Evaluation of the Stage IB Designation of the American Joint Committee on Cancer Staging System in Breast Cancer

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Published online ahead of print at www.jco.org on December 8, 2014.

Support information appears at the end of this article.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

The National Cancer Institute had no role in the design and conduct of the study; the collection, analysis, or interpretation of the data; or the preparation, review, or approval of the article.

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0732-183X/15/3310w-1119w/\$20.00

DOI: 10.1200/JCO.2014.57.2958

A B S T R A C T

Purpose

The seventh edition of the American Joint Committee on Cancer (AJCC) staging system for breast cancer differentiates patients with T1 tumors and lymph node micrometastases (stage IB) from patients with T1 tumors and negative nodes (stage IA). This study was undertaken to determine the utility of the stage IB designation.

Patients and Methods

The following two cohorts of patients with breast cancer were identified: 3,474 patients treated at The University of Texas MD Anderson Cancer Center from 1993 to 2007 and 4,590 patients from the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial. Clinicopathologic and outcomes data were recorded, and disease was staged according to the seventh edition AJCC staging system. Recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS) were determined using the Kaplan-Meier method and compared using the log-rank test.

Results

Median follow-up times were 6.1 years and 9.0 years for the MD Anderson Cancer Center and ACOSOG cohorts, respectively. In both cohorts, there were no significant differences between patients with stage IA and stage IB disease in 5- or 10-year RFS, DSS, or OS. Estrogen receptor (ER) status and grade significantly stratified patients with stage I disease with respect to RFS, DSS, and OS.

Conclusion

Among patients with T1 breast cancer, individuals with micrometastases and those with negative nodes have similar survival outcomes. ER status and grade are better discriminants of survival than the presence of small-volume nodal metastases. In preparing the next edition of the AJCC staging system, consideration should be given to eliminating the stage IB designation and incorporating biologic factors.

J Clin Oncol 33:1119-1127. © 2014 by American Society of Clinical Oncology

INTRODUCTION

For patients presenting with clinically node-negative breast cancer, [sentinel lymph node](#) dissection (SLND) is standard practice for axillary evaluation to provide staging information and guide treatment decisions.¹ One benefit of SLND is that it allows for rigorous pathologic evaluation of a small number of lymph nodes that are at greatest risk for harboring metastatic disease. Consensus statements from the American Society of Clinical Oncology and the College of American Pathologists recommend that sentinel lymph nodes (SLNs) be processed in 2.0-mm sections along the long axis and that all sections be subjected to hematoxylin and eosin (HE) staining.^{2,3} Although the guidelines do not recommend routine use of immunohistochemistry (IHC), many pathologists use IHC when processing SLNs, which results

in the identification of occult metastases in 10% to 15% of patients.^{4,5} The use of serial sectioning and IHC analysis has thus led to increased detection of small-volume nodal metastases.

To address the increased detection of small-volume metastases in the sixth edition of the [American Joint Committee on Cancer \(AJCC\)](#) staging system for breast cancer published in 2002, definitions were established for macrometastases (> 2.0 mm), micrometastases (> 0.2 mm to 2.0 mm), and isolated tumor cells (ITCs; ≤ 0.2 mm) in axillary lymph nodes.⁶ The pathologic categories pN1mi and pN0(i+) were added to indicate the presence of micrometastases and ITCs, respectively. In the seventh edition of the AJCC staging system, the definition of ITC was further refined to include the presence of less than 200 cells in a single histologic cross section.⁷ In addition, whereas in the sixth

edition, T1N1miM0 and T1N1M0 disease were both categorized as stage IIA, in the seventh edition, T1N1miM0 disease was categorized as stage IB.

The significance of small-volume nodal disease has been debated, and recent reports from the National Surgical Adjuvant Breast and Bowel (NSABP) B-32 trial and the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial have called into question routine use of IHC analysis and the utility of identification of small-volume metastases. The current study was undertaken to determine the significance of the stage IB designation using data from two large cohorts. These included patients treated at The University of Texas MD Anderson Cancer Center,

where providers were not blinded to the SLN IHC results when making treatment recommendations, and patients from the ACOSOG Z0010 trial, in which providers were blinded to IHC data.

