Significance of Micrometastases on the Survival of Women With T1 Breast Cancer

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BACKGROUND. The most important factor in predicting survival among women with newly diagnosed breast cancer is the status of the axillary lymph nodes. Although straightforward to define, the impact of micrometastases on survival remains to be completely determined.

METHODS. A review of data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute was performed using 43,921 cases diagnosed from January 1988 through December 2001. Among women with invasive breast carcinomas $\leq$2 cm undergoing a resection of the primary malignancy and an axillary lymph node dissection, there were 42,197 cases without lymph node metastases and 1724 cases with micrometastases. Survival differences among these 2 groups were evaluated and are reported here.

RESULTS. Survival at 12 years was modestly affected by the presence of either solitary (5.0%) or multiple lymph nodes (3.6%) with micrometastases when compared with lymph node-negative cases. In subgroup analyses, the decreased survival associated with micrometastases was inconsistent. The most significant survival disadvantage associated with micrometastases was found in cases with Grade 3 carcinomas.

CONCLUSIONS. The modest and variable impact of micrometastases on long-term survival indicates that micrometastases are an important, but not a dominant, prognostic indicator. ***Cancer* 2006;107:1234–9.** © *2006 American Cancer Society.*

KEYWORDS: breast cancer, micrometastases, SEER, multivariate analysis.

The most significant prognostic indicator among women with newly diagnosed breast cancer remains the status of the axillary lymph nodes. There is substantial heterogeneity in women with lymph node metastases, which is reflected in the pathologic subclassification of lymph nodes. The most subtle histologic subclass of lymph node metastases, micrometastases, has been defined as lymph nodes containing metastatic foci measuring no greater than 2 mm in diameter. This definition was first utilized by Huvos et al.[1] in 1971 and was utilized in the AJCC TNM staging system from 1984 through 2002.[2–5] In the most recent AJCC staging system, the definition of micrometastases has been further stratified to reflect the increased detection of micrometastases through use of immunohistochemical staining, reverse-transcriptase polymerase chain reaction (RT-PCR), and the uncertain clinical significance of isolated tumor cells identified as foci $<$0.2 mm.[6]

Although straightforward to define, the impact of lymph node micrometastases on survival remains an unresolved issue.[7–10] In initial series, women with micrometastases did not experience a survival disadvantage when compared with women with lymph node-negative

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breast cancer,[1,11,12] suggesting that micrometastases are not of major clinical interest.

It was subsequently recognized that these initial series were frequently limited in size and length of follow-up, and might not detect small differences in survival. The impact of study size and follow-up time was first appreciated by Rosen et al.[13] After 6 years of follow-up, Rosen[14] noted that cases with micrometastases had a survival rate that was no different than lymph node-negative cases. After 12 years of follow-up, however, the survival rates of cases with micro- or macrometastases were nearly identical, and significantly worse than that for lymph node-negative cases. In subsequent studies with more cases and longer follow-up, women with micrometastatic breast cancer experience a survival disadvantage in all but 1 series.[15–22]

The present study was performed to determine if micrometastases may be a significant prognostic indicator apart from other risk factors. Cases with micrometastases were stratified by the number of involved lymph nodes to determine if solitary lymph node metastases are associated with a survival disadvantage comparable to multiple lymph nodes with micrometastases.

TABLE 1
Sequential Exclusions

Cases excluded	Reason for exclusion	Remaining count
	Total number of breast cancer cases (1988–2001)	360,706
2319	Cases of male breast cancer	358,387
54,432	Cases of subsequent breast cancer	303,955
44,841	Cases of in situ cancer	259,114
3927	Cases not microscopically confirmed	255,187
108,565	Cases with tumor size greater than 2 cm	146,622
21,962	Cases with extension other than 05, 10, and 30	124,660
147	Cases of other histology	124,513
21,687	Cases of nodes coded 5–9	102,826
10,408	Cases of no nodes examined	92,418
23,645	Cases of less than 10 nodes examined	68,773
1089	Cases of unknown number of nodes examined	67,684
12	Cases of unknown status of nodes examined	67,672
8	Cases of number of positive nodes unknown	67,664
4871	Cases of unknown race or race other than Black or White	62,793
14,939	Cases of unknown tumor grade (other than I, II, III, or IV)	47,854
3933	Cases of pathological classification other than N0 and N1a	43,921

