Part 2—
Sentinal Node Dissections

Advancing Medical Care: The Role of Nuclear Medicine in Radioguided Surgery

"The treatment is often worse than the disease" is a motto familiar to cancer patients and researchers who are trying to alter cancer therapies to improve a patient's quality of life. Over the past two decades, radical mastectomies have given way to lumpectomies plus radiation, which can spare many patients from the emotional distress of losing a breast. More recently, a new method of analyzing lymph nodes has spared melanoma patients from full lymph node dissections and such side effects as lymphedema caused by the procedure. The technique, which also appears promising for breast cancer patients, involves the use of a gamma detection probe to locate the first node in the lymphatic chain, called the sentinel node. (A negative sentinel node generally indicates the other nodes in the chain are negative as well, whereas a positive node would necessitate the removal of additional lymph nodes.) "We've found that sentinel node resections are effective for staging and regional control in melanoma patients," said Joseph Kuhn, MD, assistant director of surgical education at Baylor University Medical Center in Dallas. "However, the question is still unanswered in breast cancer patients."

When *Newsline* first reported on sentinel node mapping 18 months ago *(J Nucl Med,* Vol. 38, No. 6, pp. 15N–20N), the technique was still largely experimental. Melanoma patients were having the lymph-node sparing surgery only by enrolling in clinical trial protocols, and breast cancer patients were still having full nodal dissections in clinical trials to test the effectiveness of sentinel node mapping. Over the past year, however, sentinel node dissection has become the standard of care for melanoma patients, according to Kuhn. And several cancer institutions are offering breast cancer patients the chance to enroll in a clinical trial which would spare them from full nodal dissections if they have a negative sentinel node. There is concern in the research community, however, that sentinel node resections might gain too swift an acceptance and that surgeons with limited training may begin performing a technique that is still being monitored in clinical trials.

Altering Treatment for Breast Cancer Patients

Sentinel node dissections are performed by injecting the patient with ^{99m}Tc sulfur colloid near the base of the tumor and using a hand-held gamma detection probe to locate the nodes with the greatest uptake. In many institutions, nuclear physicians perform lymphoscintigraphy prior to surgery to map the drainage into the lymph nodes and help the surgeon locate the sentinel node. "So far, we've had zero incidence of lymphedema in the 75 melanoma patients who participated in our earliest research trials," said David Krag, MD, chief of surgical oncology at the University of Vermont in Burlington. In a recent study of 443 breast cancer patients published in *The New England Journal of Medicine*, Krag, Kuhn and their colleagues reported that the radioguided technique was able to detect the sentinel nodes in over 93 percent of patients who participated in the multi-center trial (*NEJM*, Vol. 339, No. 14, pp. 941–946).

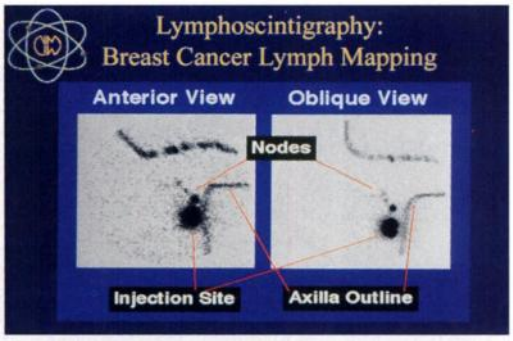

Figure 1.

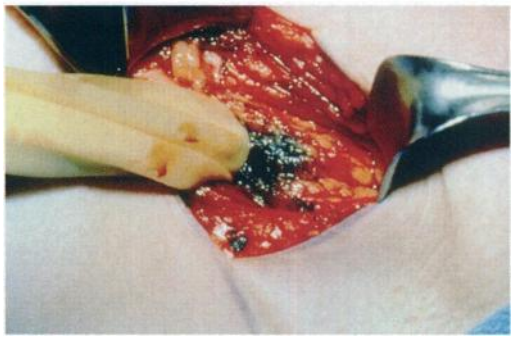

Figure 2.

Figure 3.

Figure 1. This accurate depiction of lymph flow is made possible by dynamic imaging in live patients.

Figure 2. An Axillary sentinal lymph node (SLN) is harvested in a patient with a right chest intermediate thickness melanoma. Dissection is guided by a hand-held gamma probe (middle) to locate a blue stained SLN.

Figure 3. An invasive breast cancer patient is undergoing a mastectomy to control her primary site. Radiocolloid and a vital blue dye are injected into the breast parenchyma around the primary tumor. With dissection in the axilla, a blue-stained afferent lymphatic is seen leading to a blue-stained SLN.

