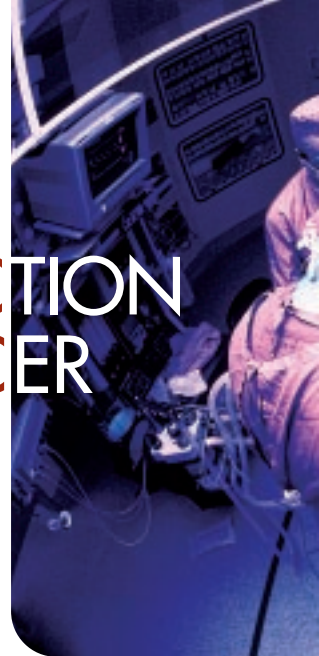


SENTINEL LYMPH NODE DISSECTION IN EARLY-STAGE BREAST CANCER

Standards, controversies and future considerations

Karen T. Lane, MD and Laura J. Esserman, MD, MBA



Top-line summary

Axillary lymph node sampling plays an important role in the evaluation and treatment of women with breast cancer. Involvement of these nodes often provides the pivotal information for making decisions about adjuvant therapy: as a significant predictor of the likelihood of developing future metastatic disease, it forecasts the absolute risk reduction afforded by either hormonal treatment or chemotherapy. Some clinicians also believe that excising the axillary nodes may improve locoregional control, although survival benefit has not been established.

How the axilla are evaluated has undergone a number of changes over the last 10 years. Sentinel lymph node dissection (SLND), which identifies the lymphatic drainage pattern of the breast, aims to determine whether tumour cells have spread outside the breast via the lymphatic system to the lymph nodes. When the SLND is found to be negative for tumour it substitutes for a more aggressive surgical procedure, axillary lymph node dissection. Experienced surgeons who perform the procedure at least twice a week are able to identify the sentinel node in over 95% of patients.

This article reviews current optimal procedures and discusses areas of ongoing debate and inquiry including injection techniques, pathologic assessment and use in various patient populations. It also describes the potential role of assessing hematogenous spread through analysis of the bone marrow.

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Sentinel lymph node dissection (SLND) was developed in an effort to find a less invasive way of evaluating axillary lymph nodes than through axillary lymph node dissection (ALND), which incurs considerable morbidity including lymphedema (10% to 20% in Level I and II ALND), damage to nerves and blood vessels, reduced arm mobility and postoperative pain.

ACCURACY AND MORBIDITY

The goal of SLND is to remove fewer lymph nodes and cause less morbidity while maintaining the accuracy of an axillary dissection. Important questions are:

- **Identification rate** — Can an SLN be identified in most patients?
- **Specificity** — Does the SLN reflect what is in the axilla? If the sentinel node is negative, are the rest of the axillary nodes negative?
- **Sensitivity** — Is metastatic disease found in the sentinel node if disease is present in the axillary node basin?
- **Morbidity and complications** — Does the more limited procedure truly achieve lower levels of these compared to ALND?

In Morton's initial 1992 published report on the first series of SLNDs in humans, 194 melanoma patients had their SLNs removed followed by completion ALND. The SLNs were found to be positive in 40 cases with a specificity of 95.2%.¹ Morton and Giuliano published preliminary results in 1994 demonstrating that SLND could also be used in breast cancer,² sparking a number of multicentre trials. Krag et al reported in 1998 that in 443 breast cancer patients who underwent SLND followed by ALND, the sentinel node identification rate was 93%, specificity was 100% and sensitivity 89%.³ The authors concluded that SLNs could routinely be identified and reasonably reflected the axillary contents in breast cancer patients. Shortly thereafter, Bass et al detailed the results of 1147 patients enrolled in a lymphatic mapping protocol:⁴ the sentinel node identification rate was 95.7% and the initial 120 patients with a negative



sentinel node had completion ALND, yielding specificity of 99.2%. From 1998–1999, Veronesi et al randomized 516 patients with breast cancers < 2 cm to SLND + ALND vs SLND with ALND only when the sentinel node was positive.⁵ The rate of SLN identification was 100% with sensitivity of 91% and specificity of 100%. Another large series, a demonstration project in which over 226 surgeons performed 2148 SLNDs followed by ALNDs, showed that after more than 20 procedures their SLN identification rates improved significantly.⁶

