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Estrogen Receptor, Progesterone Receptor, and HER2 Status Predict Lymphovascular Invasion and Lymph Node Involvement

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Abstract

Background—The ACOSOG Z0011 trial demonstrated that axillary dissection (ALND) is not necessary for local control or survival in women with T1/2cN0 cancer undergoing breast-conserving therapy. There is concern about applying these results to triple-negative (TN) cancers secondary to their high local-recurrence (LR) rate. We examined the frequency of lymphovascular invasion (LVI) and nodal metastases in TN cancers to determine whether ALND can be safely avoided in this subtype.

Methods—Data were obtained from a database of patients with invasive breast cancer treated at Memorial Sloan Kettering from 1/98–12/10. 11,596 tumors were classifiable into clinical surrogates for molecular subtype by immunohistochemical analysis: hormone receptor (HR)+/HER2+, HR+/HER2-, HR-/HER2+, and TN(HR-/HER2-). Multivariable logistic regression analysis (MVA)was used to determine associations between clinicopathologic variables and subtype.

Results—There were differences in age, tumor size, LVI, grade, and nodal involvement among groups. On MVA controlling for size, grade, and age, ER, PR, and HER2 status were significantly associated with LVI($p<.0001$). Relative to TN tumors, HR+/HER2-, HR+/HER2+, and HR-/HER2+ tumors had higher odds of demonstrating LVI of 1.8(OR,1.8; 95% CI,1.6–2.1), 2.5(2.5;2.0–3.0), and 1.7(1.7;1.4–2.1), respectively. On MVA adjusting for size, grade, LVI, and age, TN tumors had the lowest odds of having any or high-volume nodal involvement (≥4 nodes, $p<.0001$).

Conclusions—LVI and nodal metastases were least frequent in TN cancers compared with other subtypes, despite the uniformly worse prognosis and increased LR rate in TN tumors. This suggests TN cancers spread via lymphatics less frequently than other subtypes and ALND may be avoided in TN patients meeting Z0011 eligibility criteria.

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Keywords

Molecular subtype; triple negative; breast cancer; lymphovascular invasion

Introduction

Gene expression profiling has established that breast cancer comprises a group of biologically distinct diseases.[1,2] Expression levels of the estrogen and progesterone receptors, together defining hormone receptor (HR) status, and the HER2/*neu* receptor (HER2), characterize clinical surrogates for the molecular subtypes of breast cancer[3]: HR+/HER2- (luminal A-like); HR+/HER2+ (luminal B-like); HR-/HER2+ (HER2 tumors); and HR-/HER2- (triple-negative [TN], also referred to as basal-like). Expression of these receptors can be measured by immunohistochemistry (IHC), allowing subtype classification to be widely applied in the clinical setting. This information is used to guide systemic therapy as well as predict response to treatment and prognosis.[4–8]

Patterns of recurrence and outcome differ among breast cancer molecular subtypes.[8–10] HER2 tumors, prior to the use of adjuvant trastuzumab, and TN tumors were associated with higher local recurrence (LR) rates[9] and poorer overall survival (OS) than HR+ tumors.[10] With the increased use of trastuzumab in the treatment of HER2 overexpressing breast cancer (includes the HR+/HER2+ and HR-/HER2+ subtypes), the rates of local failure and prognosis in this group have improved significantly[11], while TN breast cancers continue to have a poor prognosis and an increased rate of LR. Given this, there is concern about adopting any treatment strategy with less aggressive local management for patients with TN breast cancers. In particular, there is concern about applying results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, which demonstrated that axillary lymph node dissection (ALND) is not necessary for locoregional control or survival in women with T1/2cN0 cancer undergoing breast-conserving therapy (BCT), since relatively few women with HR- tumors were included in this study and HER2 status was unknown.[12,13] Here we sought to quantify the frequency of lymphovascular invasion (LVI) and nodal metastases in each breast cancer subtype as approximated by ER, PR, and HER2, and to determine whether TN tumors have a higher risk of LVI and nodal metastases, in case this risk should preclude the application of ACOSOG Z0011 to this subtype.

