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ORIGINAL REPORT

Nodal-Stage Classification in Invasive Lobular Breast Carcinoma: Influence of Different Interpretations of the pTNM Classification

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ABSTRACT

Purpose
Application of current nodal status classification is complicated in lobular breast carcinoma metastases. The aim of this study was to define the optimal interpretation of the pTNM classification in sentinel node (SN) –positive patients to select patients with limited or with a high risk of non-SN involvement.

Patients and Methods
SN metastases of 392 patients with lobular breast carcinoma were reclassified according to interpretations of the European Working Group for Breast Screening Pathology (EWGBSP) and guidelines by Turner et al, and the predictive power for non-SN involvement was assessed.

Results
Reclassification according to definitions of EWGBSP and Turner et al resulted in different pN classification in 73 patients (19%). The rate of non-SN involvement in the 40 patients with isolated tumor cells according to Turner et al and with micrometastases according to EWGBSP was 20%, which is comparable to the established rate for micrometastases. The rate of non-SN involvement in the 29 patients with micrometastases according to Turner et al and with macrometastases according to EWGBSP was 48%, which is comparable to the established rate for macrometastases. Therefore, the EWGBSP method to classify SN tumor load better reflected the risk of non-SN involvement than the Turner et al system.

Conclusion
Compared with the guidelines by Turner et al, the EWGBSP definitions better reflect SN metastatic tumor load and allow better differentiation between patients with lobular breast carcinoma who have a limited or a high risk of non-SN metastases. Therefore, we suggest using the EWGBSP definitions in these patients to select high-risk patients who may benefit from additional local and/or systemic therapy.

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INTRODUCTION

The introduction of the sentinel node (SN) procedure in patients with breast cancer has led to an increased detection rate of small lymph node metastases[1,2] because of an intensive pathology protocol that includes step sectioning and immunohistochemistry.[3] This phenomenon is reflected by the current definitions of the International Union Against Cancer (UICC) Tumor Lymph Node Metastasis (TNM) Classification of Malignant Tumors[4] and the sixth edition of the American Joint Committee on Cancer (AJCC) Staging Manual,[5] which distinguish between isolated tumor cells (ITCs), micrometastases, and macrometastases on the basis of metastatic cluster size.

Although there is no consensus whether the distinction between ITCs and micrometastases has prognostic significance[6-8] it is important, as it directly affects decisions with regard to completion axillary lymph node dissection and adjuvant systemic therapy. Patients with SN ITC are generally considered and treated as node negative (ie, pN0[i+]), whereas patients with micrometastases (ie, pN1mi) and macrometastases (pN1) are staged as node-positive. These patients commonly receive additional axillary treatment and, in certain circumstances, adjuvant systemic therapy.

Currently, the UICC and AJCC definitions of ITC, micrometastases, and macrometastases are imprecise; therefore, different interpretations of the definitions exists, which has resulted in suboptimal reproducibility of nodal staging.[9-13] Although both the UICC and AJCC systems use size of the largest metastatic cluster, the UICC also considers some qualitative features of metastatic deposits (ie, proliferation and extravasation). Furthermore, there is no generally accepted definition for a cluster, which complicates size measurement in case of multiple clusters and/or cells. This is particularly important in patients with invasive lobular breast carcinoma, because these metastases frequently consider multiple, scattered, small clusters and/or single cells in both the sinus and the parenchyma.

Thus, new pathologic nodal staging criteria should be introduced to arrive at better reproducibility and, consequently, optimal therapeutic decision making. The European Working Group for Breast Screening Pathology (EWGBSP) offered some refinements of the current nodal staging definitions,[9] which resulted in improved (although still suboptimal) reproducibility (κ, 0.49). Turner et al[11] recently reported alternate interpretations of the same definitions, which resulted in enhanced interobserver agreement (κ, 0.92), even in the classification of lobular carcinoma SN metastases. However, a potential disadvantage of the refinements by Turner et al[11] is the classification of high SN tumor load dispersed pattern metastases as ITC, which might not optimally reflect the prediction of prognosis. This pattern is especially seen in patients with lobular breast carcinoma, which is the second most common histologic subtype of breast cancer. A comparative study on predictive value of the EWGBSP[9] and Turner et al[11] classifications of SN tumor load in patients with a lobular carcinoma has not been conducted before. Although probably only long-term follow-up studies may reveal the most optimal nodal staging definition, non-SN involvement can be regarded as a good surrogate prognostic indicator, which can be assessed instantaneously. The objective of this study, therefore, was to compare the rates of non-SN involvement associated with SN metastases (according to the classification by the EWGBSP[9] and Turner et al[11]) in patients with lobular breast carcinoma to select the most optimal method that differentiates between patients with a limited risk and those patients with a high risk of non-SN involvement.

