Review Article

The staging value of sentinel lymph node biopsy for breast cancer: translating pathologic findings to clinical practice

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Abstract: Axillary nodal status is an important prognostic factor in guiding locoregional and systemic treatment for breast cancer. Sentinel lymph node biopsy (SNB) has revolutionized axillary staging by replacing axillary lymph node dissection (ALND) in node-negative women. Even in select patients whose sentinel lymph nodes (SLNs) contain metastases, SNB alone has become an accepted method of managing the axilla. Identification of micrometastases through immunohistochemical analysis of SLNs that are tumor-free on hematoxylin and eosin staining (H&E) does not confer additional clinical benefit. The use of SNB after neoadjuvant chemotherapy (NAC) remains controversial. In addition to axillary nodal status, tumor biology plays an increasingly important role in guiding therapeutic decisions.

Keywords: Sentinel node; axillary staging; histopathologic analysis

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Introduction

Axillary nodal status is an important prognostic factor in breast cancer and is used to guide locoregional and systemic treatment decisions. Sentinel lymph node biopsy (SNB) has revolutionized axillary staging by replacing axillary lymph node dissection (ALND) in node-negative women. There is indisputable evidence that SNB is an effective and accurate method of staging the axilla in clinically node-negative breast cancer with less morbidity than ALND. SNB alone is now the standard method of managing the axilla with sentinel lymph nodes (SLNs) that are histologically free of tumor (1). In select patients with limited metastases in the SLN, SNB alone has become an acceptable approach whereas ALND has traditionally been the standard of care. Thorough pathologic interrogation of the SLN has led to increased detection of occult metastases whose clinical significance was previously greatly debated. Biologic factors play an increasingly important role in guiding therapeutic decisions, in addition to the lymph node tumor status. In this article, these issues will be addressed in detail.

Feasibility of SNB

The feasibility of intraoperative SNB in breast cancer with lymphatic mapping using isosulfan blue dye was first reported by Giuliano *et al.* in 1994 (2). Their prospective study demonstrated SNB to be a minimally invasive and highly accurate method of staging the axilla when SLNs were evaluated intraoperatively with frozen section analysis and postoperatively with hematoxylin and eosin staining (H&E) plus cytokeratin immunohistochemistry (IHC) (3). The sentinel node concept was subsequently validated by several groups. Our group reported proof of principle by performing complete histopathologic evaluation of SLNs and non-SLNs using H&E and IHC for all H&E-negative axillary lymph nodes and found the probability of non-SLN involvement to be less than 0.1% when the SLN is tumor-free by H&E and IHC. We also demonstrated the false-negative rate (FNR) of SNB to be 0.97% (4). A multicenter SLN validation study employing similar rigorous histopathologic examination of axillary lymph nodes concluded that SLNs are predicative of the final

axillary nodal status with SLNs more likely than non-SLNs to harbor occult metastases (5).

Multiple multicenter randomized SNB trials confirmed the feasibility and accuracy of SNB as an axillary staging procedure thus enabling widespread clinical application of this technique (6-9). The SLN identification rate ranged from 95% to 98.7% with accuracy of 95% to 97% and a FNR from 5.5% to 16.7%. The NSABP B-32 trial randomized 5,611 patients with clinically node-negative invasive breast cancer to either SNB plus ALND or to SNB alone with ALND only if SLNs contained metastasis. The SLNs were evaluated at 2 mm sections with H&E, and IHC was performed only in cases of suspicious or negative findings on H&E. With the use of both blue dye and radioactive tracer for lymphatic mapping, the SLN identification rate was 97.2%, accuracy 97.1%, and FNR 9.8% (6).