Data to date do not show increased axillary recurrence in women undergoing SLND alone, although more time is needed to fully evaluate this. Blanchard,⁷ Hansen⁸ and Veronesi⁵ reported 0.1% to 0.0% axillary recurrences in followups of 2.4 years, 16 months and 4 years, respectively. These rates are comparable to the axillary recurrence rate of 1.4% reported in the NSABP B-04 trial in node-negative women who were randomized to complete axillary dissection.⁹

Several large SLND series describe fewer complications than for ALND. Giuliano noted 1% lymphedema in 496 patients at 5 years followup.¹⁰ Veronesi found less postoperative pain (8% vs 39%) and improved full arm mobility (100% vs 79%) in the group that underwent SLND alone at 2 years of followup.⁵ Blanchard noted significantly more lymphedema in patients undergoing ALND (n = 164) vs SLND alone (n = 730) (34% vs 6%).⁷ Randomized trials are needed, however, to definitively answer the question of whether the complication rate is reduced when SLND is used instead of ALND.

Experience = success

A study of 5 treatment centres by Edge et al¹¹ concluded that the rate of SLND increased significantly from 8% in 1997 to 58% at the end of 2000, indicating that the use of SLND had become widespread, and raised the issue of training in the procedure. SLN identification rates, sensitivity, and specificity are all related to operator experience, both in the number of procedures the surgeon has performed and how frequently. Cox et al addressed the issue of adequacy of training and certification of surgeons performing lymphatic mapping.¹² Sixteen surgeons performed lymphatic mapping

in 2255 breast cancer patients using a combination of blue dye (isosulfan blue) and technetium-99-labeled sulfur colloid to identify the SLNs. All participants were trained in a 2-day CME-accredited course. The success rate of surgeons performing less than 3 SLNDs per month was 86%; for those performing 3–6 SLNDs per month it was 89%, and surgeons performing more than 6 SLNDs per month achieved 98% success. The conclusion: increased volume leads to decreased failure rates.

Forthcoming data

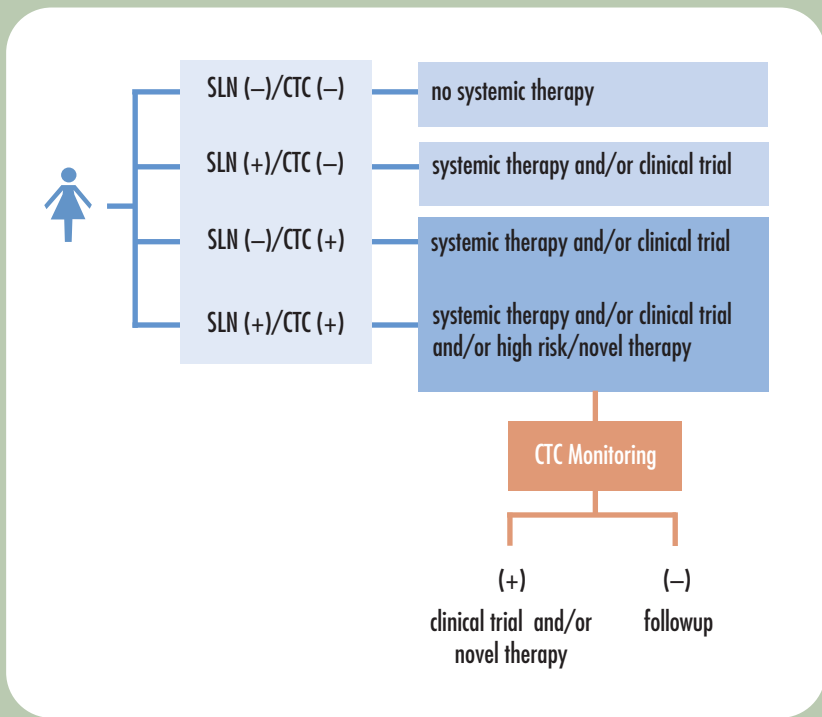
Several large U.S. SLN studies designed to further define the role of SLND in early-stage breast cancer have just completed accrual and will provide data on survival and morbidity of SLN and ALND:

- NSABP B32 randomized patients to SLND + ALND vs SLND + ALND only if the SLN was positive, a design similar to the Italian SLN randomized trial⁵ but with almost 10-fold more patients. This trial will evaluate the accuracy of SLND compared to ALND and compare impact on survival.
- The American College of Surgeons trial ACOSOG Z00011, a randomized trial of ALND vs no ALND in women with T1–2 tumours and a positive SLN, will evaluate the difference ALND makes in survival and the survival benefit associated with removing the rest of the axillary basin in node-positive patients.
- ACOSOG Z00010 is a registry of patients undergoing SLND to assess SLN identification rates as well as short- and long-term morbidity. Surgeons participating in this observational study demonstrated proficiency by having performed 20 SLNDs followed by ALND or through documented SLND training during residency or fellowship. These studies will give us survival data on SLN-positive and -negative patients who undergo no further axillary surgery vs those who undergo ALND. The ACOSOG trials will also supply critical data on the significance of microscopic deposits in the SLN, detected by immunohistochemical (IHC) stains, and on the clinical significance of circulating tumour cells (CTCs) in the bone marrow detected by staining cells for an antibody to CK19. Eventually, an algorithm evolving from one such as shown in **Figure 1** (page 8) will likely incorporate markers of metastatic disease into patient management.

TOWARDS OPTIMAL TECHNIQUE Injection sites and substances

A number of accepted techniques for SLND exist, with variation in injection sites and the use of isosulfan blue dye vs radiocolloid. Klimberg et al compared subareolar vs peritumoural injection in 68 patients undergoing SLND, finding subareolar injection of radiocolloid to be as accurate as peritumoural injection of blue dye, and easier to perform.¹³ McMasters et al evaluated peritumoural injection compared to subdermal and dermal injection of radiocolloid in 2206 patients. Radioactivity was 5- to 7-fold higher with the dermal injection, which also carried a false negative rate of 6.5% vs 9.5% for peritumoural injection.¹⁴

FIGURE 1. Algorithm for likely future breast cancer management based on markers of metastatic spread



Future staging procedures may be able to exploit information from both lymphatic and hematogenous spread. Patients with no evidence of spread will likely be able to avoid systemic therapy. Those with tumour involvement of the lymph nodes or circulating tumour cells (CTCs) will have the option of receiving systemic therapy, possibly in a clinical trial. Both CTC and lymph node involvement imply significantly worse prognosis, so participation in high-risk clinical trials with novel agents is a worthwhile possibility for this group. CTC-positive patients may be given the option of reassessing the bone marrow compartment after therapy, and trials could be specifically designed to explore optimal management of patients with persistent CTCs.

In Cox et al's evaluation of 700 patients the SLN was identified in 76% with blue dye alone, in 90% using radiocolloid alone and in 95% of subjects when both agents were employed.¹⁵ Thus, radiocolloid alone is better than blue dye, use of the 2 together is optimal, and blue dye may not add much information if the radiocolloid is successful. Further, although both substances are safe, blue dye incurs approximately a 1% chance of anaphylactic shock.¹⁶ Many surgeons therefore favour using intradermal radiocolloid injection first: after injecting 1 millicurie of technetium-99-labeled sulfur colloid, a handheld gamma probe identifies the "hot spots" to guide removal of all radioactive lymph nodes until the background radioactive count in the axilla is $\leq 10\%$ of the ex vivo count of the hottest node removed. In the absence of axillary radioactivity, or in place of radioactive colloid, 4 cc of 1% isosulfan blue dye is injected peritumourally.

