Management of the Clinically Node-Negative Axilla in Primary and Locally Recurrent Breast Cancer

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KEYWORDS
- Sentinel lymph node • Recurrence • Breast cancer • Axilla

KEY POINTS
- Axillary lymph node dissection should be performed in clinically node-negative axilla only when sentinel lymph node biopsy (SLNB) shows metastatic disease.
- Performing immunohistochemistry on routine SLNBs is not recommended.
- Sentinel lymph node biopsy on ipsilateral breast tumor recurrences is feasible and seems reliable.
- Lymphoscintigraphy provides useful information for accurately identifying the sentinel lymph node.

INTRODUCTION
For patients with primary breast cancer, nodal status remains a key determinant of overall prognosis. Thus, patients who present with metastasis to the axillary lymph nodes have a worse prognosis than those who do not. To reduce the morbidity of axillary surgery, the sentinel lymph node biopsy (SLNB) technology was introduced in the 1990s. Since then, SLNB has become the standard of care for staging patients with clinically node-negative disease. However, with the widespread implementation of SLNB technology during the past 15 years, a new dilemma has arisen: how to manage the clinically node-negative axilla in patients with ipsilateral breast tumor recurrences (IBTRs). No clear answer exists because no randomized trials have addressed the effect of SLNB remapping on locoregional recurrences and mortality. Yet, some investigators advocate for repeat SLNB in patients with an IBTR with clinically node-negative axilla.

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This article therefore discusses 2 separate issues: (1) management of the axilla in patients with clinically node-negative primary breast cancer, and (2) management of the clinically node-negative axilla in patients with IBTRs.

**SENTINEL LYMPH NODE BIOPSY IN CLINICALLY NODE-NEGATIVE PRIMARY BREAST CANCER**

Patients with clinically node-positive primary breast cancer should undergo axillary clearance. Sentinel lymph node biopsy is an option only for those with clinically node-negative breast cancer.

For patients with primary breast cancer, the management of the axilla has been a topic of considerable interest and controversy for many years. In the late 19th century, William Halsted argued that the axillary lymph nodes were the gateway for the distant spread of breast cancer. Thus, he maintained that extirpation of the breast, underlying pectoralis muscle, and the adjacent axillary lymphatics en bloc (radical mastectomy) was the optimal treatment of primary breast cancer.

The results of large randomized trials conducted under the auspices of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Cancer Research Campaign Working Party (King’s/Cambridge) have challenged this hypothesis. The NSABP B-04 trial randomized patients with clinically node-negative breast cancer to radical mastectomy versus total mastectomy with postoperative axillary radiation versus total mastectomy followed by axillary dissection only in patients who subsequently developed clinically positive nodes. In the King’s/Cambridge trial, women with clinically node-negative early breast cancer were randomized to total mastectomy with immediate axillary radiation versus total mastectomy and observation of the axilla (with delayed treatment of the axilla in patients who subsequently developed axillary recurrences).

Both of these trials demonstrated that the delayed treatment of the axilla did not adversely affect survival, and therefore called into question the notion that the axillary nodes served as the nidus for the distant spread of breast cancer. However, the NSABP B-04 and King’s/Cambridge trials do indicate that treatment of the axilla (with either surgery or radiotherapy) in patients with clinically node-negative breast cancer substantially reduces the risk of axillary recurrences. Moreover, surgery is the preferred method of treating the axilla because it also enables staging of the patient (as either node-positive or node-negative). However, patients without metastasis to the axilla needlessly undergo axillary surgery, and incur the potential morbidity associated with axillary surgery. Thus, SLNB technology was developed to reduce the risk of morbidity associated with unnecessary axillary surgery.

In 1970, Kett and colleagues published results of lymphatic mapping of the breast after periareolar injection of blue dye. This procedure identified an isolated blue node that was commonly adjacent to the axillary vein. In 1993, Krag and colleagues reported the identification of an isolated node using technetium sulfur and a gamma probe. Giuliano and colleagues described the technique of blue dye mapping of sentinel lymph nodes (SNLs) of the breast, and reported that SLNB was 95.6% accurate in predicting the status of the axilla. Albertini and colleagues combined the 2 methods (blue dye and radiocolloid), and reported a similar sentinel node identification rate of 92.0%. A randomized prospective trial by Morrow and colleagues compared the combination of blue dye and radioactive colloid versus the use of blue dye alone and showed equivalent sentinel node identification rates.