SEER (Surveillance, Epidemiology, End Results) Public-Use Database (1973–2001).
Case select: breast cancer patients diagnosed from 1973–2001 in the 11 SEER registries were used for the study. There were 360,706 breast cancer cases diagnosed from 1988–2001 in the 11 SEER registries. After exclusions there were a total of 43,921 female breast cancer patients used in the working dataset.

MATERIALS AND METHODS

Cases were identified from data collected by 11 population-based cancer registries that are part of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. The SEER Program collects data on all newly diagnosed cancers in the states of Alaska, Connecticut, Hawaii, Iowa, New Mexico, and Utah, as well as the metropolitan areas of Atlanta, Detroit, Los Angeles, San Francisco, and Seattle-Puget Sound.

Only T1 cases were included in the current study because there were adequate numbers for the subgroup analyses performed. Higher T-classification levels were not included in the study in order to minimize the probability of including cases with undetected distant metastases.

All cases of newly diagnosed breast cancer were selected from the 2003 edition of the SEER data tape. These included cases diagnosed from January, 1988, through December, 2001. Cases were excluded for a reporting source of autopsy or death certificate only, male gender, unknown age, subsequent breast cancer, in situ or histologically unconfirmed cases, size >2 cm, tumor extension to a pathologic T4 primary, examination of an unknown number or <10 lymph nodes, unknown or race other than African-American or white, unknown grade, and pathologic classification other than N0 and N1a. After exclusions, a total of 42,197 cases without lymph node metastases and 1724 cases with micrometastases were available for analysis (Table 1).

Micrometastases, N1a lymph node metastases, were defined as lymph nodes containing metastatic foci measuring no greater than 2 mm in diameter according to the AJCC TNM staging system.[2–5] Histology was classified based on the ICD-O system.[23] Grade was classified into three groups as "well," "moderate," and "poor, undifferentiated, or anaplastic." Cases were stratified into three groups bases on the lymph node status: N0 for no micrometastases, N1a(1) for 1 involved lymph node, and N1a(2+) for 2 or more involved lymph nodes.

The dependent outcome variable in this study was "death due to breast cancer." Although disease-free survival is also an appropriate endpoint, the SEER dataset does not maintain this as a unique variable. It might be possible to generate this variable for some cases by using the Date_of_last_contact variable; however, this would not be feasible in all cases.

Comparisons of general clinical and histologic characteristics were conducted utilizing chi-square

TABLE 2
General Clinical and Histologic Characteristics as a Function of the Number of Lymph Node Micrometastases

		N0	N1a(1) (1 micrometastasis)		N1a(2+) (2+micrometastases)		N1a(1) vs. N1a(2+)
		n = 41197	(*n* = 1,293) vs. N0		(*n* = 431) vs. N0		*n* = 1,290 vs. *n* = 431
		%	%	*P**	%	*P*†	*P*‡
Size, cm	1	28.3	15.6	<.001	13.2	<.001	0.228
	1.1–2.0	71.7	84.4		86.8		
	1	22.8	19.7		15.5		
Grade	2	46.3	48.8	.030	46.9	<.001	0.031
	3	30.9	31.5		37.6		
	IDC	80.3	82.9		80.0		
Histology	ILC	4.2	3.8	.067	3.5	.692	0.258
	Other	15.5	13.3		16.5		
	<50	22.7	31.5		37.6		
Age, y	50–64	36.5	36.9	<.001	38.5	<.001	0.006
	≥65	40.8	31.6		23.9		
Race	Black	6.6	8.6	.005	10.2	.003	0.307
	White	93.4	91.4		89.8		