SLND may also offer an alternative to ALND in patients with multifocal disease.¹⁷ Layeeque recently tested the use of

subareolar injection of radiocolloid and/or blue dye in 40 patients with multifocal breast cancer, successfully identifying the SLN in 100% of patients with a 0% false negative rate.

The SLN technique is robust, regardless of where in the breast the radiocolloid or blue dye is injected. While the injection site is not usually a critical factor, in cases where an upper outer quadrant biopsy has already been performed it may be important to inject the dye adjacent to the tumour, between the incision and the axilla. Both intradermal and peritumoural injections enable localization within 10 minutes. Radiocolloid remains in the sentinel lymph nodes for up to 24 hours, however, whereas blue dye diffuses into other lymph nodes within 1 hour. Blue dye must therefore be given in the operating room immediately prior to the procedure. If internal mammary nodes are to be evaluated (see below) peritumoural injections should be used because intradermal injections do not identify the first draining node in the internal mammary chain.

Internal mammary SLND

Internal mammary SLND is considered investigational: the value of identifying and removing an internal mammary SLN is yet unclear and the procedure carries risks of pneumothorax and additional scarring. In Jansen et al's review of 113 patients who underwent SLND followed by ALND,¹⁸ SLNs were found outside Levels I–II

of the axilla in 19% of patients, mostly in the internal mammary chain; 22 of the 30 SLNs at these sites were harvested. In 4 patients sentinel nodes were found only outside the axilla. The internal mammary SLN biopsy changed treatment in only 3% of patients.

Some evidence, nevertheless, points to possible significance of positive internal mammary nodes. Two recent studies found statistically significant survival benefit in radiating the nodal basins of women with any node-positive disease. In premenopausal node-positive women ($n = 1708$) randomized to mastectomy + chemotherapy + radiation vs mastectomy + chemotherapy alone, at median followup of 114 months the overall survival was 54% in the group receiving chemotherapy + radiation vs 45% in the group receiving chemotherapy alone.²⁰ In the same study, a cohort of 1375 postmenopausal node-positive women were randomized to mastectomy + tamoxifen + radiation vs mastectomy + tamoxifen alone. Radiating the chest wall,

internal mammary and supraclavicular node basins provided an overall survival benefit (45% in the group receiving tamoxifen + radiation vs 36% in those receiving tamoxifen alone).¹⁹ In Ragaz et al's study of 318 node-positive women randomized to mastectomy + chemotherapy and radiation vs mastectomy + chemotherapy alone, the group receiving radiation had increased survival (59% vs 46% at 15 years).²⁰ These findings imply that obtaining internal mammary node data might be of value if it helps identify which patients are at higher risk for positive internal mammary nodes.

When SLN mapping fails

SLND presents challenges in certain situations such as upper outer quadrant lesions, particularly after biopsy, when residual radioactivity in the primary site may create a falsely elevated count (shine-through effect), if the patient is morbidly obese or when the tumour burden is large. A prior upper outer quadrant biopsy may disrupt the lymphatics, so injections on the side of the scar closest to the axilla may be better. Looking at 2495 SLNDs between 1996 and 2001 in women with T1–3 lesions Derossis et al found 62 failed lymphatic mappings (2.48%), with increased body mass index (BMI) significantly higher in the failure group.²¹ The effect was most pronounced in women with BMI over 50. Vargas et al evaluated the number of axillary lymph node metastases in 110 patients who underwent SLND in 2001–2002.²² No SLN was identified in 7, yet ALND revealed that 5 of these had extensive axillary metastases. In contrast, only 23% of patients with successful SLN mapping showed extensive axillary metastases. The authors concluded that high lymphatic tumour burden may play a causative role in SLND failure and that ALND should be performed when the SLN cannot be identified.

