Sentinel Node Biopsy: Studies Should Bring Needed Data

Almost every day now, a breast cancer patient asks Armando Giuliano, M.D., about sentinel node biopsy. "Everybody's asking about it; it's on the Internet; patients are demanding it," said Giuliano, the surgeon at the John Wayne Cancer Institute in Santa Monica, Calif., who began studying the technique in the management of early breast cancer about 7 years ago.

It is not hard to understand why patients are interested. Taking out just one or two under-arm lymph nodes avoids the lymphedema and other complications that can accompany a more extensive axillary node dissection. In the more extensive procedure, still considered standard whether the patient has lumpectomy or mastectomy, 10 to 25 lymph nodes are removed and examined for metastases.

In the newer procedure, surgeons find and remove only the first node or cluster of nodes that drain the area of the breast surrounding the tumor. If these sentinel nodes yield no sign of cancer, the hypothesis goes, then the rest of the nodes are probably negative as well and if the sentinel node is positive, then other nodes are positive, too.

A number of small studies have confirmed this hypothesis, showing that the sentinel nodes correctly predict the status of the remaining nodes in a majority — usually a vast majority — of cases.

But that does not mean everyone is ready to give the procedure a whole-hearted vote of confidence. "Experience is limited, there are no randomized trials, and the available published data is limited to a handful of series," pointed out Robert Carlson, M.D., a Stanford University oncologist who chairs the breast cancer guidelines committee for the National Comprehensive Cancer Network.

Nobody Knows Impact

This committee of the Philadelphia-based NCCN recently voted to include sentinel node biopsy as an option for clinicians and patients to consider, but the decision was controversial, Carlson said. With no data from randomized trials, nobody knows what the long-term impact of the procedure will be on recurrence and survival rates. In addition to this fundamental issue, there are questions about the false-negative rate, how surgeons should be credentialed to perform sentinel node dissection, and which patients should be candidates to receive it.

Researchers hope upcoming studies (see sidebar, next page) will resolve issues like these, but in the meantime, the subject of sentinel node biopsy is full of hot subtopics.

Most critical of these topics may be the question of patient outcome. Two randomized trials will address this issue, one of them at the University of Vermont College of Medicine, Burlington, where David Krag, M.D., is planning a trial with the National Surgical Adjuvant Breast and Bowel Project cooperative group. Patients in this trial will be assigned randomly to receive either sentinel node or axillary node biopsy. The principal endpoints will be recurrence and survival rates.

This trial will also address the question of regional control, i.e., do women who have only sentinel nodes removed have higher rates of recurrence in the nodal area and does recurrence affect survival? Krag said he thinks regional recurrence may be higher in a small percent of women, but that a full lymphadenectomy at the time of recurrence could keep survival rates similar. The hypothesis is based in part on NSABP's experience with recurrence and survival rates in its landmark trial of lumpectomy versus mastectomy, Krag said. Recurrence rates were higher in the lumpectomy group in this trial, but survival rates were unaffected.

The other randomized trial, organized by the American College of Surgeons Oncology Group, will take a somewhat different tack. Women with positive sentinel nodes, by routine histology, will be assigned randomly to...
Four large, multicenter studies are addressing the pros and cons of sentinel node dissection. All will enroll patients who are clinically node negative — i.e., no underarm lymph nodes have palpable tumors — and whose breast tumors are no larger than 4 or 5 cm. Investigators provided the following details.

**American College of Surgeons Oncology Group.** Women whose sentinel nodes are positive by routine histology will be assigned randomly to have either axillary lymph node dissection or no further dissection. Those whose sentinel nodes are negative will have no further dissection. Groups will be compared for patient outcome, including regional recurrence of malignancy and survival. This study will also determine the significance of micrometastases that show up only on immunohistochemical (IHC) tests by comparing outcomes among IHC-positive and IHC-negative women. Participants: probably 1,500–2,000; may start enrolling late 1998. Principal Investigator: Armando Giuliano, M.D., John Wayne Cancer Institute, Santa Monica, Calif.

**Bay Area Sentinel Node Study.** This community hospital-based study is randomly assigning patients to receive one of two methods of locating sentinel nodes: blue dye alone or blue dye with radioactive tracer. All patients will have both sentinel node and standard axillary node dissection. Sentinel node identification rate, accuracy (false-negative rate) and community surgeons’ learning curves will be compared. A major objective is to determine which patients are most appropriate for sentinel node biopsy by correlating factors like tumor size and grade with the false-negative rate. It will also examine the role of preoperative lymphoscintigraphy. Participants: 800–1,200; began enrolling April 1998. PI: Stefanie S. Jeffrey, M.D., Stanford University Medical Center, Stanford, Calif.

