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# Lymphatic Mapping and Sentinel Node Biopsy: A Surgical Perspective

Ronald N. Kaleya, MD, FACS,* Jason T. Heckman, MD,* Michael Most, MD,† and Jonathan S. Zager, MD,*

**Lymphatic mapping and sentinel node biopsy has been rapidly and widely adopted by the surgical community as an oncologic equivalent elective lymphadenectomy for regional node staging in both melanoma and breast cancer. Despite being the de facto standard of care, it remains a highly unstandardized procedure surrounded by many unresolved controversies for surgeons who perform the procedure. The controversies are as basic as the definition of the real sentinel node and as specific as the appropriate localization pharmaceutical(s), site of injection, timing of the injection, and utility of external scintigraphy (dynamic versus. static). Furthermore, questions regarding surgical training, indications, and contraindications remain unanswered. Because there are few long-term studies stratified by technique and indication, the resolution of these surgical controversies are unlikely in the near future.**
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As surgical procedures have become increasing less invasive techniques during the past 2 decades, the treatment of the regional lymph nodes has followed this trend. As a result, intraoperative lymphatic mapping (IOLM) and sentinel node biopsy (SLNB) has been rapidly and widely adopted as on oncologic equivalent to elective lymph node dissection. Predicated on the assumption that solid tumors spread in an orderly progression to the regional nodes before systemic dissemination, lymphadenectomy has been used in the curative therapy for breast cancer, colon cancer, melanoma, and gynecologic malignancies, among others. This assumption, however, has not been validated for any cancer in randomized, controlled trials comparing the efficacy of routine lymphadenectomy to observation. Hematogenous spread may precede or be coincident with lymphatic spread for many solid tumors. Failing to show a survival benefit for regional lymphadenectomy, the current justifications for nodal evaluation are staging, determination of the need for additional therapy and loco-regional control of the tumor. Because at least 80% of node dissections in breast cancer and melanoma fail to show occult disease, the benefit of lymphadenectomy, when compared with morbidity and costs, may not be warranted. Sentinel node biopsy provides the same information, converts elective or prophylactic node dissections into directed therapeutic node dissections, and confines the morbidity of the procedure to those patients who could potentially benefit from removal of involved lymph nodes.

Not only does the definition of what constitutes the real sentinel node vary from study to study, but the protocols used for localization and harvesting of the sentinel node differ between institutions, making comparison of results difficult. IOLM and SLNB has, therefore, become an unstandardized standard of care. Thus, from the surgeon's viewpoint, the critical issues and controversies surrounding IOLM and SLNB include the following (Table 1): validation as an oncologically equivalent to elective lymphadenectomy, site of injection for the mapping procedure, appropriate localizing pharmaceutical(s), timing of the injection, the utility of external scintigraphy (dynamic versus. static), and value of IOLM and SLNB in several specialized situation (ie, large tumors or following neoadjuvant chemotherapy).

## The Sentinel Node: A Precise Definition

The sentinel node is the first draining lymph node on the direct drainage pathway from the primary tumor site.[1] However, there are several surrogate definitions depending on the mapping technique used to localize the SLN. Clinical definitions include (1) nodes that stain blue and have a blue-stained afferent lymphatic, (2) a blue-stained node, (3) a

*Department of Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.
†Department of Surgery, Beth Israel Medical Center, New York, NY.
Address reprint requests to Ronald Kaleya, MD, 440 East 79th Street, New York, NY 10021. E-mail: rkaleya@chpnet.org

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**Table 1** Surgical Controversies

| |
|---|
| Validation of the concept of lymphatic mapping and sentinel node biopsy |
| Definition of the "real" sentinel node |
| Localizing pharmaceutical |
| Radiocolloid |
| Vital dye |
| Both |
| Site of injection |
| Peritumoral |
| Intradermal |
| Periareolar |
| Subareolar |
| Timing of injection |
| Intraoperative |
| Same day |
| Prior day |
| External lymphoscintigraphy |
| Dynamic |
| Static |
| Unnecessary |
| Training requirements and learning curve |
| Indications in special cases (breast cancer) |
| Large tumors |
| Multifocal/multicentric disease |
| After incisional biopsy |
| After neoadjuvant chemotherapy |

node with 10 to 25 counts in 10 seconds, (4) a node with 300 to 3000 CPS, (5) an in vivo node to background count >2 to 3, or (6) an ex vivo node to background count >10. Although many of the nodes found using these definitions overlap, not all blue or hot nodes are sentinel nodes. Therefore, although the theoretic definition of the sentinel node is clear, the clinical application is much more ambiguous.

