



Adrian Deckbar. *Intimacies #3*. Serigraph, 39" × 27". Courtesy of the Hanson Gallery, New Orleans, Louisiana.

*The significance of micrometastases found in sentinel nodes is being studied in several clinical trials.*

# Breast Cancer Sentinel Node Metastases: Histopathologic Detection and Clinical Significance

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**Background:** *Lymphatic mapping with sentinel lymphadenectomy (LM/SL) is an accurate and less morbid means of determining the tumor status of the axilla in breast cancer patients than standard level I and II axillary lymph node dissection (ALND). This review addresses the handling and pathologic examination of the sentinel node (SN), the clinical significance of tumor within the SN, and the risk factors for non-SN tumor involvement.*

**Methods:** *The seminal works that have addressed pathologic examination of ALND specimens and SN specimens are summarized, and the important studies attempting to identify predictors of non-SN metastases in patients with a tumor-involved SN are reviewed.*

**Results:** *Standard single-section hematoxylin-eosin (H&E) examination is inadequate for reliable detection of axillary or SN metastases. Large studies appropriately powered to detect a survival difference for patients with micrometastatic disease are reviewed. The current data on the clinical significance of micrometastatic nodal disease is inconclusive. While several strong predictors of non-SN tumor involvement have been identified, none is reliable enough to allow omission of ALND in patients with a tumor-involved SN.*

**Conclusions:** *Routine examination of the SN specimen should include serial sections with H&E stain. Ongoing prospective clinical trials should help to define the clinical significance of SN micrometastases. Furthermore, these trials could help identify predictors of non-SN metastasis that would allow a subset of patients with a tumor-involved SN to avoid the morbidity of ALND.*

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## Introduction

The sentinel node (SN) era is upon us. Intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL), first described by Morton and colleagues<sup>1</sup> for patients with cutaneous melanoma and also by Giuliano et al<sup>2</sup> for patients with invasive breast cancer, has been shown to be a less invasive and more accurate

method for staging the regional nodal basin. LM/SL offers the ability to identify a direct lymphatic channel between the primary tumor and the regional nodal basin. By following this channel, the SN can be identified. Thus, the SN is the first lymph node receiving efferent lymphatic drainage from the primary tumor. The SN hypothesis is based on the idea that malignant cells shed from the primary tumor will also travel this same direct lymphatic pathway. Therefore, the SN will be the most likely site of nodal disease, if it exists.

Using slightly varying techniques, numerous single institutions<sup>3,5</sup> and multi-institution studies<sup>6,7</sup> have confirmed that at experienced centers, LM/SL is an accurate method for determining the tumor status of the axilla than a standard level I and II axillary lymph node dissection (ALND). The varying technical details of LM/SL are well described, including blue dye alone, radiocolloid alone, combined blue dye and radiocolloid, peritumoral injection, periareolar injection, and intradermal injection. We have previously critically reviewed the various techniques examining the advantages and disadvantages of each method.<sup>8</sup> The purpose of this monograph is to step beyond the technical aspects of how to perform LM/SL and locate the SN. Rather, we discuss how the SN should be sectioned and examined for metastatic disease, the significance of tumor in the SN, and the risk factors for non-SN metastatic tumor involvement.

## Sectioning and Staining of Axillary Lymph Nodes

### *Axillary Lymph Node Dissection Specimens*

In 1948, Saphir and Amromin<sup>9</sup> first suggested that standard pathologic evaluation of a lymph node, ie, bisecting the node and examining each face with hematoxylin-eosin (H&E) stain, was inadequate for consistent detection of axillary metastases in breast cancer patients. They hypothesized that examination of serial sections taken systematically through the entire lymph node would increase the detection rate of metastatic breast cancer compared with examination of a random section stained with H&E. They sectioned the entire lymph node from patients who had previously been determined to have tumor-free lymph nodes by standard pathologic examination. Examining an average of 332 H&E stained sections per block, they detected previously occult metastases in 33% of the axillary node specimens. They concluded that a single, random H&E section of a lymph node was inadequate to accurately determine the tumor status of a breast cancer patient's axillary lymph nodes. Many subsequent studies have

duplicated their work.<sup>10,11</sup> While no standard definition for serial sectioning exists, a variety of protocols have demonstrated that evaluating a lymph node specimen with serial sections increases the metastatic tumor detection rate from 7% to 33% compared to examination of a single H&E section.<sup>10</sup> Nevertheless, a single section with H&E stain remains the standard pathologic evaluation of the axillary nodes in an ALND specimen. Routine serial sections on all lymph nodes in an ALND specimen is cost prohibitive, labor intensive, and time consuming. Other than as part of a research protocol or clinical trial, this cannot be considered efficient use of a pathologist's time or resources.

