

LYMPHATIC MAPPING: finding the SENTINEL NODE



By CHARLES LEVENBACK, MD

Lymphatic mapping can identify the sentinel node in 90% to 95% of patients with solid tumors, making it possible to detect smaller metastases than ever before. Among the latest techniques are preoperative lymphoscintigraphy and intraoperative mapping and node removal.

Not all regional lymph nodes surrounding a primary solid tumor have the same likelihood of containing metastatic disease. Rather, 1 node or a small group of nodes is at highest risk by virtue of a direct lymphatic connection to the tumor. These lymph nodes are identified by a procedure called lymphatic mapping. Mapping techniques involve the injection of a dye or other material that can be detected in a regional lymph node at a site adjacent to the primary tumor. The lymph node identified using this technique is termed the "sentinel" node (*Figures 1 to 3*).

A brief history

The Halstedian model of cancer surgery, introduced at the beginning of the 20th century, was a dramatic improvement over previous local surgical procedures. This model required removal of the primary tumor, the afferent lymphatic channels with the surrounding skin and fat, and all the regional lymph nodes. Procedures following Halstedian concepts—e.g., radical mastectomy with axillary lymphadenectomy and radical vulvectomy with inguinal femoral lymphadenectomy—cured many patients who otherwise would have suffered painful deaths due to locally advanced disease.

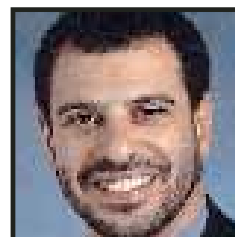
The Halstedian model was based in part on cadaver studies. These studies involved the injection of heavy metals such as mercu-

ry into lymphatic channels, followed by tedious dissection to locate both the lymphatic channels and the regional lymph nodes. At the time of these studies, no in vivo anatomic studies had been conducted; therefore, each lymph node in a regional nodal basin was thought to have an equal chance of containing metastatic disease. Thus followed the principle that all regional lymph nodes needed to be removed as part of cancer treatment.

Small in vivo studies of lymphatic anatomy were begun in the mid-20th century. Zeit and Wilcoxon used cervical injections of India ink to help identify pelvic nodes in patients undergoing radical hysterectomy.¹ Eichner and associates intraoperatively injected ions of blue dye into various gynecologic sites and documented in vivo drainage patterns of the reproductive organs.^{2,5} Parry-Jones used in vivo lymphatic mapping to correct errors in the classical anatomists' description of the paths of vulvar lymphatics.⁶

Riveros et al were the first to describe the

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modern concept of lymphatic mapping and sentinel node biopsy.⁷ Since they treated many patients with advanced penile cancers, these Paraguayan urologists were seeking a technique to reduce the extent of groin dissection. They performed penile lymphography by injecting a blue dye into the phallus and cutting down to the dorsal lymphatic of the penis. They cannulated this vessel and injected ethiodized oil. When the oil was taken up in a lymph node, it could be imaged by plain radiography and was designated as the sentinel node. Cabanas studied this technique in a series of more than 70 patients and found that a negative sentinel node accurately predicted that all the remaining regional nodes were negative.⁸

The sentinel node concept languished until the early 1990s, when investigators sought new ways of addressing the surgical treatment of cutaneous melanoma. One problem they faced was related to lesions at sites with ambiguous lymphatic drainage, e.g., melanomas adjacent to the umbilicus, which can drain to the groins or the axillae. Morton and colleagues utilized a procedure called lymphoscintigraphy to determine the lymphatic drainage patterns of these lesions and ascertain the appropriate target for surgical dissection.⁹ In lymphoscintigraphy, a small amount of radionuclide is injected near the lesion. This radionuclide is transported by the lymphatics to the sentinel node and can be imaged by standard nuclear medicine scanning.

