Effect of Very Small Tumor Size on Cancer-Specific Mortality in Node-Positive Breast Cancer

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ABSTRACT

Purpose

Traditionally, larger tumor size and increasing lymph node (LN) involvement have been considered independent predictors of increased breast cancer–specific mortality (BCSM). We sought to characterize the interaction between tumor size and LN involvement in determination of BCSM. In particular, we evaluated whether very small tumor size may predict for increased BCSM relative to larger tumors in patients with extensive LN involvement.

Patients and Methods

Using Surveillance, Epidemiology and End Results registry data, we identified 50,949 female patients diagnosed between 1990 and 2002 with nonmetastatic T1/T2 invasive breast cancer treated with surgery and axillary LN dissection. Primary study variables were tumor size, degree of LN involvement, and their corresponding interaction term. Kaplan-Meier methods, adjusted Cox proportional hazards models with interaction terms, and a linear trend test across nodal categories were performed.

Results

Median follow-up was 99 months. In multivariable analysis, there was significant interaction between tumor size and LN involvement ($P < .001$). Using T1aN0 as reference, T1aN2+ conferred significantly higher BCSM compared with T1bN2+ (hazard ratio [HR], 20.66 v 12.53; $P = .02$). A similar pattern was seen among estrogen receptor (ER) –negative patients with T1aN2+ compared with T1bN2+ (HR, 24.16 v 12.67; $P = .03$), but not ER-positive patients ($P = .52$). The effect of very small tumor size on BCSM was intermediate among N1 cancers, between that of N0 and N2+ cancers.

Conclusion

Very small tumors with four positive LNs may predict for higher BCSM compared with larger tumors. In extensive node-positive disease, very small tumor size may be a surrogate for biologically aggressive disease. These results should be validated in future database studies.

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INTRODUCTION

As adjuvant therapy options for breast cancer expand, accurate estimates of cancer-specific outcomes are increasingly important in order to appropriately tailor therapy. To date, numerous prognostic factors have been identified including tumor size, degree of axillary lymph node (LN) involvement, age, histologic grade, hormone receptor status, HER2/*neu* status, and presence of lymphovascular invasion (LVI).¹⁻⁶ Of these, extent of axillary LN involvement and tumor size are two of the most important baseline prognostic determinants, and consequently, along with presence of distant metastases, establish the basis of the American Joint Committee on Cancer (AJCC) staging system.⁷

Among node-negative patients, increasing tumor size has been associated with increased breast

cancer–specific mortality (BCSM).⁸ In addition, increasing tumor size has been correlated with a higher risk of axillary LN involvement.⁹ Although larger tumor size and increasing LN involvement have traditionally been considered independent predictors of higher BCSM, tumors which metastasize to lymph nodes early in the disease process (ie, at small tumor size) may reflect a more biologically aggressive phenotype, and may paradoxically be associated with a higher risk of distant spread.

Timing of acquisition of metastatic potential and its possible implications is an area of active research. Although traditionally, distant spread has been considered a late event in tumor progression, recent studies suggest that for some tumors, acquisition of metastatic potential may occur early in cancer development, even in the absence of detectable primary tumors.¹⁰⁻¹⁴ Similarly, the presence of a

very small primary tumor with significant LN involvement may suggest early acquisition of metastatic potential.

The relationship between tumor size and BCSM in the subset of patients with axillary LN involvement has not been comprehensively examined. We sought to determine whether there is significant interaction between tumor size and LN involvement in predicting BCSM. In particular, we examined whether very small tumor size may predict for increased BCSM compared with larger tumor size among patients with breast cancer with extensive LN involvement. We hypothesized that very small tumor size in the context of extensive LN involvement may be a surrogate for biologically aggressive disease.

PATIENTS AND METHODS

Patient Selection

Breast cancer records were obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Cancer database.¹⁵ Collected from nine population-based cancer registries, the SEER database includes 3.5 million cancer cases from areas comprising 26% of the United States population. We identified 50,949 female patients diagnosed with invasive breast cancer between January 1, 1990, and December 31, 2002. Patients diagnosed after 2002 were excluded to ensure a minimum follow-up of 4 years. Patients diagnosed before 1990 were excluded because of lack of hormone receptor data within the SEER registry.