Methods

Patient Population

A total of 11,449 patients with 11,715 invasive breast cancers were treated at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1998 and December 2010. Of these, estrogen receptor (ER), progesterone receptor (PR), and HER2 status was available in all but 119 tumors, in which the HER2 status was equivocal, leaving 11,596 tumors which were classifiable into surrogates for molecular subtype on the basis of their biomarker profiles. Patients with prior malignancy were included, as long as their breast cancer was a primary breast cancer. In patients who had bilateral breast cancers, each cancer was included as a separate event and its biomarker profile recorded. Patients who were treated with

neoadjuvant systemic therapy were excluded. Data were obtained from a prospectively maintained registered database. This study was approved by the MSKCC institutional review board.

Classification of Groups

Tumors were classified as follows: HR+/HER2- (ER+ or PR+ and HER2-), HR+/HER2+ (ER+ or PR+ and HER2+), HR-/HER2+ (ER- and PR- and HER2+), and TN HR-/HER2- (ER- and PR- and HER2-). ER and PR status was determined by IHC. ER and PR positivity was defined as the presence of staining of ≥1% of tumor cells. Tumors were considered HER2+ if they scored "3+" by IHC or if they were HER2 amplified (ratio≥2.2) on the basis of fluorescence in situ hybridization. Grade was defined as nuclear grade when available. When nuclear grade was not available or reported, histologic grade was used as a surrogate. If the histology was compatible with classic lobular carcinoma, the tumor was assigned "low" grade. Nodal positivity was defined as the presence of any tumor cells in a lymph node and included macrometastases, micrometastases, and isolated tumor cells.

Statistical Analysis

The x^2 test was used for categorical variables and analysis of variance for continuous variables to compare the distribution of clinicopathologic characteristics among the four subtypes. All percentages and statistical tests were based on available data. Multivariable logistic regression analysis (MVA) was used to examine whether subtype was independently associated with three outcomes of interest: LVI; any nodal involvement; and high-volume nodal involvement. All models were adjusted for tumor size (continuous), grade (high vs. intermediate/low), age (at time of surgery, continuous), and for the two nodal involvement models considered, LVI. TN was the reference group. Patients with missing co-variate data (n=571) were excluded from the MVA. All statistical tests were two sided, and a p-value of ≤0.05 was considered significant. All statistical analyses were performed using SAS Version 0.1 (SAS Institute, Cary, NC).

Results

The distribution of subtype in the study population was 74% HR+/HER2-, 8% HR+/HER2+, 5% HR-/HER2+, and 13% TN. The presenting characteristics of the entire population are summarized in Table 1. Patient and tumor characteristics divided by subtype are displayed in Table 2. Among the four subtypes, there were significant differences in age, tumor size, LVI, grade, and nodal involvement (all $p<0.0001$). Patients with HR+/HER2- tumors presented at an older median age than the other subtypes with a median age of 57.5 (range, 22–96) years. HR-/HER2+ and TN- tumors were larger and more frequently high grade than the HR+ tumors. 25% of HR+/HER2- tumors were high grade compared to 89% and 86% of HR-/HER2+ and TN tumors, respectively. On univariate analysis, HR+/HER2- and TN tumors had lower rates of LVI than the HER2 overexpressing subtypes. HR+/HER2- and TN tumors were also less likely to have ≥1 lymph node involved and to have high-volume lymph node involvement (≥4 nodes involved) than HER2 overexpressing tumors.

On MVA, after controlling for tumor size, grade, and age, subtype was independently associated with LVI ($p<0.0001$) (Table 3). Specifically, patients with the TN subtype had the lowest odds of demonstrating LVI, with patients with the HR+/HER2+ subtype being 2.5 times more likely than those with the TN subtype to have LVI (odds ratio [OR], 2.5; 95% confidence interval [CI], 2.0–3.0). Patients with the HR+/HER2- subtype were 80% more likely (OR, 1.8; 95% CI, 1.6–2.1) and patients with HR-/HER2+ were 70% more likely (OR, 1.7; 95% CI, 1.4–2.1) to have LVI than those with the TN subtype.

On MVA, after controlling for tumor size, grade, LVI, and age, subtype was independently associated with any lymph node involvement and high-volume lymph node involvement (≥4 lymph nodes involved, $p<0.0001$) (Table 4). Specifically, patients with the HR-/HER2- subtype had the lowest odds of having ≥1 positive node and of having high-volume lymph node involvement. HR-/HER2+ tumors were 2.0 times more likely than HR-/HER2- tumors to be associated with any nodal involvement (OR, 2.0; 95% CI, 1.6–2.5) and were 2.3 times more likely than HR-/HER2- tumors to have ≥4 nodes involved (OR, 2.3; 95% CI, 1.7–3.1).