Cytokeratin immunohistochemical (IHC) staining of axillary nodes has also been shown to enhance the tumor detection rate in breast cancer patients. Many retrospective studies have shown an increased tumor detection rate of 10%-15% when IHC staining is added to routine H&E evaluation of axillary nodes.<sup>10,12-16</sup> For example, by staining a single level of each tumor-free lymph node with a cocktail of monoclonal antibodies against epithelial cell antigens, de Mascarel et al<sup>17</sup> detected occult micrometastases in 41% of previously node-negative invasive lobular carcinoma patients and 10% of previously node-negative invasive ductal carcinoma patients. McGuckin and colleagues<sup>18</sup> detected occult metastases in 25% of specimens examined by performing both serial sectioning and IHC staining on axillary nodes previously determined to be tumor-free by routine H&E. Overall, there is strong data to support the use of serial sectioning and IHC to enhance the detection of axillary nodal metastases. However, like serial sectioning with H&E stain, IHC examination has not been incorporated into the standard pathologic evaluation of axillary lymph nodes. Due to the high monetary and labor expense of these techniques, they have not been practical for routine use in examination of ALND specimens.

### *Sentinel Node Specimens*

In the era of LM/SL, where only one or two SNs are retrieved in the majority of patients,<sup>3,5,12</sup> pathologists can focus their time and resources on a thorough evaluation of SN specimens. Sectioning and staining of the SN vary significantly from study to study.<sup>3,5,12,19</sup> Most pathologists agree that the first step in the handling and sectioning of the SN is to bivalve the node. From that point, however, considerable variations exist. Some groups bivalve the SN with half being processed in pathology and the other half being cryopreserved and banked for research purposes. Other groups perform routine step-sectioning on each half of the node with alternating levels of the node going to pathology and being saved in tissue banks. Still other groups use

portions of the node for intraoperative examination.<sup>3,5,20</sup> The manner in which these portions are obtained, including quantity of tissue and depth of sections, are not standardized.

In our experience, proper handling and pathologic evaluation of the SN have been imperative for reliable detection of metastatic tumor. In our initial SN protocol, the SN was bisected, and half was sent to surgical pathology and the other half was cryopreserved and stored for ongoing and future research studies. In our institutional breast cancer SN validation trial, each patient underwent LM/SL followed by completion ALND. Early in the trial, two patients were found to have non-SN metastases despite having SNs that were tumor-free. When the cryopreserved tissue from these cases was retrieved and examined, an SN metastasis was identified in both specimens. Realizing that histopathologic examination of only one half of each bisected SN was inadequate, we changed our protocol for SN handling and sectioning. Our current protocol<sup>21</sup> requires alternating levels (each  $\leq 1$  mm) to be submitted to surgical pathology and to the tissue procurement facility. From each level sent to surgical pathology, a 5- $\mu$ m-thick section is obtained and examined with H&E stain. Since implementation of the new protocol, no non-SN metastases have been identified in cases with a tumor-free SN.

Standard histopathologic examination of the SN varies among institutions. Based on the data from ALND specimens, several groups<sup>19,22-27</sup> have suggested that the addition of serial sectioning and/or IHC staining to the SN workup would increase the metastatic tumor detection rate. Nahrig et al<sup>22</sup> examined the impact of serial sections with only H&E staining. With the examination of an additional five H&E-stained sections at 150  $\mu$ m intervals, they demonstrated an increase in the metastatic tumor detection rate in the SN from 45% to 55%.

Investigators have consistently shown an increased metastatic tumor detection rate with the addition of serial sectioning and cytokeratin IHC stain to the histopathologic evaluation of the SN. By performing serial sectioning of the SN at 0.5-mm intervals with subsequent H&E and IHC staining, Jannink and colleagues<sup>23</sup> increased the metastatic detection rate from 32% to 47%. Czerniecki et al<sup>24</sup> added four IHC levels at unspecified intervals to the standard H&E examination of the SN. These additional sections increased the SN metastatic detection rate from 29% to 37%. Kelley and group<sup>25</sup> added four additional H&E stained sections and two IHC stained sections to the SN workup and increased the SN metastatic detection rate from 25% to 32%. Dowlatshahi et al<sup>26</sup> demonstrated a dramatic

increase in the metastatic tumor detection rate from 12% to 58% with the addition of IHC and serial sections at 0.25-mm intervals. Turner and colleagues<sup>27</sup> demonstrated an increase in the metastatic detection rate from 19% to 37% with a total of four H&E and 10 IHC stained sections at 40  $\mu$ m intervals. Most recently, Weaver et al<sup>19</sup> demonstrated an increase in metastatic tumor detection from 31% to 36% with the addition of two H&E-stained sections and one IHC-stained section at 100  $\mu$ m intervals to the SN workup. This increase may be falsely small, as 24% of the tumor-free SN specimens were not available for serial sectioning and IHC staining.