PATIENTS AND METHODS

Data Acquisition

Members of the EWGBSP that contributed to a previous multicenter study[14] were asked to participate in this study. This study group was updated and supplemented with patient cases from several other members of this working group, which resulted in an overlap of 10% and made this study independent from this previous study. All contributors were asked to extract data from their own archives and to reclassify the positive SN metastases of the tumors according to the interpretations defined by the EWGBSP[9] and Turner et al.[11] A detailed, step-wise protocol; a data-extraction form (via Microsoft Excel sheet); and digital training programs (via Microsoft PowerPoint) were distributed to all contributors. None of those patient cases evaluated in these training programs were included in this study. The two main differences between these two classifications are the definition of a cluster (which results in different diameters of metastases) and the role of the microanatomic location of tumor deposits. Details of these two interpretations are listed in Table 1.

The following criteria for study inclusion had to be fulfilled. First, patients had to be diagnosed with any type of invasive lobular breast carcinoma. Second, patients had to be diagnosed previously with a tumor-positive SN (ie, ITC, micrometastases, or macrometastases), followed by an axillary lymph node dissection (including $\geq$ six lymph nodes, additionally denoted as non-SNs). Data extracted from the original reports included primary tumor features (ie, diameter, lymphovascular invasion, unifocality, or multifocality), the number of (tumor-positive) SNs, and the number of (tumor-positive) non-SNs. All contributors reclassified tumor-positive SNs according to both the EWGBSP[9] and Turner et al[11] classifications, and they were blinded to the status of the non-SN. The detection method of these metastases (ie, hematoxylin and eosin [H&E] or immunohistochemistry) and the presence or absence of extranodal extension also was recorded. In occurrences of discordance between both classifications, the reason (either diameter or microanatomic location) was recorded to evaluate the effect of these features separately.

Table 1. Main Differences in the EWGBSP[9] and Turner et al[11] Definitions to Classify SN Metastases

Term	Definitions	
	EWGBSP[9]	Turner et al[11]
Cluster	Single tumor cells or clusters are arranged in a continuous manner or separated by only a few cells distance Cells or clusters arranged in a discontinuous manner but dispersed homogeneously in a definable part of the lymph node should be measured as one focus Cells, clusters, or foci arranged in a discontinuous manner and dispersed unevenly should be considered as one if the distance between clusters or foci is smaller than the smallest cluster or focus; if the distance between these cells, clusters, or foci is larger than the smallest cluster or focus, it should be characterized by the size of the largest cluster or focus Three-dimensional information is used: single cluster in corresponding areas of two consecutive sections at $>$ 0.2 mm interval is measured as one	Confluent focus of tumor cells that are touching other tumor cells Clusters or cells separated by a single benign cell or a spatial gap are measured as separate clusters, except when fibroblastic reaction of the tumor has caused this separation Single cells represent ITC; densely crowded cells when contiguous/touching are measured and classified according to the largest group of contiguous/touching cells Only the two-dimensional image of the microscopic section is considered
Microanatomic location	Tumor cells localized in the parenchyma are considered micrometastases (except with $\leq$ five single cells), even if the largest diameter is $<$ 0.2 mm Metastatic cells in extranodal lymph vessels should not be recorded as nodal involvement	Microanatomic location is not a factor in classification; ITC may be found in nodal parenchyma Metastatic cells in extranodal lymph vessels are classified as nodal disease on the basis of size of deposit
Proliferation	Mitotic activity is considered as a feature reflecting malignant/metastatic activity	Mitotic activity is not considered

Abbreviations: EWGBSP, European Working Group for Breast Screening Pathology; ITC, isolated tumor cell.

