Selective Lymphoscintigraphy

A Necessary Adjunct to Dye-Directed Sentinel Node Biopsy for Breast Cancer?

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**Background:** Dye-directed sentinel node biopsy (SNB) for breast cancer provides accurate staging with low morbidity, but for tumors distant from the axilla, its use has been questioned.

**Hypothesis:** Can preoperative breast lymphoscintigraphy (BL) applied selectively to medial hemisphere tumors predict a subset of patients who may not require surgical staging of the axilla?

**Design:** Prospective cohort study.

**Setting:** Tertiary, multidisciplinary breast center.

**Patients:** Thirty-two women with breast tumors located in the medial hemisphere (30) or inframammary crease (2).

**Intervention:** Peritumoral injection of 500 µCi of technetium Tc 99m sulfur colloid and biplanar imaging. Nonpalpable lesions were localized with ultrasound or mammography. At the time of definitive breast surgery, isosulfan blue dye-directed SNB was performed. Axillary dissection was performed when the SN contained a tumor or could not be identified.

**Main Outcome Measures:** Regional nodal basins identified by BL; success rate of SNB.

**Results:** Preoperative BL demonstrated axillary drainage in 28 patients (88%); 2 patients (6%) had isolated internal mammary radionuclide uptake, and 2 patients had no nodal uptake. Dye-directed axillary SNB succeeded in 27 (87%) of 31 patients, including both patients with failed BL. Breast lymphoscintigraphy had predicted isolated internal mammary drainage in 2 of 4 patients whose SNs could not be identified. Metastases were found in 5 patients (16%).

**Conclusions:** Axillary radionuclide uptake predicts but does not augment dye-directed SN identification. In those few patients with isolated internal mammary drainage, BL may obviate the need for surgical staging of the axilla.

Arch Surg. 2000;135:1101-1105

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The microscopic analysis of regional lymph nodes remains the most important prognostic variable for patients with breast cancer. At present, neither advances in molecular biology nor improved imaging techniques have provided clinicians with an alternative test that is as reliable as nodal analysis. Still, the morbidity of a negative axillary dissection may be considerable. Furthermore, conventional pathologic analysis of axillary lymph nodes may be compromised by a substantial false-negative rate, since intensive examination of the axillary contents yields 9% to 29% more axillary metastases than does routine testing.  

Sentinel node biopsy (SNB) for breast cancer has been demonstrated to provide the prognostic benefit of sensitive axillary staging while avoiding the morbidity of lymphedema for the substantial proportion of patients without axillary nodal metastases who previously would have undergone axillary lymph node dissection. Lymphatic mapping (LM) and SNB (LM/SNB) was originally described using a vital dye only; with surgeon experience and selection criteria, the procedure has been shown to be reproducible, accurate, and sensitive. Some authors have suggested that combined techniques employing both blue dye and peritumoral injection of radioisotopes enhances the identification of SNs and shortens the learning phase for the surgeon by providing a safety net should dye-directed efforts fail. An additional potential benefit of the combined techniques is the demonstration of nonaxillary drainage when present. Disadvantages of the combined techniques in-
PATIENTS AND METHODS

Patients diagnosed with invasive breast cancer were treated and followed up prospectively between October 1997 and October 1999 in a multidisciplinary, comprehensive breast cancer center. A subset of patients with tumors located in the medial hemisphere of the breast or tumors in the inframammary crease was identified clinically by the treating surgeon. The medial hemisphere was defined as the portion of the breast located medial to a sagittal plane passing through the medial edge of the areola.

A total of 32 patients with tumors located in the medial hemisphere or inframammary crease were selected from about 300 patients with primary breast cancer who were considered for LM/SNB during the study interval. All patients were women. The mean age was 56 years (age range, 35-73 years). Fifteen patients (47%) had palpable tumors, with the preoperative diagnosis made by means of fine needle aspiration or core biopsy; 9 patients (28%) had undergone previous excisional biopsy. The remaining 8 patients (25%) underwent image-guided core needle biopsies for diagnosis of nonpalpable lesions prior to surgical intervention.

Thirty (94%) of 32 patients had tumors located in the medial hemisphere of the breast and 2 had tumors located in the inframammary crease, as depicted in Figure 1. Nearly all patients (97% [31/32]) had ductal carcinomas; a single patient (3%) had lobular carcinoma. Most tumors (72% [23/32]) were moderately or poorly differentiated and most had receptors for estrogen (62% [18/30]). The mean tumor size was 1.7 cm (median, 1.5 cm; range, 0.2-3.0 cm).

All 32 patients underwent preoperative BL in the Department of Nuclear Medicine, Kaiser Permanente Los Angeles Medical Center, Los Angeles, Calif. A mean dose of 488 μCi (range, 166-550 μCi) of technetium Tc 99m sulfur colloid mixed in 4 to 5 mL of isotonic sodium chloride solution was injected into the parenchyma surrounding the breast tumor. The isotope was injected into the wall of the biopsy cavity if the primary tumor had been previously excised. Patients with nonpalpable lesions underwent image-guided localization of the lesion with mammography or ultrasound to ensure precise radioisotope injection. Patients were instructed to perform self-breast massage prior to imaging. Early and delayed biplanar scintiscanning of the upper thorax and axillary regions was performed. Sentinel node locations were marked on the overlying skin using scintigraphic guidance. Examples are included in Figure 2. Handheld gamma probes were not used.

