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Sentinel Node Biopsy and Improved Patient Care

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■ **Abstract:** Sentinel lymph node biopsy (SLNB) is based on the hypothesis that the sentinel lymph node (SLN) reflects the lymph-node status and a negative SLN might allow complete axillary lymph node dissection (ALND) to be avoided. Past and current sentinel lymph node clinical trials for breast carcinoma have addressed the prognostic and therapeutic benefits of this technique and as such, SLNB has become a standard of care for select breast cancer patients. This article reviews the history of SLNB as well as current guidelines and recent controversies. ■

Key Words: breast cancer, lymphatic system, sentinel node, sentinel node biopsy

Lymphatic tumor spread and its relationship with patient treatment and survival has been studied for centuries. In 1643, Bartholin was the first to note the presence of lymphatic channels. In 1848, Virchow described the prominent supraclavicular node that was associated with advanced gastric cancer. His findings led him to formulate the theory that lymph nodes filtered particulate matter from lymph and that there were associations between lymphatic channels and lymph nodes. It was not until the twentieth century, however, that these initial hypotheses were studied in more detail. Gould, in 1960, published his description of the sentinel node (SN) in partoid cancer and Cabanas followed in penile cancer in 1977 (1,2). Despite their findings, it was not until Morton et al. used cutaneous lymphoscintigraphy to identify lymphatic drainage patterns of melanomas that the value of lymphatic staging in the management of cancer was recognized. Morton's findings resulted in development of the SN biopsy technique, by which intraoperative lymphatic mapping allowed for removal of lymph nodes on the direct drainage pathway from primary melanoma (3). The sentinel lymph node biopsy (SNB) is based on the fact that a tumor drains in an orderly manner to the lymphatic system, first to only one or two nodes. Therefore, the first lymph node (the SN) is the first to be affected by metastasis if the tumor has spread.

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SLN IN BREAST CANCER

The feasibility of identifying a SN intraoperatively in breast cancer was first investigated by our group (4). In October 1991, a clinical study began to determine the safety and feasibility of lymphatic mapping and SN biopsy in breast cancer. The hypothesis was that the SNB may be an accurate and less morbid approach to staging the regional lymph nodes in breast cancer than completion axillary lymph node dissection (ALND). This prospective study demonstrated that SNB is technically feasible, safe, and when a SN could be identified, highly accurate (5). In addition to blue dye directed lymphatic mapping, other technical approaches for SN identification in breast cancer were reported using radioisotopes. The accuracy rates for SNB with preoperative lymphoscintigraphy, and the combination of blue dye and isotope were found to be safe and reproducible. A variety of technical factors, which include type of dye or radioisotope, filtered versus unfiltered isotope, timing of surgery after injection, site of injection (peritumoral, subdermal, intradermal, sub-areolar), and histopathologic processing, influence the performance of SNB. In the multi-institutional American College of Surgeons (ACOSOG) Z0010 trial 198 surgeons enrolled 5,237 patients and used blue dye with radiocolloid in 79.4% of cases, blue dye alone in 14.8%, and radiocolloid alone in 5.7% with a success rate of 98.7% of identifying SNs, corresponding to a failure rate of 1.3%. The percent of failed SNB with blue dye was 1.4%, radiocolloid 2.3%, and the combination 1.2% ($p = 0.28$) (6). Reliable staging with SNB depends on the success of SN identification, a low false-negative rate, and reliable histopathologic assessment of SLNs.

After technical refinement of the procedure, a number of multi-institutional randomized studies were conducted. The first was from Milan by Veronesi et al. followed later by the larger NSABP B32 trial which included 5,611 women (7,8). These studies demonstrated that a SN could be identified in 98% of women with clinically node-negative stage I/II breast cancer and could replace ALND for SN-negative women. Both studies had the same design and the NSABP B-32 trial randomized patients with clinically node-negative invasive breast cancer to either SNB followed by a level I or II ALND, or observation of the axilla if the SN was tumor free (group 2). In both studies there was no significant difference between ALND or just SLNB with respect to overall survival (OS), disease-free survival (DFS), and regional control. Over two decades of experience with SNB and several prospective randomized trials with long follow-up prove that this is as safe, accurate, effective, and less morbid than conventional lymph node staging with ALND for early clinical node-negative breast cancer. The SNB procedure was adopted early by surgeons in both academic and community settings throughout the world even prior to a randomized trial.