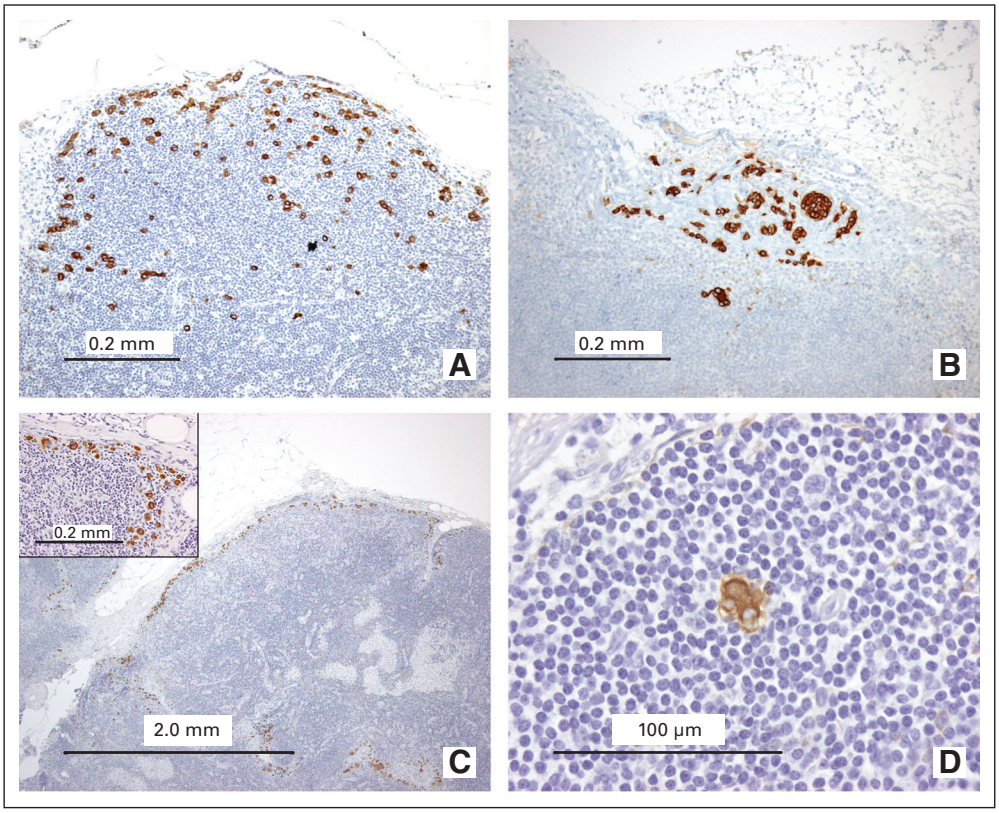

Fig 1. Examples of sentinel node (SN) metastases from lobular breast carcinoma that caused difficulty in nodal classification and discordance between different interpretations. SNs with multiple single cells and clusters arranged in a discontinuous manner but dispersed homogeneously in a definable part of the lymph node, classified as (A, B) micrometastases or (C) macrometastasis according to the European Working Group for Breast Screening Pathology (EWGBSP) interpretations[9] versus ITC according to Turner et al.[11] (D) SN with a tumor cluster less than 0.2 mm located in the parenchyma, classified as a micrometastasis according to the EWGBSP interpretation[9] versus isolated tumor cells according to Turner et al.[11]

SN Processing

The pathologic work-up of SNs was somewhat heterogeneous, but all laboratories used a multilevel assessment and performed immunohistochemistry for patient cases with a negative SN on H&E staining, which was generally performed on multiple levels. Non-SNs were evaluated by a single to a few H&E–stained sections without the routine use of immunohistochemistry.

Statistical Analysis

The 95% CIs were calculated by use of the Rothman spreadsheet.[15] Univariate analysis with the χ^2 test was used to correlate covariates with non-SN involvement. The Spearman correlation coefficient was used as a measure of correlation between the total number of SNs and the number of positive non-SNs. In those patient cases with more than one SN involved, the largest deposit was used for statistical analysis. Statistical analyses were performed by using SPSS for Windows (version 13.0; SPSS, Chicago, IL). Two-sided *P* values less than .05 were considered significant.

RESULTS

Clinicopathologic Features

Overall, 392 patients with invasive lobular breast carcinoma and a positive SN were included in this study, and the median tumor size was 2.2 cm. The median numbers of SNs and non-SN assessed per patient were two (range, one to seven) and 15 (range, six to 50), respectively. The overall rate of non-SN involvement was 183 (47%; 95% CI, 41.8 to 51.6) of 392 patients.

SN Staging

The originally diagnosed SN metastases were classified as ITC (n = 31; 6%), micrometastases (n = 132; 26%), or macrometastases (n = 274; 54%), or they remained unclassified (n = 74; 14%). The majority of these metastases (ie, 286 [73%] of 392) were detected by H&E staining.