Discussion

Our study confirms and expands upon our previous work indicating that presenting tumor features vary by breast cancer molecular subtype approximated by ER, PR, and HER2 status.[14] These features include age, tumor size, LVI, grade, and nodal involvement. The previous study by Wiechmann et al included 6,072 breast tumors (the majority of which are included in the current study) and showed that TN tumors had the lowest risk of having any nodal disease and high-volume nodal disease. This observation is consistent with several published series relating these characteristics to molecular subtype. Crabb et al demonstrated in a retrospective analysis of 3,441 early-stage breast cancers that subtype as approximated by ER, PR, and HER2 was predictive of nodal involvement, independent of grade and tumor size.[15] The TN subtype had the lowest odds of having axillary lymph node involvement, with an OR of 0.53 (95% CI, 0.41–0.6; $p<0.0001$) relative to the HR+/HER2- subtype. The current study, which includes 11,596 breast cancers and expands our group of TN cancers to 1517, represents the largest series classified by subtype and analyzed for features of lymphatic invasion and nodal involvement to the best of our knowledge. An additional finding in the current analysis is that TN tumors also have the lowest rate of LVI of all subtypes. To the best of our knowledge, this has not been previously demonstrated in any large series.

The finding of a low incidence of LVI calls into question the means through which TN tumors express their aggressive phenotype. Several studies link TN tumors to a high risk of LR and poor survival.[10,16,17] Nguyen et al studied 793 patients with invasive breast cancer and clinically approximated molecular subtype and found that the 5-year cumulative incidence of LR was 7.1% for the TN tumor group and 8.4% for the HR-/HER2+ group compared to 0.8% and 1.5% for the HR+/HER2- and HR+/HER2+ groups, respectively.[8] Lowery et al quantified the influence of subtype on locoregional recurrence following BCT and mastectomy by performing a meta-analysis of 12,592 patients.[9] They found HR+ tumors had a lower risk of LR than TN (risk ratio (RR), 0.38; 95% CI, 0.23–0.61) and HER2 tumors (RR, 0.34; 95% CI, 0.26–0.45) following BCT. Following mastectomy, HR+ tumors had a

lower risk of LR than TN (OR, 0.61; 95% CI, 0.46–0.79) and HER2 tumors (OR, 0.69; 95% CI, 0.54–0.89). HER2 tumors had a higher risk of LR than TN tumors following BCT, but there was no difference between HER2 and TN tumors following mastectomy. Adjuvant trastuzumab was not used in the studies included in this analysis, and it is likely that since trastuzumab decreases LR in HER2 overexpressing breast cancer[11], TN tumors would be associated with the highest risk of LR if patients treated with more modern regimens were included in the analysis. A retrospective analysis of 2 prospective clinical trials performed by the Danish Breast Cancer Cooperative Group showed a significant improvement in overall survival in patients with HR+ and HER2- tumors that were treated with postmastectomy radiotherapy, but no significant improvement in patients with TN cancers or HER2 overexpressing cancers prior to the use of trastuzumab.. Smaller reductions in locoregional recurrence after PMRT were also seen in TN and HR-/HER2+ patients compared to those with HR+/HER2- tumors.[18]

In contrast to the increased rates of in breast recurrence and postmastectomy chest wall recurrence reported for TN cancers, evidence that rates of nodal recurrence are increased is lacking.. For instance, the ACOSOG Z0011 trial demonstrated that among patients with limited sentinel lymph node (SLN) metastases undergoing BCT, SLN biopsy alone resulted in rates of locoregional recurrence, disease-free survival (DFS), and OS similar to ALND, but with decreased morbidity.[12,13] This was attributed to the effectiveness of the radiation therapy and systemic therapy (given to over 95% of patients) at reducing locoregional recurrence. Of the patients randomized into ACOSOG Z0011, 83% were ER+. HER2 status was not routinely determined during the time period of that study, raising concerns about the applicability of the results to TN breast cancers. No differences in DFS or OS were noted on the basis of HR status[19], and the number of regional failures was too small to analyze based on HR status.