Patients met the following inclusion criteria for the study: female sex; age of diagnosis between 18 and 70 years; treatment with either breast conserving surgery or mastectomy; AJCC stages I, II, or III; invasive ductal histology; $\geq$ six axillary LNs dissected; unilateral breast cancer; known estrogen receptor (ER) status; pathologic confirmation; known diagnosis date; diagnosis not obtained through death certificate or autopsy; breast cancer as first and only cancer diagnosis; and known tumor size.

Outcome Measures

The primary study outcome was BCSM. Vital status code established whether the patient was alive or dead. Cause of death was categorized as breast cancer-specific or nonbreast cancer-related death. BCSM was calculated from the date of diagnosis to the date of breast cancer death. Patients who died from other causes were censored at date of death for BCSM analysis.

Statistical Analysis

To determine whether there was significant interaction between tumor size and degree of LN involvement in predicting BCSM, we defined an interaction term, ie, tumor size $\times$ LN status, as the primary study variable. Additional study variables included year of diagnosis, age, race, histologic grade, ER status, progesterone receptor (PR) status, number of LNs dissected, degree of LN involvement, and tumor size (Appendix, online only). Degree of LN involvement was analyzed as a categorical variable determined by AJCC nodal criteria (N0 or 0 positive ν N1 or one to three positive ν N2 or four positive LNs).⁷ Tumor size was analyzed as a continuous and categorical variable according to AJCC tumor category size criteria (T1a or $\leq$ 0.5 cm ν T1b or $>$ 0.5 and $\leq$ 1.0 cm, ν T1c or $>$ 1.0 and $\leq$ 2.0 cm ν T2 or $>$ 2.0 and $\leq$ 5.0 cm).⁷ Nonlinear effect of continuous tumor size on BCSM was assessed using a B-spline transformation with two evenly spaced knots. Based on the median follow-up of 8.3 years, we reported 8-year actuarial rates for BCSM.

Comparisons of patient and tumor characteristics by LN involvement were performed using χ^2 tests.¹⁶ Survival outcomes were estimated using the Kaplan-Meier product limit method and compared using log-rank statistics. Adjusted hazard ratios (HR) were calculated using Cox proportional hazards models.¹⁷

Overall presence of interaction between tumor size and LN involvement was evaluated by the Wald test. Pair-wise comparisons were performed between different combinations of LN involvement and tumor size to determine the presence of significant BCSM differences. Exploratory analysis was performed with stratification by ER status because ER status has clinical relevance

with respect to treatment implications and is a known modulator of clinical outcomes.¹⁸ The likelihood ratio test for the covariate representing LN status was performed to determine the significance of a linear trend in the effect of tumor size across nodal stage categories (Appendix, online only).

All computed *P* values were two sided. For the overall analysis, a Bonferroni correction of 2 was applied in order to adjust for multiple comparisons, and statistical significance was defined as a *P* value lower than .025. On exploratory subgroup analysis by ER status, because of the small number of patients, no attempt was made to correct for multiple comparisons, with statistical significance defined as a *P* value lower than .05. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC) and R 2.4.0 (<http://www.R-project.org>). This study was submitted and determined to qualify for institutional review board exemption.

RESULTS

Descriptive Statistics

We identified 50,949 patients who met eligibility criteria for our study. In total, 6,997 patients (13.7%) died secondary to breast cancer. Table 1 summarizes the patient and tumor characteristics by LN involvement. Categories of LN involvement significantly differed with respect to tumor size, histologic grade, ER status, PR status, and number of LNs dissected. Absence of nodal involvement was correlated with older age, non-African American race, smaller tumor size, lower histologic grade, ER positivity, PR positivity, and limited LN dissection.

Determination of Interaction Between Tumor Size and LN Status

On univariate analysis, year of diagnosis, patient age, race, tumor size, LN involvement, tumor grade, ER status, PR status, and number of LNs dissected were significantly associated with breast cancer-specific survival (BCSS; Appendix Table A1, online only). On multivariate analysis, there was significant interaction between tumor size and LN involvement in determining BCSM ($P < .001$; Table 2). In addition, earlier year of diagnosis, older age, African American race, higher tumor grade, absence of ER status, absence of PR status, more extensive LN dissection, larger tumor size, and greater LN involvement were independently associated with increased BCSM (Table 2). Separate Kaplan-Meier curves for N0, N1, and N2+ patients stratified by categorical tumor size are provided in Figure 1.