Considerable evidence now shows that SLNB is a much less morbid procedure than the standard ALND, and that the 2 procedures are associated with similar survival
rates and risk of local recurrences. The NSABP B-32 trial randomized 5611 women with clinically node-negative breast cancer to ALND versus SLNB plus ALND (with ALND performed only if evidence showed metastasis to the SLN). The study used both blue dye and radiotracer to identify the SLN. Patients in the SLNB arm of the trial had equivalent survival and regional control to those in the standard ALND arm. In addition, patients in the SLNB arm had a lower risk of morbidity compared with those in the standard ALND arm. Significantly fewer shoulder abduction deficits (75% vs 41%; \( P < .001 \)), lymphedema (7%–9% vs 13%–14%), arm numbness (31.0% vs 8.1%; \( P < .001 \)), and tingling (13.5% vs 7.5%; \( P < .001 \)) were associated with SLNB versus ALND.

Several other randomized control trials have demonstrated the reduced morbidity of SLNB compared with ALND. In the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, Mansel and colleagues showed that the SLNB group had a lower incidence of lymphedema, shorter time of drain usage, shorter hospital stay, and faster resumption of everyday activities compared with the ALND group. The absolute risk of developing lymphedema 12 months after SLNB was 5% versus 13% (relative risk [RR], 0.37; 95% CI, 0.23–0.60) in those who underwent an ALND. Similarly, the absolute risk of experiencing sensory loss at 12 months after SLNB was 11% compared with 31% of patients who had ALND (RR, 0.37; 95% CI, 0.27–0.50).

Veronesi and colleagues reported the results of their trial undertaken in Milan, which randomized 512 patients to ALND versus SLNB (with ALND only in patients with positive SLNs) and followed them for 24 months after surgery. The patients randomized to the SLNB arm of the trial had significantly less axillary pain (8% vs 39%), less numbness (1% vs 68%), and better overall arm mobility (0% vs 21%) than those randomized to the ALND arm of the trial.

Purushotham and colleagues randomized 298 patients with tumors smaller than 3 cm to similar groups (ALND vs SLNB followed by ALND if sentinel node–positive). They reported decreased sensory deficits, decreased seroma occurrence, and reduction in lymphedema in the SLNB arm. Similarly, the GIVOM (Gruppo Interdisciplinare Veneto di Oncologia Mammaria) trial in Italy randomized 697 patients to ALND versus SLNB (with ALND in node-positive cases). In addition to the decrease in lymphedema and numbness and better range of motion, they noted improved quality of life for patients randomized to SLNB.

The Sentinel Node versus Axillary Clearance (SNAC) trial randomized 1083 patients either to SLNB followed by axillary clearance if the SLN was positive or not detected, or to routine axillary clearance. A significant decrease in wound infection, seroma formation, impairment of range of motion, and numbness was seen in the group randomized to SLNB.

Kell and colleagues published a meta-analysis of 7 randomized controlled trials with a total of 9608 patients comparing standard ALND versus SLNB. The goal of this overview was to determine morbidity reduction with SLNB versus standard ALND. This meta-analysis showed a reduction in risk of infection (odds ratio [OR], 0.58; 95% CI, 0.42–0.80; \( P = .0011 \)), seroma (OR, 0.40; 95% CI, 0.31–0.51; \( P = .0071 \)), arm swelling (OR, 0.30; 95% CI, 0.14–0.66; \( P = .0028 \)), and numbness (OR, 0.25; 95% CI, 0.1–0.59; \( P = .0018 \)) in patients in the SLNB arm compared with those in the standard ALND arm.

These results indicate that standard ALND can no longer be justified as the standard means of staging patients with clinically node-negative primary breast cancer (Table 1). Rather, SLNB is the standard method of staging these patients.

However, the results of the American College of Surgeons Oncology Group (ACSOG) Z0011 trial suggests that not all patients with positive SLNs need to proceed with
axillary lymph node dissection. Specifically, this trial suggests that selected patients with SLN-positive disease who undergo lumpectomy and radiotherapy may not require a formal axillary clearance. Although this study has limitations (the study did not meet its targeted accrual goal; follow-up was only 6 years; and a disproportionately large number of patients in this study had estrogen receptor–positive tumors), it does suggest that selected patients with sentinel node–positive tumors can avoid ALND.