Dengel et al recently analyzed 287 patients who met ACOSOG Z0011 eligibility criteria and were treated with SLN biopsy alone if metastases were present in <3 sentinel nodes and gross extracapsular extension was not identified intraoperatively.[20] 84% of patients met indications for SLN biopsy alone and avoided ALND. The study demonstrated that age, HR status, HER2 status, and grade did not differ between the SLN biopsy-only and ALND groups ($p<0.0001$). Our study provides further reassurance that application of the ACOSOG Z0011 findings to patients with TN breast cancer is appropriate by demonstrating that they are actually less likely to have a heavy nodal disease burden than patients with other tumor subtypes. This conclusion is further supported by two large studies specifically examining predictors of nodal recurrence in patients undergoing ALND. Grills et al and Yates et al examined predictors of nodal recurrence in multivariate models which included HR status in 1500 and 1065 patients, respectively. In neither study was HR status found to be significant.[21,22] In aggregate, the literature and the current study do not suggest a propensity for heavy nodal disease burden or an increased risk of isolated nodal recurrence in TN patients, and we routinely perform sentinel lymph node biopsy alone in patients meeting ACOSOG Z0011 eligibility criteria, regardless of HR and HER2 status. Thus, the elevated rates of locoregional recurrence reported for TN cancer likely reflects the excess of in-breast and chest wall recurrences in these patients.

Our study confirms the results of other studies indicating that presence of LVI is associated with an increased risk of nodal involvement (Table 4).[15,23–27] When LVI was absent, the risk of any nodal involvement was 0.28 (95% CI, 0.26–0.31) compared to when it was present. Additionally, LVI is well documented to be a risk factor for local recurrence after both BCT and mastectomy[28–30], raising the possibility that an increased frequency of LVI could be responsible for the higher rates of local recurrence in the breast and chest wall seen with TN breast cancer. However, we found that of all the subtypes, TN cancers were least likely to have LVI.

A question that remains unanswered is the means through which TN breast cancers achieve their higher rate of LR. The findings of our study suggest that high-risk features of the primary tumor are unlikely to be the explanation. An alternative explanation is the lack of targeted therapy. The dramatic effect of targeted therapy on local outcomes is illustrated by the decrease in locoregional recurrence seen in HER2 overexpressing patients with the addition of trastuzumab to chemotherapy after both BCT and mastectomy. Kiess et al reported that rates of locoregional recurrence at 3 years after BCT decreased from 7% to 1% with the addition of trastuzumab treatment[31] and a similar reduction was seen in patients undergoing mastectomy.[32] The benefit of endocrine therapy in reducing local recurrence is well documented[33,34], with a 50% reduction in locoregional recurrence after 5 years of tamoxifen compared to placebo, with additional incremental benefit observed with the use of the aromatase inhibitors or switching strategies. The hypothesis that features of the primary tumor are unlikely to be responsible for the increased rates of local recurrence seen in TN breast cancer is further supported by observations that larger surgical procedures do not improve outcomes in TN breast cancer. Pilewskie et al demonstrated that margins >2mm do not decrease local recurrence compared to margins <2mm in size in TN patients undergoing BCT[35], and 3 retrospective studies have failed to demonstrate that mastectomy improves local control compared to BCT.[28,36,37] Strengths of our study include its large size and the performance of ER, PR, and HER2 testing in a single pathology laboratory. However, there are several potential limitations to this study. First, the data used in this study are retrospective, although this is unlikely to influence the ascertainment of nodal metastases. Second, classification of subtype was based on IHC, which only approximates the genotype-based breast cancer subtype, such that there may be some level of misclassification of tumors.[38,39] However, at this time, IHC surrogates are used for clinical decision making, so this approach provides information relevant to patient care.[4–6,8]

In summary, our study demonstrates that TN tumors have the lowest risk of any subtype of having LVI or LN metastases, despite the uniformly worse prognosis and increased rate of local recurrence in these tumors. This implies the mode of recurrence of TN tumors is not driven by lymphatic invasion. We believe that among patients with early TN tumors and limited SLN metastatic breast cancer, treatment with BCT and SLNB alone, and not ALND, according to the ACOSOG Z0011 trial results, is adequate, safe, and reduces morbidity.

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Synopsis

Triple-negative breast cancers have higher locoregional recurrence rates than other subtypes. We found they are the least likely subtype to have lymphovascular invasion and nodal metastases, suggesting axillary dissection may be avoided in cases meeting ACOSOG Z0011 eligibility criteria.