Although the handling, sectioning, and staining in these studies have varied widely, it is clear that the addition of serial H&E-stained sections and IHC-staining to the histopathologic evaluation of the SN increases the metastatic tumor detection rate. Therefore, the use of IHC stains by pathologists for the evaluation of the SN should be used as a focused tool to avoid false-negative examinations rather than as a predictor of clinical outcomes. H&E examination of a single SN section is inadequate and should not remain the standard. However, studies to determine the optimal SN sectioning and staining protocol are necessary with the goal of maximizing tumor detection while minimizing labor and cost.

## Clinical Significance of Micrometastases

### *Axillary Lymph Node Dissection Micrometastases*

In both ALND and SN specimens, many of the metastases identified by serial sectioning and IHC examination are micrometastases ( $\leq 2$  mm). The clinical significance of detecting occult micrometastatic disease in patients previously deemed to have single section H&E node-negative breast cancer remains controversial. Since 15%-30% of patients with H&E node-negative breast cancer will develop recurrent disease,<sup>28,29</sup> one can hypothesize that the patients with previously occult micrometastases are the patients most likely to develop recurrent breast cancer. Many studies<sup>17,18,30-36</sup> have retrospectively examined single-section H&E node-negative ALND specimens with a more thorough pathologic evaluation of the entire node. This more intensive histopathologic evaluation identified previously occult tumor in 7%-33% of cases. Based on this retrospective data, attempts have been made to determine the prognostic significance of detecting this previously occult micrometastatic disease. Unfortunately, many of the studies are underpowered to detect a significant difference in overall survival (OS). More than 250 patients would be required to detect even a 20%

difference in survival between those with and those without occult micrometastases. Some studies have not thoroughly and systematically examined the entire node for micrometastases. For these reasons, only studies with at least 200 patients and a clearly defined and thorough sectioning schema are discussed.

Wilkinson and colleagues<sup>30</sup> retrospectively examined multiple H&E-stained sections (mean 24 sections per node) from the axillary specimens of 525 node-negative patients and identified previously occult micrometastases in 89 patients (17%). However, there was no statistically significant difference in the 5- and 10-year disease-free survival (DFS) rate and OS rate in patients with previous occult micrometastatic disease as compared to those whose nodes remained tumor-free. In the International (Ludwig) Breast Cancer Study Group<sup>32,35</sup> of 736 single-section H&E node-negative breast cancer patients, serial sections of six levels stained with H&E identified occult micrometastatic disease in 83 patients (9%). At 6 years, both the DFS rate (53% vs 71%) and OS rate (70% vs 86%) were worse in those patients with occult tumor compared to those without occult tumor. Friedman et al<sup>31</sup> examined an average of four levels per node from 1,153 patients and found a 70% increase in the risk of distant relapse at 10 years for patients with occult H&E-detected micrometastases compared to those without occult micrometastatic disease.

De Mascarel et al<sup>17</sup> examined nodes from 785 patients with an average of three H&E sections per node. The 10-year DFS and OS rates were worse for those patients with micrometastatic disease compared to those without micrometastatic disease; however, this association was not significant on multivariate analysis. Overall, three of the four large studies that included thorough evaluation of the entire node found at least some association between micrometastatic disease and clinical outcome.