Reclassification according to the definitions of the EWGBSP[9] and Turner et al[11] resulted in a discordance in nodal staging in 86 (22%) of 392 patients because of a difference in either diameter (n = 42; 49%), microanatomic location (n = 29; 34%), or both (n = 15; 17%). This resulted in a different pN classification in 73 patients (19%). Overall, the rates of SN ITC, micrometastases, and macrometastases were 7%, 27%, and 66% according to the interpretation of the EWGBSP,[9] compared with 18%, 25%, and 57% on the basis of the definitions by Turner et al.[11] Figure 1 shows some examples of metastatic deposits causing discordance between both staging definitions. The majority of these discordantly staged cases (40 [55%] of 73 patients) were classified as micrometastases according to the interpretation of the EWGBSP,[9] whereas they were classified as ITC according to the interpretation by Turner et al[11] (Table 2). The rest of these discrepancies were caused by a difference between micrometastases (Turner et al[11]) versus macrometastases (EWGBSP[9]; 40%) or between ITC (Turner et al[11]) versus macrometastases (EWGBSP[9]; 5%). Taking the total number of patients into account revealed a discordance in 40 (37%) of 107 of all patients with micrometastases according to the EWGBSP.[9] The rate of discordances in the group of patients classified as macrometastases according to EWGBSP was only 13% (33 of 258 patients).

Non-SN Involvement

Univariate analysis showed that the diameter of the primary tumor and the presence of lymphovascular invasion were significantly

Table 2. Comparison of SN Staging According to the Interpretations of EWGBSP[9] and Turner et al[11] Criteria in a Group of 392 Patients With Invasive Lobular Breast Cancer

EWGBSP Criteria[9]	Turner et al[11] Criteria			
	ITC	Micrometastases	Macrometastases	Total
ITC	27	0	0	27
Micrometastases	40	67	0	107
Macrometastases	4	29	225	258
Total	71	96	225	392

Abbreviations: EWGBSP, European Working Group for Breast Screening Pathology; ITC, isolated tumor cell.

Table 3. Comparison of Clinicopathologic and SN Characteristics in Patients With Lobular Breast Carcinoma Without and With Non-SN Involvement

Variable	Patients by SN Involvement				
	Non-SN Negative (n = 209)		Non-SN Positive (n = 183)		
	No.	%	No.	%	*P*
Primary tumor feature					
Tumor stage					
pT1	107	51	62	34	.002
pT2	89	43	102	56	
pT3	13	6	19	10	
Lymphovascular invasion					.001
No	138	66	93	51	
Yes	58	28	81	44	
Unknown	13	6	9	5	
Growth pattern					.14
Unifocal	115	55	87	48	
Multifocal	78	37	81	44	
Unknown	16	8	15	8	
SN feature					
No. of SNs					
Median	2		2		.92
Range	1-5		1-5		
No. of involved SNs					.07
Median	1		1		
Range	1-3		1-5		
Detection method					< .001
H&E	130	62	156	85	
Immunohistochemistry	79	38	27	15	
Extracapsular extension					< .001
No	159	76	103	56	
Yes	38	18	77	42	
Unknown	12	6	3	2	
SN classification according to EWGBSP[9]					< .001
ITC	24	10	3	2	
Micrometastases	85	41	22	12	
Macrometastases	100	48	158	86	
SN classification according to Turner et al[11]					< .001
ITC	62	30	11	6	
Micrometastases	66	32	28	15	
Macrometastases	81	39	144	79	
No. of non-SNs					.069
≤ 10	39	19	25	14	
> 10 to ≤ 15	81	39	59	32	
> 15	89	43	99	54	

Abbreviations: SN, sentinel node; H&E, hematoxylin and eosin; ITC, isolated tumor cell; EWGBSP, European Working Group for Breast Screening Pathology.

associated with non-SN involvement ($P = .002$ and $P = .001$, respectively). SN features that were significantly associated with non-SN involvement included the detection method ($P < .001$), the presence of extracapsular extension ($P < .001$), SN staging according to the EWGBSP[9], as well as Turner et al[11] ($P < .001$ for both; Table 3). There was no significant correlation between the total number of SNs and the number of positive non-SNs ($P = .32$).