* Chi-square analysis of N0 vs. N1a(1) for each strata (size, grade, histology, age, and race).
† Chi-square analysis of N0 vs. N1a(2+) for each of the 5 strata.
‡ Chi-square analysis of N1a(1) vs. N1a(2+) for each of the 5 strata.

analysis. Six univariate analyses were conducted utilizing the Kaplan–Meier[24] survival methods with log rank tests for the strata: lymph node status, size, grade, histology, age, and race. A single multivariate survival analysis was done with the Cox regression method,[25] also utilizing the same six strata. In all survival analyses, death due to breast cancer was the outcome of interest as the dependent variable. Censoring variable for survival analyses was the Date_of_last_contact. Right-side censoring was invoked when lost to follow-up occurred or if the last date of contact extended beyond the end of the study, meaning the patient survived to the end of the study. All statistical analyses were conducted using the SAS v. 8 program (Cary, NC).

RESULTS

Clinical and histologic characteristics of cases are shown in Table 2. In cases with no micrometastases, at least 70% were the larger breast cancer size, 1.1 to 2.0 cm. This compares with at least 84% in the 2 groups [N1a(1) and N1a(2+)] with micrometastases and also with the larger breast cancer size. The highest proportion of cases, >46%, had moderately differentiated (Grade 2) carcinomas. Infiltrating ductal carcinomas (IDC) was the most common histologic subtype, with at least 80% of the cases. More than 89% of the cases were white. Note that for most covariates, the 2 micrometastases groups, N1a(1) and N1a(2+), had similar distributions; however, both these groups were different from the group with no micrometastases.

The full follow-up in this study was 14 years. To give a sense of full follow-up, 5-year and 12-year survival of N0 compared with N1a(1) and N0 compared with N1a(2+) cases are shown in Table 3. Log rank tests were conducted using the full 14 years of follow-up. Probability values listed in Table 3 are for the full follow-up and not just for the 5-year or 12-year survival. Overall, cases with either solitary and multiple lymph node micrometastases experienced a statistically significant decrease in 12-year survival to 88% and 89%, respectively, compared with the decrease in lymph node-negative cases of 93%. This represents a 5.0% and a 3.6% survival disadvantage, respectively, compared with lymph node-negative cases (Fig. 1). In stratified analyses, the decreased survival associated with the presence of 1 or more micrometastases was generally modest and variable. The most significant survival disadvantage associated with micrometastases was in 12-year survival of cases with Grade 3 carcinoma. Survival of solitary and multiple lymph node micrometastases cases declined by 13.7% and 9.1%, respectively. This was seen as a survival percentage of 76% and 81%, respectively, compared with 90% for 12-year survival in lymph node-negative cases.

TABLE 3
Kaplan-Meier Survival Associated with Micrometastases by Selected Risk Factors

		N0		N1a(1)			N1a(2+)		
		5-Year Survival	12-Year Survival	5-Year Survival	12-Year Survival	*P**	5-Year Survival	12-Year Survival	*P*†
LN status		0.97	0.93	0.95	0.88	<.001	0.94	0.89	<.001
Size, cm	≤1	0.99	0.96	0.96	0.96	.013	1.00	0.96	.765
	1.1–2	0.97	0.92	0.95	0.86	.001	0.93	0.88	.002
	1	0.99	0.97	1.00	1.00	.137	1.00	1.00	.459
Grade	2	0.98	0.93	0.98	0.92	.085	0.94	0.94	.028
	3	0.95	0.90	0.88	0.76	<.001	0.91	0.81	.008
	IDC	0.97	0.92	0.95	0.88	<.001	0.95	0.89	.015
Histology	ILC	0.98	0.95	1.00	1.00	.411	1.00	1.00	.690
	Other	0.98	0.94	0.97	0.80	.349	0.86	0.86	<.001
	<50	0.96	0.92	0.95	0.87	.155	0.93	0.84	.019
Age, y	50–64	0.98	0.93	0.95	0.92	.001	0.93	0.93	.025
	≥65	0.97	0.93	0.95	0.86	.006	0.95	0.92	.161
Race	Black	0.94	0.88	0.94	0.87	.708	0.88	0.88	.418
	White	0.97	0.93	0.95	0.89	<.001	0.94	0.89	<.001

LN, lymph node; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma.