While retrospective data suggest occult H&E-detected micrometastases are associated with decreased survival, the clinical significance of cytokeratin IHC micrometastases is uncertain. Of the three largest retrospective studies of IHC-detected axillary micrometastases and outcome, only one shows a clear impact of IHC-detected micrometastases on prognosis. For 216 of their 785 patients, de Mascarel et al<sup>17</sup> examined one level of each axillary lymph node with an anti-cytokeratin antibody cocktail and identified occult metastases in 50 patients (23%). While the detection of cytokeratin IHC metastases was not associated with a poorer OS, there was an increased incidence in recurrence at 15 years in patients found to have cytokeratin IHC micrometastases. Of note, this association was true

only for patients whose primary tumor was invasive ductal carcinoma. In patients with invasive lobular carcinoma, there was no significant association between occult IHC-detected micrometastasis and DFS or OS. For patients in the International (Ludwig) Breast Cancer Study Group with H&E-determined node-negative breast cancer, Cote and colleagues<sup>34</sup> examined a single level of each axillary node stained with two anticytokeratin antibodies. Cytokeratin IHC micrometastases were identified in 148 (20%) of 736 patients, but they were not associated with decreased DFS or OS at 10 years. However, in a subset analysis, there was a statistically significant DFS and OS difference for postmenopausal women. McGuckin et al<sup>18</sup> combined serial sectioning with IHC staining and examined nodes from 216 patients with anticytokeratin antibodies at four levels. Occult micrometastases were identified in 25% of patients. A clear decrease in 5-year DFS for patients with occult micrometastases was identified. However, there was no statistically significant difference in OS. In summary, to date, there is no clear association between IHC detected micrometastases and clinical outcome.

### *Sentinel Node Micrometastases*

Hansen and colleagues<sup>37</sup> presented the initial data from the John Wayne Cancer Institute on the clinical significance of SN micrometastases at the 2001 meeting of American Society of Clinical Oncologists. The SNs from 696 patients were serially sectioned and examined with both H&E and cytokeratin IHC stains. At 5 years, patients with H&E-detected macrometastases (>2 mm) demonstrated a decreased DFS rate (75.2% vs 94.5%,  $P=.0001$ ) but not OS rate (96.5% vs 100%,  $P=.0520$ ) compared to patients with micrometastases ( $\leq 2$  mm). There was no difference in DFS rate (98.3% vs 95.1%,  $P=NS$ ) or OS rate (100% vs 99.7%,  $P=NS$ ) for patients with cytokeratin IHC-detected SN metastases compared to patients with no SN tumor involvement. Additionally, there did not appear to be a difference in DFS rate (94.5% vs 95.1%,  $P=NS$ ) or OS rate (100% vs 99.7%,  $P=NS$ ) for patients with H&E-detected SN micrometastases compared to patients with no SN tumor involvement. Notably, the total number of tumor-involved axillary nodes was not considered in this analysis. This is significant because the size of the SN metastasis has been shown to be significantly associated with the total number of tumor-involved axillary nodes. Since it is commonly held that the number of tumor-involved axillary nodes is significantly associated with DFS and OS, this variable must be accounted for in future studies examining the clinical significance of SN metastases.

Large prospective clinical trials are necessary to answer whether micrometastases, especially those

detected by cytokeratin IHC, are clinically relevant. Two well-designed clinical trials — ACOSOG Z0010<sup>38</sup> and NSABP B-32<sup>39</sup> — should answer definitively whether cytokeratin IHC should be included as the national standard for evaluating the regional nodes in breast cancer patients. Until the true clinical significance is established, we believe the use of cytokeratin IHC should not be used routinely as a guide to clinical therapy.

## Predictors of Nonsentinel Node Tumor Involvement

The true benefit of LM/SL is that an accurate histopathologic status of the axilla can be determined without having the patient incur the morbidities associated with ALND. At experienced centers with a documented low false-negative rate, for patients whose SN is tumor-free, no additional axillary therapy is necessary. However, for patients with a tumor-involved SN, the true extent of axillary involvement is not known until a completion ALND is performed. Unfortunately, completion ALND is currently the only surgical option available for patients with a tumor-involved SN. Surgeons do not have a reliable technique to map or identify the next lymph node in the lymphatic chain after the SN. The potential efferent pathways leaving the SN are too numerous and variable for the surgeon to consistently identify. Moreover, these efferent pathways will invariably have been disrupted during the original SN procedure. Thus, a completion ALND remains the standard for patients with a tumor-involved SN.

As the technique of LM/SL has matured and become more widely practiced, several groups have reported that only approximately half the patients with a tumor-involved SN have associated non-SN metastases.<sup>10,12-16</sup> Approximately 50% of patients with a tumor-involved SN will have no metastatic tumor detected in the completion ALND specimen. If there were a way to reliably predict which patients with a tumor-involved SN will have non-SN tumor involvement, then completion ALND could be reserved for these cases. Conversely, ALND could be omitted in patients for whom the SN metastasis represents the only axillary nodal tumor involvement.