Among patients with four or more positive LNs, those with T1b tumors experienced significantly lower BCSM relative to patients with T1a tumors ($P = .02$; HR, 0.60; 95% CI, 0.39 to 0.91). Unadjusted 8-year BCSS was 62% in patients with T1aN2+ disease, compared with 74%, 69%, and 57%, in patients with T1bN2+, T1cN2+, and T2N2+ disease, respectively. In contrast, there was no significant difference in BCSM among patients with T1aN2+ versus T1cN2+ or T2N2+ tumors. Patient and tumor characteristics among N2+ patients stratified by tumor category are highlighted in Appendix Table A2 (online only).

Among patients with one to three positive LNs, there was no significant difference in BCSM between patients with T1a tumors relative to patients with either T1b or T1c tumors ($P = .20$ and $P = .70$, respectively). Patients with T2N1 tumors had significantly increased BCSM compared with T1aN1 tumors (HR, 2.01; 95% CI, 1.38 to 2.93; $P < .001$). The relationship between continuous tumor size and 8-year BCSM stratified by LN involvement status depicting the presence of effect modification is graphically illustrated in Figure 2. Figures 2B and 2C, which include N1 and N2 patients respectively, reveal a pattern of

Table 1. Patient Characteristics by LN Involvement (N = 50,949)

Patient Characteristic	Patients								P
	Total (N = 50,949)		Node Negative (n = 32,074)		1-3 Positive LNs (n = 12,443)		≥4 Positive LNs (n = 6,432)		
	No.	%	No.	%	No.	%	No.	%	
Median follow-up, months			106.0		90.0		74.0		
IQR			76-145		62-130		46-115		
Year of diagnosis									< .001
1990-1994	16,571	32.5	10,610	33.1	3,735	30.0	2,226	34.6	
1995-1999	21,834	42.9	14,256	44.4	5,059	40.7	2,519	39.2	
2000-2002	12,544	24.6	7,208	22.5	3,649	29.3	1,687	26.2	
Patient age, years									.10
≤ 50	20,494	40.2	11,841	36.9	5,680	45.7	2,973	46.2	
> 50	30,455	59.8	20,233	63.1	6,763	54.3	3,459	53.8	
Race									.42
White	41,963	82.4	26,727	83.3	10,056	80.8	5,180	80.5	
Black	4,160	8.2	2,289	7.1	1,207	9.7	664	10.3	
Other	4,826	9.5	3,058	9.6	1,180	9.5	588	9.1	
Tumor size									< .001
T1	34,237	67.2	24,727	77.1	7006	56.3	2,504	38.9	
T1a	2,536	5.0	2,208	6.9	247	2.0	81	1.2	
T1b	9,313	18.3	7,760	24.2	1,233	9.9	320	5.0	
T1c	22,388	43.9	14,759	46.0	5,526	44.4	2,103	32.7	
T2	16,712	32.8	7,347	22.9	5,437	43.7	3,928	61.1	
Grade									< .001
1	6,287	12.3	4,888	15.2	1,131	9.1	268	4.2	
2	19,197	37.7	12,476	38.9	4,769	38.3	1,952	30.4	
3	19,177	37.6	10,583	33.0	5,176	41.6	3,418	53.1	
Unknown	6,288	12.3	4,127	12.9	1,367	11.0	794	12.3	
ER status									< .001
Positive	36,978	72.6	23,507	73.3	9,113	73.2	4,358	67.8	
Negative	13,971	27.4	8,567	26.7	3,330	26.8	2,074	32.2	
PR status									< .001
Positive	32,391	63.6	20,597	64.2	8,004	64.3	3,790	58.9	
Negative	17,240	33.8	10,583	33.0	4,139	33.3	2,518	39.2	
Unknown	1,318	2.6	894	2.8	300	2.4	124	1.9	
No. of LNs dissected									< .001
6-10	11,767	23.1	7,955	24.8	2,969	23.9	843	13.1	
11-20	29,691	58.3	18,736	58.4	7,205	57.9	3,750	58.3	
≥ 21	9,491	18.6	5,383	16.8	2,269	18.2	1,839	28.6	

Abbreviations: LN, lymph node; IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor.

decreasing 8-year BCSM with increasing tumor size at very small sizes, until a threshold size is reached, at which point, increasing tumor size and 8-year BCSM follow a monotonic relationship (8-year BCSM for all node-positive patients depicted in Appendix Fig A1, online only). The likelihood ratio test revealed a significant linear trend in the effect of tumor size on BCSM across nodal categories ($P < .001$, Appendix, online only), suggesting that N1 cancers had an intermediate effect between that of N0 and N2+ tumors with respect to very small tumor size conferring increased BCSM.