Histopathologic processing of SLNs

Guidelines were established on focused histopathologic analysis of SLNs for more accurate axillary staging through more intensive histopathologic review to detect more SLN metastases (10). The SLN should be bivalved along the longitudinal axis, serially sectioned at 1.5 to 2 mm intervals, and each interval block is serially sectioned at three levels. Metastases in the SLN detected by H&E or IHC are classified by size: macrometastases (>2 mm), micrometastases (≤2 and >0.2 mm), or isolated tumor cells (ITCs) (≤0.2 mm). ITCs were further defined by the 7th edition of the American Joint Committee on Cancer (AJCC) as clusters of cells ≤0.2 mm or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic cross section of a lymph node (11).

Impact of SNB with negative SLNs

Multiple randomized trials have demonstrated that when the SLN is tumor-free, observation alone confers similar regional control and survival compared to SNB followed by ALND (12-15). In NSABP-B32, 3,089 patients had pathologically negative SLNs, 99.9% of whom had follow-up data. At 95.6 months, there was no statistically significant difference between the SNB plus ALND group and the SNB-only group with respect to regional recurrence (RR) (0.4% *vs.* 0.7%), 8-year overall survival (OS) (91.8% *vs.* 90.3%) and 8-year disease-free survival (DFS) (82.4% *vs.* 81.5%) (12). Veronesi *et al.* demonstrated in their single-institution randomized trial similar results comparing SNB plus ALND to SNB-only when the SLN is free of metastasis. At 102 months, there was no statistically significant difference in OS (89.7% *vs.* 93.5%) or in DFS (89.9% *vs.* 88.8%) with only 2 axillary recurrences both in the SNB-only group (13). Intraoperative frozen sections followed by permanent section analyses were performed on SLNs in both studies. Like NSABP-B32, Veronesi *et al.* examined the SLN in multiple sections with H&E and used IHC only in case of negative or suspicious SLNs. These results demonstrate that SNB provides regional nodal control equivalent to ALND when the SLN is free of tumor. In the Sentinella trial, despite the high FNR of 16.7%, only one axillary recurrence in the SNB-only group occurred at 55.6 months, and there was no difference in OS and DFS (15). Hence, some occult lymph node metastases may not progress to become clinically significant, especially in the modern day era of systemic therapy. SNB has been proven to be safe, reliable and effective and has become the standard procedure for staging clinically node-negative invasive breast cancer.

Management of the axilla with positive SLNs

The standard management of a patient with metastasis in the SLN has traditionally been ALND. However, several retrospective studies have documented similar regional recurrence and survival rates in select patients with a tumor-positive SLN who did not undergo completion ALND compared to those who did. Bilimoria *et al.* identified 97,314 clinically node-negative patients found to have SLN metastases from the National Cancer Database from 1998–2005, of whom 20.8% underwent SNB alone. Amongst patients with SLNs containing micrometastases, there was no difference in RR and survival between the SNB-only group and the SNB plus completion ALND group at 63 months. With respect to nodal macrometastases, the outcomes were better with ALND, but the difference was not statistically significant (16). Similar results were reported from a review of the Surveillance, Epidemiology, and End Results (SEER) database with 26,986 SLN-positive patients, among whom 16.4% had SNB alone. From 1998 to 2004, the proportion of patients with SLN micrometastases increased from 21% to 37.8%. At a median follow up of 50 months, no survival advantage was seen with completion ALND among those with micrometastases in the SLNs (17).

Nomograms based on histopathologic data have been

developed to predict the risk of additional nodal disease beyond the SLN and to help the clinician determine who may be at increased risk for harboring non-SLN metastases and therefore might benefit from a completion ALND (18-20). The clinical usefulness of nomograms has been met with variable degree of success. Memorial Sloan-Kettering Cancer Center conducted a retrospective review of 1,960 SLN-positive patients from 1997 to 2004. The 287 patients who did not have completion ALND were older, had more favorable tumors, a higher rate of breast conservation, and had a lower risk of residual axillary disease as predicted by their nomogram. At 23–30 months follow-up, the axillary recurrence was marginally higher in the SNB-only group than in the SNB plus ALND group (2% *vs.* 0.4%, P=0.004) (21).

