–6.7%). This included 15 patients with bilateral disease, either simultaneous or metachronous who developed LRR: 11 chest wall, 3 supraclavicular, and one axilla. There were no internal mammary node recurrences. All instances of bilateral disease were considered LRR from the same side treated. The distribution of failures is presented in Table 2.

Lymphatic vessel invasion

When cases where lymphatic vessel invasion (LVI) was not specifically reported were considered as negative, menopausal status ($p = 0.006$), age ≥ 50 ($p = 0.015$), tumor size ≥ 2 cm ($p = 0.006$), poor tumor grade ($p = 0.035$), close or positive margins ($p < 0.0001$), and LVI ($p = 0.0001$) were associated with an increased risk of LRR on univariate analysis. Tumor stage (T1 vs. T2), systemic therapy and the number of lymph nodes removed at axillary dissection (<10 vs. ≥ 10) were not associated with LRR (Table 3). All analyzed variables were included in the multivariate analysis. The final multivariate model included only those variables that remained significant at the 0.05 level in the presence of other variables. The variables associated with increased risk of LRR on multivariate analysis were positive LVI ($p = 0.002$), close or positive margins ($p = 0.001$), tumor size ≥ 2 cm ($p = 0.011$), age ≥ 50 ($p = 0.018$), and no systemic therapy ($p = 0.036$) (Table 4).

The total LRR rate at 10 years in the absence of any of these risk factors; that is, for those with negative LVI, negative margins, tumor size <2 cm, age >50 , and with systemic therapy was 2.0% (95% CI: 0.5–5.2%; $n = 165$) increasing to 3.3% (95% CI: 1.8–5.5%; $n = 450$) in the presence of one of these risk factors, 5.8% (95% CI: 3.4–9.0%; $n = 313$) with two risk factors and 19.7% (95% CI: 12.2–28.6%; $n = 99$) with three or more risk factors (Fig. 1).

When excluding cases in which LVI was not reported, positive LVI ($p = 0.001$), tumor size ≥ 2 cm ($p = 0.022$), age ≥ 50 ($p = 0.042$), and no systemic therapy ($p = 0.030$) were associated with increased risk of LRR on multivariate analysis. Margin was the only variable that became non-significant ($p = 0.24$) (Table 4). The 10-year total LRR rate was 0.8% (95% CI: 0.7–3.9%; $n = 134$) for patients with no risk factor, 3.9% (95% CI: 1.8–7.1%; $n = 290$) for patients with one risk factor, 6.9% (95% CI: 3.6–11.6%; $n = 196$) for patients with two risk factors and 15.4% (95% CI: 8.1–24.8%; $n = 77$) for patients with three or more risk factors (Fig. 2).

DISCUSSION

The delivery of PMRT for women with T1-T2 tumors and negative axillary nodes is not generally warranted because of the low risk of recurrence in this population as a whole. However, in the setting of multiple adverse prognostic factors, the risk of LRR approaches and in some cases surpasses the risk of recurrence documented for patients with one to three positive lymph nodes (13, 14).

The present study has identified a number of clinicopathological variables associated with an increased risk of LRR and subsets of T1-T2N0 patients with LRR rates close to 20%, in

contrast to the 5.2% incidence described in the entire T1-T2N0 population. A multitude of studies has demonstrated the prognostic importance of grade, LVI, tumor size, menopausal status or age, systemic therapy, and surgical margins for predicting risk of LRR (18–23). A caveat in the applicability of these studies is that these series have included (either within the cohort or exclusively) positive lymph nodes, tumor size ≤ 5 cm, or breast-conserving surgery.

The current study confirms our prior finding that the presence of LVI in this population predisposes affected patients to local recurrence (13). Some studies have even suggested that the LRR of patients with LN– disease and LVI who do not receive PMRT is worse than that of patients with node-positive disease receiving adjuvant radiotherapy (18). In a more recent study from the Danish group, LVI was not found to be a sufficient prognostic factor to move patients from the low- to high-risk group (24). The controversial implications of vascular invasion on recurrence have prompted a great deal of debate at the Saint Gallen International Expert Consensus over the years. In 2007, LVI was finally accepted as a discriminatory feature of increased risk for LN– disease, but only when extensive invasion is present (25).

Our data suggest that tumor size is associated with increased LRR rates, confirming findings from earlier studies, by Pinder *et al.*, reporting both tumor grade and size as strong predictors of LRR in LN– patients (26). More specifically, in LN– mastectomy patients, Rosen *et al.* showed that grade was associated with an increased risk of LRR in T1 tumors (27). In contrast, Janni failed to correlate local recurrence with either grade or tumor size for patients with T1-T2N0 having undergone mastectomy (28). In our study, histological grade was not a prognostic factor for failure on multivariate analysis.