Determination of Interaction After Stratification by ER Status

After stratifying by ER status, 13,971 patients and 36,978 patients were found to have ER-negative and ER-positive disease, respectively. Among both ER-negative and ER-positive patients, significant interaction between tumor size and LN involvement was identified.

ER-Negative Subgroup

Among ER-negative patients with four or more positive LNs (Table 3), those with T1b tumors experienced significantly lower BCSM relative to patients with T1a tumors ($P = .03$; HR, 0.52; 95% CI, 0.29 to 0.94). There was no significant difference in BCSM among patients with T1a tumors relative to patients with T1c or T2 tumors ($P = .12$ and $P = .39$, respectively). In contrast, consistent with results in the overall study analysis, for patients with N1 disease, there was no significant difference in BCSM among those with T1a, T1b, or T1c tumors. Patients with T2N1 tumors (HR, 1.66; 95% CI, 0.99 to 2.78, $P = .05$) experienced increased BCSM compared with patients with T1aN1 tumors.

ER-Positive Subgroup

Among ER-positive patients with four or more positive LNs (Table 4), tumor stage did not contribute additional prognostic information. Specifically, there was no significant difference in BCSM

Table 2. Breast Cancer–Specific Mortality With Interaction Term Between Tumor Category and Nodal Stage

Variable	Hazard Ratio	95% CI	P	Pairwise		
				Hazard Ratio	95% CI	P
Year of diagnosis			< .001			
1990-1994	1.00					
1995-1999	0.76	0.72 to 0.81				
2000-2002	0.61	0.56 to 0.66				
Age, years			< .001			
≤ 50	1.00					
> 50	1.10	1.04 to 1.14				
Race			< .001			
White	1.00					
Black	1.45	1.35 to 1.56				
Other	0.91	0.84 to 1.00				
Grade			< .001			
I	1.00					
II	2.78	2.33 to 3.31				
III	4.21	3.54 to 5.01				
Unknown	3.89	3.25 to 4.66				
ER status			< .001			
Positive	1.00					
Negative	1.41	1.32 to 1.51				
PR status			< .001			
Positive	1.00					
Negative	1.33	1.24 to 1.42				
Unknown	1.10	0.94 to 1.29				
No. of LNs dissected			< .001			
6-10	1.00					
11-20	0.87	0.82 to 0.92				
≥ 21	0.84	0.78 to 0.90				
Tumor*nodal stage			< .001			
Tumor category			< .001			
Nodal stage			< .001			
T1aN0	1.00					
T1bN0	1.53	1.12 to 2.07				
T1cN0	2.72	2.04 to 3.62				
T2N0	5.42	4.07 to 7.22				
T1aN1	5.22	3.28 to 8.31				
T1bN1	3.98	2.83 to 5.60		0.76	0.50 to 1.15	.20*
T1cN1	5.62	4.21 to 7.52		1.07	0.74 to 1.57	.70*
T2N1	10.49	7.88 to 13.96		2.01	1.38 to 2.93	< .001*
T1aN2+	20.66	13.05 to 32.72				
T1bN2+	12.53	8.82 to 17.80		0.60	0.39 to 0.91	.02†
T1cN2+	15.27	11.41 to 20.42		0.73	0.51 to 1.07	.11†
T2N2+	21.53	16.19 to 28.63		1.04	0.72 to 1.50	.83†

Abbreviations: HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; LN, lymph node.

*Referent group: T1aN1.

†Referent group: T1aN2+.

between patients with T1a, T1b, T1c, or T2 tumors. Among patients with one to three positive LNs, those with T2N1 tumors had significantly higher BCSM compared with T1aN1 patients ($P = .002$). There was no significant difference in BCSM for patients with T1bN1 ($P = .52$) or T1cN1 tumors ($P = .57$) compared with T1aN1 tumors.