PATIENTS AND METHODS

MD Anderson Cancer Center

A prospectively maintained database of patients treated at MD Anderson was used to identify the study population, which included clinically node-negative patients undergoing SLND between 1993 and 2007. Clinicopathologic data were recorded, including age, histology, grade, estrogen receptor

Table 1. Clinicopathologic Characteristics of Patients With Stage IA, IB, or IIA Disease in The University of Texas MD Anderson Cancer Center Cohort

Characteristic	Stage IA (n = 2,246)		Stage IB (n = 207)		Stage IIA (n = 685)		P* (IA v IB)	P* (IB v IIA)
	No. of Patients	%	No. of Patients	%	No. of Patients	%		
Age, years								
Median	57		54		55		< .001	.04
Range	22-92		29-88		23-91			
Histology							.005†	.018†
IDC	1,780	79.3	165	79.7	505	73.7		
ILC	151	6.7	13	6.3	75	10.9		
IDC/ILC	143	6.4	23	11.1	58	8.5		
Other	172	7.6	6	2.9	47	6.9		
Grade							.3†	.018
I	384	17.1	27	13.0	77	11.2		
II	1,205	53.7	121	58.5	339	49.5		
III	654	29.2	59	28.5	269	39.3		
Unknown	3		0		0			
ER status							.04†	.003
Positive	1,679	79.6	174	85.7	508	76.2		
Negative	430	20.4	29	14.3	159	23.8		
Unknown	137		4		18			
PR status							.2†	.5†
Positive	1,342	63.9	139	68.5	421	63.0		
Negative	759	36.1	64	31.5	247	37.0		
Unknown	145		4		17			
HER2 status							.7†	1.0†
Positive	217	11.2	23	12.2	77	12.3		
Negative	1,716	88.8	166	87.8	549	87.7		
Unknown	313		18		59			
LVI							< .001	< .001
Present	174	7.7	51	24.6	139	20.3		
Absent	2,072	92.3	156	75.4	546	79.7		
Breast surgery							< .001	.20†
Total mastectomy	650	28.9	88	42.5	257	37.5		
Segmental mastectomy	1,596	71.1	119	57.5	428	62.5		
ALND							< .001	.09†
Yes	257	11.4	97	46.9	275	40.1		
No	1,989	88.6	110	53.1	410	59.5		
Adjuvant chemotherapy							< .001	.5
Yes	603	26.9	146	70.5	467	68.3		
No	1,640	73.1	61	29.5	217	31.7		
Unknown	3		0		1			
Adjuvant endocrine therapy							.04	.2
Yes	1,462	65.2	150	72.5	461	67.4		
No	781	34.8	57	27.5	223	32.6		
Unknown	3		0		1			

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor.

*P values were calculated after unknown values were excluded.

†Fisher's exact test.

(ER) status, progesterone receptor status, and human epidermal growth factor receptor 2 (HER2) status. During the period covered by this study, ER positivity and progesterone receptor positivity were defined as greater than 10% of cells positive by IHC staining. Tumors were considered to be HER2 positive if they were 3+ by IHC analysis or positive for *HER2* gene amplification by fluorescence in situ hybridization. Trastuzumab was not routinely used in patients with HER2-positive disease during the study period. SLND was performed as previously described.⁸⁻¹¹ Pathologic evaluation of the SLNs included serial sectioning of each node at 2- to 3-mm intervals. Each section was paraffin embedded, and three 5- μ m sections were cut, two for HE evaluation and one for IHC analysis. The MD Anderson Cancer Center Institutional Review Board approved this study.

ACOSOG Z0010

ACOSOG Z0010 was a prospective phase II trial conducted between 1999 and 2003 to determine the incidence and prognostic significance of occult metastases in the SLNs and bone marrow of patients with early-stage breast cancer. The study enrolled patients with clinical T1-2N0M0 breast cancer undergoing breast-conserving surgery followed by whole-breast irradiation. SLNs were evaluated locally by HE staining and, when negative on HE, by IHC analysis at a central laboratory. Adjuvant therapy was administered at the discretion of the treating physician, who was blinded to the IHC results. Clinicopathologic and outcomes data from patients enrolled on Z0010 were recorded. The institutional review boards of all participating institutions approved the ACOSOG Z0010 study, and informed consent was obtained from each patient.