The current study also suggests that patient's age was a significant predictor for LRR. Truong *et al.* also found young age to predict for increased LRR (14). In contrast, the data reported by Voogd do not show any significant influence of age on the occurrence of local recurrence in LN– patients treated with mastectomy (29).

Our study has identified positive/close margins as a risk factor for LRR in patients treated with mastectomy who have small tumors and LN–. Even though Ahlborn and Mentzer failed to recognize close margins as a predictor for an increased risk of chest wall failure (30, 31), other studies have underlined the prognostic value of close and positive margins in younger patients (32) and when positive margin occurs in the presence of other aggressive tumor characteristics (33). Given this controversy, in clinical practice today, patients with a close or positive surgical margin after mastectomy are likely to be treated with chest wall irradiation.

In contrast to our previous findings (13), systemic treatment is found to be an independent prognostic factor for LRR in multivariate analysis. The results of recent randomized trials (1–3) have emphasized the importance of systemic therapy in conjunction with radiation therapy not only in improving survival, but also in achieving better local control.

In a study conducted by the International Breast Cancer Study Group on 1275 LN– breast cancer patients treated with mastectomy, systemic therapy conferred a significant improvement in locoregional control in premenopausal patients (34). In this population as a whole, the LRR rate remains low. However, in the setting of T1-T2N0 patients with multiple risk factors undergoing mastectomy, our data concur with recent publications indicating that the risk of LRR may be as high as 20%; a rate that warrants strong consideration of PMRT (13, 14, 35). Truong *et al.* (14) and Yildirim *et al.* (35) identified LVI, tumor size, and grade as factors associated with a greater LRR in T1-T2 patients. Truong *et al.* (14) reported less than 15% LRR risk when these factors were examined individually, and Yildirim *et al.* (35) classified patients with only one of those risk factors in the low-risk group. Combination of

two or more of these risk factors, however, was associated with higher rate of LRR reaching 53% in some instances (35). In a series of 763 T1-T2N0 patients, postmastectomy locoregional relapse was <10% among patients with one of the following characteristics: age <50, premenopausal status, Grade 3 histology, or ER-negative disease when LVI was absent. In the presence of LVI, this risk increased to 15–20% (36). LRR risks of approximately 20% were observed when positive surgical margins occurred in association with young patient age, T2 tumor size, high histologic grade, or the presence of LVI (33).

Our results have shown a LRR rate close to 20% when three or more of the following adverse factors were present simultaneously: age $\geq$ 50, tumor size $\geq$ 2 cm, positive LVI, close or positive margins, and absence of adjuvant systemic treatment. Truong et al. have reported a rate in excess of 20% when Grade 3 tumors were associated with LVI, and in the absence of LVI, combination of T2 tumors with high grade could yield similar rates if systemic therapy was omitted (14). Taken together, these data seem to confirm that the concomitant presence of multiple risk factors contributes to higher than expected risk of LRR in T1-T2N0 mastectomy patients.

This retrospective study carries several limitations; primarily the missing information in some variables not routinely reported in the 1980s, affecting 392 cases, where LVI was not reported. Including those cases as negative LVI or excluding them yielded different multivariate models. Another limitation is that biases have certainly hampered patient selection; this study probably does not reflect specific interventions that would have taken place in our era, more specifically the systemic treatment which was much less used for LN – patients than it is today. One last limitation to consider is the relatively small number of patients or events in certain subgroups of interest which could limit our analysis, such as the pattern of LRR in different biological phenotypes. Several studies have emphasized the role of biological subtypes of breast cancer in predicting LRR (37) and the effect of PMRT on reducing LRR and increasing survival in the various subtypes (38). This question could not be addressed in our series, because in the 162 cases with readily available estrogen receptor, progesterone receptor and Her2 status information, only six LRR occurred.

These obstacles can only be avoided in prospective trials that are designed to investigate biological subtypes and other factors potentially influencing LRR. In the meantime, we must use the tools within reach to identify the patients at significantly high risk of LRR to justify use of PMRT. T1-T2N0 mastectomy patients have always been perceived as a low-risk population who would not benefit from radiotherapy. However our data, as well as others (14, 35), have demonstrated that not all these patients are at truly low risk. Particularly, 50 years old patients and younger with tumor size $\geq$ 2 cm, positive LVI, close or positive margins, and lack of systemic therapy conferred a higher than accepted risk of LRR. In clinical practice, identifying this high-risk subpopulation for potential postmastectomy chest wall radiation should be considered.