Another conundrum is the presence of micrometastases in the SLN. The American Joint Committee on Cancer (AJCC) defines macrometastases as foci of tumor cells greater than 2.0 mm, micrometastases are those foci measuring between 0.2 and 2.0 mm (pN1mi), and isolated tumor cells (pN0(i+)) foci measuring 0.2 mm or less. Micrometastases are found using deeper cross-sections and immunohistochemistry (IHC), and their significance has been investigated in patients from the NSABP B-32 trial. The occult metastases or micrometastases were found using deeper cuts and IHC, whereas the standard metastases were found using standard 2-mm intervals and hematoxylin-eosin (H&E) staining. The 5-year overall survival rate among patients with occult metastases detected was 94.6% using the Kaplan-Meier method, compared with 95.8% in patients without detectable metastases. Although this difference attains statistical significance, it has little clinical relevance.

The relevance of micrometastases in the SLN detected with IHC was further investigated in the ACOSOG Z0010 study. The study enrolled 5210 patients with early-stage breast cancer who were treated with breast-conservation therapy and SLNB. In 10.5% of patients (349 of 3326 patients) whose SLNs were negative on H&E

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<th>Table 1</th>
<th>Outcomes of randomized controlled trials comparing rate of complications with SLNB versus ALND</th>
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<tr>
<td></td>
<td>Number of Patients</td>
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<tr>
<td>NSABP-B32 N = 5611</td>
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<tr>
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<td>Milan N = 516</td>
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<td>SLNB</td>
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<td>ALND</td>
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Abbreviation: N/A, not available.
staining, micrometastases were detected by IHC. However, the presence of these micrometastases did not alter the 5-year survival rates (95.7%; 95% CI, 95.0%–96.5% for IHC-negative, and 95.1%; 95% CI, 92.7%–97.5% for IHC-positive disease).

The International Breast Cancer Study Group (IBCSG) recently reported the results of a large trial randomizing 934 patients with sentinel node micrometastasis to undergo either axillary dissection or not. The 5-year disease-free survival rate was 87.8% in the group who did not undergo axillary dissection (95% CI, 84.4–91.2), and 84.4% (95% CI, 80.7–88.1) in the group who did. More long-term surgical complications were seen in the axillary dissection group (lymphedema, neuropathy). These results suggest that ALND can be avoided in patients with micrometastasis to the sentinel node. Moreover, one might argue that standard H&E staining of the sentinel nodes is sufficient, and that IHC staining should be avoided because it leads to potential overstaging.

MANAGEMENT OF THE CLINICALLY NODE-NEGATIVE AXILLA IN LOCALLY RECURRENT BREAST CANCER

As women with breast cancer continue to live longer, new challenges are arising regarding the management of the axilla in patients with an IBTR after breast-conservation therapy. With the more widespread use of SLNB, management of the axilla in patients with IBTR after breast-conservation therapy has generated controversy. Approximately 10% to 15% of all patients treated with breast-conservation therapy will experience an IBTR within a 10-year period, although these rates are decreasing with improvements in adjuvant systemic therapy. The standard management of IBTR after breast-conservation therapy has been a salvage mastectomy. However, the question has arisen whether sentinel node remapping should be undertaken in patients with clinically node-negative breast cancer who present with IBTR. To date, no randomized controlled trials have addressed this issue. Thus, whether sentinel node remapping ultimately results in improved outcomes (reduction in risk of mortality or recurrences) for these patients is currently unknown. However, several observational studies suggest that a repeat SLNB is feasible in patients who subsequently experience an IBTR after surgery for primary breast cancer.

Cox and colleagues performed a retrospective review of their dataset for patients from 1994 to 2006 who underwent SLNB and then underwent reoperative SLNB. This study identified 56 patients with IBTR who had a previous lumpectomy and a negative SLNB, and 52 of these underwent a repeat SLNB. In this study, the SLN was successfully identified in 80.4% of cases using both blue dye and radiocolloid. Of the patients with clinically node-negative breast cancer who underwent successful remapping, 9 of 45 (20%) had positive SLNs and underwent formal ALND, whereas the remaining 80% were spared ALND. At 26 months of mean follow-up, no axillary recurrences were seen, suggesting that ALND could be avoided in patients who are SLNB-negative after IBTR.