The rates of non-SN involvement in patients with SN ITC, micrometastases, and macrometastases were 11%, 21%, and 61% according to the interpretation of the EWGBSP,[9] compared with 15%, 29% and 64% on the basis of the definitions by Turner et al[11] (Table 4). None of these differences were statistically significant ($P = .82$, $P = .21$, and $P = .6$, respectively). SN metastases with a diameter of less than 0.2 mm that were classified as micrometastases on the basis of microanatomic location according to the EWGBSP[9] were associated with non-SN involvement in four (16%; 25 patient cases; 95% CI, 6.4% to 34.7%), compared with three patient cases (11%; 95% CI, 3.9% to 28.1%) with metastases with a diameter of less than 0.2 mm located in the sinus, classified as ITC.

Table 5 shows the rates of non-SN involvement in those 73 patient cases with a discrepant classification between EWGBSP[9] and Turner et al.[11] The rate of non-SN involvement in the 40 patients with ITC according to Turner and micrometastases according to EWGBSP was 20%, which is comparable to the established rate for micrometastases. The rate of non-SN involvement in the 29 patients with micrometastases according to Turner et al[11] and macrometastases according to EWGBSP[9] was 48%, which is comparable to the established rate for macrometastases. However, none of those four patient cases classified as having macrometastases according to EWGBSP[9] versus ITC according to Turner et al[11] had detected non-SN involvement (Fig 1C). Overall, the EWGBSP method to classify SN tumor load thereby better reflected the risk of non-SN involvement than the Turner et al[11] system in these discrepant patients.

DISCUSSION

Lymph node metastases from lobular invasive breast cancer often show a pattern with multiple scattered clusters and/or single cells in both sinus and parenchyma of (sentinel) lymph nodes, which complicates nodal staging. This study is the first to evaluate nodal staging in this specific group of patients by assessing the frequency of non-SN involvement for two different interpretations of nodal staging guidelines.

Overall, the rates of non-SN involvement in patients with a lobular breast carcinoma and SN ITC, micrometastases, or macrometastases were consistent with results from previous breast cancer studies including all histologic subtypes.[16,17] Several features of the primary tumor (ie, diameter, lymphovascular invasion) and the SN (ie, number of involved SNs, extracapsular extension) were also significantly associated with non-SN involvement, which is consistent with previous breast cancer studies.[18-21]

Table 4. Frequency and Comparison of Non-SN Involvement According to Two Different Interpretations of the N Staging System

	Patients With Non-SN Involvement									
	EWGBSP[9]				Turner et al[11]				Difference	
SN Classification	No.	No. Evaluated	%	95% CI	No.	No. Evaluated	%	95% CI	%	95% CI
ITC	3	27	11	3.9 to 28.1	11	71	15	8.9 to 25.7	4	−13.8 to 16.9
Micrometastases	22	107	21	14.0 to 29.2	28	96	29	21.0 to 38.9	9	−3.3 to 20.4
Macrometastases	158	258	61	55.2 to 67.0	144	225	64	57.5 to 70.0	3	−5.9 to 11.3

Abbreviations: SN, sentinel node; EWGBSP, European Working Group for Breast Screening Pathology; ITC, isolated tumor cell.

SN reclassification according to the definitions of the EWGBSP[9] and Turner et al[11] resulted in a different pN classification in 73 patients (19%). Not all discrepancies resulted in a different pN classification, because patients were staged according to the largest metastatic deposit; for example, a patient with two macrometastases according to the EWGBSP interpretation[9] was classified as having one macrometastases and one micrometastasis according to Turner et al.[11]

In general, the EWGBSP[9] interpretation designates more often metastases into a higher category than the Turner et al[11] system. This is because metastatic cell clusters that have a size compatible with ITC are yet classified as micrometastases when the microanatomic location is in the SN parenchyma. Second, a dispersed pattern of generally small tumor clusters or single metastatic cells is considered ITC or micrometastases in the Turner et al[11] classification depending on size of the largest cluster, whereas these are often designated micrometastases or macrometastases in the EWGBSP system.[9] Of 107 patient cases classified as micrometastases according to the EWGBSP definitions,[9] 40 patients (37%) were staged as having ITC according to Turner et al.[11] This is higher than the discordance rate of 24% previously reported by Cserni et al,[14] which was expected, as we considered only lobular breast cancers whereas the study of Cserni et al[14] included all breast cancer subtypes. The discrepancy between micrometastases (Turner et al[11]) versus macrometastases (EWGBSP[9]) or between ITC (Turner et al[11]) versus macrometastases (EWGBSP[9]), conversely, was relatively limited. The main explanation for this finding is that a substantial proportion of macrometastases show a compact pattern of single cells and/or a fibroblastic reaction, which precludes a discrepancy between both interpretations.