DISCUSSION

We sought to determine whether there was significant interaction between tumor size and LN involvement in predicting BCSM. We hypothesized that for tumors with very small primary lesions (defined

as T1a tumors) and four or more positive LNs at presentation, tumor size may be a surrogate for biologically aggressive disease and thus, predict for higher BCSM compared with larger tumors with a similar degree of nodal involvement. After adjusting for known breast cancer prognostic factors and accounting for multiple comparisons, we observed that patients with T1bN2+ cancers had significantly lower BCSM compared with those with T1aN2+ cancers (HR, 0.60; 95% CI, 0.39 to 0.91; $P = .02$). This association of smaller tumor size and higher BCSM was not seen, however, in patients with less extensive nodal involvement. However, we identified a significant linear trend in the effect of tumor size on BCSM for increasing nodal categories (ie,

Fig 1. (A, B, C) Kaplan-Meier curves for N0, N1, and N2+ patients stratified by categorical tumor size, respectively. (C) Demonstrates that among patients with four or more positive nodes, those with T1a tumors experienced significantly lower breast cancer-specific survival (BCSS) relative to patients with T1b tumors. The 8-year BCSS is lower among patients with T1aN2+ disease, compared with patients with T1bN2+ and T1cN2+ disease, respectively.

Fig 2. Relationship between continuous tumor size and 8-year breast cancer-specific mortality (BCSM) stratified by lymph node involvement status depicting the presence of effect modification: (A) N0 patients; (B) N1 patients; (C) N2+ patients. In contrast to (A), panels (B) and (C), which include N1 and N2 patients, respectively, reveal a pattern of decreasing 8-year BCSM with increasing tumor size at very small sizes until a threshold size is reached, at which point increasing tumor size and 8-year BCSM follow a monotonic relationship. The gray line represents the estimated 8-year BCSM, and the dashed blue lines represent the 95% confidence band.

Table 3. Breast Cancer–Specific Mortality With Interaction Term Among Patients With ER-Negative Disease (n = 13,971)

Variable	Hazard Ratio	95% CI	P	Pairwise		
				Hazard Ratio	95% CI	P
Year of diagnosis			< .001			
1990-1994	1.00					
1995-1999	0.82	0.76 to 0.89				
2000-2002	0.71	0.64 to 0.79				
Age, years			.004			
≤ 50	1.00					
> 50	1.11	1.04 to 1.20				
Race			< .001			
White	1.00					
Black	1.42	1.29 to 1.57				
Other	0.94	0.82 to 1.08				
Grade			< .001			
I	1.00					
II	1.93	1.36 to 2.76				
III	2.18	1.54 to 3.09				
Unknown	2.20	1.54 to 3.09				
PR status			.002			
Positive	1.00					
Negative	1.22	1.09 to 1.38				
Unknown	1.07	0.81 to 1.41				
No. of LNs dissected			< .001			
6-10	1.00					
11-20	0.84	0.77 to 0.92				
≥ 21	0.78	0.69 to 0.87				
Tumor nodal stage*			< .001			
Tumor category			< .001			
Nodal stage			< .001			
T1aN0	1.00					
T1bN0	2.06	1.30 to 3.25				
T1cN0	2.80	1.82 to 4.30				
T2N0	5.18	3.38 to 7.93				
T1aN1	5.81	3.01 to 11.20				
T1bN1	4.38	2.60 to 7.39		0.75	0.42 to 1.37	.35*
T1cN1	5.92	3.83 to 9.15		1.02	0.61 to 1.72	.94*
T2N1	9.67	6.31 to 14.82		1.66	0.99 to 2.78	.05*
T1aN2+	24.16	12.68 to 26.05				
T1bN2+	12.67	7.49 to 21.44		0.52	0.29 to 0.94	.03†
T1cN2+	16.24	10.51 to 25.08		0.67	0.41 to 1.11	.12†
T2N2+	19.47	12.71 to 29.81		0.81	0.49 to 1.32	.39†

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; LN, lymph node.

*Referent group: T1aN1.

†Referent group: T1aN2+.