Surgical procedures were carried out under the guidance of 4 surgeons with varied experience, performing LM/SNB in a tertiary hospital residency teaching program. Informed consent was obtained in all cases.

Intraoperative LM consisted of the injection of about 5 mL of isosulfan blue dye (Lymphazurin; US Surgical Corporation, Norwalk, Conn) in 1-mL aliquots into the tumor-breast interface or biopsy cavity wall. Adjustments in the amount of dye used were related to the distance of the tumor from the axilla; as much as 7 mL was injected for more medially located tumors. Dye injection was followed by 5 to 7 minutes of active breast compression to stimulate lymphatic flow.

A limited transverse axillary incision was made below the hair-bearing portion of the axilla, and a blue lymphatic channel was sought with gentle dissection. Once identified, the channel was traced to a blue-stained lymph node. The node was dissected in a lateral to medial fashion to preserve the afferent lymphatic flow. The channel was traced proximally into the tail of the breast to ensure that the node identified was in fact the SN. Additional blue-stained nodes were sought to ensure the primacy of the node(s) removed. An axillary dissection was performed if the SN contained a metastasis or if a blue-stained node could not be identified. Definitive breast surgery was performed under the same anesthetic.

Sentinel nodes underwent serial sectioning at a minimum of 3 levels with hematoxylin-eosin staining after frozen-section analysis. Immunohistochemical staining for cytokeratin was performed on hematoxylin-eosin–negative SNs on at least 2 additional levels. Radioactive specimens were not examined until 48 hours had elapsed.

RESULTS

Radioisotope uptake patterns in relation to tumor location are depicted schematically in Figure 1 and in tabular form in Figure 2. Two patients had no tracer migration from the primary site and were considered BL failures. In the remaining 30 patients, BL revealed drainage to a total of 38 primary basins. Axillary drainage alone was
noted in 21 patients (70%). Two patients (7%) had isolated internal mammary (IM) nodal drainage. Seven patients (23%) had primary lymphatic drainage to 2 or more nodal basins identified (5 patients with both axillary and IM drainage; 1 patient with axillary/infraclavicular drainage; and 1 patient with axillary/IM/infraclavicular drainage). Overall, 28 (93%) of 30 patients’ tumors had axillary drainage alone or in combination. Eight (27%) of 30 patients had IM drainage alone or in combination (Figure 3).

Lymphatic mapping and SN biopsy was attempted in 31 of 32 patients; 1 patient declined axillary surgery. Axillary SNs were detected in 27 (87%) of 31 patients, including both patients with unsuccessful BL. Five (19%) of these patients had tumor-positive SNs. Three SN metastases (60%) were identified with frozen section, which permitted immediate axillary dissection at the original operation; the other nodes contained micrometastatic disease not apparent on frozen section. The remaining 22 patients had negative SNs. Results of LM/SNB biopsy are summarized in Figure 4.

Four patients underwent axillary dissection when no blue dye was seen in the axilla. Two patients with BL-predicted isolated IM drainage had negative axillary dissections; 2 patients with predicted axillary drainage also had tumor-free axillary nodes.

There was no apparent correlation between the exact tumor location in the breast and the finding of IM drainage by radioisotope uptake. Of the 2 patients with isolated IM sentinel nodes, 1 had a tumor in the parasternal region and the other had a tumor in the lower, inner quadrant of the breast. Both inframammary lesions drained to the axilla.

Axillary drainage as predicted by BL augured well for surgical identification of the SN. Dye-directed LM/SNB was successful in 25 (93%) of the 27 patients with axillary SNs. Conversely, neither patient with isolated IM drainage by preoperative BL was found to have a blue lymphatic channel or a tumor-positive node in the axilla.

The sensitivity of BL in predicting successful axillary SNB was 93% (25/27). The specificity was 50% (2/4). The positive predictive value of BL in predicting axillary SN identification was 93% (25/27). The negative predictive value was 50% (2/4).

In a previous study,12 we identified medial tumor locations as a risk factor for unsuccessful dye-directed LM/SNB when compared with other tumor locations. Because patients in whom an SN could not be identified were at risk for a substantial axillary nodal tumor burden, axillary dissection was strongly encouraged in this scenario. Although it is possible that technical errors such as insufficient dye volume or inadequate breast compression led to some LM/SNB failures, it is clear that some tumors do not drain to the axilla. The lymphatic drainage of the breast is complex; even tumors in the inframammary crease may have accessory lymphatic drainage in a rosette pattern along the ribs toward the sternal chain.13 The existence of alternate drainage patterns has important implications for preoperative decision-making.