Several cancer institutions, monitored by their hospital's investigational review boards, are beginning to perform sentinel node dissections in breast cancer patients with stage I disease, sparing those with negative nodes from full lymphadenectomies. Surgeons at the University of Washington Medical Center in Seattle have offered sentinel node resections to more than 100 breast cancer patients since the spring of this year. "We've been able to detect the sentinel node in over 90% of patients with a 1% rate of skip metastases, which our surgeons find acceptable," said Janet Eary, MD, a professor of radiology and pathology at the University of Washington Medical Center. (Skip metastases occur when the first node in the chain does not contain metastatic disease, but more distal lymph nodes do.) "We will continue to follow patients to see if those who have had partial node removal will have a greater rate of local recurrence over the years."

A caveat to the sentinel node surgery: Patients with positive sentinel nodes need to undergo a second surgery under general anesthesia to remove the remaining nodes. "Patients with tumors that are 1 cm or smaller are good candidates for the procedure because they have a low likelihood of having lymph node spread," Eary said. On the other hand, patients whose tumors are larger than 2 cm have a greater likelihood of lymph node metastases and may not want to take the chance of having a repeat surgery or having a skip metastasis.

The major factor that will determine whether sentinel node dissections become the standard of care for breast cancer patients is the false negative rate. If too many patients have malignant nodes missed by sentinel node dissections, the procedure will be deemed unacceptable. For instance, in *The New England Journal of Medicine* study, 11% of patients who had spread to their lymph nodes had a pathologically negative sentinel node. "We were concerned that this rate is too high," said Kuhn. Krag said he expects the rate to decrease in future studies since adjustments have been made to the technique. For instance, the researchers found that doubling the volume of the sulfur colloid injected yields significantly higher counts in the sentinel node. "We also developed a better understanding about the drainage network," Krag said. "It's much more complex than one sentinel node draining into the axillary lymph node chain. We often find two or even three sentinel nodes, and we have found that about 8% of patients have drainage exclusively in sentinel nodes that are outside the axillary chain." The false negative rate may also be improved by performing more sensitive pathological exams on the sentinel nodes. (See box on left.)

Two large-scale clinical trials, slated to begin early next year, should help researchers determine the true rate of false negatives. One study is sponsored by the American College of Surgeons (ACS) Oncology Group, and the other is sponsored by the National Cancer Institute (NCI). Both will involve more than 3,000 patients from 50 to 100 centers throughout the country. In the ACS study, all patients will be offered sentinel node biopsies and only those patients with positive nodes will go on to have fully axillary dissections. In the NCI study, breast cancer patients will be randomly divided into two groups, with one group having a sentinel node dissection plus a full axillary node

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New Pathological Techniques

Since surgeons remove just one, or at most, two or three sentinel nodes when performing partial node dissections on melanoma and breast cancer patients, they need to make sure that the nodes are examined extremely carefully for signs of malignant spread. When patients have complete lymph node dissections, pathologists routinely perform permanent sections, which detect one abnormal cell for every 10,000 normal cells. A newer technique called immuno histio chemical (IHC) staining, which involves taking multiple crosswise slices, can detect malignant cells with a sensitivity of 1 in 100,000. The technique will be used in two new multicenter research trials of sentinel node dissections in breast cancer patients. "We want to see if IHC staining can lower the rate of skip metastases," said Douglas Reintgen, MD, director of the cutaneous oncology center at the Moffitt Cancer Center in Tampa, FL who is a researcher participating in the American College of Surgeons' trial. The theory is that micrometastases may form in the sentinel node that are too small to detect on a traditional frozen section. These metastases, however, could still spread to other lymph nodes or more distant sites.

An even more sensitive pathological exam, called polymerase chain reaction (PCR), can identify one abnormal cell for every 1 million normal cells. The PCR technique, a DNA amplification method, is somewhat controversial because researchers do not know if an abnormal cell marker indicates a micrometastasis that could alter a patient's prognosis. "About 20% of patients with an intermediate thickness melanoma have positive lymph nodes," says Joseph Kuhn, MD, assistant director of surgical education at Baylor University Medical Center in Dallas. "With PCR, an additional 20% will have abnormalities in the sentinel node. The question is: Should these patients be treated more aggressively than those with negative nodes?" said Kuhn.