**Moffitt Cancer Center/Department of Defense Study.** This prospective, nonrandomized study is tracking two groups of patients who have sentinel node biopsies: those whose sentinel nodes are positive, who receive axillary node dissection, and those whose sentinel nodes are negative, who have no further dissection. Regional recurrence, disease-free survival, and overall survival will be compared. The study is also comparing two assays for micrometastases — immunohistochemistry and polymerase chain reaction in nodes, blood, and bone marrow — to learn how they correlate with each other and with outcome. Participants: 700; began enrolling mid-1997. PI: Douglas Reintgen, M.D., H. Lee Moffitt Cancer Center, Tampa.

**University of Vermont/National Surgical Adjuvant Breast and Bowel Project.** This trial will randomly assign patients to two groups, one to have axillary node dissection and one to have sentinel node biopsy. Groups will be compared for disease-free and overall survival, lymphedema and other side effects, and long-term regional control of the disease. Participants: probably 3,600; may start enrolling late 1998. PI: David Krag, M.D., University of Vermont College of Medicine, Burlington.

— Caroline McNeil
but other nodes were positive — has been too small to calculate a meaningful false-negative rate. Dr. Stefanie Jeffrey

Jeffrey has designed a trial with 800 to 1,000 patients, in which all participants will have both sentinel nodes and other nodes removed and compared. With this number of cases, statisticians should be able to determine the rate of skipped metastases within a reasonable 95% confidence interval, she said. Determining the false-negative rate is also one goal of a current large trial at the H. Lee Moffitt Cancer Center in Tampa, which will enroll about 700 women.

While researchers are tackling questions of patient outcome and accuracy, a clutch of other issues also demand attention. There is patient eligibility, for example: Which early breast cancer patients are the best candidates for sentinel node dissection? No one disputes that the nodes must be clinically negative, i.e., not palpable, before a patient can be considered for sentinel node biopsy. But what about other factors, such as size of the breast tumor?

Currently, cutoff points for tumor size vary — 4 cm for Giuliano’s patients at the John Wayne Cancer Institute, both on and off protocol; 5 cm for patients at Moffitt; 3 cm according to the new NCCN guidelines. Data to help resolve this issue could come from Jeffrey’s Stanford trial, which will correlate false negatives with tumor size, grade, and location in the breast and the size of the biopsy cavity.

Still another topic of debate centers on how surgeons become proficient in sentinel node mapping. The techniques for locating the first node or nodes into which a tumor has drained require expertise, and in general, surgeons are acquiring it by performing both sentinel and axillary node biopsies. That is, they first locate and remove the sentinel nodes but then go on to perform the more standard procedure, as a safety net for patients and themselves.

But how many of these procedures do surgeons need to do before they are experienced enough to remove the sentinel node only? Estimates currently vary widely, ranging from five to 30 procedures. One of the aims of the Stanford trial is to train and then track the learning curves of community hospital surgeons as they gain experience.

Different Techniques

Complicating the learning curve issue is the availability of several different techniques used to locate sentinel nodes. One of these involves a blue dye, which is injected in the area of the tumor. The other method uses a radioactive tracer, injected and then tracked by means of a hand-held gamma camera. A lymph imaging technique, called lymphoscintigraphy, which also uses a radioactive tracer, can supplement the dye or the gamma camera.

Each method has its proponents, and again, the Stanford trial should add data to the debate. Patients will be randomly assigned to either blue dye alone or blue dye with radioactive tracer so that success rates and learning curves with each technique can be compared.

Still another question arises once the sentinel node is found and removed: How should it be examined? A method in common use is serial sectioning, cutting the node into several sections and testing it with standard histology, often supplemented by immunohistochemistry.

More experimental is the use of polymerase chain reaction to detect breast cancer markers in the sentinel node, blood, and bone marrow. PCR may be more sensitive than immunohistochemistry at detecting occult metastases, and the two are now being compared in the trial at Moffitt, which is headed by Douglas Reintgen, M.D. This study is designed to show how the assays correlate with each other and with patient outcome, according to the trial’s clinical coordinator, Fadi Hadad, M.D.

The new and more sensitive assays have prompted some thinking about future strategies in which sentinel node biopsy, in conjunction with these assays, might be used to inform treatment decisions. At a strategy meeting for sentinel node researchers at the National Cancer Institute last fall, Giuliano speculated that if a woman had negative sentinel nodes, a tumor under a certain size, plus negative immunohistochemistry and PCR tests, she might be able to forego systemic treatment because of an extremely low risk of distant metastases.

Other investigators agreed that ultimately there would be a need for a trial that could relate the question of sentinel node positivity or negativity to the need for further treatment. The trend in sentinel node research, said Reintgen, will be towards detecting a subgroup of early breast cancer patients who do not need adjuvant therapy.

“That will be the next set of trials,” Giuliano said.

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Journal of the National Cancer Institute, Vol. 90, No. 10, May 20, 1998