## Sentinel Node Biopsy: Validation of the Concept

If metastatic involvement of lymph nodes progress in a stepwise manner, biopsy of the first node in the lymphatic chain at risk for metastasis should reflect the involvement of the remainder of the nodal basin. Morton[2] initially described the use of blue dye to identify the sentinel lymph nodes in melanoma, and Krag[3] reported its first application in early-stage breast cancer. Since the introduction of sentinel node biopsy, several investigators have compared the results of sentinel node biopsy to completion lymph node dissection in both melanoma and breast cancer.[4-13] The results have consistently shown that sentinel node biopsy can be identified in 80% to 100% of patients, that there is a learning curve for the procedure, and that the sentinel node is representative of the presence or absence of metastases in remainder of the nodal basin. The false-negative rate for this technique in both breast cancer and melanoma is less than 2% in most series. In addition, the sentinel node is the only involved node in two-thirds of patients with nodal metastases (Table 2),[13-21] supporting the theory that, in some patients, there is an orderly progression of lymph node metastasis. Thus, the concept that a sentinel node exists for breast cancer and melanoma, and that the sentinel node is predictive of the status of the remainder of the nodal basin has been clearly verified in prospective evaluations.

## Localizing the Sentinel Node

IOLM and SLNB presupposes that lymphatic tumor dissemination and lymphatic flow follow the same pathways. There are several methods to identify the sentinel node including vital dyes and radiopharmaceuticals. The pattern of lymph drainage is by no means predictable. The most common pattern of lymphatic drainage is through a single channel to a single node. However, other patterns exist, including multiple channels draining to a single node, a divergent channel to several nodes and several channels to several nodes. In addition, these drainage patterns can lead to more than one nodal basin. Preoperative scintigraphy identified aberrant lymphatic drainage (as compared with clinical prediction) in 48%, 23%, 12%, and 8% of head and neck, trunk, upper extremity, and lower extremity melanomas, respectively.[22,23]

## The Site of Injection

The site of injection can significantly affect the surgeons's ability to detect the proper node. For cutaneous diseases, intradermal injections are validated and are standard.[24,25] In the case of breast cancer, the site of injection is less clear. The current protocols for breast cancer include injections into the peritumoral breast parenchyma, intradermally over the tumor, the periareolar (PA) skin in the same quadrant as the primary tumor, and the subareolar plexus (SAP).

Several conflicting theories exist concerning the lymph drainage in the human breast. Among the more commonly held theories is that proposed by Sappey[26] in 1834. After mercury injections into cadaver breast parenchyma, most of the mercury flowed centripetally, entering the subareolar plexus and then to the axilla via one or more major lymphatic trunks. This pattern of flow was subsequently strengthened by the anatomic findings of Rouviere[27] and Grant et al.[28] Turner-Warwick[29] challenged this theory suggesting that the

**Table 2** The Sentinel Node as the Only Node Harboring Metastases in Malignant Melanoma and Breast Cancer

| Author | Total (%) |
|---|---|
| Melanoma | |
| Morton[14] | 25/40 (63) |
| Krag[15] | 10/15 (67) |
| Pijpers[16] | 22/30 (73) |
| Wells[17] | 6/6 (100) |
| Leong[18] | 18/22 (82) |
| Breast cancer | |
| Krag[19] | 86/162 (53) |
| Guiliano[20] | 44/84 (52) |
| Borgstein[21] | 35/59 (59) |
| Leiberman[13] (collected series) | 296/641 (46) |

mercury injections may have entered the mammary ducts and thereby traversed the breast within the ductal system to the subareolar plexus. In our study of 145 dynamic lymphoscintigrams, in which we used both IP and SD injections, we were unable to demonstrate the SAP despite visualizing distinct lymphatic channels in 37% of cases,[30] which suggests that the SAP is not a physiologic intermediary connecting the deep lymphatics of the breast to the ipsilateral axillary nodal basin.

An alternative pattern of breast lymphatic flow from the breast parenchyma has been described.[26,28,31,32] By using dye and isotope injections into resected breast specimens, anatomic dissections, patterns of tumor dissemination within the breast and external lymphoscintigraphy, these investigators found that lymph flows from the entire breast and overlying soft tissues primarily and directly to the ipsilateral axilla without traversing the subareolar plexus. Furthermore, additional drainage pathways are found leading directly to the internal mammary and interpectoral node groups.