Researchers have already begun the search for the answer. Reintgen and his colleagues evaluated the PCR technique by re-examining the sentinel node tissue samples on 15 melanoma patients who had local recurrences within two years after having a negative sentinel node biopsy. "We found abnormal cell markers in 10 of the 15 patients," said Reintgen. Kuhn is involved in an ongoing study sponsored by the University of Louisville, which will evaluate PCR in melanoma patients who have pathologically negative sentinel nodes (based on a routine permanent section). If exams detect abnormal markers, one group will be observed only, a second will receive the drug interferon and a third will receive additional lymph node surgery as well as interferon.

Sentinel Node Dissections

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dissection and the other group having just the sentinel node dissection. (Women in either group with spread detected in the sentinel node will go on to have full axillary node dissections.) "We will follow patients for at least five years to see whether sentinel node dissections increase the risk of local recurrences or distant metastases," said Krag who is heading the NCI-sponsored trial.

Which Technique is Best?

As is the case with any new surgical procedure, the technique of locating and removing sentinel lymph nodes varies from researcher to researcher. (Usually, the most reliable method is determined before the experimental procedure becomes the standard of care.) For instance, researchers do not agree on the best way to locate the sentinel node: Some prefer to use the gamma detection probe, whereas others prefer to locate sentinel nodes by injecting a 1% isosulfan blue dye. Several studies suggest that using both techniques in combination yields a better detection rate than using either one alone.

The use of lymphoscintigraphy also varies from place to place. Many surgeons work together with nuclear physicians who perform lymphoscintigraphy prior to surgery to map the drainage through the various lymph node chains and determine if there is drainage in the internal mammary chain. Douglas Reintgen, MD, director of the Cutaneous Oncology Center at the Moffitt Cancer Center, instructs surgeons that lymphoscintigraphy is a necessary component of sentinel node dissections at a sentinel node dissection training program he heads at Moffitt. "It decreases the amount of time a surgeon spends in the operating room which saves money and minimizes the risk to the patient," Reintgen said. Krag, on the other hand, said he does not think lymphoscintigraphy improves the detection rate of the gamma probe, so he does not include the nuclear imaging procedure in his research protocols.

Another point of contention is over the removal of sentinel nodes located in the internal mammary chain. Traditionally, surgeons have not biopsied these nodes because removing the entire chain requires extensive surgical maneuvering deep within the chest, causing increased morbidity. Using the radioguided probe, Krag has been able to modify the technique to remove just the sentinel node in the internal chain. "If the probe detects an area of increased uptake in the internal chain, we make a tiny incision and remove the single node," said Krag. "In our most recent study, we found that 3% of positive sentinel nodes are in the internal chain." Reintgen, however, does not think internal sentinel node dissections are necessary. "The clinical probability of an internal mammary chain recurrence is rare, especially since the vast majority of patients have some form of adjuvant therapy such as radiation which would kill off stray cancer cells in that localized area," he said.

Dealing with the Learning Curve

With the ease of use and patient benefits that sentinel node dissections offer, surgeons at community-based hospitals throughout the country are eager to perform the technique in breast cancer patients. Researchers have become alarmed that some surgeons have decided to offer partial node removals to patients even though the jury is still out on whether the technique is as reliable as traditional node surgery. "I know of several surgeons in northern Texas and Dallas who are now offering sentinel node dissections as a marketing tool, and they're taking an extreme risk," said Kuhn. "If a patient has a local recurrence after her surgeon performs a sentinel node dissection outside of a clinical trial, she could have grounds for a malpractice suit. Plenty of surgeons would testify that this procedure is experimental and not considered the standard of care."

Kuhn also emphasizes that physicians need to be properly trained to evaluate sentinel nodes through one of the courses offered by several cancer centers throughout the country. "After training in our course at Baylor, we recommend physicians perform at least 30 procedures to locate the sentinel node during full nodal dissections before considering themselves proficient enough to do partial dissections," said Kuhn.

In a study conducted last year by Kaiser Permanente Medical Center in Los Angeles on the feasibility of performing sentinel node dissections in a community setting, researchers documented a "procedural learning curve" and found that the rate of false negatives dropped dramatically as surgeons became more familiar with the technique. The researchers concluded that the technique was "feasible, economical, and reproducible within the context of a community managed care facility while not placing exacting demands on operating room, pathology or nuclear medicine personnel" (*Cancer J Sci Am* 1997 Nov-Dec; 336–340). That kind of endorsement may be a telling predictor of the acceptance that sentinel node dissections will have in the near future.

—Deborah Kotz

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