The omission of completion ALND in SLN-positive patents was examined in American College of Surgeons Oncology Group (ACOSOG) Z0011 and After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trials, both prospective randomized clinical trials. The ACOSOG Z0011 was a prospective multicenter Phase III non-inferiority trial that randomized 891 patients with clinical T1-2N0M0 disease but pathologically tumor-positive SLNs to completion ALND or to SNB alone (22). The SLN was documented to contain metastasis by frozen section, touch preparation, or H&E on permanent section. Positive SLNs by IHC alone were excluded. All patients received breast conservation surgery (BCS) and whole breast irradiation (WBI), and 97% received adjuvant systemic therapy. The SNB-only group had more micrometastases than the ALND group (44.8% *vs.* 37.5%, P=0.05), and 27% of the ALND patients had additional lymph node metastases beyond the SLN. At a median follow-up of 6.3 years, there was no statistically significant difference between the two groups in terms of locoregional recurrence (1.6% with SNB and 3.1% with ALND), DFS (83.9% with SNB and 82.2% with ALND), and OS (92.5% with SNB and 91.8% with ALND). The AMAROS trial was also a prospective, multicenter Phase III non-inferiority trial that enrolled 4,823 patients between 2001 and 2010 (9). Of the 1,425 patients with a positive SLN, 744 had been assigned to receive ALND, and 681 to axillary radiotherapy. The SLN was considered to have metastasis if any tumor deposit was found, including that identified on IHC which was employed when H&E was negative. Eighty-two percent of the patients in each arm had BCS with WBI while the remaining 18% had mastectomy with or without chest wall radiation. Thirty-three percent of the ALND group had additional lymph node metastases removed by ALND. At a median follow up of 6.1 years, there was no statistically significant difference in axillary recurrence (0.4% with ALND and 1.2% with axillary radiotherapy), DFS (86.9% *vs.* 82.7%), and OS (93.3% *vs.* 92.5%). Significantly higher rates of morbidities with ALND compared to either SNB-alone or axillary radiotherapy were demonstrated. These studies provided level one evidence that completion ALND may be omitted in select patients with early stage breast cancer with limited SLN metastasis who are treated with BCS with WBI and adjuvant systemic therapy without compromising locoregional control or survival. The AMAROS trial further demonstrated that perhaps in select mastectomy patients, completion ALND may be omitted as well.

SLN micrometastases

SNB not only revolutionized the approach to axillary staging in early stage invasive breast cancer, but it also led to more intensive evaluation of the SLN and higher rates of detection of micrometastases and ITCs. These tumor cells are usually not detected on initial H&E stains but on further pathologic evaluation with deeper-cut H&E analysis, IHC stains, or molecular testing. Multiple sectioning of the SLN and evaluation with IHC have been shown to improve the accuracy of axillary staging, especially in the detection of micrometastases, compared to routine histologic examination of non-SLN in ALND with one or two sections (23).

Molecular analysis of SLNs with reverse transcription-polymerase chain reaction (RT-PCR) has been shown to be more sensitive and more accurate for lymph node metastases compared to standard histologic evaluation. In a prospective multisite study, quantitative RT-PCR detected 98% of metastases >2 mm and 88% of metastases greater than >0.2 mm, a superior result to frozen section histology (24). The molecular assay could also be performed in 36–46 minutes for one to three nodes (25). Despite its higher sensitivity than standard histology, molecular analysis of SLNs has not been shown to provide additional prognostic information. In a prospective multicenter study of 547 patients with a mean follow-up of 7 years, molecular staging predicted only 26% of recurrences in patients with negative SLNs by conventional histology, and it was not a statistically significant independent predictor of distant recurrence (26). Similar results were observed in another prospective study of 501 patients with a follow-up of 5 years, which failed to demonstrate a significant clinical impact

with molecular overexpression of breast cancer-associated genes in lymph nodes (27).

