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Impact of Molecular Subtype on Locoregional Recurrence in Mastectomy Patients with T1-2 Breast Cancer and 1-3 Positive Lymph Nodes

Tracy-Ann Moo, MD¹, Robert McMillan, MPH, MD¹, Michele Lee, BS², Michelle Stempel, MPH¹, Alice Ho, MD³, Sujata Patil, PhD⁴, and Mahmoud El-Tamer, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

²Weill Cornell Medical College, New York, NY 10021

³Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

⁴Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

Abstract

Introduction—Postmastectomy radiation (PMRT) in T1-T2 tumors with 1-3 positive axillary lymph nodes (ALNs) is controversial. Impact of molecular subtype (MST) on locoregional recurrence (LRR) and PMRT benefit is uncertain. We examined the association between MST and LRR, recurrence-free survival (RFS), and overall survival (OS), in T1-T2 tumors with 1-3 positive ALNs.

Methods—From an institutional database, we identified mastectomy patients with 1-3 positive ALNs between 1995-2006. Patients who received neoadjuvant chemotherapy, had T3-4 tumors, or 4 positive ALNs were excluded. MST was defined as: hormone receptor (HR)+/HER2-(Luminal A/B), HR+/HER2+(Luminal HER2), HR-/HER2+(HER2), and HR-/HER2-(basal). Kaplan-Meier method and Cox regression analysis were used to examine association between MST and LRR, RFS, and OS.

Results—884 patients (700 no PMRT, 141 PMRT) were included: 72.8% luminal A/B, 7.8% luminal HER2, 6.8% HER2, and 12.6% basal. Median follow-up was 6.3 years; 39 LRRs occurred. Luminal A/B subtype had the smallest tumors ($p=0.03$), lowest intraductal component ($p=0.01$), histologic grade ($p<0.0001$), lymphovascular invasion (LVI) ($p=0.008$) and multifocality/multicentricity ($p=0.02$). On univariate analyses, there was no association between MST and LRR. MST was associated with RFS and OS; the basal and HER2 subtype had the lowest RFS ($p=0.0002$) and OS ($p<0.0001$). On multivariate analysis, only age ≥ 50 years ($p=0.002$) and presence of LVI ($p=0.0003$) were predictive of LRR; MST was not ($p=0.38$).

Conclusion—In patients with T1-2 breast cancer and 1-3 positive lymph nodes who did not receive PMRT, MST was not a independent predictor of LRR and may not be useful in selecting PMRT candidates in that group.

Keywords

molecular subtype; locoregional recurrence; mastectomy; axillary lymph nodes

INTRODUCTION

Although postmastectomy radiation (PMRT) has been shown to decrease rates of locoregional recurrence (LRR) in high-risk mastectomy patients,¹⁻³ the issue of PMRT in patients with early breast cancer and 1-3 positive axillary lymph nodes (ALNs) is debated. Randomized trials conducted in the 1980s and early 1990s reported LRR rates of 12-30%.^{1,4,5} The Oxford overview showed improved LRR rates in 1-3 positive ALN patients receiving PMRT—4% in the group who received PMRT compared to 16% in those who did not.³ However, more recent retrospective analysis of patients with 1-3 positive ALNs treated with mastectomy and current adjuvant systemic therapy have reported LRR rates of 5-10%.^{6,7} With such low LRR rates in the modern era, PMRT may not benefit all patients with 1-3 positive ALNs.

In order to identify patients with 1-3 positive ALNs who would benefit from PMRT, prior retrospective studies have examined various clinicopathologic features associated with a higher risk of LRR. Studies have identified features, such as age, LVI, and size of axillary nodal metastases, as high risk; these features are often used to select patients for PMRT.^{6,8,9} However, current treatment of breast cancer uses not only clinicopathologic criteria, but also incorporates biologic features of the tumor into clinical decision making. Molecular subtyping has emerged as an important tool in determining prognosis and therapeutic options in breast cancer, and has been shown to correlate with differences in survival with the HER2 amplified and triple negative groups having the poorest outcomes.¹⁰⁻¹² In patients with early tumors (T1-T2) and limited lymph node involvement (1-3 positive lymph nodes), the impact of molecular subtype (MST) on LRR and PMRT benefit is unclear. Here we examine the association between subtype and LRR in a cohort of patients with T1-2 tumors and 1-3 positive lymph nodes who were treated with current standards for adjuvant systemic therapy.

MATERIALS AND METHODS

From an institutional database, we identified all patients who underwent total mastectomy with sentinel and or axillary lymph node dissection between January 1995 and December 2006. Patients who received neoadjuvant chemotherapy, had T3-4 tumors, or had 4 positive lymph nodes were excluded. Patients with isolated tumor cells only on final pathology were classified as N0 and also excluded. In those patients with bilateral breast cancer, clinicopathologic data were included for the side meeting study inclusion criteria. Clinicopathologic and patient follow-up data were obtained from the electronic medical

record. This study was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board.