CONTROVERSIES IN PATHOLOGIC ASSESSMENT

One of SLND's major benefits is that it allows more accurate assessment of the lymph nodes removed. A single 5-micron section has traditionally served as the standard for histologic analysis of tissue. SLND makes examination of multiple, deeper-level sections of a given lymph node feasible, enabling identification of occult lymph-node metastases. Defined as metastases found on sections of deeper levels of the lymph node stained with hematoxylin and eosin (H & E), occult metastases are important for breast cancer staging. They differ from micrometastases, which are deposits of < 2-mm metastatic tumour. As the clinical significance of micrometastases is controversial we currently do not perform completion axillary dissection on patients who have them.

Frozen section

The primary goal of frozen section for the intraoperative evaluation of SLNs is to minimize the patient's chances of requiring a second surgery. The practice carries a risk of

Factoring haematogenous spread into staging

Tumour spreads beyond the primary site in breast cancer via 2 routes, lymphatic and haematogenous, yet staging currently focuses on the assessment of lymphatic spread alone.

A number of investigators, principally in Germany, have begun incorporating detection of circulating tumour cells (CTCs) in bone marrow into routine staging of breast cancer, and prospective studies show that the presence of CTCs correlates with outcome. Braun and Pantel performed bone marrow aspirates in 552 patients with Stage 1, 2 or 3 disease and found that 36% (199/552) had CTCs.⁴⁴ CTCs occurred in patients both with (36%) and without (33%) lymph node metastases; the group of patients with positive lymph nodes was 2.5 times larger than the group with negative lymph nodes, explaining the overall rate of 36%. At median followup of 4 years the impact of either positive lymph nodes or CTCs on survival was very similar. Although treatments were not standardized based on the presence of either CTCs or positive lymph nodes, the difference in survival probabilities was quite striking: 97% in patients without evidence of tumour in either nodes or bone marrow, 85% in those with one or the other, and 50% in women with both. A recent meta-analysis of 4199 patients from several German institutions, using various methods for CTC detection, showed similar results.⁴⁵

An important advantage of CTC evaluation is that it can be repeated and used to monitor response to therapy or reassess future risk, as it is performed on a renewable source. Some groups are beginning to evaluate CTCs after neoadjuvant therapy as a marker to guide secondary adjuvant therapy.⁴⁶

A range of methods now in use yield considerable variation in results. Ongoing studies comparing techniques and greater standardization of the assays will be required before this test can be incorporated into standard practice. As CTCs have the capacity to further stratify risk of recurrence, improve treatment decisions, focus clinical trials on patients at risk for metastatic recurrence and can be repeated to reassess risk and evaluate options for post-primary and extended treatment, they will likely gain a place in breast cancer staging and monitoring.

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false positives, however.^{23–25} Sensitivity ranges from 44% to 90%,^{25–28} depending on expertise. The use of frozen sections improves patient management if accuracy is sufficient to prevent a second surgery for patients with a positive SLN (sensitivity \geq 90%) and avoid unnecessary ALND in patients without metastatic deposits (specificity > 95%). When examination of lymph nodes on permanent section using standard H & E stain reveals macrometastases > 2 mm that were not seen on frozen section, the patient should be offered a completion axillary dissection. Other arguments against frozen section evaluation of SLNs are that it uses too much tissue and that it introduces freeze-thaw artifact into the permanent section.

IHC analysis

Besides obtaining additional sections of a given node, SLND offers more thorough evaluation because, at many institutions, microscopic metastases are sought using immunohistochemical (IHC) analysis. Macrometastases > 2 mm appear to negatively impact outcome, regardless of whether they are found by serial or single section. The significance of micrometastases, particularly random cells identified only by IHC, is unknown. Current recommendations call for IHC analysis of SLNs that appear potentially positive on H & E staining.^{29–31} Current American Joint Committee on Cancer (AJCC) staging considers nodes to be negative if they are negative on H & E but show micrometastases by IHC staining alone. While some institutions advocate IHC staining to evaluate SLN metastases, the data do not currently support its use in standard management. Early results from 2 large multicentre studies addressing the influence of IHC-only positive SLNs on survival suggest insufficient impact on prognosis to justify including IHC-only positivity in lymph node evaluation³² and treatment decisions.

