

Cancer Staging Technique Holds Promise

Using gamma probes to identify sentinel lymph nodes, researchers are evaluating a new technique that could provide a less invasive way to evaluate lymph node metastases. How will this affect the practice of nuclear medicine?

Two years ago, John Lantman, MD, a retired family physician from Williston, Vermont, was bending down to pull a weed from his garden when his wife noticed an irregularly shaped black spot on the back of his neck. He immediately went to see his dermatologist, and a biopsy revealed that the growth was a melanoma. "He referred me to a surgeon at the University of Vermont who he said was performing a new technique on melanoma patients."

Lantman met with David Krag, MD, chief of surgical oncology at the University of Vermont in Burlington, who told him about a clinical trial he was conducting to evaluate a technique that identifies the sentinel lymph node, the first node that collects lymph drainage from the tumor site. Krag explained that the technique can be helpful in staging melanoma patients in whom prophylactic lymph node dissection remains controversial. Traditionally, some oncologists opt not to biopsy any lymph nodes in melanoma patients, which can spare overtreatment in 80% of patients who have no nodal involvement but also reduces the survival rate in those 20% of patients who have lymph node metastases that go undetected. Other oncologists remove all the surrounding lymph nodes, which can increase survival in some but lead to unnecessary complications such as lymphedema in those 80% of patients with clear nodes.

The beauty of sentinel node detection is that the surgeon can remove just the one lymph node—which is usually the first site of spread—reliably evaluating for the presence of metastatic involvement while leaving all of the other nodes intact. This would then avoid the complication of lymphedema. Lantman was told that the technique had been studied in research trials for the past five years. He was told the results had consistently showed that the technique was reliable, although it was still deemed by the medical establishment to be experimental.

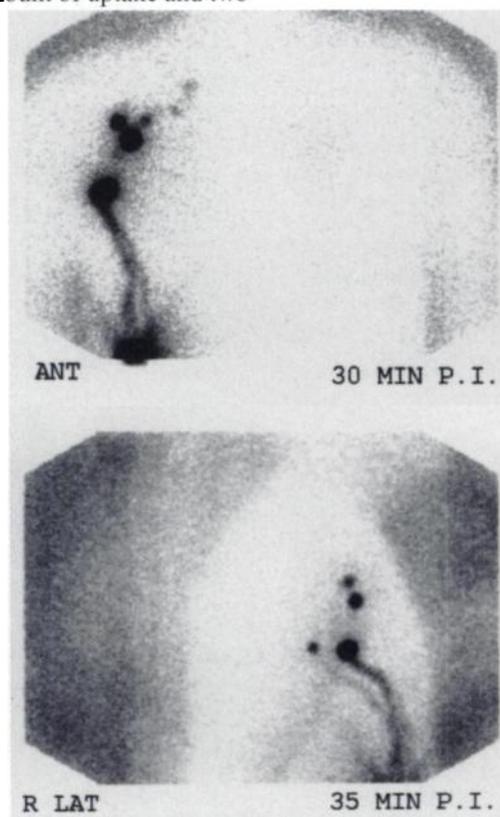
After weighing his options, Lantman decided to participate in the clinical trial. Two hours before surgery, he was injected with a ^{99m}Tc -nanocolloid

near the base of the melanoma; over the next hour, a nuclear physician performed lymphoscintigraphy to locate the nodes with the greatest activity. Krag decided to remove three nodes—one with the greatest amount of uptake and two others with a moderate level of uptake—to ensure that he did not miss the sentinel node. While performing the surgery, Krag used a hand-held gamma probe to locate the three nodes directly without additional radiopharmaceutical injection.

A frozen section was initially analyzed for the presence of metastases, and three days later, the pathologist's final report revealed that all three nodes were negative. "I was glad to have the reassurance that the three nodes were negative," said Lantman. "If I hadn't entered the study, I would have been left worrying about my prognosis." Now he spends his days gardening and skiing with his wife when he is not visiting his four daughters and seven grandchildren.

