infraclavicular node groups can be marked, although it may be difficult to determine which nodes are actually sentinel nodes in the internal mammary node field when multiple nodes are seen on delayed scans.

The exact role of lymphoscintigraphy in sentinel node biopsy of the axilla in patients with breast cancer requires further study and several questions still need to be answered. Can axillary dissection be avoided in patients who do not show lymph drainage to the axilla? Can selective lymphadenectomy with sentinel node biopsy adequately stage the patient's breast cancer and give the needed prognostic information, thus reducing the morbidity from surgery in these patients? Does knowledge of lymph drainage to the internal mammary, supraclavicular or infraclavicular nodes alter the management of patients with breast cancer? These question can only be answered by studies with larger patient populations in which the scintigraphic results are correlated with surgical findings.

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EDITORIAL

Lymphoscintigraphy and the Intraoperative Gamma Probe

Lymphoscintigraphy is not a new procedure, but one which has been in clinical use for decades. Yet, only now is this radionuclide imaging test gaining attention and enthusiasm from surgeons and the nuclear medicine community. This turn of events is largely related to the sentinel node concept (*1*) and appreciation for the impact of the lymphoscintigram on cost-effective patient management coupled with availability of a tool, the intraoperative hand-held gamma probe (*2*). Lymphoscintigraphy in conjunction with the probe, used to facilitate surgical localization and excision of the sentinel node, is finding a niche in the surgical management of patients with early melanoma and breast cancer.

The lymphoscintigram, performed as a two-phase study of dynamic followed by static imaging, defines the physiology of lymphatic flow through lymph channels to lymph nodes. The fact that functional imaging defines lymphatic pathways and nodal bed drainage from the tumor site which would not have been predicted from classical anatomic approaches (*3–5*) is changing surgical management in early clinical Stage I/II melanoma. The same potential for breast cancer surgical management also exists (*6*).

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Management based on the sentinel node concept offers the following:

1. It is cost-effective.
2. It has the potential to improve survival (although this has yet to be proven).
3. It provides a more rational approach to selecting patients for lymph node dissection as well as to defining the lymph node beds to be dissected.

In clinical Stage I/II melanoma, the therapeutic value of elective lymph node dissection has been debated because only 16% of electively dissected lymph nodes show metastases, and elective lymph node dissections do not consistently prevent recurrent nodal disease (*7*).

Eliminating the cost of performing unnecessary lymphadenectomy is a cost-saving value of the lymphoscintigram-sentinel node approach to restricting elective lymph node dissection to those patients with clinical Stage I/II tumor-positive sentinel node(s). The lymphoscintigram identifies the sentinel node(s) that should be excised and biopsied. Those nodal bed(s) are dissected only if the sentinel node shows tumor. Many of those nodes would not have been removed as part of a conventional lymph node dissection in the absence of the lymphoscintigram because lymphatic drainage from the tumor to those sites would not have been predicted. Thus, the rationality, cost-effectiveness and potential for improving patient outcomes based on the lymphoscintigram and intraoperative gamma probe sentinel node localization and excision have converged to alter surgical management. Intraoperative probe detection of the sentinel node and surgical excision is performed at the same time as the wide excisional resection of the primary melanoma tumor, thus no additional surgical procedure is required. In fact, probe localization of the sentinel node and its excision can be outpatient procedures in some cases where the node is superficial and the primary tumor resection is relatively simple.

The champions of the intraoperative gamma probe procedure are the surgeons. The sentinel node concept was developed by a surgeon (*1*) and surgeons use the intraoperative gamma probe in the operating room to locate the sentinel node. Dependency on nuclear medicine is based on imaging (a road map), radiopharmaceutical availability and radiation safety regulatory concerns. We are convinced that dynamic imaging to define the flow patterns of lymphatics to lymph node basins is important for accurate identification of the sentinel node (*8*). We need to make sure that our surgical partners also view the images and appreciate the contributions of dynamic images. Displayed in cine format, the dynamic images dramatize definition of the first draining node from the tumor site. Static delayed images alone do not accomplish the same result, unless only one node per node basin is visualized. In that case, there can be no confusion in identifying the sentinel node and static images are sufficient. Static images must include multiple projections, however, to insure that attenuation does not mask imageability of a node which has trapped radiocolloid.