It seems that both dye-directed SNB and BL require a learning phase to be successful. The 2 unsuccessful BL procedures occurred early in our study and were likely related to insufficient breast massage. We have not had problems with BL after initiating patient self-breast massage after isotope injection, nor have we failed to identify axillary SNs in patients with failed BL. We are confident, however, that the negative predictive value of BL ultimately will prove to be substantially higher than 50% as more lymphoscintigrams are performed and more experience is gained. Based on these early data, and recognizing that exclusively nonaxillary drainage is a rare event, we emphasize the high probability of axillary drainage for nearly all breast tumors and continue to recommend dye-directed axillary staging for patients with failed BL (ie, BL that fails to show lymphatic mapping).

Lymphoscintigraphic detection of axillary drainage was strongly predictive of successful surgical identification of SNs. Dye-directed LM of unfavorably located breast tumors yielded axillary SNs in 25 (93%) of 27 patients with BL-detected axillary drainage. This compares favorably with SN success rates for breast tumors in all locations using combined techniques. Although the success rate for SN identification is high, we still emphasize the need to perform a standard axillary dissection if the SN cannot be identified when axillary drainage is predicted.
Our study confirms that the vast majority of breast tumors drain to the axilla, alone or in combination with other nodal basins. Even in this select subset of tumors in unusual locations within the breast, more than 93% drained to the axilla. While nonaxillary drainage may be clinically relevant, it is clear that the axilla remains the dominant basin at risk, as well as the most accessible for surgical staging. Furthermore, BL validated but did not augment our ability to successfully identify SNs.

The trend in using LM/SNB has been moving toward proliferation of a combined dye and radioisotope injection that may enhance the ability to identify SNs. Despite the current enthusiasm for a combined technique,8,10,14-16 there are many practical advantages of using only isosulfan blue dye for LM. The chief benefits of dye-directed LM/SNB are time and cost efficiency. Patients and surgeons may be spared time-consuming trips to the nuclear medicine department on the morning of surgery, and avoid significant delays in the histologic analysis of nodes while awaiting the decay of radioisotopes. Indeed, patients whose nonradioactive nodes are found to contain a tumor on frozen section may undergo immediate axillary dissection and thus reduce or eliminate the need for additional surgical procedures. The material costs of isosulfan blue dye are minimal, especially when compared with the expenses of radioisotope procurement, injection, imaging, additional professional fees, and the disposal of hazardous waste. Furthermore, vital dye is nontoxic and well tolerated by patients. Because of its technical ease, dye-directed SN identification is particularly well-suited to the majority of breast tumors that are located in the lateral portion of the breast.

Probe-guided SNB is plagued by the “shine-through” or “blast effect” of the relatively high radioactivity in the primary breast site, which may obscure the axilla and true SNs. Krag et al11 have reported a large study using only radioisotope injection in which all 13 falsely negative SNs (11.4%) occurred in patients with lateral hemisphere primaries. In contrast, the axilla is relatively unaffected by shine-through from medial hemisphere BL. Several large studies have reported false-negative rates from 0% to 10% using only blue dye.1,6,7,17 We suggest that blue dye alone may be a superior mapping material for lateral tumor locations, if for no other reason then by virtue of avoiding shine-through effects.

The clinical relevance and necessity of nonaxillary lymph node staging is unknown and intriguing. Although there are surgeons performing and recommending IM SNB,10,11 there are abundant oncologic, technical, selection, and cosmetic considerations. Several interesting questions arise. Would patients with primary lymphatic drainage to 3 different nodal basins undergo 4 separate incisions in the context of breast conservation? If the axillary SN is tumor-free, might an IM SNB be indicated? Is a delayed IM or infraclavicular node dissection reasonable when permanent sections reveal SN metastasis a week after a mastectomy has been performed?

In contrast, a patient with a medial hemisphere tumor undergoing segmentectomy might be an excellent candidate for IM node sampling and/or dissection through a single incision. It seems logical to continue clinical trials of nonaxillary SNB until further experience and analysis is available. It is likely, however, that probe-guided LM/SNB would be the procedure of choice for patients in whom this method of staging was employed.

Proponents of BL emphasize the particular suitability of probe-guided LM/SNB for medial tumors with an improved ability to identify SNs. Our study has demon-


Figure 4. Results of dye-directed lymphatic mapping and sentinel node biopsy. LM/SNB indicates lymphatic mapping and sentinel node biopsy; SN, sentinel node; BL, breast lymphoscintigraphy; ALND, axillary lymph node dissection; and IM, internal mammary.
strated that breast tumors found in challenging locations drain to the axilla alone or in combination with other locations. In fact, even in this selected subset of tumors, dye-directed LM/SNB had a success rate of 93% (27/29). This success rate compares favorably with that of combined technique and probe-guided efforts.\textsuperscript{10,11,18} Clearly, dye-directed LM/SLB is feasible for difficult primary locations when proper technical maneuvers are employed. In addition, very few patients are spared axillary staging with routine BL. Most importantly, routine BL predicts but does not improve the surgeon’s ability to perform dye-directed LM/SNB.

Presented at the 71st Annual Session of the Pacific Coast Surgical Association, San Francisco, Calif, February 20, 2000.

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REFERENCES


Surgical Anatomy

The abdominal aorta originates at the level of the twelfth thoracic vertebra and bifurcates at lumbar vertebra 4. The bifurcation of the aorta with respect to an external landmark is at the level of the umbilicus.