The risk of non-SN involvement in patients with SN ITC overall did not differ significantly between both interpretations, a finding similar to that of Cserni et al[14] and dealing with all histologic breast cancer types and only low volume metastases. We demonstrated that the interpretation of Turner et al[11] is associated with a higher positive predictive value of having non-SN metastases after finding either ITC or micrometastases in the SN. However, a high positive predictive value is not desirable in these groups of patients, because the objective is to select those patients with a limited risk of non-SN involvement, which correlates better with results of the EWGBSP definitions.[9] In those patients with a discordant classification between both definitions, the EWGBSP method to classify SN tumor load better reflected the risk of non-SN involvement than the Turner system, which leads to the conclusion that the EWGBSP method is better for the subgroup of invasive lobular carcinomas. Second, the rate of non-SN metastases in patients with SN metastases less than 0.2 mm but located in the parenchyma was 16%, which is relatively high compared with the risk for non-SN metastases in patients with SN metastases less than 0.2 mm located in the sinus (11%). These clusters located in the parenchyma were designated micrometastases according to EWGBSP,[9] whereas they are regarded as ITC by Turner et al.[11] Although the limited number of patients and the wide CIs do not allow definitive conclusions, these seem to support the hypothesis that extravasation of metastatic tumor deposits from the sinus into the parenchyma is a sign of the potential to generate additional metastatic spread. One must realize that the absence of a capsule deeper in the tissue block, immediately behind these deposits that seem to be located purely in the parenchyma, cannot be excluded. However, the potential risk of overstaging these patient cases was reduced by serial sectioning of the SN.

Table 5. Frequency of Non-SN Involvement for 73 Invasive Lobular Carcinoma Cases With Dissimilar N Classification According to Two Different Interpretations of the N Staging System

Turner et al[11] Criteria	EWGBSP Criteria[9]	No. of Patients	Patients With Non-SN Involvement	
			No.	%
ITC	Micrometastases	40	8	20
ITC	Macrometastases	4	0	0
Micrometastases	Macrometastases	29	14	48

Abbreviations: SN, sentinel node; EWGBSP, European Working Group for Breast Screening Pathology; ITC, isolated tumor cell.

It was interesting to note that none of the four patient cases classified as SN ITC according to Turner et al[11] and as macrometastases according to EWGBSP[9] had non-SN metastases. This could imply that in these patient cases, the Turner[11] classification may perform better, although it is more likely that the main underlying cause is the number of patient cases studied being too low to draw any conclusions. In addition, non-SN metastases with a dispersed pattern may have remained undetected in these cases, since non-SNs were not routinely examined by immunohistochemistry.

Another difference between both classifications is the interpretation of metastatic cells in extranodal lymph vessels without nodal involvement. These patient cases were classified as having nodal disease according to Turner et al,[11] whereas they were classified as node negative according to the EWGBSP[9] interpretation. The effect of this difference with regard to the rate of non-SN involvement is probably limited. In this study, it was not evaluated, because these patient cases were not selected as having a positive

SN. The capsular and subcapsular lymphatic space on the other hand is regarded as part of the lymph node according to both definitions. These metastatic deposits are classified as either ITC or micrometastases, depending on size.

The definitions by Turner et al[11] are superior to those by the EWGBSP[9] regarding reproducibility in small metastases (κ,0.92 ν 0.49). However, they tend to understage high-volume metastases. Because the EWGBSP definitions[9] reflect the total metastatic tumor load, especially in patients with lobular breast carcinoma, we suggest using these definitions at least in patients with lobular breast carcinoma for nodal staging to select high-risk patients that may benefit from additional local and/or systemic therapy. Clarifications regarding the measurement of nodal metastases, supplemented by visual examples, should be included in future staging manuals (or well worked out on Web sites) to achieve reproducible nodal staging. Although an improved interobserver agreement does not necessarily mean better treatment, it is required to make a better prognostic separation. Findings from large studies assessing the effect of ITC and micrometastases on survival will provide greater clinical evidence regarding policies on local and systemic treatment in patients with either ITC or micrometastases in their SNs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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