Port and colleagues undertook a retrospective study at Memorial Sloan-Kettering Cancer Center of 117 patients who experienced IBTR after breast-conservation therapy (previously treated with either SLNB or ALND). All of these patients underwent SLNB, irrespective of whether they had previously undergone SLNB or ALND. Their SLN remapping success rate was 55% (64 of 117). Because of the larger sample size, the investigators were able to detect a significant difference in the success rate of the remapping between patients who underwent previous SLNB alone versus ALND. The success rate of identifying an SLN after a previous SLNB was significantly higher than if the patient had undergone an ALND at the time of primary diagnosis.
(74% vs 38%; $P = .0002$). No axillary recurrences were seen in any of these patients at a mean follow-up of 2.2 years, suggesting that ALND can be avoided in patients who undergo remapping with SLNB. These investigators performed lymphoscintigraphy preoperatively on most patients undergoing remapping, and found that the success of the reoperative SLNB correlated with a positive lymphoscintigraphy (79% vs 24%; $P<.0001$). In the earlier study, lymphoscintigraphy showed that 30% of the patients with IBTR had drainage to other nodal basins, such as the internal mammary or supraclavicular basins.

Axelsson and Jonsson\textsuperscript{25} undertook a nonrandomized prospective trial in Denmark of 50 patients with IBTR after either lumpectomy or mastectomy who were all mapped preoperatively with lymphoscintigraphy. In this study, 45% of patients had SLNs detected at surgery (and 83% of these had a positive preoperative lymphoscintigraphy). Sentinel lymph nodes contained metastases in 16%, and these patients went on to completion ALND.

The use of preoperative lymphoscintigraphy was further supported by Taback and colleagues\textsuperscript{26} who reviewed 15 patients who developed an IBTR after undergoing breast-conservation surgery, SLNB and/or ALND, and adjuvant breast radiation therapy. All patients underwent preoperative lymphoscintigraphy, and 7 cases of aberrant nodal drainage were reported. These basins include the internal mammary, supraclavicular, interpectoral, and contralateral axilla. The authors postulated that this is likely because of the combination of prior axillary surgery and breast irradiation, which can alter the drainage pathways. Not surprisingly, 2 of the 3 patients who had the SLN identified in the contralateral axilla had undergone ipsilateral ALND as part of their initial treatment. Thus, preoperative lymphoscintigraphy may provide useful information regarding ipsilateral axillary SLN identification.

Maaskant-Braat and colleagues\textsuperscript{28} undertook a meta-analysis of SLNBs in patients with IBTR, involving a total of 692 patients from 25 studies. In this study, 301 patients had previous SLNB, 361 with previous ALND, and 30 had no previous axillary surgery. Sentinel node was identified in 65.3%. Higher identification rates were reported in patients with previous SLNB compared with previous ALND (81.0% vs 52.2%; $P<.0001$). The lymphoscintigraphy-directed repeat SLNB altered treatment plans in 16.5% of patients, and 50.0% of patients with previous negative SLNB results were spared ALND.

These studies raise an important issue: what impact does SLN identification have on the ultimate outcome in patients with IBTR? In these studies, patients with clinically node-negative IBTR who were SLN-positive underwent ALND (whereas those who were SLN-negative did not), but whether this strategy has any overall benefit on local recurrence or mortality is unknown. Ultimately, this question can only be resolved through a large randomized prospective trial with long-term follow-up.

**SUMMARY**

In patients with primary breast cancer, axillary surgery is an important staging tool, and substantially reduces the risk of axillary recurrences. The SLNB is the preferred
method of staging the axilla compared with standard ALND, because it results in significantly less morbidity. In the years ahead, the number of breast cancer survivors will continue to increase as treatment modalities improve. Moreover, larger numbers of patients who experience IBTR after surgery for primary breast cancer will likely be seen, and the role of SLN remapping in this setting remains controversial. No randomized controlled trial exists to define the exact algorithm that should be followed, but observational studies have indicated that SLNB is feasible in the setting of IBTR (Table 2). Most studies would also suggest the use of lymphoscintigraphy to help guide the remapping of the lymphatic drainage, particularly in those who have undergone prior ALND. This information may allow more patients to continue to avoid the morbidity associated with ALND, even in the setting of IBTR. However, the overall impact of SLNB (on mortality and local recurrence) in the setting of IBTR is not known, as no randomized trials have addressed this issue.

REFERENCES


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<th>Table 2</th>
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Abbreviation: N/A, not available.