Statistical Analysis

In both cohorts, disease was staged according to the seventh edition AJCC staging system, and recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS) were determined using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards models were used to generate point estimates and CIs for hazard

ratios. The assumption of proportional hazards was checked and held for RFS and DSS in both cohorts.

RESULTS

MD Anderson Cancer Center

The MD Anderson Cancer Center cohort included 3,474 patients, 2,246 (64.6%) with stage IA disease, 207 (6.0%) with stage IB disease, 685 (19.7%) with stage IIA disease, 209 (6.0%) with stage IIB disease, and 127 (3.7%) with stage III disease. Clinicopathologic characteristics of patients with stage IA, IB, and IIA disease are listed in Table 1.

The SLN was negative in 2,518 patients (72.5%) and contained ITCs in 169 patients (4.9%), micrometastases in 307 patients (8.8%), and macrometastases in 481 patients (13.8%). All instances of ITCs were identified by IHC. In 58 patients (18.9%) with a micrometastasis in an SLN, the disease was detected only by IHC; in other words, use of IHC led to disease upstaging. A completion axillary lymph node dissection (ALND) was performed in 25 (43%) of the 58 patients, and only three patients had additional nodal disease identified (a second micrometastasis in two patients and a macrometastasis in the third patient). When looked at by AJCC stage, for patients with stage IA disease, the SLN was negative in 2,115 patients (94%) and contained ITCs in 131 patients (6%). For patients with stage IB disease, all patients had a micrometastasis in their SLN, identified by IHC in 34 patients (16%) and by HE in 173 patients (84%). For patients with stage IIA disease, 378 patients (55%) had a negative SLN and thus stage was dictated by tumor size, and 307 patients (45%) had a positive SLN.

Table 2. Survival Outcomes of Patients With Early-Stage Breast Cancer

Outcome	Stage IA	Stage IB	Stage IIA	IA v IB			IB v IIA		
				HR	95% CI	P	HR	95% CI	P
MD Anderson Cancer Center									
No. of patients	2,246	207	685						
RFS, %				1.1	0.5 to 2.3	.90	2.3	1.03 to 5.0	.04
5 years	97.5	98.0	93.8						
10 years	95.4	94.8	89.1						
DSS, %				1.2	0.5 to 2.8	.70	2.5	1.05 to 5.8	.03
5 years	98.7	99.5	95.4						
10 years	95.8	94.0	89.8						
OS, %				1.1	0.6 to 1.8	.80	1.5	0.9 to 2.6	.2
5 years	96.2	95.9	93.2						
10 years	89.1	87.5	83.6						
ACOSOG Z0010									
No. of patients	2,849	376	878						
RFS, %				1.03	0.67 to 1.59	.89	1.69	1.07 to 2.68	.03
5 years	95.5	97.0	91.6						
10 years	92.4	91.6	88.0						
DSS, %				1.52	0.63 to 3.64	.35	1.68	0.68 to 4.12	.26
5 years	99.3	98.9	98.2						
10 years	98.9	98.3	97.1						
OS, %				0.69	0.44 to 1.11	.13	2.32	1.42 to 3.80	< .001
5 years	96.6	96.7	93.2						
10 years	91.7	93.8	86.8						

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; DSS, disease-specific survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.

Median follow-up time for patients with stage IA, IB, or IIA disease was 6.5 years (range, 0 to 16.7 years). The 5- and 10-year RFS, DSS, and OS rates are listed in Table 2. Patients with stage IA and stage IB disease had similar RFS ($P = .90$), DSS ($P = .70$), and OS ($P = .80$). Patients with stage IA disease had better RFS ($P < .001$), DSS ($P < .001$), and OS ($P = .001$) than patients with stage IIA disease, and patients with stage IB disease had better RFS ($P = .04$) and DSS ($P = .03$) than patients with stage IIA disease (Fig 1).