The removal of one SN led to increased histopathologic processing with immunohistochemical staining (IHC) which identified micrometastases within SNs. The significance of these small metastases and their impact on treatment was unclear. In the ACOSOG Z0010 trial, patients with stage I or II clinically node-negative invasive breast cancer were treated with breast conservation, SNB, and bilateral iliac crest bone marrow aspirations. If the SN was free of tumor by hematoxylin and eosin (H&E) examination, no further ALND was undertaken. The aim of this study was to determine the prevalence and biologic significance of IHC-positive micrometastases in lymph nodes and immunocytochemistry (ICC) positive bone marrow metastases, and to determine the impact of micrometastases on survival. The secondary aim was to determine the morbidity associated with SNB. Blinded analysis of the SN by IHC and bone marrow by ICC was performed in a central laboratory. Among 5,184 patients, 1,239 (23.9%) had lymph node metastases identified by routine H&E. Of the remaining 3,945 patients whose sentinel lymph nodes were negative, 350 (9%) were found to have occult metastases by IHC. Five-year survival rates slightly favored patients with IHC detected SLN metastases in (95.8% versus 95.1%; $p = 0.53$) (6). Additionally, the NSABP examined outcomes for patients in their B32 study and compared survival for patients with and without occult metastases. Although disease-free and distant disease-free survival were significantly worse for IHC-positive than for IHC-negative patients, the absolute difference in OS was only 1.2% (94.6% versus 95.8%, $p = 0.03$) (8). The upstaging of sentinel lymph nodes by IHC appears to have no clinically meaningful prognostic information which suggests that IHC is not required when SLN is negative with H&E stain. Therefore, the presence or absence of micrometastases should not affect the use of systemic therapy. Following reports of the ACOSOG Z010 and NSABP-B32 trials, the American Society of Breast Surgeons released a position statement on SN micrometastases in August 2011, stating that SN micrometastases detected only by IHC are clinically insignificant and that routine use of IHC staining of SNs is unnecessary and should be limited to selective use at the discretion of the pathologist. IHC is of value to detect metastases from infiltrating lobular carcinoma which may be difficult to detect with H & E alone and should still be performed for patients with infiltrating lobular carcinoma.

ERADICATION OF AXILLARY DISSECTION

Several studies soon reported short-term outcomes in SN-positive patients who declined ALND and had no treatment of the axilla (9,10). These studies were small with short follow-up. The appropriate management of the axilla after a tumor-positive SN was subsequently addressed prospectively in the ACOSOG Z0011 trial. This prospective Phase III noninferiority trial randomized women with clinical T1 or T2N0M0 breast cancer who had a tumor-positive SN to completion ALND or observation of the axilla (11). The patients were treated with breast conserving surgery, radiation therapy (RT), and neo-adjuvant systemic therapy This addressed the controversial topic of the role of ALND in clinically node-negative women found to have metastases in the SN with conventional pathologic processing. The primary end point of this study was OS. Morbidity and DFS were secondary end points. Important considerations in study design included the recognition that systemic therapy contributes to local control, that opposing tangential field RT used to treat the breast also treats a portion of the axilla and that adjuvant systemic therapy decreases local-regional failure. Despite all the evidence support-

ing the need to reevaluate the necessity of axillary dissection in the current era, ACOSOG Z0011 was considered a radical and potentially dangerous study, and many large institutions declined to participate which resulted in the studies early closure due to poor accrual (only 47% of the targeted 1,900 patients) and a low event rate. Despite the early closure, the findings were highly statistically significant (12).