The concept of the sentinel node as the first node to drain lymphatic flow from the tumor site, and the best biopsy indicator of the presence or absence of tumor in lymph nodes, was first introduced by Morton et al. (*1*). They used a blue dye (isolsulfan blue) injected at the time of surgery to visualize lymphatic drainage from the tumor to the lymph nodes. The first lymph node to turn blue, or the node closest to the tumor, was presumed the sentinel node. Excision and biopsy of the sentinel node are reliable indicators of presence or absence of lymph node metastases (*9*). The blue dye, however, travels rapidly through the lymphatics and may not always remain in the nodes long enough for surgical identification and excision. Also, the surgeon may find it difficult to identify a blue-stained node in a sea of tissue. Thus, the use of ^{99m}Tc-sulfur colloid was introduced by Alex and Krag (*2,10*) to provide a lymphoscintigraphic image, combined with a hand-held gamma probe for detection and excision of the sentinel node at surgery. Several studies have documented the utility, reliability and impact of lymphoscintigraphy on surgical management of patients with clinical Stage I/II melanoma. Reports indicate surgical changes in management, including location and extent of node dissection in 30%–60% (*3,4*) of patients (*4*). In melanoma, recent reports indicate that most patients show lymph drainage to one or two node groups and 10% to three or more node groups (*5*). The discordance between imaged nodal drainage sites and sites which would have been predicted by the conventional approach is particularly high: 64%–73% in head and neck melanoma (*4*) and slightly lower (44%–54%) for truncal lesions (*3*). Combined with use of the intraoperative gamma probe to find the sentinel node and excise it, the impact on surgical management has been to save on cost, morbidity and perhaps improve therapeutic response (yet unproven).

Reproducibility studies have been presented (*11,12*) that show good reproducibility (85%–88%) of sentinel node identification by lymphoscintigraphy. Causes for nonreproducibility are likely related to several factors, including: radiopharmaceutical particle size and label efficiency variabilities, injection dose and volume, location of melanoma (head versus trunk), camera acquisition and display parameters, timing of imaging and variable disruption of lymphatic flow from previous excisional biopsy of the primary melanoma.

Clinical experience with lymphoscintigraphy and intraoperative gamma probe sentinel node localization has been primarily in malignant melanoma, with a few reports in breast cancer. Because axillary lymph node dissection is a basic, routine procedure in breast cancer management of clinically localized disease (Stage I/II), the same rationales applicable for melanoma are relevant in breast cancer.

Twenty-three years ago, Vendrell-Torne et al. (*13*) published a study using colloidal ^{198}Au to assess lymph drainage patterns in the breast. They showed that intramammary injectate

in all four quadrants of the breast, and in the subareolar region, resulted in different lymph drainage patterns. Kaplan (*14*) summarized those data and his experience with radionuclide lymphoscintigraphy in breast cancer patients. Internal mammary nodes may drain from all quadrants of the breast. Upper outer breast quadrant sites drain to axillary node(s) exclusively in 38% of patients, internal mammary node(s) exclusively in 6%, and a combination of those in 50%, and to supraclavicular node(s) in addition to axillary and internal mammary in 6% (*13*).

In this issue of the *Journal*, Uren et al. (*15*) report on 34 patients with suspected breast cancer who were studied with lymphoscintigraphy using ^{99m}Tc-antimony sulfide colloid. They report unexpected drainage across the center of the breast to axillary or internal mammary nodes in 32% of patients with inner or outer quadrant lesions; drainage to supraclavicular or intraclavicular nodes in 20% of upper quadrant lesions, drainage to ipsilateral axilla in 85% of cases where a single sentinel node was seen. Solin (*16*) has shown that the frequency of internal mammary node metastases in breast cancer parallels metastases to axillary nodes and correlates with the size of the tumor. Certainly, the implications of drainage to unpredicted lymph nodes for patient surgical management are profound. Current practice does not include lymphoscintigraphy to identify lymphatic drainage from the breast cancer site, but does include ipsilateral axillary lymph node dissection for all invasive breast cancers, regardless of location. Clinical trials to evaluate the therapeutic impact of sentinel node excision and biopsy directed by lymphoscintigraphy to guide lymph node dissection(s) of all nodal beds involved with tumor are underway. If the frequency of metastases to axillary, internal mammary and other nodal groups is proportional to the frequency of lymph drainage to those node groups, then surgical management will probably be modified to include internal mammary and other nodal bed dissections. Of course, if the sentinel node biopsy of those nodal groups is tumor-free, the lymph node dissection of those node beds would not be warranted.