We previously showed that the combination of ER status, grade, and AJCC stage resulted in better stratification of patients with respect to survival outcomes than AJCC stage alone.¹² Therefore, within the group of patients with stage I disease (IA and IB), we evaluated the utility of the biologic factors of ER status and grade to stratify patients with respect to survival outcomes. As shown in Figure 2, ER status and grade stratified stage I patients with respect to RFS, DSS, and OS.

ACOSOG Z0010

Complete pathologic data enabling determination of the AJCC stage were known in 4,595 patients enrolled onto the ACOSOG Z0010 trial. Of these patients, 2,849 (62.0%) had stage IA, 376 (8.2%) had stage IB, 878 (19.1%) had stage IIA, 322 (7.0%) had stage IIB, and (3.7%) had stage III. Clinicopathologic characteristics of patients with stage IA and IB disease are listed in Table 3. Median follow-up for the entire cohort was 9.0 years (range, 0 to 12.7 years). There were no significant differences between patients with stage IA and stage IB disease with respect to RFS ($P = .89$), DSS ($P = .35$), or OS ($P = .13$; Table 2). Comparing patients with stage IB disease to those with stage IIA disease, there was a significant difference with respect to RFS ($P = .03$) and OS ($P < .001$) but not DSS ($P = .26$), which was outstanding in all three stage groups (stage IA, 99.3%; stage IB, 98.9%; stage IIA, 98.2%). In patients with stage I disease (stage IA and IB), stratification of patients with respect to RFS by incorporating ER status and histologic grade was highly statistically significant (Fig 3).

DISCUSSION

With the widespread use of SLND in patients with breast cancer and enhanced pathologic evaluation of SLNs, including serial sectioning and IHC, there has been an increase in detection of small-volume nodal metastases. To address this, the AJCC staging system was modified; first, small-volume metastases were designated as ITC [pN0(i+)] or micrometastases (pN1mi), and then T1N1miM0 disease was designated as stage IB.^{6,7} One primary goal of the AJCC staging system is to stratify patients with respect to prognosis, suggesting that patients with stage IB disease should have a prognosis intermediate between that of patients with stage IA and stage IIA disease. In the current study, using both a large single-institution data set and data from the ACOSOG Z0010 trial, we have shown that RFS, DSS, and OS are not different between patients with stage IA and stage IB disease, indicating that patients with small primary tumors and micrometastases in their lymph nodes have the same prognosis as patients with pathologically negative lymph nodes. In addition, in an evaluation limited to stage I (IA and IB) patients, biologic factors, including ER status and grade, better stratified patients with respect to RFS, DSS, and OS than did the presence versus absence of micrometastasis in the lymph nodes. Taken together, these data suggest that

Fig 1. Survival outcomes for patients with stage IA, IB, and IIA breast cancer. Kaplan-Meier curves for (A) recurrence-free survival, (B) disease-specific survival, and (C) overall survival. HR, hazard ratio.

Fig 2. Survival outcomes for patients with stage I disease in the MD Anderson Cancer Center cohort by biologic factors. Kaplan-Meier curves for (A and D) recurrence-free survival, (B and E) disease-specific survival, and (C and F) overall survival of patients with stage I disease stratified by (A to C) estrogen receptor (ER) status or (D to F) histologic grade. HR, hazard ratio.

Table 3. Clinicopathologic Characteristics of Patients With Stage IA, IB, or IIA Disease Enrolled Onto the ACOSOG Z0010 Trial

Characteristic	Stage IA (n = 2,849)		Stage IB (n = 376)		Stage IIA (n = 878)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	58		55		55	
Range	25-95		27-87		23-87	
ER status						
Positive	2,277	83.7	307	86.0	621	73.4
Negative	442	16.3	50	14.0	225	26.6
Missing	130		19		32	
PR status						
Positive	1,845	69.5	256	73.1	511	61.2
Negative	810	30.5	94	26.9	324	38.8
Missing	194		26		43	
LVI						
Yes	243	9.7	63	19.0	211	26.2
No	2,255	90.3	269	81.0	595	73.8
Missing	351		44		72	
Grade						
I	1,016	38.0	95	27.9	144	17.4
II	1,082	40.5	171	50.1	368	44.4
III	573	21.5	75	22.0	316	38.2
Missing	178		35		50	
Chemotherapy						
Yes	918	38.1	169	52.6	555	78.3
No	1,492	61.9	152	47.4	154	21.7
Missing	439		55		169	
Endocrine therapy						
Yes	1,650	68.5	233	72.6	462	65.2
No	760	31.5	88	27.4	247	34.8
Missing	439		55		169	

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor.

biologic factors are more significant than the presence of small-volume nodal disease with respect to determining prognosis in patients with early-stage breast cancer.