TABLE 1

Population characteristics

Characteristic	Value (%)
Tumor stage, n (%)	
T0	16 (0%)
T1	4379 (74%)
T2	1339 (23%)
T3	91 (2%)
TX	35 (1%)
No. of positive nodes, n (%)	
0	6737 (58%)
1–3	3592 (31%)
≥ 4	1267 (11%)
Nuclear grade, n (%)	
High	3889 (38%)
Intermediate	4717 (46%)
Low	1598 (16%)
Histologic grade, n (%)	
High	4411 (39%)
Intermediate	5117 (46%)
Low	1691 (15%)
LVI, n (%)	
No	8104 (70%)
Yes	3492 (30%)
Age, years	
≤ 45	2270 (20%)
45–65	6042 (52%)
≥ 65 and up	3284 (28%)

LVI, lymphovascular invasion

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TABLE 2

Patient and tumor characteristics by subtype*

Clinicopathologic variable	HR+/HER2-	HR+/HER2+	HR-/HER2+	HR-/HER2-	p-value
N	8526	928	625	1517	<.0001
	74%	8%	5%	13%	
Age					
No. missing	0	0	0	0	
Median (range)	57.5 (22–96)	51.5 (21–89)	53.3 (25–90)	54.9 (19–95)	<.0001
Tumor size					
No. missing	142	18	17	40	
Median (cm)	1.3	1.5	1.6	1.7	<.0001
LVI					
No. missing	0	0	0	0	
% Yes	28%	43%	40%	32%	<.0001
Grade **					
No. missing	253	38	41	45	
% High grade	25%	63%	89%	86%	<.0001
Nodal involvement					
No. missing	0	0	0	0	
% ≥ 1 positive LN	40%	49%	53%	41%	<.0001
% ≥ 4 positive LN	9%	16%	22%	13%	<.0001

* Percentages and statistical tests are based on available data for subtypes.

** Nuclear grade when available, otherwise histologic grade. Classic lobular histology was assigned low grade.

LVI, lymphovascular invasion; LN, lymph node

TABLE 3

Multivariate logistic regression of LVI (n = 11,025) (Covariates = subtype, tumor size, grade, age)

Variable		Outcome	
		LVI	
		Adjusted OR (95% CI)	p-value
Subtype	HR-/HER2-	1.0	<.0001
	HR+/HER2-	1.8 (1.6–2.1)	
	HR+/HER2+	2.5 (2.0–3.0)	
	HR-/HER2+	1.7 (1.4–2.1)	
Tumor size (cm) *		1.8 (1.7–1.9)	<.0001
Grade **	Low/intermediate	1.0	<.0001
	High	2.1 (1.9–2.4)	
Age		0.983 (0.980–0.987)	<.0001

* Odds of outcome occurrence with a 1 cm increase in tumor size.

** Nuclear grade when available, otherwise histologic grade. Classic lobular histology was assigned low grade.

LVI, lymphovascular invasion; CI, confidence interval; OR, odds ratio

TABLE 4

Multivariate logistic regression of nodal involvement (n = 11,025) (Covariates = subtype, tumor size, grade, LVI, age)

Variable		Outcome			
		Any nodal involvement (≥1 positive LN)		High-volume nodal involvement (≥4 positive LN)	
		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Subtype	**HR-/HER2-**	1.0	<.0001	1.0	<.0001
	HR+/HER2-	1.7 (1.4–1.9)		1.3 (1.0–1.6)	
	HR+/HER2+	1.6 (1.3–2.0)		1.4 (1.1–1.9)	
	HR-/HER2+	2.0 (1.6–2.5)		2.3 (1.7–3.1)	
Tumor size (cm)		1.9 (1.8–2.0)	<.0001	1.7 (1.7–1.8)	
Grade	**Low/intermediate**	1.0	0.0065	1.0	0.0009
	High	1.2 (1.0–1.3)		1.3 (1.1–1.5)	
LVI	**Yes**	1.0	<.0001	1.0	<.0001
	No	0.28 (0.26–0.31)		0.22 (0.19–0.25)	
Age		0.985 (0.982–0.988)	<.0001	0.922 (0.987–0.997)	0.0021

LN, lymph node; OR, odds ratio; CI, confidence interval; LVI, lymphovascular invasion