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Fig. 1. Cumulative incidence of locoregional recurrence by risk groups (cases in which lymphovascular invasion not specifically reported included as negative).

Fig. 2. Cumulative incidence of locoregional recurrence by risk groups (cases in which lymphovascular invasion not specifically reported excluded from the analysis).

Table 1

Patient, tumor, and treatment characteristics

Total number of patients	1,136
Age median (range)	62 (25–92)
Menopausal status	
Premenopausal	234
Postmenopausal	830
Peri-menopausal	38
Unknown	34
Margin status	
Positive	10
Close (<2 mm)	60
Negative (≥ 2 mm)	1,021
Unknown	45
Tumor stage	
T1	855
T2	281
Tumor size	
Median	1.5
0.1–1.9 cm	711
2–5 cm	353
Unknown	72 [*]
Lymphovascular invasion	
Present	125
Absent	596
Suspicious	23
Not described	392
Grade	
1	113
2	462
3	239
Unknown grade	322
Number of nodes examined	
Median	14
<10	240
10	885
Unknown	11
ER status	
Positive	634
Negative	216
Unknown	286
Her2 status	

Total number of patients	1,136
Positive	25
Negative	139
Unknown	972
Systemic treatment	
Endocrine therapy alone	270
Chemotherapy alone	77
Both chemo and endocrine therapy	89
Neither chemo nor endocrine therapy	700

* 72 unknown size (classified as 40 T1 and 32 T2 according to oncologist notes).

Table 2

Sites of failures

	Number of isolated LRR (%)	Number of total LRR (%)
Chest wall	30 (77%)	41 (71%)
Axilla	4 (10%)	6 (10%)
Supraclavicular nodes	1 (3%)	7 (12%)
Internal mammary chain	2 (5%)	3 (5%)
Chest wall/axilla	1 (3%)	0 (0%)
Chest wall/supraclavicular nodes	1 (3%)	0 (0%)
Chest wall/internal mammary chain/supraclavicular nodes	0 (0%)	1 (2%)
Total	39 (100%)	58 (100%)

Abbreviation: LRR = locoregional recurrences.

Table 3

Total locoregional failures according to patients, tumor, and treatment characteristics

	Number of patients	Total LRR	
		n (%)	p value
Menopausal status			
Postmenopausal	830	34 (4.1)	0.0063
Peri-premenopausal	272	23 (8.5)	
Age			
Continuous variable			0.002
40	82	8 (9.8)	0.032
>40	1,054	40 (4.7)	
50	287	22 (7.7)	
>50	849	36 (4.2)	
Tumor stage			
T1	855	42 (4.9)	0.43
T2	281	16 (5.7)	
Tumor size			
Continuous variable			0.023
2	353	28 (7.9)	0.0059
<2	711	29 (4.1)	
Grade			
Well	113	1 (0.9)	0.007
Moderate	462	27 (5.8)	
Poor	239	21 (8.8)	
Well/moderate	575	28 (4.9)	
Poor	239	21 (8.8)	0.035
Margins			
Positive/close	70	12 (17.1)	<0.0001
Negative	1,021	44 (4.3)	
Lymphovascular invasion			
Positive	125	15 (12)	0.0001
Negative/suspicious/not reported	1011	43 (4.3)	
Positive	125	15 (12)	0.0002
Negative/suspicious	619	23 (3.7)	
Estrogen receptor status			
Positive	634	32 (5)	0.23
Negative	216	16 (7.4)	
Nodes removed			
10	293	14 (4.8)	0.77
>10	832	44 (5.3)	
Systemic therapy			
Yes	436	18 (4.1)	0.38

	Number of patients	Total LRR	
		<i>n</i> (%)	<i>p</i> value
No	700	40 (5.7)	

Some variables are missing, therefore isolated and total locoregional recurrences do not always add to 39 and 58, respectively.

Table 4

Multivariate analysis

	Patients with positive, negative, and unknown LVI			Patients with positive or negative LVI		
	HR	95% CI	p	HR	95% CI	p
Systemic treatment (yes vs. no)	0.5	0.3–0.96	0.036	0.5	0.2–0.9	0.030
Margins (2 mm vs. <2 mm)	3.3	1.7–6.5	0.001	1.8	0.7–4.7	0.237
Tumor size (2 cm vs. < 2 cm)	2.0	1.2–3.4	0.011	2.2	1.1–4.2	0.022
Age (>50 vs. 50)	0.5	0.3–0.9	0.018	0.5	0.2–0.98	0.042
Lymphovascular invasion (positive vs negative)	2.7	1.5–5.1	0.002	3.2	1.6–6.2	0.001

Abbreviations: HR = hazards ratio; LVI = lymphovascular invasion.