From May 1999 through December 2004, 891 node-negative women with clinical T1 and T2 cancers and no palpable metastases were enrolled from 115 sites: 445 were randomized to ALND, 446 were randomized to no further axillary treatment. There was no significant difference between the 2 groups with respect to patient age, T size, ER status, LVI, grade or histology of the primary. Ninety-seven percent of patients received adjuvant systemic therapy reflecting practice patterns in the U.S. The 2 groups varied naturally by number of LNs removed with a median of two axillary nodes removed in the SNB-only group compared to 17 in those randomized to ALND ($p < 0.001$). Additional tumor-positive axillary nodes were found in 27% of the ALND patients. At a median 6.3 years of follow-up, there was no difference between the SNB-only and SNB plus ALND groups in the rates of nodal (0.9% versus 0.5%), in breast (1.9 versus 3.6%), or overall local-regional recurrence (LRR; 2.8 versus 4.9%; $p = 0.53$). Neither DFS (83.9.2% versus 82.2%) nor OS (92.5% versus 91.9%) differed significantly between groups, leading us to conclude that for patients meeting study criteria, the routine use of ALND after the finding of metastasis in the sentinel lymph node may no longer be justified. Noninferiority between the 2 arms was achieved with high statistical significance ($p < 0.008$) showing that SNB alone is not inferior to ALND for these patients.

Results of this study created a significant amount of controversy in the oncologic community. Many questioned whether radiation oncologists irradiated the axillary nodes in the SNB alone group, even though axillary irradiation was prohibited in the protocol. A recent analysis of those patients who had detailed RT records available ($n = 228$), showed that most patients received tangential field RT alone with no significant differences in tangential field height between the two study arms, that 18.9% of patients in both arms received directed nodal irradiation via a third field, which was out of study protocol. Additionally, there were a subgroup of patients who received no RT at all. These findings have prompted the need for additional studies to evaluate whether certain patients might safely avoid RT while others might benefit from more extensive treatment (13). Concerns were also raised regarding the number of patients accrued, length of follow-up, and the applicability of the results to the general population since the majority of patients in the Z011 trial had early ER-positive metastatic disease. However, not only was noninferiority achieved with statistical significance ($p < 0.008$), total local-regional recurrence, DFS, and OS were in favor of the SNB alone group, suggesting that observed results are not likely to change with an increase in sample size. The excellent local-regional control in the Z011 trial was probably due to numerous factors, including early disease, whole breast irradiation, routine use of adjuvant systemic therapy, and low burden of nodal metastases.

Another concern that critics have expressed about this trial is the length of follow-up. Many argued that death from early ER-positive breast cancer tends to occur late and a median follow-up of 6.3 years is not long enough for this study. However, axillary recurrences do tend to occur early. There is an abundance of data demonstrating that the median time to axillary recurrence ranges from 14 to 33 months (11,14). The median follow-up of 6.3 years should be more than enough time to detect a majority of regional recurrences. Further arguments included the fact that the large majority of the study population were older patients with ER+, less aggressive tumors and that the higher risk populations were under-represented in the trial. Therefore, many concluded that completion ALND should still be performed for younger patients with high-risk, ER-negative tumors. In Z0011, patient age ranged from 24 to 92 with 38% of participants under the age of 50. Among the younger patients, there was no difference between the two groups with respect to LRR, and most of the recurrences among these younger women were in-breast recurrences—not nodal recurrences. In fact, younger women were not at increased risk for isolated nodal recurrences, but did have increased risk for in breast tumor recurrence. Investigators argued that age should not limit the application of this study to the general population. Patients with ER/PR negative tumors represented about 16% of the study population. In a subset analysis, there was no difference in survival between the two arms whether they had ER+ or ER− tumors or were older or younger than 50 years.