Several groups have searched for potential predictors of non-SN metastasis in patients with an SN metastasis.<sup>12-16</sup> While the exact characteristics examined by each group varied, all attempted to identify predictors on non-SN metastases in patients with a tumor-involved SN. Numerous clinical and histopathologic characteristics have been examined at various institutions, yet only four characteristics have demonstrated any significant association with non-SN metastases: size of the SN

metastasis, extracapsular extension of the SN metastasis, size of the primary tumor, and peritumoral lymphovascular invasion.

## Size of Sentinel Node Metastasis

Size of SN metastasis has been examined repeatedly as a predictor of non-SN tumor involvement. Consistently, studies have supported size of SN metastasis as a predictor of non-SN tumor involvement. Most groups have examined the number of non-SN metastases in patients with micrometastases (SN metastasis  $\leq 2$  mm) vs patients with macrometastases (SN metastasis  $> 2$  mm) as opposed to examining size of the SN metastasis as a continuous variable. In a study involving 157 women with a tumor-involved SN, Chu et al<sup>13</sup> demonstrated non-SN tumor involvement in 44.4% of patients with macrometastases ( $> 2$  mm) vs only 24.4% of patients with micrometastases ( $\leq 2$  mm,  $P=.014$ ). Weiser et al<sup>16</sup> demonstrated that while 45% of patients with macrometastases had non-SN tumor involvement, only 18% of patients with micrometastases demonstrated non-SN tumor involvement ( $P=.0002$ ). Reynolds and associates<sup>15</sup> analyzed data from 60 patients with tumor-involved SNs and found non-SN tumor involvement in 66.7% of patients with macrometastases vs 22.2% of patients with micrometastases ( $P=.002$ ). In our institutional validation study<sup>12</sup> of 76 patients, we examined size of the SN metastasis as a continuous variable. We found patients with non-SN tumor involvement tended to have larger SN metastases (mean 10.2 vs 3.8 mm,  $P=NS$ ), but this did not reach statistical significance because of the relatively small sample size. In our expanded experience<sup>40</sup> with 182 patients, increasing size of SN metastasis, examined as a continuous variable, was associated with non-SN tumor involvement (mean 9.9 vs 4.4 mm,  $P=.001$ ) and was statistically significant in the larger sample size. Turner et al<sup>14</sup> also examined size of SN metastasis as a continuous variable and found that increasing size of SN metastasis was significantly associated with non-SN tumor involvement (median 6.5 vs 0.8 mm,  $P=.0001$ ).

## Extracapsular Extension

Extracapsular extension (ECE) of axillary node metastases, defined as tumor extension through the capsule of a node, was first identified as a prognostic factor by Fisher et al<sup>41</sup> in 1976. In their report from the NSABP-04 trial, they noted that ECE of an axillary nodal metastasis was associated with tumor involvement of four or more lymph nodes ( $P=.002$ ). Since that initial report, the presence of ECE has been repeatedly associated with a greater number of tumor-involved axillary nodes.<sup>42-46</sup> Prompted by the association between ECE

and the total number of tumor-involved axillary nodes, we examined ECE of the SN metastasis as a predictor of non-SN metastasis.<sup>12</sup>

In our initial experience<sup>12</sup> with 76 patients, we were able to demonstrate a significant association between non-SN tumor involvement and ECE of the SN metastasis. In fact, after multivariate analysis, ECE of the SN metastasis was the only clinical or histopathologic characteristic that was significantly associated with non-SN tumor involvement ( $P=.04$ ). Similar to studies of ALND specimens, ECE of the SN metastasis was also significantly associated with the total number of tumor-involved axillary nodes (6.0 vs 1.7,  $P=.006$ ). Our expanded experience<sup>40</sup> with 182 patients demonstrated again that patients with ECE of the SN metastasis were significantly more likely to have non-SN tumor involvement (80.0% vs 32.4%,  $P=.002$ ) than were patients without ECE of the SN metastasis. Similarly, we again demonstrated that patients with ECE of the SN metastasis averaged a greater total number of tumor-involved nodes (6.5 vs 1.9,  $P=.001$ ) than did patients without ECE of the SN metastasis.

No other studies have addressed ECE as a potential predictor of non-SN tumor involvement. Turner and colleagues<sup>14</sup> examined extranodal hilar tissue invasion (HTI), a similar but not identical histopathologic characteristic. HTI was defined as either efferent lymphovascular invasion or extension of tumor into hilar adipose tissue. Of the 194 patients with a tumor-involved SN, 89% of cases with extratumoral HTI had non-SN involvement vs 29% of cases without extratumoral HTI ( $P=.001$ ). Together, these studies strongly suggest that tumor extending through the capsule or present outside the capsule is a strong predictor of non-SN tumor involvement.