Another problem in the treatment of cutaneous melanoma is centered on the therapeutic efficacy of regional lymphadenectomy. Morton and colleagues investigated whether lymphatic mapping and sentinel node biopsy would lead to the more accurate detection of metastases and reduce the morbidity of lymphadenectomy. They intraoperatively injected blue dye to allow visual identification of the sentinel node. In a series of more than 200 patients, the incidence of

false-negative sentinel nodes (negative sentinel nodes in a patient with metastases in other regional nodes) was less than 1%.⁹

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The work of Morton et al led to an explosion of interest in lymphatic mapping. Today, the growing consensus is that lymphatic mapping can identify the sentinel node in 90% to 95% of patients with a variety of solid tumors. In addition, the incidence of false-negative sentinel nodes is low—less than 5% of patients with positive nodes. Although lymphatic mapping has become part of the standard surgical evaluation of patients with breast cancer and melanoma, regional lymphadenectomy con-

tinues to be performed. Several large phase III trials in breast cancer and melanoma patients are exploring whether regional lymphadenectomy can be omitted in patients with a negative sentinel node.

Techniques

Preoperative lymphoscintigraphy. When primary tumors occur in locations where the route of lymphatic drainage is ambiguous, preoperative lymphoscintigraphy is a vital element of lymphatic mapping. Such tumors include head and neck primary tumors; melanomas of the head, neck, and trunk; breast cancers in the medial third of the breast, which may have drainage to internal mammary lymph nodes; and, perhaps, periclitral vulvar tumors, which may have unilateral or bilateral lymphatic drainage.

Intraoperative mapping and node removal.

Although there remains some debate over the relative merits of intraoperative lymphoscintigraphy versus lymphatic mapping with blue dye, most experts agree that combining the 2 techniques helps shorten the learning curve for surgeons new to the procedure. Since most radionuclides have a half-life of 6 hours, injections as early as 18 hours prior to surgery are acceptable. Typically, the radionuclide is injected 1 to 6 hours prior to surgery. As for the blue dye, which is visible

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for only about 30 to 45 minutes in most cases, it is injected just prior to the incision, after the induction of anesthesia. A handheld gamma probe is inserted into the wound to detect radioactivity. High levels of radioactivity and visualization of blue dye are used to identify the sentinel node.

Pathologic examination of sentinel nodes. Standard practice after regional lymphadenectomy is to send the lymph-node-containing fat pad, unoriented, to the surgical pathologist. The nodes are teased from the fat, usually divided in half, and mounted on slides.

Biopsying the sentinel node yields further opportunities for study. Sentinel nodes are subjected to serial-step sectioning, which greatly increases the number of cells actually reviewed by the pathologist. Typically, the sentinel lymph node is cut into 2- or 3-mm sections using a “bread-loaf” technique. Each block is then cut into multiple slices, which are placed on slides for review by a pathologist. Techniques such as immunohistochemical staining also can be performed to search for micrometastases. Immunohistochemical staining has proved especially important in patients with melanoma or breast cancer, because small nests of malignant cells from these tumors are difficult to detect on standard hematoxylin- and eosin-stained slides.

Breast cancer

Although lymphatic mapping and sentinel node biopsy were pioneered in patients with cutaneous melanoma, the techniques are most widely practiced in patients with breast cancer. Along with breast-conserving surgery, sentinel node biopsy is becoming a standard element of the surgical treatment of early breast cancer. Patients with a positive sentinel node receive additional treatment. It has not yet been determined whether patients with negative sentinel nodes can safely be spared further axillary treatment. Several large randomized trials are studying this issue. One of those trials—the American College of Surgeons (ACS) Oncology Group protocol Z-10—will enroll more than 7,000 patients over the next 4 years.

In patients with small primary breast

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Figure 1



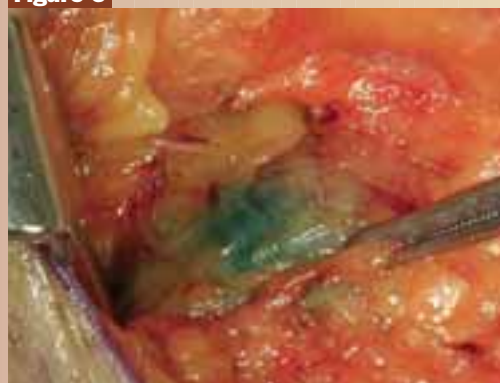
Stage II squamous carcinoma of the vulva involving midline.

Figure 2



Peritumoral injection of isosulfan blue. The dye is taken up immediately by the cutaneous lymphatic channels.

Figure 3



Blue-stained sentinel node. The dye remains visible for 30 to 45 minutes.