Two investigators recently reported relevant data that support the logic presented above. Krag (*17*) reported 100% sensitivity and specificity for tumor detection by sentinel node biopsy compared to axillary nodal dissections in 50 patients who had sentinel lymph node biopsy and regional lymph node dissections following lymphoscintigraphy and intraoperative gamma probe use (21 patients had lymph node metastases and 29 did not). The major problem encountered was the diffusion of radioactivity injected around the tumor into the breast, which may, have precluded identification of a sentinel node near the tumor site. Investigators have found that larger volumes of injecate (about eight times the amount) to the breast are needed than intradermally around melanoma, i.e., a total of about 3 cc of radiocolloid for breast lymphoscintigraphy versus 0.4–0.5 cc for melanoma studies.

At the 48th annual meeting of the Society of Surgical Oncology, Guilliano (*18*) reported data comparing the yield of metastatic lymph nodes found at elective axillary lymph node dissection versus sentinel node biopsy with lymphatic mapping (blue dye). In 269 patients, 136 had sentinel lymph node biopsy following blue dye lymphatic mapping and 133 had axillary node dissection. Sentinel nodes showed tumor in 43% (58/136), while the axillary dissections revealed tumor in only 29% (38/133). The investigators summarized the surgical advantages of lymphoscintigraphic sentinel node identification preoperatively followed by biopsy:

1. The location of the sentinel node(s) can be identified prior to any incisions.
2. A small incision can be made to excise the sentinel node rapidly and easily.
3. Morbidity from axillary node dissection is minimized if axillary node dissection can be avoided, as it can when the sentinel node is tumor negative. Expense as well as substantial morbidity are thereby saved. Axillary node dissection removes a large bulk of tissue, necessitating drains and limiting physical activity for an extended time. Most women suffer some arm complication from the procedure.
4. Staging is improved over axillary node dissection staging.

From the surgeon's perspective, the disadvantages of lymphoscintigraphy and the intraoperative probe are cost and radiation exposure. It is therefore important for nuclear medicine clinicians to keep the cost as low as possible, reassure the surgeon and pathology about radiation and provide good radiation safety support.

Another application of lymphoscintigraphy in breast cancer patients has been guidance in radiation portal coverage for internal mammary chain inclusion (*14*). Kaplan described three-dimensional localization of the internal mammary nodal groups with lymphoscintigraphy as unique to each patient. Ohtake et al. (*19*) applied a stereo lymphoscintigraphic technique using bilateral slant-hole collimation to achieve depth determination of each lymph node imaged to optimize determination of radiation therapy portal coverage. The internal mammary node chain can be imaged when the injection of the radiocolloid is made subcostal, just anterior to the posterior rectus sheath. The needle traverses skin, subcutaneous tissue and the rectus muscle and stops short of the peritoneal cavity. This approach is quite different from lymphoscintigraphy to identify lymphatic drainage pathways from tumor sites in the breast and is used only to accurately localize the internal mammary nodes to be included in the radiation port.

As we work with our surgical colleagues to develop our protocols for breast tumor lymphoscintigraphy, sentinel node(s) identification and intraoperative gamma probe localization and excision of sentinel node(s), we must be alert to the surgeon's temp-

tation to inject radiocolloid around the tumor at the time of surgery (a radiation safety nightmare) and immediately use the probe to search "blindly" for hot nodes without imaging. Quality and success of sentinel node localizations will be enhanced by the image as a road map for using the probe. Nuclear medicine should be flexible in accommodating surgical schedules to perform imaging 1–2 hr before the patient goes to the operating room. The patient's skin should be marked to identify all sentinel nodes seen on the images, so that the surgeon knows how many and which nodal groups drain the tumor prior to using the probe.

Breast lymphoscintigraphy is not difficult to perform but requires palpation of the tumor and correlation with the mammogram to estimate depth and localization of appropriate injection sites at four peripheral points that border and surround the tumor. Ultrasound may be warranted in some cases. At the time of the surgical lumpectomy or mastectomy, sentinel node localization and excisional biopsy can be performed. The sentinel node concept needs further validation in breast cancer. Until such data are available, surgeons will continue to perform ipsilateral axillary lymph node dissections in most cases. I urge surgeons to use the lymphoscintigram and the probe to direct biopsy of sentinel node(s) and possible dissection of all nodal groups identified by lymphoscintigraphy as drainage pathways from the tumor site if the sentinel node(s) show tumor.

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