MST was categorized using immunohistochemical surrogates: hormone receptor (HR) positive (-)/HER2 negative (-) (Luminal A/B), HR+/HER2+ (Luminal HER2), HR-/HER2+ (HER2), HR-/HER2- (Basal). HR + included ER+ and/or PR+ tumors, HR- were ER- and PR-. HER2 positive was defined as immunohistochemical staining score of 3+ or 2+ with an amplification ratio of ≥ 2.2 on fluorescence in situ hybridization.

Adjuvant chemotherapy and/or hormonal therapy were delivered at the discretion of the treating medical oncologist. HER2 testing and trastuzumab treatment was not standard for most of the study period; however, 129 patients had known HER2 status and 52 were treated with trastuzumab between 1995 and 2006. Postmastectomy radiation was delivered according to physician discretion. There were no formal institutional guidelines for which patients with 1-3 positive lymph nodes should receive PMRT.

Proportions with each clinicopathological variable by subtype were tested using the chi-square test. The primary endpoint of this study was locoregional recurrence. Locoregional recurrence was defined as tumor recurrence in the ipsilateral chest wall, axilla, and infraclavicular, supraclavicular, or internal mammary lymph nodes. Secondary endpoints were recurrence-free survival (RFS) and overall survival (OS). RFS was calculated as time from surgery to LRR, distant metastasis, or death. OS was defined as time from surgery to date of last follow-up or death. The date of last follow-up was defined as the last office visit at MSKCC which documented disease status, correspondence documenting disease status, or death notification.

The Kaplan Meier method and log-rank test were used to examine the univariate association between MST and other clinicopathologic variables with LRR, RFS, and OS. The Cox proportional hazards model was used to examine whether MST was independently associated with outcome in a multivariate model. P-values less than .05 were considered significant.

RESULTS

Between 1995 and 2006, 1331 mastectomy patients with 1-3 positive lymph nodes were identified in our database. A total of 884 patients met study inclusion criteria and were classified into different MSTs. The luminal A/B subtype consisted of 644 patients (72.8%), the luminal HER2 subtype consisted of 69 patients (7.8%), the basal subtype consisted of 111 patients (12.6%), and the HER2 subtype consisted of 60 patients (6.8%). With a median follow-up of 6.3 years (range, 0-16 years), 39 locoregional events were identified. A total of 141 patients (16%) received PMRT. There was no significant difference among the subtypes in terms of the proportion of patients receiving PMRT ($p=0.39$). Table 1 compares clinicopathologic features among the MSTs. These features differed among subtypes with respect to tumor size, age, histologic grade, lymphovascular invasion (LVI), and multifocality. The luminal A/B subtype had smaller tumor size ($p=0.03$), lower histologic grade ($p<0.0001$) and LVI ($p=0.008$). The basal subtype was more likely to have a larger

tumor size, higher histologic grade, and presence of LVI. The majority of patients received an axillary lymph node dissection; 40 patients (4.5%) received only a sentinel lymph node dissection and had fewer than 7 lymph nodes removed.

LRR

Overall, there was no significant difference in LRR among the subtypes (Figure 1). The basal and HER2 subtypes had the highest 5-year LRR (5.4% and 8.8%, respectively), while the luminal A/B and luminal HER2 subtypes had lower rates of LRR (2.9% and 3.1%, respectively). These differences did not reach statistical significance. In multivariate analysis, age ≥ 50 years ($p=0.002$) and presence of LVI ($p=0.0003$) were associated with LRR; MST was not associated with LRR ($p=0.38$) (Table 2). When LRR recurrence was examined based on receipt of PMRT, there remained no difference in LRR among the subtypes who were not radiated. However, in the group that was radiated, the HER2 subtype continued to do significantly worse, with a LRR of 16.7% in the PMRT group compared to 7% in the no-PMRT group ($p=0.05$).

RFS and OS

On univariate and multivariate analysis, MST had a significant association with RFS (univariate, $p=0.002$; multivariate $p<0.0001$) and OS (univariate and multivariate, $p<0.001$). (Figures 2 and 3) The HER2 and basal subtypes had the lowest 5-year RFS (69% and 72%, respectively), compared to the 81% and 88% in the luminal HER2 and luminal A/B groups. In terms of OS, the basal subtype had the poorest outcome, with a 5-year OS of 78.5%.

Adjuvant Therapy

Most patients received some form of adjuvant systemic therapy. 753 (85%) received systemic chemotherapy. The luminal A/B subtype had the lowest proportion of patients receiving chemotherapy (82% compared to 91% in the luminal HER2, 92% in the HER2, and 95% in the basal group [$p=0.0004$]). Most patients who received chemotherapy received an anthracycline/taxane based regimen (67%). 37% of the HER2+ patients received trastuzumab, 39% of the HER2+ patients in the luminal/HER2 group received trastuzumab, and 35% of the HER2+ patients in the HER2 group received trastuzumab. 668 (76%) patients received hormonal therapy, 589 (89%) of whom were in the luminal A/B group (Table 1).