Advancement in Cancer Staging

Two years after Lantman was a participant in the melanoma study, "sentinel node mapping has become common practice at most major cancer institutions," said Joseph Kuhn, MD, the assistant director of surgical education at Baylor University Medical Center in Dallas. More and more research is suggesting that the technique is extremely reliable: Researchers from the Netherlands Cancer



Lymphoscintigram of a 56-yr-old man with a melanoma on the right trunk. (Top) Anterior image shows lymphatic drainage to a sentinel node in the right axilla. (Bottom) Lateral image shows another sentinel node with a separate drainage duct.

(Reprinted from Kapteijn et al. Validation of gamma probe detection of the sentinel node in melanoma. *J Nucl Med* 1997;38:362-366).



The C-Trak[®] Surgical Guidance System by Care Wise, Morgan Hill, CA, is designed to detect small sites of radioisotope uptake in the high-scatter, highly variable background environments found with nuclear medicine imaging radiolabels such as ¹¹¹In and ^{99m}Tc.

Institute in Amsterdam recently reported that scintigraphy combined with the use of a gamma detection probe and a blue dye mapping technique can identify almost 100% of sentinel nodes in patients with melanoma (*J Nucl Med* 1997;38:362-365).

Moreover, researchers have found that the technique has potential for staging breast cancer patients. A recent study published in the *Journal of the American Medical Association (JAMA)* 1996; 278:1818-1822) found that the use of the gamma detection probe with radiocolloid injection and the injection of 1% isosulfan blue dye successfully identified the sentinel nodes in 92% of a total of 62 patients. A larger multicenter trial, sponsored by the National Cancer Institute is currently underway to study sentinel node mapping in 300 breast cancer patients. The technique is also being investigated for gastrointestinal tumors, solid tumors and head and neck cancers in pilot studies, according to Krag.

If the procedure proves to be reliable for breast cancer, "this could revolutionize the treatment of breast cancer in much the same way lumpectomies altered the course of radical surgery," said Clau-

dia Berman, MD, an associate professor of radiology at the University of South Florida in Tampa and a co-author of the *JAMA* study. Instead of undergoing routine axillary lymph node dissections, breast cancer patients could have just the one sentinel node removed and then analyzed by a pathologist before a decision is made on whether to remove the other nodes. If the node is negative, patients could be spared the removal of the remaining nodes which causes lymphedema in about half of all patients. If the node is positive, patients might have the rest of their axillary nodes excisionally biopsied to determine the extent of metastatic disease.

Although sentinel node mapping appears to offer many benefits, whether it will have any significant effect on nuclear physicians' practices remains to be seen. The widespread use of the procedure could usher in routine lymphoscintigrams. Nuclear physicians may also be needed to inject the radiopharmaceutical since many surgeons may be reluctant to obtain the required Nuclear Regulatory Commission (NRC) license. The actual handling of the probe, though, will probably be performed by surgeons since the procedure is straightforward and easy to learn, according to Krag.

Current Status of Breast Cancer Staging

To locate a sentinel node in a breast cancer patient, the radiopharmaceutical is injected into four sites surrounding the tumor. Surgeons then use the gamma probe to audibly locate the area or areas with the highest counts of radioactivity. An actual measurement (counts) for a short period of set time is then recorded and compared to an adjacent area 1 cm away to verify the location of the sentinel node.

Since sentinel node detection in breast cancer patients is still under clinical investigation, patients must undergo complete axillary node dissections—regardless of the status of their sentinel nodes. These dissections are standard in almost all breast cancer patients who have surgery to remove their
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Marketing of the Gamma Probe

Two companies in the U.S. are manufacturing gamma probes for sentinel node identification. Care Wise Medical Products Corporation in Morgan Hill, CA, is manufacturing the C-Trak probe and the Neoprobe Corporation in Dublin, OH is manufacturing the Neoprobe. Both companies received Food and Drug Administration permission several years ago to market the probes for the finding of radiolabeled tissues.

"So far, we've sold around 150-200 probes," estimated Robin Wise, Jr., president of Care Wise. "We've principally sold probes to surgery departments, although we've sold some to nuclear medicine departments as well." He remarked that sales outside the U.S. have been

almost exclusively to nuclear medicine departments since most foreign countries have severe restrictions on who is permitted to perform procedures involving radionuclides. In countries such as Germany and Japan, only nuclear physicians are allowed to handle the gamma probes.