These data are consistent with recent reports from the ACOSOG Z0010 and NSABP B-32 trials. The ACOSOG Z0010 trial enrolled 5,210 patients with clinical T1-2N0 breast cancer undergoing breast-conserving therapy. An SLN was identified in 5,119 patients, 3,904 (76.3%) of whom had negative SLNs by HE. Of those, 3,326 patients (85.2%) were assessed centrally by IHC analysis, and 349 patients (10.5%) had occult metastases detected. The ACOSOG investigators reported that at a median follow-up of 6.3 years, occult disease had no significant association with recurrence or death.⁴ Similarly, in the NSABP B-32 trial, in which patients with clinically node-negative breast cancer were randomly assigned to SLND plus ALND or SLND with ALND only if an SLN was positive for metastatic disease on HE staining, negative SLNs were sent to a central laboratory for IHC analysis. Of 3,884 patients with HE-negative SLNs in whom SLN blocks for IHC and follow-up data were available, 616 patients (15.9%) had occult metastases—430 (11.1%) had ITC, 172 (4.4%) had micrometastases, and 14 (0.4%) had macrometastases. The estimated 5-year OS and disease-free survival (DFS) rates of patients with occult metastases were lower than those of patients without occult

metastases (OS: 94.6% v 95.8%, respectively; $P = .03$; and DFS: 86.4% v 89.2%, respectively; $P = .01$).⁵ However, these differences are attributable to the study's large sample size and, given the small absolute differences in OS (1.2%) and DFS (2.8%) rates, are not likely clinically relevant. Our data support this interpretation in that we found that patients with T1 tumors and micrometastases, whether identified by IHC or HE, had RFS, DSS, and OS rates similar to those of patients with negative SLNs. Therefore, our data provide additional evidence that routine use of IHC analysis is not indicated in evaluation of the SLNs in patients with early-stage breast cancer.

Our data have implications for the clinical care of patients with micrometastases identified in an SLN. In a review published in 2007, after the AJCC had defined micrometastases but before data from the ACOSOG Z0010 and NSABP B-32 trials, as well as the ACOSOG Z0011 trial (described later), were available, we advocated for completion ALND in patients with micrometastasis in an SLN.¹³ That recommendation was made largely because the AJCC had designated micrometastases as node-positive (pN1mi) disease. However, data from our current study showing that patients with T1N1mi disease have survival outcomes similar to those of patients with T1N0 disease provide support for omitting ALND in patients with small-volume disease. Additional support for omitting ALND in patients with minimal axillary disease burden comes from large multicenter trials. The International Breast Cancer Study Group 23-01 trial was designed to evaluate the significance of SLN micrometastases. The study randomly assigned 931 patients with micrometastases in their SLN to ALND or no further surgery and reported no differences in 5-year DFS rates (84.4% in the ALND group v 87.8% in the SLND-only group).¹⁴ The ACOSOG Z0011 trial was conducted to determine whether patients with a positive SLN require ALND. Patients with clinical T1-2N0M0 breast cancer undergoing breast-conserving therapy with one or two HE-positive SLNs were randomly assigned to completion ALND or no further axillary treatment.^{15,16} At a median follow-up of 6.3 years, the OS rates for the ALND group (91.8%) and SLND-only group (92.5%) did not differ significantly. There were also no significant differences in DFS rates, and ipsilateral axillary recurrences were uncommon, reported in less than 1% of patients. On the basis of these data, ALND is now omitted in selected patients with clinically node-negative disease when one or two positive SLNs are identified.¹