DISCUSSION

Current treatment guidelines for invasive breast cancer recommend PMRT for patients with tumors that are locally advanced ($>5\text{cm}$), with positive lymph nodes or extensive axillary lymph node involvement (≥ 4 positive lymph nodes).¹³ Guidelines are less clear in patients with 1-3 positive ALNs and tumors less than 5 cm; the National Comprehensive Cancer Network recommends strong consideration of PMRT in this group.¹⁴ In practice, there is controversy as to whether PMRT is necessary in patients treated with current adjuvant chemotherapy and hormonal therapy, and only about 20% of patients with 1-3 positive lymph nodes actually receive PMRT.¹⁵

MST has been shown to predict recurrence and survival in breast cancer.^{11,16-19} However, there are limited reports on MST association with LRR in the 1-3 positive ALN group. Using immunohistochemical surrogates, we investigated the association of MST with LRR, and PMRT effect among patients with early breast cancer and 1-3 positive lymph nodes.

In our analysis, MST was associated with OS and RFS as previously reported.^{16,17,19} The basal and HER2 subtypes had significantly lower OS and RFS compared to the luminal subtypes. There was a trend toward an increase in LRR in the HER2 and basal subtypes (LRR, 5.4% and 8.8%, respectively) compared to the luminal A/B and luminal HER2 subtypes (LRR, 2.9% and 3.1%, respectively). However, on univariate and multivariate analysis, this association was not significant ($p=0.35$ and $p=0.38$, respectively). Our 5-year LRR rates ranged from 2.9-8.8% in the entire cohort. This is in contrast to the higher rates reported in previous studies which have looked at MST and LRR in postmastectomy patients treated in the 1980s and early 1990s.¹⁷⁻²⁰ Voduc et al. looked at 2,985 tumors between 1986 and 1992 treated with either BCT or mastectomy and found 10-year rates of local recurrence ranging from 8% in the luminal A subtype to 13-20% among the other subtypes. Notably, this study had a very low utilization of systemic therapy, with only 26% of patients receiving systemic chemotherapy. LRR rates comparable to ours were found by Dominici et al. who retrospectively reviewed 819 postmastectomy patients. Recurrence rates were 1% for HR+/HER2-, 6.5% for HR+/HER2+, 2% for HR-/HER2+, and 10.9% for HR-/HER2- subtypes; this difference was significant ($p<0.01$). While this group represented a modern series of patients, it was much more heterogeneous, as it included patients with both negative and positive nodal status, possibly explaining the wider range in LRR rates.²¹ This is the first study to specifically examine the 1-3 lymph node positive subset of patients, eliminating the influence of the node-negative and 4 positive lymph node groups. As such, these patients have a lower nodal disease burden, but are often treated with chemotherapy and/or hormonal therapy. In our study, 85% of patients overall received systemic chemotherapy; this was highest rate in the triple negative group where 95% received chemotherapy. In the HR+ subtypes (luminal A/B and luminal HER2), 89-92% of patients received hormonal therapy. 37% percent of our HER2 patients were treated with adjuvant trastuzumab.

Among patients who did receive PMRT, the HER2 subtype had the poorest 5-year LRR outcomes (17% versus 7% in the no-PMRT group). This was observed previously by Kyndi et al., who looked at 1000 breast cancer patients randomly assigned to PMRT versus no PMRT in the Danish Breast Cancer Cooperative Group (DBCG) trial. When patients were analyzed by subtype, the HER2 group did not show a significant improvement in LRR with PMRT (21% versus 33%, $p=0.2$). However, they did not take into account treatment with adjuvant trastuzumab, which has been shown to decrease rates of LRR by 50%.²² As standard treatment of HER2+ patients with tumors >5 mm now includes adjuvant trastuzumab, LRR rates should improve.