Another relevant point is that ER-negative tumors were not more likely to metastasize to the nodes. Wiechmann et al. performed immunohistochemical staining to determine subtype on over 6,000 breast tumors that had information on nodal status. They found that the basal subtype, or triple-negative subtype, was less likely than the other subtypes (luminal A, B, or Her2) to have nodal involvement (15). Therefore, it is unlikely that patients in this subset would truly benefit from completion ALND anymore than low-risk patients. A more recent study by Gangi et al., found tumor subtype was not an independent predictor of lymph node positivity, and when compared to the Luminal A subtype the odds ratio of LN positivity was greater for Her2 and Luminal B subtypes (16). Additionally, Dengel et al. recently applied Z0011 selection criteria to 287 SN-positive patients undergoing BCT and found age, ER, and HER2 status were not predictive of axillary metastases. In their study, they found that 84% of consecutive patients at Memorial Sloan Kettering Cancer Center met criteria for SLNB alone thereby avoiding the morbidity of ALND (17).

In summary, patients with a tumor-positive SN who may avoid ALND are those with clinical T1-2, N0 breast cancer with 1 or 2 tumor-positive SN who were treated with lumpectomy, whole breast irradiation and systemic therapy. Patients in whom completion ALND should still be recommended include those who receive neo-adjuvant therapy, those who have a tumor-positive SN and are treated with mastectomy, those with 3 or more tumor-positive SNs, those with significant extra-nodal extension, those who do not receive adjuvant systemic therapy or whole breast irradiation, and those with clinically palpable nodes. The results of the Z0011 trial represent level I data that should result in clinical practice changes and render nomogram models obsolete (18). In addition, although the Z0011 trial excluded patients who's SN had micrometastases detected only by IHC, the results can rationally be applied to patients with SN micrometastases. Further, the International Breast Cancer Study Group (IBCSG), recently completed a phase III randomized control trial to determine whether no axillary dissection was noninferior to axillary dissection in patients with one or more micrometastatic ($\leq$2 mm) SNs and tumors $\leq$5 cm. At a median follow-up of 5 years, Galimberti et al. found no difference between the axillary dissection and no axillary dissection groups with respect to disease-free survival. The IBCSG 23-01 results support those of the ACOSOG Z0011 study and show that with minimal SN involvement axillary dissection is unjustified in those patients who receive whole breast irradiation and systemic adjuvant treatment (12). In the Galimberti study, some patients were treated with mastectomy but too few to make the results appropriate to mastectomy patients.

Another topic of controversy since ACOSOG Z0011 has been the utility of frozen section analysis to evaluate SNs. Weber and colleagues evaluated time trends and variation between surgeons in the use of frozen sections for SNB and ALND in over 7,500 patients with clinically node-negative invasive breast cancer (19). From 1997 through 2006, the use of frozen section analysis of SNs decreased from 100% to 62% ($p < 0.0001$) and varied widely by surgeon preference, demonstrating a diminishing rate of frozen section analysis of SNs over time. While there was no significant trend in ALND with a tumor-positive SN detected by frozen section or routine H&E during this time period, the investigators did observe a significant decrease in ALND for those with metastases detected by serial sectioning or IHC. Kapoor et al. applied the ACOSOG Z0011 selection criteria to a cohort of patients and calculated that 66% of SN frozen sections (4,159 of 6,327) and 48% of ALND (939 of 1,953) would have been avoided, sparing 13% of all patients the morbidity of ALND (20). Several factors are known contraindications for SLNB, including grossly palpable nodes, inflammatory breast cancer, or patients in whom the status of the SN is irrelevant or accurate removal of the SN is impossible secondary to prior surgery or radiation. If the cytology or histology of the node is negative, staging with SNB is reasonable, as long as the palpable node is also removed. The American Society of Breast Surgeons released a position statement on the management of axillary lymph nodes following the presentation of ACOSOG Z011 results, stating that intraoperative frozen section analysis of SN can be avoided if clinical suspicion of additional nodal involvement is low and the patient otherwise meets the entry criteria for the Z011 trial (21). A recent ASCO clinical practice guideline update recommended omission of ALND for patients with one or two H&E positive SNs (22). The SN biopsy during the past 25 years has replaced the century of axillary dissection as effective staging and treatment for most women with

early breast cancer greatly improving care for patients worldwide.

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