N0, N1, and N2). This trend describes the intermediate effect of tumor size on BCSM between T1aN1 versus T1bN1 patients, relative to the difference between T1aN2+ and T1bN2+ patients, and that of T1aN0 and T1bN0 patients. Although the conventional view of cancer spread is that cancer gains metastatic ability through an accumulation of mutations as they grow to large size,¹⁹ we hypothesize that very small cancers with extensive nodal spread represent a subset of cancers where the invasion/metastases pathways are more prominent than those of “self-seeding to the primary tumor.”¹⁹

Our study supports a growing body of literature which suggests that African American women, even after adjusting for other known prognostic factors, have worse breast cancer-specific outcomes.²⁰⁻²² In our study, African American race was an independent predictor of increased BCSM (HR, 1.45; $P < .01$). Similarly, Albain et al²⁰ reported

that African American race was associated with increased mortality among patients with breast cancer enrolled and treated on prospective Southwest Oncology Group trials. In addition, our study highlights the decrease in BCSM over time. More recent year of diagnosis was an independent predictor of lower BCSM after adjusting for other factors ($P < .001$). Our findings support other population-based studies demonstrating a significant decline in mortality rates over time, which have largely been attributed to advancements in adjuvant systemic therapy.^{18,23,24} Our study also support the excellent prognosis for patients with small node-negative tumors with an unadjusted 8-year BCSS of 93.3%. These results support a recent population based study of 1,187 node-negative, LVI-negative patients from British Columbia Cancer Agency with reported BCSS of 92% and 90%, respectively for T1 and T2 tumors.⁸

Table 4. Breast Cancer–Specific Mortality With Interaction Term Among Patients With ER-Positive Disease (n = 36,978)

Variable	Hazard Ratio	95% CI	P	Pairwise		
				Hazard Ratio	95% CI	P
Year of diagnosis			< .001			
1990-1994	1.00					
1995-1999	0.74	0.69 to 0.79				
2000-2002	0.52	0.46 to 0.58				
Age, years			.08			
≤ 50	1.00					
> 50	1.06	0.99 to 1.13				
Race			< .001			
White	1.00					
Black	1.48	1.33 to 1.64				
Other	0.88	0.79 to 0.99				
Grade			< .001			
I	1.00					
II	2.84	2.32 to 3.47				
III	4.90	4.01 to 5.98				
Unknown	4.11	3.33 to 5.06				
PR status			< .001			
Positive	1.00					
Negative	1.36	1.26 to 1.47				
Unknown	1.13	0.93 to 1.36				
No. of LNs dissected			.02			
6-10	1.00					
11-20	0.89	0.82 to 0.97				
≥ 21	0.92	0.83 to 1.01				
Tumor*nodal stage			< .001			
Tumor category			< .001			
Nodal stage			< .001			
T1aN0	1.00					
T1bN0	1.27	0.84 to 1.92				
T1cN0	2.69	1.83 to 3.96				
T2N0	5.81	3.94 to 8.55				
T1aN1	4.68	2.42 to 9.08				
T1bN1	3.84	2.45 to 6.03		0.82	0.45 to 1.49	.52*
T1cN1	5.49	3.71 to 8.10		1.17	0.67 to 2.04	.57*
T2N1	11.16	7.59 to 16.40		2.38	1.38 to 4.12	.002*
T1aN2+	15.27	7.87 to 29.61				
T1bN2+	12.14	7.57 to 19.46		0.79	0.43 to 1.47	.46†
T1cN2+	14.48	9.79 to 21.41		0.95	0.55 to 1.65	.85†
T2N2+	23.05	15.71 to 33.83		1.51	0.87 to 2.61	.14†

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; LN, lymph node.

*Referent group: T1aN1.

†Referent group: T1aN2+.

Our results suggest that very small tumor size in the presence of extensive nodal disease may be a surrogate for inherent biologic aggressiveness. With the discovery and validation of prognostic categorization of breast tumors into distinct biologic subtypes by microarray gene expression studies,^{3,25} there is increasing awareness of tumor biology in predicting patient outcome. Although some of the significance of our findings may be attributed to inability to adjust for HER2/*neu* status, this is unlikely to explain all of the increased mortality found with T1a tumors with nodal involvement seen in our study, suggesting that additional biologic markers not yet identified may aid in prognostic determination. These markers may be related to the metastatic potential of breast tumors.