DILEMMAS IN APPLICATION Neoadjuvant therapy

The accuracy of assessing the SLN in patients with large tumours undergoing neoadjuvant chemotherapy has

been questioned. In 33 patients who underwent neoadjuvant chemotherapy Haid et al identified 29 (88%) SLNs with no false negatives.³³ All subjects had completion ALND as well as SLND with an average of 13 lymph nodes harvested during dissection. Studies by Nason, Breslin and Reitsamer report successful SLN identification in 84% to 100% of patients, with a false negative rate of 3% to 9%.^{34–37} In a recent study at our institution, 53 patients were treated with neoadjuvant therapy followed by SLND and ALND between 1995 and 2003.³⁸ All surgeons performing SLND were experienced, dedicated breast surgeons in high-volume practice. The SLN identification rate was 94% (50/53 patients) with a specificity of 98%. It thus appears that SLND following neoadjuvant chemotherapy is reliable with acceptable identification rates and specificity, particularly in women with clinically negative disease at the time of diagnosis. Additional multicentre trials would help to further validate the use of this technique in this population.

SLND can also be performed prior to starting neoadjuvant therapy if there is a compelling reason to know the node status at this time, such as for determining radiation fields. In most patients, however, nodal status is probably most predictive after chemotherapy, with the persistence of nodes after treatment portending poor prognosis.^{39,40}


DCIS

Women with ductal carcinoma in situ (DCIS) present another controversial population in the use of SLND. Careful examination reveals tumour cells in the SLNs of many women with DCIS, but their impact on outcome is unknown. Intra et al examined 223 pure DCIS patients who underwent SLND between 1998 and 2001 and found metastases in the SLN of only 7 (3.1%).⁴¹ Five of these had only micrometastases in the SLN. Six patients had completion ALND with no additional nodal metastases identified. The authors concluded that SLND should only be performed in patients with DCIS who are undergoing mastectomy. On the

other hand, Cox et al found that 13% of women with pure DCIS had a positive SLN and concluded that all DCIS patients should undergo SLND.⁴² Klauber-DeMore et al reported that 12% of patients with DCIS had SLN metastases, and recommended that those with high-grade DCIS should undergo SLND.⁴³

Survival in pure DCIS approaches 100% but finding SLN metastases potentially subjects these women to the morbidity of a complete axillary dissection or adjuvant therapy — without providing any demonstrated survival benefit. SLND has a place in DCIS patients who chose mastectomy for extensive or multifocal disease, as final pathology finds invasive disease in 10% of these women. Since SLND cannot be performed after mastectomy they would require ALND for staging, but SLND done at the same time as mastectomy adds very little morbidity. At this time, SLND plays no role in patients with DCIS undergoing lumpectomy. If evaluation of the lumpectomy specimen finds microinvasion SLND can be offered at a second surgery.

WHERE SLND STANDS NOW

SLND is a robust technique that in many cases allows substitution of a less morbid procedure for a more aggressive surgical one. Experienced surgeons who routinely perform the operation, at least twice a week, can identify the SLN in over 95% of patients. Recently completed and/or closed clinical trials will soon provide valuable information about the sensitivity and specificity of SLND among a large cross-section of North American surgeons. The NSABP and ACOSOG trials will provide definitive evidence about morbidity in patients with SLND vs ALND. ACOSOG Z-11 will help answer whether the finding of a positive SLN means that patients can avoid ALND. We are confident that the impact on mortality will become clear over the next 5–10 years. 

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