The gamma probes cost between \$20,000 and \$40,000 depending on the size, and separate sizes are needed for breast and melanoma imaging. Several cancer centers are sponsoring educational training programs, and Care Wise offers an instructional video to teach physicians how to use the probe.

smaller consequence.

In these times of constricted resources, it is unlikely that other departments will follow the example that has been set at the Albert Einstein College of Medicine and a few other medical centers. However, the directors of nuclear medicine must impress upon their radiology or medicine chairpersons, or whatever academic department they relate to, the importance of the specialty and the need for financial and moral support and growth.

Even more important is the need for us to overcome the endless question that arises whenever we meet someone socially (or even at medical functions) who asks us what we do and we respond, "we are nuclear medicine physicians." The reaction varies from "what is that" to "oh, you are a radiologist" or even "oh, you mean you treat cancer." The public must be made aware of who we are, what we do and how important it is. This means spending money. I realize that the ACNP and the SNM are facing financial problems, but we all have financial problems. Therefore, it is time to set priorities. I believe that the single most important

priority any organization in the field has is to make people aware of its existence and importance. This can only be done with an influx of a large amount of capital and with experienced direction through a professional public relations firms.

It is time to stop crying and time to stand up and fight for a field which we believe to be vital to the progress of medicine and of the advancement of our ability to diagnose and treat illness. Let us clarify and solidify the pathways into nuclear medicine as required by the ABNM. Let us make the public aware of our existence and our importance. Let's stop the surveys that list all of the board-certified medical specialties that invariably do not bother to mention nuclear medicine.

If we do not stop crying, we are going to drown in our tears.

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tumors, and many patients experience complications. For instance in the *JAMA* study, 40% of patients experienced lymphedema, 5% had chronic lymphedema, 40% had paresthesia of the arm and 10% had a seroma formation. In addition, lymph node removal can raise the risk of postoperative complications. "In Stage I cancers, where only 10% to 15% of patients have positive nodes, you're subjecting an unacceptably large number of women to unnecessary surgery," said Kuhn.

A Lack of a Standard Method

Until the NCI trial is completed early next year, the sentinel node technique will remain in the hands of researchers or in limited clinical settings. "So far, the preliminary studies have yielded good results," said Kuhn. "The rate of skip metastases is on the order of about 2%, and most oncologists would consider this an acceptable amount." (Skip metastases occur when the first node in the chain does not contain metastatic disease, but more distal lymph nodes do.)

Sentinel node detection, with all its ease and simplicity, has many nuances that have researchers debating about the best way to perform the technique. Previous research has documented the superiority of the gamma probe over the blue dye, a conclusion that researchers agree upon. A point of debate is whether the gamma probe is sufficient on its own or whether it needs to be combined with the blue dye. "The *JAMA* study didn't compare the two techniques with each other. It combined both techniques,

and I don't agree that this is necessary," said Krag. Commenting on the *JAMA* study which she co-authored, Berman pointed out that "there definitely is an advantage to the combined technique since previous research has shown that the gamma probe alone detects the sentinel node in 71% of cases, while the blue dye alone detects the node in 65% of cases." In the *JAMA* study, the combined technique successfully identified the sentinel node in 92% of patients.

Another point of contention is whether lymphoscintigraphy before surgery is necessary in breast cancer patients. Berman said she "strongly advocates" doing the imaging procedure because "a lymphoscintigram will indicate whether drainage is in the axillary lymph node chain or internal mammary chain. It will also tell the surgeon what to expect during surgery and provide information to the radiation oncologist to help determine the necessity or extent of radiation treatments." Krag, on the other hand, said that he "hasn't found imaging to be of benefit" in his research experience. He feels the probe is precise enough on its own to adequately locate the sentinel node.

The researchers' divergent views will probably come closer together once larger studies are published on sentinel node mapping in breast cancer patients. Some nuclear physicians could experience an increase in volume if lymphoscintigraphy is adopted as part of the mapping technique. In this era of medical cost reductions, however, health care managers may be reluctant to pay for lymphoscintigraphy—unless someone is willing to perform a study to show that it is "cost-effective."

Deborah Kotz