Lymphatic mapping of the vulva: results of published series

TABLE 1

SERIES	PATIENTS IN WHOM SN IDENTIFIED (%)	TOTAL NUMBER OF CASES	GROINS IN WHICH SN IDENTIFIED (%)	TOTAL NUMBER OF GROINS
Barton et al ¹⁵	90	10	--	Not stated
DeCesare et al ¹⁶	100	11	100	14
Terada et al ¹⁷	100	9	100	12
DeCicco et al ¹³	100	37	100	55
Ansink et al ¹⁸	Not stated	51	56	93
de Hullu et al ¹²	100	59	89	107
Levenback et al ¹⁴	88	52	75	76

SN=sentinel node

tumors, the risk of lymph node metastases is low, perhaps 20%. This means that if sentinel node biopsy is performed routinely in all such patients, 80% of them will receive no benefit yet will be exposed to the risk of lymphedema, which remains a common and incurable complication of regional lymphadenectomy for breast cancer despite improved surgical techniques, antibiotics, and wound drains. Patient should review their risk of nodal metastases and indications for adjuvant treatments with their physician before deciding on sentinel node biopsy alone or axillary lymphadenectomy.

Vulvar cancer

Because vulvar cancer is the only cutaneous malignancy treated by gynecologic oncologists, it was an obvious first choice for gynecologic lymphatic mapping and sentinel node biopsy. Progress has been slow, in part because of the infrequency of the disease, which has an incidence of fewer than 4,000 cases per year in the United States.¹⁰ Several studies have demonstrated the feasibility of lymphatic mapping in patients with vulvar cancer (*Table 1*).¹¹⁻¹⁸ Results of a validation study of lymphatic mapping and sentinel node biopsy in patients with early squamous carcinoma of the vulva (Gynecologic Oncology Group protocol 173) are probably several years away. At present, the standard of care for patients with vulvar cancer remains inguinal femoral lymphadenectomy, although sentinel node biopsy alone is an option in patients at extreme risk for metastases or in whom prolonged anesthesia is inadvisable.

Lymphatic mapping is not recommended for patients with advanced tumors and no obvious injection site, patients with grossly involved lymph nodes, or patients who have undergone previous vulvar or groin surgery that may have altered the lymphatic drainage. Because wide local excision may interfere with lymphatic mapping in patients with vulvar cancer, it is advisable to perform only a punch biopsy when suspicious vulvar

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Key points

- Lymphatic mapping identifies the sentinel node—the node most likely to contain metastatic disease—in patients with primary solid tumors.
- In lymphatic mapping, a dye or other material that can be detected in a regional lymph node is injected at a site adjacent to the primary tumor.
- Lymphatic mapping can identify the sentinel node in 90% to 95% of patients with solid tumors, with a false-negative rate of less than 5%.
- Along with breast-conserving surgery, sentinel node biopsy is becoming a standard element of the surgical treatment of early breast cancer. It also is used in the treatment of vulvar and cervical cancers.

lesions are present before referring the patient to a gynecologic oncologist.

Cervical cancer

The cervix is a midline structure with complex lymphatic drainage. Thus, in patients with cervical cancer, an extensive nodal dissection is required to remove all potential sites of metastatic disease. Regional therapy is curative if the extent of disease is accurately established.

Several feasibility trials have been reported.¹⁹⁻²⁵ In addition, the first laparoscopic gamma probes are now available, allowing 2 minimally invasive techniques to be combined: lymphatic mapping and operative laparoscopy.

Unfortunately, questions remain about the usefulness of lymphatic mapping in cervical cancer patients. That is because lower-extremity lymphedema is not as common following pelvic lymphadenectomy as it is following inguinal femoral lymphadenectomy. However, the determination of lymph node status could help triage patients between radical surgery and regional radiotherapy.

Future directions

In the coming years, gynecologists should look for increasing use of lymphatic mapping in patients with solid tumors. One of the great promises of lymphatic mapping is the ability to detect smaller and smaller metastases. For example, investigators have found human *Papillomavirus* DNA and cytokeratin RNA in lymph nodes from cervical cancer patients with “negative” biopsy findings after standard histologic examination. The clinical significance of these so-called biologically positive lymph nodes is not known at present. However, there will be increasing application of new molecular biologic techniques to the analysis of sentinel nodes. ■

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