The prognostic significance of micrometastases has been largely debated. Some older retrospective data associated occult metastases with worse survival, but those patients were not treated with current standards of adjuvant systemic therapy. The Ludwig Breast Cancer Study Group identified occult nodal metastases in 20% of the study patients (28). Less than half of them received adjuvant systemic therapy in the form of cyclophosphamide, methotrexate and fluorouracil as part of the randomization process. A SEER database review demonstrated nodal micrometastasis as a prognostic survival indictor, intermediate to N0 and N1 disease (29). A retrospective Dutch study showed nodal ITCs and micrometastases to be associated with decreased survival, but only in patients who did not receive adjuvant systemic therapy (30).

The ACOSOG Z0010 trial was a prospective clinical trial undertaken to resolve the conflicting data on micrometastases (31). This was a prospective observational study of patients with clinical T1,2N0M0 invasive breast cancer treated with breast conservation, SNB, and bilateral iliac crest bone marrow aspirations. Between 1999 and 2003, 5,538 patients were enrolled in the study, and 5,519 patients were eligible and had a SLN identified, of whom 23.7% had SLN metastases detected by H&E. Of the remaining H&E-negative SLNs that were evaluated centrally and blindly by IHC, 349 (10.5%) had tumor detected immunohistochemically. At a median follow up of 6.3 years, SLN metastases detected by IHC alone did not have a significant impact on DFS or OS. A subset analysis of the NSABP-B32 trial evaluated the prognostic significance of occult metastases (32). Of 3,887 tissue blocks of pathologically negative SLN specimen that were re-examined with serial sectioning and with IHC, 15.9% were detected with occult metastases. The estimated 5-year overall survival was 94.6% with occult metastases and 95.8% without (P=0.03). Despite the statistically significant difference, the authors concluded, based on the very small absolute difference in OS, that further evaluation of H&E-negative SLNs would not provide additional clinical benefit. This conclusion was reinforced by the IBCSG 23-01 trial that randomized patients with SLN micrometastases, 464 to the ALND arm and 467 to no-ALND, from 2001 to 2010 (33). The SLNs were evaluated on frozen or permanent sections with H&E on multiple sections and with IHC only in cases of suspicious or negative H&E findings. ITCs were included but not macrometastatic disease. At a median follow-up of 5 years, there was no statistically significant difference in DFS (87.8% with no ALND *vs.* 84.4% with ALND) and OS (97.5% *vs.* 97.6%) with a similar 5-year cumulative incidence of breast cancer events.

The most recent 7th edition of the AJCC TNM staging system on breast cancer incorporated changes reflecting the prognostic significance of micrometastases (11). Stage I has been subdivided into stage 1A and stage 1B to differentiate T1 tumors with micrometastases (N1mic, Stage 1B) from those with negative nodes (Stage 1A). The stage 1B designation has been challenged by Mittendorf *et al.* who analyzed over 8,000 patients from two prospective cohorts, an MD Anderson Cancer Center series and the ACOSOG Z0010 cohort (34). Five thousand stage 1A patients and 580 stage 1B patients were identified with a median follow-up of 6.1 to 9 years. There was no statistically significant difference between the two stages with respect to recurrence-free survival, DFS and OS. One of the limitations of the study was the increased use of adjuvant systemic therapy in stage 1B patients compared to stage 1A. Despite this, the study calls into question the current staging nomenclature that reflects only the anatomical classification whereas treatment of breast cancer is increasingly driven by tumor biology with growing use of genomic assays irrespective of tumor stage.