* Separate survival curves were constructed for each of the 6 strata, risk factors, presented in Table 3. Log rank analysis of N0 vs. N1a(1) for each strata, (LN status, size, grade, histology, age, and race).

† Log rank analysis of N0 vs. N1a(2+) for each of the 6 strata.

Results of a multivariate analysis are shown in Table 4. The hazard risk of death due to breast cancer was 1.62 in cases with micrometastases involving 1 lymph node compared with breast cancer cases without micrometastases. This risk increased to 1.78 in cases with 2 or more micrometastases. White women were only at about half the risk of death due to breast cancer compared with African-American women. Those women at greatest risk of dying in this study were those who had: 1) larger initial tumor size (1.1–2.0 cm), 2) a Grade 3 carcinoma, and 3) micrometastases.

TABLE 4
Multivariate Cox Analysis by Selected Risk Factors

		Hazard ratio	95% CI	*P*
LN classification	N0	1.00		
	N1a(1)	1.62	1.26–2.10	<.001
	N1a(2+)	1.78	1.19–2.66	.005
Tumor size, cm	≤1.0	1.00		
	1.1–2.0	2.04	1.76–2.36	<.001
	1	1.00		
Grade	2	2.27	1.85–2.79	<.001
	3	4.48	3.65–5.48	<.001
	Other	1.00		
Histology	IDC	1.10	0.95–1.28	.207
	ILC	0.60	0.41–0.88	.009
	<50	1.00		
Age, y	50–64	0.83	0.73–0.94	.004
	≥65	1.05	0.93–1.18	.471
Race	Black	1.00		
	White	0.58	0.49–0.68	<.001

CI, confidence interval; LN, lymph node.

A survival disadvantage was associated with the presence of one or multiple micrometastases in addition to other known risk factors. Probability values based on the hazard ratio in each strata.

DISCUSSION

For the past 100 years management of invasive breast malignancies has included the performance of an axillary lymph node dissection and histologic examination of representative sections from each lymph node. The major limitation of this approach is the potential to miss small metastatic foci. Despite the limitations of routine histologic examination, micrometastases have been noted in 8% to 10% of lymph node-positive cases.[26,27]

Recognizing the potential to miss subtle metastatic foci using standard techniques, serial sectioning can be employed to examine a greater proportion of the axillary lymph node volume. In series utilizing serial sectioning with hematoxylin and eosin (H&E) staining, the frequency of occult lymph node metastases was noted to increase in the range of 8% to 24% among previously lymph node-negative cases.[11,12,28]

When initially negative H&E-stained, but immunohistochemically positive, slides are retrospectively examined, a number of cases with occult metastases can be detected.[29] Utilization of immunohistochemical staining has also resulted in an increase in the

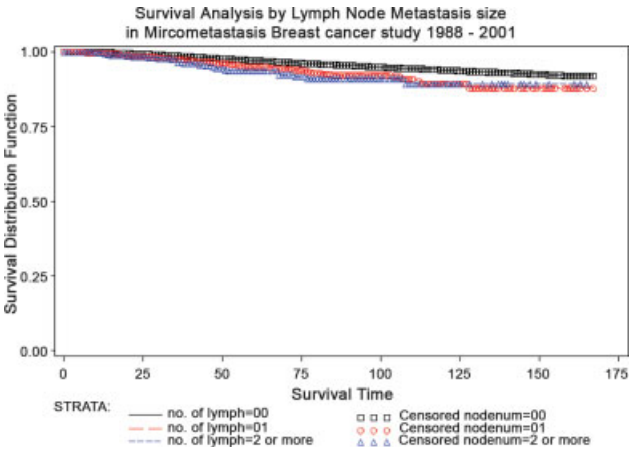

FIGURE 1. Kaplan–Meier survival curve.