Although traditionally, metastasis has been considered a late event in tumor progression, recent studies suggest that metastasis may

also occur as an early event in the course of cancer development.¹¹⁻¹⁴ Van't Veer et al¹¹ recently described a gene expression signature strongly predictive of short interval to distant metastases (ie, poor prognosis signature). Genes involved in cell cycle, invasion, angiogenesis, and signal transduction were significantly upregulated in the poor prognosis signature.¹¹ In addition, Husemann et al¹² demonstrated that the earliest transformed cells with epithelial alterations in *HER2* are capable of dissemination, thereby challenging the framework of late-disseminating cells as the only potential source of metastases. Extensive LN involvement with a very small tumor suggests that these tumor cells may have earlier acquisition of metastatic potential. Future studies evaluating patients with T1aN2 tumors may help elucidate genetic or molecular differences that contribute to development of metastatic potential. For these tumor cells with early metastatic

potential, determination of how tumor dormancy and metastatic outgrowth is regulated will play an integral role in developing targeted therapies.¹³

In addition, our study reinforces that patients with very small tumors with significant LN involvement have substantial risk of BCSM and should be treated aggressively. Although we expect that most patients with significant LN involvement would receive aggressive systemic and locoregional therapy, our study reinforces that this patient population remains at substantial risk for breast cancer-related death, and should not be undertreated.

Our study had several limitations. First, there is a potential for miscoding of study variables within the SEER database. However, miscoding would likely be random and thus, unlikely to introduce systematic misclassification bias. In order to minimize misclassification bias, we included only patients with pathologically determined tumor size and patients with six or more axillary LNs removed. In addition, our study was limited to invasive ductal histology, and thus our findings cannot be extrapolated to other histologies. The SEER database also lacks several important tumor characteristics, cancer therapy, and patient outcome variables. Pathologic features including HER2/*neu* status, LVI, and biologic subtype, which have been shown to predict for LN involvement and BCSM, are not available through SEER. Thus, our analyses could not adjust for these potential confounding factors.

Next, the SEER database provides only limited treatment information. Consequently, we cannot be certain that these results do not reflect undertreatment of patients with small tumors, despite node-positive disease. However, the effect of tumor size on BCSM was demonstrated in patients with four or more positive LNs. In the era in which this study was performed, it is highly unlikely that patients with extensive nodal involvement would not have received aggressive systemic therapy and comprehensive nodal irradiation. Lastly, our results remained significant after adjusting for year of diagnosis as a surrogate for type of therapy.

Because of the long natural history of breast cancer, a median follow-up of 8.3 years may not detect long-term survival differences. Among ER-negative patients, most breast cancer events may occur within 5 to 7 years.²⁶ In contrast, among ER-positive patients, breast cancer events can occur through 15 years.¹⁸ This may partly explain our significant findings among ER-negative tumors, but not ER-positive tumors. With longer follow-up, similar results demonstrating increased BCSM for very small tumors in N2+ patients may emerge among the ER-positive patient cohort.

Despite a large initial study population, with substratification by tumor size, LN involvement, and ER status, individual subgroups become small, yielding limited statistical power. Hence,

small numbers in certain subgroups resulted in wide overlapping CIs and limited our ability to detect meaningful differences between groups. Moreover, no attempt was made to adjust for multiple comparisons on subgroup analysis by ER status, and thus these results should be considered exploratory in nature.

Finally, our study challenges retrospective series that suggest similar or improved outcomes among patients with occult breast cancer with axillary metastases compared with stage II patients with detectable disease.²⁷⁻²⁹ These studies, however, are limited by small patient numbers, short follow-up, and outdated imaging techniques.

Despite these limitations, use of a population-based registry such as SEER provides the opportunity to analyze a large number of patients with significant follow-up. Our data represents the most robust evaluation of interaction between tumor size and LN involvement in breast cancer. However, our findings should be interpreted with caution and validated within other large databases.

In conclusion, our study reveals that very small tumors with four or more positive LNs may have increased BCSM compared with larger tumors, suggesting that very small tumor size in the context of LN-positive disease may be a surrogate for biologically aggressive disease. If our finding is validated in other databases, further correlative studies should focus on the subset of patients with T1aN2+ tumors to help elucidate genetic or molecular differences that contribute to development of metastatic potential. Obtaining a deeper understanding of the timing and acquisition of metastatic process is critical for developing more effective and personalized systemic therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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