This study is limited by its retrospective design. We did not find a significant difference in LRR between different subtypes, and this may be difficult to demonstrate in a group of this size. However, with such low event rates, our cohort represents one of the largest studies of the 1-3 lymph node positive group. We did not perform genotype-based tumor subtyping in

this study. Tumor subtypes were approximated based on immunohistochemical surrogates for genotype-based MSTs. While MSTs were initially identified using gene expression analysis, IHC surrogates were later validated by comparing gene expression and IHC analysis.²³ We did not separate luminal A and B tumors, as there is no reliable and consistent method of differentiating between luminal A and B using IHC surrogates. Studies have shown that in the luminal B subtype approximately 30-50% of genotype-based luminal B tumors do not overexpress HER2, and so this group can be misclassified as luminal A when using IHC surrogates.²⁴ Furthermore, current treatment of both luminal A and B subtypes are similar and include hormonal therapy. Thus, luminal HER2 was used to describe the HR+/HER2 overexpressing group. Another limitation is the selection bias in the PMRT group, as these patients were likely a higher-risk group selected due to the presence of clinicopathologic risk factors for recurrence. However, there was no difference in the proportion of patients among the different subtypes receiving PMRT, and for all except the HER2 subtype, outcomes were comparable. The HER2 and luminal HER2 subtypes had the smallest numbers of patients, and standard treatment now includes trastuzumab for all HER2 positive patients. As such, we cannot draw definitive conclusions from this heterogeneous cohort, and we expect that outcomes in these patients will change in the future. Another limitation of this study is the inclusion of patients who underwent PMRT: they represent a small group (n = 141), and PMRT is a treatment variable not inherently part of the pathology. The result of the analysis, however, was similar with or without PMRT patients.

Conclusions

The treatment of breast cancer continues to change, requiring constant re-evaluation of current practice. Patients with T1-2 tumors with 1-3 positive lymph nodes represent an intermediate group that has a limited nodal disease burden and that is currently treated with systemic chemotherapy and hormonal therapy with or without PMRT. The benefit of administering PMRT to all patients with 1-3 positive lymph nodes seems to be an overtreatment with the low LRR rates (<10%) reported in modern series. Although MST does predict survival and systemic metastasis, it does not seem to be a useful tool to identify patients who would benefit from PMRT in this subgroup. Among those patients who did receive PMRT, the HER2 subtype continued to have the poorest outcomes, a finding which will likely change with current standards for administering adjuvant trastuzumab.

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Synopsis

In patients with T1-2 breast cancer and 1-3 positive lymph nodes who did not receive postmastectomy radiation, molecular subtype was not a independent predictor of locoregional recurrence and may not be useful in selecting postmastectomy radiation candidates in that group.

FIG 1.
Association of molecular subtype and locoregional recurrence.

FIG 2.
Association of molecular subtype and recurrence-free survival.

FIG 3.
Association of molecular subtype and overall survival.

TABLE 1

Comparison of clinicopathologic features among molecular subtypes.

		Luminal A/B (%)	Luminal HER2 (%)	Basal (%)	HER2 (%)	p-value
		n = 644	n = 69	n = 111	n = 60	
Age	50	44	67	43	53	
	> 50	56	33	57	47	0.002
Tumor size	< .5	4	3	6	7	
	.5 to 1	10	13	6	10	
	1 to 2	41	43	24	38	
	2 to 5	45	41	63	45	0.033
Histological grade	I	2	0	0	0	
	II	24	13	5	8	
	III	57	84	87	92	
	Unknown	17	3	8	0	< .0001
Nuclear grade	I	2	0	1	0	
	II	49	29	13	8	
	III	29	59	77	87	
	Unknown	20	12	9	5	< .0001
# Positive nodes	1	59	59	56	45	
	2	27	28	27	42	
	3	14	13	17	13	0.340
LVI	No	54	35	44	53	
	Yes	46	65	56	47	0.009
Multifocal/centric	No	54	51	68	47	
	Yes	46	49	32	53	0.022
Extranodal invasion	No	82	83	87	78	
	Yes	18	17	13	22	0.486
Size of ALN metastasis	Micro	30	23	21	20	
	Macro	69	75	78	80	
	Unknown	1	2	1	0	0.071
Chemotherapy	No	14	6	4	3	
	Yes	82	91	95	92	
	Unknown	4	3	1	5	0.0004
Hormonal therapy	No	4	7	86	83	
	Yes	92	89	11	10	
	Unknown	4	4	3	7	< 0.0001
Trastuzumab	No	95	57	96	58	
	Yes	0	39	0	35	
	Unknown	5	4	4	7	< .0001
RT	No	80	80	77	75	

		Luminal A/B (%)	Luminal HER2 (%)	Basal (%)	HER2 (%)	p-value
		n = 644	n = 69	n = 111	n = 60	
	Yes	15	16	21	20	
	Unknown	5	4	2	5	0.398

LVI, lymphovascular invasion; ALN, axillary lymph node; RT, radiation therapy

TABLE 2

Multivariate analysis: clinicopathologic features associated with locoregional recurrence.

	HR	95% CI	p-value
PMRT	1.7	0.72-4.2	0.22
Age < 50 years	0.33	0.16-0.68	0.003
LVI	4.03	1.9-8.6	0.0003
Subtype			
Luminal A/B	ref		
Luminal HER2	0.69	0.21-2.32	
Basal	1.51	0.62-3.70	
HER2	1.86	0.75-5.15	0.38

HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; LVI, lymphovascular invasion