These 2 interdependent, yet-distinct, patterns of lymph flow have been substantiated in recent studies of sentinel node detection. Several investigators have shown discordant drainage patterns from injections of localizing agents into the SAP, subdermal breast tissue and the deep breast parenchyma.[33-36] The intraparenchymal injections consistently visualize a more diverse pattern of lymph flow. Specifically, the internal mammary chain and supraclavicular nodes are commonly seen after IP injection and rarely, if ever after SAP or SD injections. IP injection in different quadrants of the breast also show different patterns of localization.[34] The axilla is the only site of lymph flow in less than 80% of cases, ranging from 78% for upper outer lesions to 42% for the lower inner lesions. Similarly, the IMN and clavicular nodes were visualized 10% to 52% and 2.3% to 3.6%, respectively, depending on the site of injection of the localizing pharmaceutical. Others have found flow to areas outside of the axilla in a quarter to half of patients.[35,37]

Nonetheless, using dual injection techniques followed by completion axillary dissection injection, has reproducibly identified the same axillary sentinel node regardless of whether the injection was SA, SD, or IP.[9] Kern reported that subareolar injection of blue dye alone accurately demonstrates a the SLN in 98% of cases with no false-negative sentinel nodes.[38,39] Similarly, Klimberg[6] confirmed that subareolar injection of technetium is equivalent to peritumoral injection of blue dye.[40] Intradermal radiocolloid injected directly over breast tumors drained to the same LN as blue dye injected intraparenchymally in a different quadrant of the breast in 92% of cases as compared with 93.9% if the dye and radiocolloid were injected into the same quadrant.[41]

Proponents on the SAP/PA injection discount the importance of extra-axillary lymph node identification, and describe this technique as easier and more efficient. SAP/PA injection protocols facilitate IOLM and SLNB in patients with mammographically detected tumors because there is no need to inject the localizing pharmaceutical into the site of the tumor. Despite varying anatomic and clinical descriptions of the pattern of lymph flow, the rates of sentinel node localization, accuracy and predictive value of sentinel node biopsy seem to be unaffected by the site of injection of the localizing pharmaceutical. A difference may become apparent with long-term follow-up that examines the pattern of axillary failure stratified by injection site used for IOLM and SLNB. Until we have durable long-term outcome data of this nature, we use the IP/SD injection technique because it more accurately reflects all lymphatic flow from breast tumor and excise all extra-axillary sentinel nodes when identified on lymphoscintigraphy.

## Mapping Pharmaceuticals

The choices of the agent for lymphatic mapping and lymphoscintigraphy are numerous. The dyes include patent blue, methylene blue, and isosulfan blue, whereas the radiopharmaceuticals include radiolabeled human serum albumin, filtered and unfiltered sulfur colloid, and dextran. The particle size, target affinity, and retention by the lymph node affects the identification of the sentinel node by the radiopharmaceutical agent. Ideally, the mapping pharmaceutical migrates rapidly and stays in the node. In practice, those agents that migrate rapidly tend to label several nodes and those that travel slowly fail to identify any nodes in a larger percentage of cases. Both filtered and unfiltered Tc sulfur colloids have been used with great success and it is, at present, unreasonable to advocate the use of one over the other.

At present, very few centers rely on either vital dyes or radiopharmaceuticals alone because most studies show that the combination of the 2 agents are complementary, reducing the learning curve, and increasing the sentinel node yield.[42] The relative contribution of the vital dye does, however, diminishes with extensive (>1000 cases) LMSNB experience.[43]

## Timing of the Injection

The options for injection timing include intraoperative, same-day and day-before surgery. Intraoperative injection is not as reliable as either of the other methods. In addition, intraoperative injection requires transfer of radiopharmaceuticals to the operating suite that is complicated by radiation safety issues and training for inadvertent radiation spills.

Comparisons of prior day and same day injection show no difference regarding the number of nodes harvested, success rate of identification of a sentinel node and the percentage of nodes containing metastatic disease. Each protocol has distinct advantages and disadvantages.[44] The use of a prior-day injection allows more convenient operating room scheduling including early morning cases. The use of a same-day injection allows for dynamic scintigraphy, which may increase accuracy of IOLM and SLNB when more than one regional node basin is visualized.

The radiopharmaceutical must appropriate for the different tasks. Unfiltered sulfur colloid is optimal for prior-day injections because it migrates slowly, whereas the filtered radiocolloid, which travels faster, is better for the same-day

injection. Dosing is important as well. Because of the half life of Tc99, higher doses are usually used in day before injections when compared those of same day injections (1.5 $\mu$Ci versus 0.5 $\mu$Ci)

## External Scintigraphy

Most of the objections to external scintigraphy are made on the basis of cost and logistics. Because lymph drainage from a given site can be unpredictable, external lymphoscintigraphy is an essential component of sentinel node identification. The drainage from the tumor site to the nodal basin can be followed in most cases, and the very first node can be localized. This provides the surgeon with an accurate roadmap of the sentinel node and limits the number of nonsentinel nodes harvested during the SLN dissection.