### *Size of Primary Tumor*

Some studies have shown significant associations between size of primary tumor and non-SN tumor involvement. Turner et al<sup>14</sup> found a median primary tumor size of 2.2 cm in patients with non-SN tumor involvement vs 1.8 cm in patients without non-SN tumor involvement ( $P=.0008$ ). As with size of SN metastases, other studies have not examined size of primary tumor as a continuous variable. Weiser and group<sup>16</sup> showed non-SN tumor involvement in 18.2% of patients with T1a/T1b tumors vs 30.5% of patients with T1c/T2 tumors ( $P=.007$ ). Chu et al<sup>13</sup> and Reynolds et al<sup>15</sup> compared T1 vs T2 and found cases with a primary T2 tumor were associated with a significantly increased occurrence of non-SN metastasis when compared to cases with a primary T1 tumor (44.4% vs 24.4%,  $P=.014$  and 79.2% vs 25.0%,  $P=.0004$ , respectively).

### *Peritumoral Lymphovascular Invasion*

Two groups have demonstrated an association between non-SN tumor involvement and peritumoral lymphovascular invasion (LVI). Weiser and colleagues<sup>16</sup> analyzed clinical and histopathologic characteristics from 206 patients treated over a 2½-year period. In this study, they demonstrated that on univariate analysis, LVI was significantly associated with non-SN tumor involvement (41% vs 26%,  $P=.021$ ). However, they were unable to show LVI as an independent predictor of non-SN metastasis after multivariate analysis. Turner et al<sup>14</sup> also examined LVI and demonstrated a strong association between LVI and non-SN tumor involvement (65% vs 37%,  $P=.001$ ). We did not examine LVI in our multivariate analysis of predictors of non-SN tumor involvement.

### *Significance of Predictors*

While size of SN metastasis, ECE of SN metastasis, size of primary tumor, and peritumoral LVI have all been shown to be associated with non-SN tumor involvement, none of these characteristics alone are strong enough to identify exclusively the patients with an SN metastasis who have non-SN tumor involvement. For example, in our experience,<sup>40</sup> while 80% of patients with ECE of the SN metastasis have non-SN tumor involvement, so do 32.4% of patients without ECE of the SN metastasis. Clearly, ALND cannot be omitted based solely on the absence of ECE of the SN metastasis.

As no one characteristic has sufficient strength by itself to predict the presence or absence of non-SN tumor involvement, studies have attempted to identify combinations of predictors that might serve as strong predictors. Reynolds et al<sup>15</sup> reported that no patients with T1 primary tumors and SN micrometastases had non-SN tumor involvement. Chu and colleagues<sup>13</sup> similarly reported no non-SN tumor involvement in patients with primary tumor  $\leq 1$  cm and SN micrometastases. In contrast, Weiser et al<sup>16</sup> reported non-SN metastases in 7% of cases with primary tumor  $\leq 1$  cm and SN micrometastases. However, by adding a third variable to the combination, Weiser et al<sup>16</sup> report no non-SN tumor involvement in cases with primary tumor  $\leq 1$  cm, SN micrometastases, and no LVI. Unfortunately, this combination of characteristics identified only 24 (17%) of 140 patients with a tumor-involved SN and a tumor-free non-SN specimen. While no combination of characteristics has been identified to date that is 100% predictive of non-SN tumor status, it is clear that there are certain characteristics that are strongly associated with non-SN tumor involvement. Until future studies identify a combination of characteristics that is both sensitive and specific for non-SN tumor involvement, all patients with a

tumor-involved SN should undergo completion ALND, unless ALND is omitted as part of a study protocol.

## Conclusions

The advent of LM/SL for breast cancer patients has allowed more thorough histopathologic examination of axillary specimens. Data from the era of ALND show the value of serial sectioning to enhance the metastatic tumor detection rate and are supported by earlier data from serial sectioning of SN specimens. As a result, serial sectioning with H&E staining should be routine for histopathologic evaluation of the SN specimen. Data supporting IHC staining are less clear. While IHC staining does detect occult metastases, the clinical significance of these metastases is unclear. Until further prospective information is available (ACOSOG Z0010,<sup>38</sup> NSABP B-32<sup>39</sup>), routine IHC staining of the SN specimen should be performed only as part of a clinical trial, and clinical decisions should not be made on the basis of IHC results alone except in the setting of a clinical trial.