SNB after neoadjuvant chemotherapy (NAC)

Controversy exists regarding SNB after NAC as it is unclear how NAC affects lymphatic drainage patterns or if it leads to non-uniform eradication of disease which would result in reduced accuracy and high FNRs. In the NSABP-B27 study which compared three arms of NAC, 428 patients had SNB attempted before the required ALND with a SLN identification rate of 85% (35). Of 343 patients who had both SNB and ALND, the FNR was 10.7%, similar to that reported in NSABP-B32. More than 75% of the patients who had SNB were clinically node-negative prior to NAC. One limitation of the study is the lack of a predetermined protocol for the SNB procedure and of standardized pathologic assessment of SLNs. In a meta-analysis of 21 studies with 1,273 patients who had SNB followed by ALND after NAC, the SLN identification rate was 90% with a FNR of 12% (36). A small retrospective study of 69 patients who had cytologically proven axillary lymph node disease prior to NAC reported a FNR of 25%, much higher than that observed in clinically node-negative patients (37).

The ACOSOG Z1071 trial was designed to evaluate the

role of SNB following NAC for initially clinically node-positive disease (38). Between 2009 to 2011, 756 patients with clinical T0–4, N1–2, M0 breast cancer were enrolled. Of the 649 patients with cN1 disease who underwent NAC followed by SNB and ALND, the SLN identification rate was 92.9%. With the removal of 2 or more SLNs, the FNR was 12.6% which was higher than the preset acceptable threshold of 10%. In the SENTINA trial, a four-arm prospective cohort study designed to assess the optimal algorithm for SNB in relation to NAC, one of the arms consisted of 592 patients with clinically node-positive disease who converted to clinically node-negative status following NAC (39). These patients underwent SNB followed by ALND after NAC with a SLN identification rate of 80.1% and a FNR of 14.2%. Both studies concluded that SNB may not be a reliable alternative to ALND following NAC for initially clinically node-positive breast cancer.

Recommendations

In light of results from ACOSOG Z0010, Z0011, and NSABP-B32, the American Society of Breast Surgeons (ASBS) released a position statement on management of the axilla in August 2011 (https://www.breastsurgeons.org/statements/PDF_Statements/Axillary_Management.pdf). It states that ALND may no longer be routinely required for patients with T1-2 tumors, 1 to 2 positive SLNs without extracapsular extension, who are treated with BCS, WBI and adjuvant systemic therapy. It recommended against routine use of IHC on SLNs. In addition, intraoperative frozen section analysis of the SLN can be avoided if clinical suspicion of nodal involvement is low and the patient otherwise would meet the entry criteria for the Z0011 trial.

In 2014, the American Society of Clinical Oncology (ASCO) updated its evidence-based guidelines on SNB for early stage breast cancer based on nine randomized clinical trials and 13 cohort studies between 2004 and 2013 (1). It recommended against ALND for patients with one or two metastatic SLNs who are undergoing BCS followed by WBI. Patients with metastatic SLNs undergoing mastectomy should be offered ALND. It also stated that SNB may be offered in selected patients with multicentric tumors, DCIS with planned mastectomy, prior axillary surgery, and NAC. SNB is not recommended for large or locally advanced invasive breast cancers, inflammatory breast cancer, DCIS with planned breast conservation surgery, or in pregnancy. The updates recommended against the routine use of multiple sectioning or IHC for detection of occult metastases that may be present in SLNs that are tumor-free on initial pathology evaluation of a single routinely stained section. They acknowledged the lack of standardized methods to evaluate SLNs in different studies and the varied practice patterns across regions in the world. Thus the authors, based on the expert opinion of the Update Committee, recommended quantification of nodal tumor burden by the pathologist as part of the standard analysis.

Conclusions

The advent of SNB represents one of the greatest achievements in breast cancer management in the past decades. It has replaced ALND for axillary staging in clinically node-negative patients and even in some who have positive SLNs. Even though axillary nodal status remains one of the most important prognostic factors in breast cancer, the importance of biology in prognosis and guiding therapy is being increasingly recognized. In addition, the importance of radiotherapy and systemic therapy in optimizing breast cancer management cannot be understated. Clinicians and pathologists should be aware of the significance of metastases in SLNs, even single tumor cells, and formulate therapeutic plans based on not only the exact extent of nodal disease but also the molecular subtype of the tumor and genomic analyses.

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Footnote

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