The fact that there were no differences in survival outcomes between patients with stage IA and stage IB disease in our current study could be attributable to differences in receipt of chemotherapy. In the MD Anderson Cancer Center cohort, 70.5% of patients with stage IB disease received chemotherapy versus 26.9% of patients with stage IA disease. Similar to the rationale described earlier for previously recommending ALND for patients with pN1mi disease, this difference is likely a result of oncologists considering pN1mi disease node positive. In the ACOSOG Z0010 cohort, 52.6% of patients with stage IB disease received chemotherapy versus 38.1% of patients with stage IA disease. The differences between the MD Anderson Cancer Center and ACOSOG Z0010 cohorts with respect to the rates of chemotherapy administration may be attributable to the patients with micrometastases identified only by IHC evaluation. In the MD Anderson Cancer Center cohort, in the majority of patients, clinicians were aware of the IHC data and may have recommended chemotherapy for patients with IHC-positive nodes. In contrast, clinicians enrolling patients on ACOSOG Z0010 were blinded to the IHC results and thus

Fig 3. Survival outcomes for patients with stage I disease in the American College of Surgeons Oncology Group Z0010 cohort by biologic factors. Kaplan-Meier curves for (A and D) recurrence-free survival, (B and E) disease-specific survival, and (C and F) overall survival of patients with stage I disease stratified by (A to C) estrogen receptor (ER) status or (D to E) histologic grade. HR, hazard ratio.

would not have recommended chemotherapy for patients with micro-metastases based on IHC evaluation. As discussed further later in this section, the benefit of adjuvant therapy is now thought to be determined primarily by biology, not stage of disease. Because the biologic subgroups are fairly evenly distributed for stage IA and IB patients in this study, the greater use of adjuvant chemotherapy in stage IB patients would not likely change survival outcomes. Because this was a retrospective study, we could not discern the indications for chemotherapy in individual patients. We note, however, that since the time period covered in the current study, the use of adjuvant systemic therapy has increased. Currently, treatment decisions are largely guided by the size of the primary tumor, receptor status, molecular subtypes, and genomic tools; thus, SLND results are often not required to guide recommendations. The majority of patients with breast cancer, even those with T1 tumors with pathologically negative nodes, are given adjuvant systemic therapy. For patients with triple-negative tumors,¹⁷ this therapy includes chemotherapy, and for patients with HER2-positive tumors,¹⁸⁻²⁰ chemotherapy plus HER2-directed therapy is recommended. Therefore, for these breast cancer subtypes, the results of SLN evaluation often will not provide information required to guide adjuvant systemic therapy. For patients with hormone receptor-positive tumors that are pathologically node negative, endocrine therapy will be advised, and chemotherapy recommendations are often guided by a genomic predictive assay.²¹ The RxPonder trial is evaluating the utility of one of these genomic assays, Oncotype DX, in patients with hormone receptor-positive tumors with one to three positive lymph nodes.²² At the time the RxPonder trial began accrual, the definition of node-positive patients included those with pN1mi disease. A recent amendment to the protocol now requires that patients have macrometastases in their lymph nodes and excludes patients who only have pN1mi disease.

The changes in recommendations regarding use of systemic therapy reflect the growing appreciation that the biology of the primary tumor is the most important determinant of treatment response and outcome. Intrinsic breast cancer subtypes with distinct gene profiles have been identified using microarray analyses.^{23,24} These subtypes, including luminal A, luminal B, HER2 enriched, and basal, can be approximated using IHC markers available in a patient's pathology report. These constructed subtypes have been used to effectively stratify patients with respect to distant RFS, DSS, and locoregional outcomes.²⁵⁻²⁸ In another recent study evaluating the significance of tumor biology, Bagaria et al²⁹ categorized patients by TNM stage and whether the tumor was triple-receptor negative. Incorporation of whether the tumor was triple negative was superior to TNM staging

alone with respect to prognostic accuracy. Previous studies by our group have shown that the prognosis of patients undergoing surgery as a first intervention and patients receiving neoadjuvant chemotherapy could be stratified better when ER status and grade were incorporated along with anatomic factors including T and N stage.^{12,30,31} Although grading of breast cancer, much like other morphology-based evaluations such as size determination, has an element of subjectivity and interobserver variability, studies have shown that, with training and strict application of histologic criteria, grading can be a reproducible parameter in breast cancer.^{32,33} Like patients from the previous studies from our institution, patients in the current study were treated in an era that predated the routine use of trastuzumab; therefore, the impact of HER2 status and treatment with trastuzumab could not be determined.