At this time, level I and II ALND must be considered the standard of care for patients with a tumor-involved SN. Omission of routine ALND should occur only as part of an approved clinical protocol such as ACOSOG Z0011.<sup>47</sup> However, as more data mature, we may be able to reliably predict which patients with tumor-involved SN have little, if any, risk for additional concurrent axillary node tumor involvement.

## References

1. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127:392-399.
2. Giuliano AE, Kirgan DM, Guenther JM, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220:391-401.
3. Giuliano AE, Jones RC, Brennan M, et al. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol*. 1997;15:2345-2350.
4. Albertini JJ, Lyman GH, Cox C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. *JAMA*. 1996;276:1818-1822.
5. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997;349:1864-1867.
6. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med*. 1998;339:941-946.
7. Tafta L, Lannin DR, Swanson MS, et al. Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. *Ann Surg*. 2001;233:51-59.
8. Ollila DW, Rager EL. Lymphatic mapping and sentinel lymphadenectomy: critical review of technique. *Breast Dis*. In press.
9. Saphir O, Amromin GD. Occult axillary lymph-node metastasis in carcinoma of the breast. *Cancer*. 1948;238-241.
10. Dowlatsahi K, Fan M, Snider HC, et al. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. *Cancer*. 1997;80:1188-1197.
11. Pickren JW. Significance of occult metastases: a study of breast cancer. *Cancer*. 1961;14:1266-1271.

12. Stitzenberg KB, Calvo BE, Nealon BH, et al. Predictors of non-sentinel node metastasis in breast cancer patients: size and extracapsular extension of the sentinel node metastasis. Presented at the 23rd Annual San Antonio Breast Cancer Symposium; San Antonio, Texas: December 6-9, 2000.
13. Chu KU, Turner RR, Hansen NM, et al. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg*. 1999;229:536-541.
14. Turner RR, Chu KU, Qi K, et al. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. *Cancer*. 2000;89:574-581.
15. Reynolds C, Mick R, Donohue JH, et al. Sentinel lymph node biopsy with metastasis: can axillary dissection be avoided in some patients with breast cancer? *J Clin Oncol*. 1999;17:1720-1726.
16. Weiser MR, Montgomery LL, Tan LK, et al. Lymphovascular invasion enhances the prediction of non-sentinel node metastases in breast cancer patients with positive sentinel nodes. *Ann Surg Oncol*. 2001;8:145-149.
17. de Mascarel I, Bonichon F, Coindre JM, et al. Prognostic significance of breast cancer axillary lymph node micrometastases assessed by two special techniques: reevaluation with longer follow-up. *Br J Cancer*. 1992;66:523-527.
18. McGuckin MA, Cummings MC, Walsh MD, et al. Occult axillary node metastases in breast cancer: their detection and prognostic significance. *Br J Cancer*. 1996;73:88-95.
19. Weaver DL, Krag DN, Ashikaga T, et al. Pathologic analysis of sentinel and nonsentinel lymph nodes in breast carcinoma: a multicenter study. *Cancer*. 2000;88:1099-1107.
20. Kamath VJ, Giuliano R, Dauway EL, et al. Characteristics of the sentinel lymph node in breast cancer predict further involvement of higher-echelon nodes in the axilla: a study to evaluate the need for complete axillary lymph node dissection. *Arch Surg*. 2001;136:688-692.
21. Amjadi D, Calvo B, Dressler L, et al. Sentinel lymphadenectomy: immunohistologic validation and improved axillary staging for breast carcinoma: the Chapel Hill experience. *Am J Clin Pathol*. 1999;112:538-539.
22. Nahrig J, Richter T, Kowolik J, et al. Comparison of different histopathological methods for the examination of sentinel lymph nodes in breast cancer. *Anticancer Res*. 2000;20:2209-2212.
23. Jannink I, Fan M, Nagy S, et al. Serial sectioning of sentinel nodes in patients with breast cancer: a pilot study. *Ann Surg Oncol*. 1998;5:310-314.
24. Czerniecki BJ, Scheff AM, Callans LS, et al. Immunohistochemistry with pancytokeratins improves the sensitivity of sentinel lymph node biopsy in patients with breast carcinoma. *Cancer*. 1999;85:1098-1103.
25. Kelley SW, Komorowski RA, Dayer AM. Axillary sentinel lymph node examination in breast carcinoma. *Arch Pathol Lab Med*. 1999;123:533-535.
26. Dowlatsahi K, Fan M, Bloom KJ, et al. Occult metastases in the sentinel lymph nodes of patients with early stage breast carcinoma: a preliminary study. *Cancer*. 1999;86:990-996.
27. Turner RR, Ollila DW, Stern S, et al. Optimal histopathologic examination of the sentinel lymph node for breast carcinoma staging. *Am J Surg Pathol*. 1999;23:263-267.
28. Fisher B, Bauer M, Wickerham DL, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: an NSABP update. *Cancer*. 1983;52:1551-1557.
29. Rosen PP, Groshen S, Saigo PE, et al. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: a study of 644 patients with median follow-up of 18 years. *J Clin Oncol*. 1989;7:1239-1251.
30. Wilkinson EJ, Hause LL, Hoffman RG, et al. Occult axillary lymph node metastases in invasive breast carcinoma: characteristics of the primary tumor and significance of the metastases. *Pathol Annu*. 1982;17:67-91.
31. Friedman S, Bertin E, Mouriesse H, et al. Importance of tumor cells in axillary node sinus margins ('clandestine' metastases) discovered by serial sectioning in operable breast carcinoma. *Acta Oncol*. 1988;27:483-487.
32. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. International (Ludwig) Breast