High-resolution collimators should be used, and the camera should be placed as close to the patient as possible to achieve optimal discriminating ability.[45] The images should be done in at least 2 planes to limit superimposed nodal images. When more than one node appears simultaneously, the surgeon should be advised to look for all of them. In addition, the site(s) of the sentinel node should be marked on the patients' skin in the nuclear medicine facility using both external imaging and a hand-held gamma probe. If the site of the injection is close to the nodal basin, shielding may be necessary to visualize the sentinel node. Most importantly, the nuclear medicine physician should communicate their findings directly to the operating surgeon.

## The Intraoperative Gamma Probe

The ideal probe should have these characteristics: (1) high sensitivity; (2) excellent collimation; (3) excessive shielding; (4) small probe size; (5) simplicity and (6) low cost. In our opinion, sensitivity is less important than collimation and shielding. A sensitive but poorly collimated probe makes finding the general area easier and quicker, whereas a well-collimated probe allows precise localization. Good collimation and specific localization facilitates the placement of the incision, thus minimizing unnecessary tissue dissection. The head of the probe should be as compact as possible so that it can be placed within a small incision.

In addition, the probe should be purchased and maintained by the nuclear medicine department rather than the operating room. This insures proper function and quality control of the instrument. In our institution, the nuclear medicine technician who performs the lymphoscintigraphy brings the probe to the operating room and directs the localization.

## The Learning Curve

As with all new procedures, there is a learning curve at the inception of a new sentinel node program. Some have suggested that each surgeon perform 20 to 30 sentinel node biopsies followed by completion axillary dissection to assure a false negative rate $<5\%$ and an identification rate $>90\%$.[4,46,47] This obligates an enormous number of breast cancer patients to unnecessary axillary node dissections. It may be more reasonable to validate an institutional sentinel node program inclusive of the nuclear medicine, mammography, pathology and surgery rather than certifying individual surgeons. Validated members of the sentinel node program then proctor the cases of new additions to the program. Using this protocol, the rate of localization for every surgeon at our institution has been $>96\%$ since the initiation of our sentinel node program.

## Special Cases

Sentinel node biopsy may not be appropriate in all circumstances. In each of the clinical scenarios outlined subsequently, the data supporting use of this technique is limited, selected and controversial. Larger and more durable studies are required before accepting SLNB as a standard procedure in these circumstances.

### Previous Excisional Biopsy

The localization rate following open biopsy (85% to 91%) is slightly less than that found in biopsy naive breast, presumably because of disruption of normal lymphatic pathways. However, in prospective studies using completion axillary dissection, the accuracy, sensitivity and predictive value of IOLM and SLNB is unchanged when a SN is visualized on the preoperative lymphoscintigram.[48,49]

### Large Primary Tumor Size

Thirty percent of patients with breast tumors greater than 4 cm with have no lymph node metastases. In small prospective studies of IOLM and SLNB followed by completion axillary dissection for breast cancers larger than 4 cm, both the localization rate and sensitivity is equivalent to those patients with smaller tumors.[10] One caveat must be made, the axilla must be digitally explored at the time of SNB and all palpable nodes should be removed.

### Multifocal Breast Cancer

Following injection of both blue dye and radiocolloid into all tumors, SN localization is $>94\%$ and, when compared with completion axillary dissection, IOLM and SLNB is an accurate predictor of nodal status.[50] This setting may be the most appropriate situation for periareolar or subareolar injection protocols.

### LMSNB After Neoadjuvant Chemotherapy for Breast Cancer

The localization rate is slightly lower than that seen in the chemotherapy naïve patient; however, when a SN is visualized, IOLM and SLNB is a reasonable predictor of the nodal status when compared with completion axillary dissection.[51,52]

## Summary

Although sentinel node dissections are standard practice for melanoma and breast cancer, they are far from standardized procedures. At present, accuracy and reproducibility are best achieved using external scintigraphy, intraoperative blue dye mapping along with intraoperative gamma probe detection. Refinements in injection techniques, radiotracer pharmacology, imaging procedures will extend sentinel lymph node dissections to several other solid tumors. This technology directs the attention of the surgeon and the pathologist to the nodes most likely involved with cancer and confines potential complications associated with the ablative surgical procedures to those who may most likely benefit from them.

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