In conclusion, we have shown that biologic factors, including ER status and grade, may stratify patients with early-stage breast cancer with respect to prognosis better than the presence of small-volume nodal metastases. This is consistent with the growing appreciation that biology may be more important than anatomy as dictated by the TNM stage to both guide treatment and stratify patients with respect to prognosis. The AJCC staging system is being revised, and the eighth edition is scheduled to be published in 2016. The data from our study suggest that the stage IB designation be reconsidered and that biologic factors be incorporated in the eighth edition of the AJCC staging system for breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Elizabeth A. Mittendorf, Kelly K. Hunt
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REFERENCES

1. Lyman GH, Temin S, Edge SB, et al: Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 32:1365-1383, 2014
2. Fitzgibbons PL, Page DL, Weaver D, et al: Prognostic factors in breast cancer: College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 124:966-978, 2000
3. Lyman GH, Giuliano AE, Somerfield MR, et al: American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 23:7703-7720, 2005
4. Giuliano AE, Hawes D, Ballman KV, et al: Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA* 306:385-393, 2011
5. Weaver DL, Ashikaga T, Krag DN, et al: Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med* 364:412-421, 2011
6. Greene FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Handbook. New York, NY, Springer, 2002
7. Edge SB, Compton CC, Fritz AG, et al (eds): AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
8. Breslin TM, Cohen L, Sahin A, et al: Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 18: 3480-3486, 2000
9. Hunt KK, Yi M, Mittendorf EA, et al: Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. *Ann Surg* 250: 558-566, 2009
10. Lambert LA, Ayers GD, Hwang RF, et al: Validation of a breast cancer nomogram for predicting nonsentinel lymph node metastases after a positive sentinel node biopsy. *Ann Surg Oncol* 13: 310-320, 2006
11. Mittendorf EA, Sahin AA, Tucker SL, et al: Lymphovascular invasion and lobular histology are associated with increased incidence of isolated tumor cells in sentinel lymph nodes from early-stage

breast cancer patients. *Ann Surg Oncol* 15:3369-3377, 2008

12. Yi M, Mittendorf EA, Cormier JN, et al: Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: Time to modify the current American Joint Committee on Cancer staging system. *J Clin Oncol* 29:4654-4661, 2011

13. Mittendorf EA, Hunt KK: Significance and management of micrometastases in patients with breast cancer. *Expert Rev Anticancer Ther* 7:1451-1461, 2007

14. Galimberti V, Cole BF, Zurrada S, et al: Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. *Lancet Oncol* 14:297-305, 2013

15. Giuliano AE, Hunt KK, Ballman KV, et al: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. *JAMA* 305:569-575, 2011

16. Giuliano AE, McCall L, Beitsch P, et al: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 252:426-432, 2010

17. Theriault RL, Litton JK, Mittendorf EA, et al: Age and survival estimates in patients who have node-negative T1ab breast cancer by breast cancer subtype. *Clin Breast Cancer* 11:325-331, 2011

18. Curigliano G, Viale G, Bagnardi V, et al: Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol* 27:5693-5699, 2009

19. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al: High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol* 27:5700-5706, 2009

20. McArthur HL, Mahoney KM, Morris PG, et al: Adjuvant trastuzumab with chemotherapy is effective in women with small, node-negative, HER2-positive breast cancer. *Cancer* 117:5461-5468, 2011

21. Mamounas EP, Tang G, Fisher B, et al: Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: Results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 28:1677-1683, 2010

22. ClinicalTrials.gov: RxPONDER: A phase III, randomized clinical trial of standard adjuvant endocrine therapy ± chemotherapy in patients with 1-3 positive nodes, hormone receptor-positive and HER2-negative breast cancer with recurrence score (RS) of 25 or less. <http://clinicaltrials.gov/show/NCT01272037>

23. Perou CM, Sørlie T, Eisen MB, et al: Molecular portraits of human breast tumours. *Nature* 406:747-752, 2000

24. Sørlie T, Perou CM, Tibshirani R, et al: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 98:10869-10874, 2001

25. Carey LA, Perou CM, Livasy CA, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 295:2492-2502, 2006

26. Cuzick J, Dowsett M, Pineda S, et al: Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal

growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. *J Clin Oncol* 29:4273-4278, 2011