frequency of occult lymph node metastases from 9% to 31% among H&E lymph node-negative cases.[17,21,30] Routine utilization of serial sectioning and immunohistochemical staining is time-consuming and expensive; therefore, it has not been practical to utilize routinely after performance of an axillary lymph node dissection.

The current study includes cases with long-term follow-up that predate the widespread utilization of the sentinel lymph node biopsy technique. This study therefore allows one to examine the long-term impact of micrometastases detected by H&E staining. The histologic and clinical characteristics utilized in this study were chosen based on their known impact on survival. In order to minimize the potential impact of undetected lymph node metastases, cases were excluded if fewer than 10 lymph nodes were examined.

The shortcomings of this study are related to a lack of a central pathologic review. Undefined histologic factors of interest include the size of tumor deposits and the location of metastatic tumor deposits within the lymph node.[10,16] Additionally, cases identified by immunohistochemical staining cannot be identified, but likely involve a minimal number of cases with long-term follow-up.

In this series, there is potential for error in determining the survival rates. The frequency of micrometastases is underestimated in the lymph node-negative group, as in all studies not utilizing serial sectioning or immunohistochemical staining. The low mortality rate of the lymph node-negative group mitigates against a potential Will Rogers effect, narrowing the survival between the groups with and without micrometastases. In this study, breast cancer mortality was the main endpoint. In an audit of SEER data, the accuracy of the data was ascertained to be 98%.[31] Based on the these assumptions, systematic errors would most likely have a minimal impact on the conclusions of this study.

The majority of lymph node micrometastases are solitary.[20,22] Articles by Huvos et al.[1] and Fisher et al.[12,26] indicate that solitary lymph node metastases do not adversely impact survival. This opinion has been reflected in the notation in the AJCC TNM staging system manual that invasive breast cancers associated with solitary lymph node micrometastases are associated with the same survival as cases without lymph node metastases. In contrast, Rosen[14] noted that at 12 years follow-up the survival of groups with solitary micro- and macrometastases was nearly identical. In the current study, solitary lymph node micrometastases were associated with a modest 5% (statistically significant) overall survival disadvantage after 12 years.

In contrast, the presence of an increasing number of occult metastases was associated with a decrease in disease-free survival in several studies.[20,22] Multiple occult metastases including cases detected by immunohistochemistry alone have been found to be the most significant predictor of disease-free and overall survival.[20] Consistent with these studies, the current study found the presence of multiple micrometastases to be a predictor for survival. The current study shows that the presence of 2 or more lymph node micrometastases is associated with a modest 3.6% (statistically significant) survival disadvantage after 12 years.

Heterogeneity in previous reported studies precludes the conclusion that micrometastases are an independent prognostic indicator.[7] The overall survival for cases with micrometastases detected by H&E staining after an adequate axillary lymph node dissection is modestly reduced compared with lymph node-negative cases among T1 breast cancer carcinomas. The adverse impact on survival of micrometastases associated with Grade 3 carcinomas indicates the highest risk of systemic disease seen in this study. The modest survival disadvantage due to micrometastases among the remaining subgroups indicates that micrometastases in general are not determinants of survival, but are a significant risk factor.

The questions for the future include: What is the impact of micrometastases detected by sentinel lymph node biopsy, and is there a need for a complete axillary lymph node dissection in cases with micrometastases? Ongoing clinical trials have been designed to address these questions. The current study, with subgroup analyses, will provide a context to evaluate the results of these pending clinical trials.

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