Cancer Study Group. *Lancet*. 1990;335:1565-1568.

33. Hainsworth PJ, Tjandra JJ, Stillwell RG, et al. Detection and significance of occult metastases in node-negative breast cancer. *Br J Surg*. 1993;80:459-463.

34. Cote RJ, Peterson HF, Chaiwun B, et al. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. *Lancet*. 1999;354:896-900.

35. Neville AM, Price KN, Gelber RD, et al. Axillary node micrometastases and breast cancer. *Lancet*. 1991;337:1110.

36. Fisher ER, Palekar A, Rockette H, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). V. Significance of axillary nodal micro- and macrometastases. *Cancer*. 1978;42:2032-2038.

37. Hansen NM, Grube BJ, Te W, et al. Clinical significance of axillary micrometastases in breast cancer: how small is too small? *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:91a.

38. Protocol ACOSOG-Z0010, GUMC-00152. Phase III Prognostic Study of Sentinel Node and Bone Marrow Micrometastases in Women With Stage I or IIA Breast Cancer. CancerNet PDQ Web site. Available at: <http://cancer.net.nci.nih.gov/trialsrch.shtml>. Accessed August 2, 2001.

39. Protocol NSABP B-32. Phase III Randomized Study of Sentinel Node Dissection With or Without Conventional Axillary Dissection in Women With Clinically Node Negative Breast Cancer. CancerNet PDQ Web site. Available at: <http://cancer.net.nci.nih.gov/trialsrch.shtml>. Accessed August 2, 2001.

40. Ollila DW, Stitzenberg KB, Iacocca MV, et al. Sentinel node metastasis with extracapsular extension can predict risk of nonsentinel node involvement in breast cancer patients (poster presentation). Presented at the 53rd Annual Cancer Symposium of the Society of Surgical Oncology; New Orleans, La: March 16-19, 2000.

41. Fisher ER, Gregorio RM, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project. (Protocol No. 4). III. The significance of extranodal extension of axillary metastases. *Am J Clin Pathol*. 1976;65:439-444.

42. Donegan WL, Stine SB, Samter TG. Implications of extracapsular nodal metastases for treatment and prognosis of breast cancer. *Cancer*. 1993;72:778-782.

43. Mignano JE, Zahurak ML, Chakravarthy A, et al. Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. *Cancer*. 1999;86:1258-1262.

44. Vicini FA, Horwitz EM, Lacerna MD, et al. The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. 1997;39:1069-1076.

45. Leonard C, Corkill M, Tompkin J, et al. Are axillary recurrence and overall survival affected by axillary extranodal tumor extension in breast cancer? Implications for radiation therapy. *J Clin Oncol*. 1995;13:47-53.

46. Mambo NC, Gallager HS. Carcinoma of the breast: the prognostic significance of extranodal extension of axillary disease. *Cancer*. 1977;39:2280-2285.

47. Protocol ACOSAG-Z0011, GUMC-00153. Phase III Randomized Study of Axillary Lymph Node Dissection in Women With Stage I or IIA Breast Cancer Who Have a Positive Sentinel Node. CancerNet PDQ Web site. Available at: <http://cancer.net.nci.nih.gov/trialsrch.shtml>. Accessed August 2, 2001.