27. Dawood S, Hu R, Homes MD, et al: Defining breast cancer prognosis based on molecular phenotypes: Results from a large cohort study. *Breast Cancer Res Treat* 126:185-192, 2011

28. Nguyen PL, Taghian AG, Katz MS, et al: Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. *J Clin Oncol* 26:2373-2378, 2008

29. Bagaria SP, Ray PS, Sim MS, et al: Personalizing breast cancer staging by the inclusion of ER, PR, and HER2. *JAMA Surg* 149:125-129, 2014

30. Jeruss JS, Mittendorf EA, Tucker SL, et al: Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. *J Clin Oncol* 26:246-252, 2008

31. Mittendorf EA, Jeruss JS, Tucker SL, et al: Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol* 29:1956-1962, 2011

32. Fanshawe TR, Lynch AG, Ellis IO, et al: Assessing agreement between multiple raters with missing rating information, applied to breast cancer tumour grading. *PLoS One* 3:e2925, 2008

33. Rakha EA, El-Sayed ME, Lee AH, et al: Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. *J Clin Oncol* 26:3153-3158, 2008

Support

Supported in part by grants from the National Cancer Institute to The University of Texas MD Anderson Cancer Center (Grant No. CA016672), the American College of Surgeons Oncology Group (Grant No. CA76001), the Alliance for Clinical Trials in Oncology (Monica M. Bertagnoli, MD, Chair, Grant No. CA31946), and the Alliance Statistics and Data Center (Daniel J. Sargent, PhD, Grant No. CA33601). E.A.M. is an R. Lee Clark Fellow of The University of Texas MD Anderson Cancer Center supported by the Jeanne F. Shelby Scholarship Fund.

GLOSSARY TERMS

American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC)

TNM staging: a cancer staging system that describes the extent of cancer in a patient's body. "T" describes the size of the tumor and whether it has invaded nearby tissue; "N" describes regional lymph nodes that are involved; "M" describes distant metastasis (spread of cancer from one body part to another). The TNM Classification of Malignant Tumours was developed and maintained by the UICC to achieve consensus on one globally recognized standard for classifying the extent of spread of cancer. The TNM classification was also used by the AJCC. In 1987, the UICC and AJCC staging systems were unified into a single staging system. Prognosis of a patient is defined by TNM classification.

macrometastasis: a cohesive cluster of metastatic tumor cells more than 2 mm in the largest dimension within a lymph node.

micrometastasis: a cohesive cluster of metastatic tumor cells measuring more than 0.2 mm and up to 2.0 mm in the largest dimension found within a lymph node.

sentinel lymph node: the lymph node that is anatomically located such that it is the first site of lymph drainage from the location of the primary tumor. It is suspected and assumed that if a malignancy is going to disseminate via the lymphatic system, metastases will first be evident in the sentinel lymph node. In this manner, this lymph node is said to stand guard or sentinel over the metastatic state of the tumor. For many cancers, the sentinel lymph node is biopsied as part of the staging process and presence of macro- or micrometastases in the sentinel lymph node is a negative prognostic factor.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Evaluation of the Stage IB Designation of the American Joint Committee on Cancer Staging System in Breast Cancer**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Elizabeth A. Mittendorf**Honoraria:** Galena Biopharma**Research Funding:** Galena Biopharma (Inst), Antigen Express (Inst)**Karla V. Ballman**

No relationship to disclose

Linda M. McCall

No relationship to disclose

Min Yi

No relationship to disclose

Aysegul A. Sahin

No relationship to disclose

Isabelle Bedrosian**Consulting or Advisory Role:** Bayer Healthcare MRI advisory board**Travel, Accommodations, Expenses:** Bayer Healthcare**Nora Hansen****Speakers' Bureau:** Genentech**Sheryl Gabram**

No relationship to disclose

Thelma Hurd

No relationship to disclose

Armando E. Giuliano

No relationship to disclose

Kelly K. Hunt

No relationship to disclose