# How To Handle Positive Sentinel Nodes?

**By Charlie Schmidt**

Many women can now avoid what was once standard practice in breast cancer staging: removal of all axillary lymph nodes in the armpit. Instead, surgeons look for metastases in the few lymph nodes into which the tumor is most likely to drain—the so-called sentinel nodes. A negative sentinel node biopsy (SNB) does not require removal or biopsy of the other nodes, according to many studies, including large, randomized trials, which have ended the controversy that used to surround SNB.

But now, when the SNB is positive, clinicians face a different quandary. Often the sentinel nodes are the only ones that are positive. So when surgeons remove all the remaining lymph nodes, it can turn out to have been unnecessary, and patients may be left with side effects, including numbness, swelling, pain, and infections. On the other hand, if surgeons don't perform the full axillary lymph node dissection (ALND), they run the risk of leaving positive nodes in place, possibly as a staging area for further metastases.

Apart from surgical removal and biopsy, clinicians have no error-free ways to find out whether the lymph nodes beyond the sentinel nodes are positive, said Lisa Newman, M.D., director of the Breast Care Center at the University of Michigan Comprehensive Cancer Center in Ann Arbor. "With physical exam, you're wrong about the presence of cancer in the axilla anywhere from 25% to 50% of the time," Newman said. Imaging is better at finding positive nodes, but the nodes can look abnormal for reasons unrelated to cancer, such as reactive hyperplasia.

*"We bring each node-positive case to our tumor board for discussion. . .These decisions have to be made on an individual basis."*

## Matter of Debate

With that uncertainty, the appropriate clinical response to positive SNB is now a matter of debate. Taking a conservative view, which assumes that the rest of the axilla may also be cancerous, most consensus statements—including those from the American Society of Clinical Oncology and the National Comprehensive Cancer Network—recommend ALND when the sentinel nodes are positive. Yet studies show that in roughly half of all newly diagnosed breast cancer patients who undergo ALND, only the sentinel nodes are positive, indicating that the procedure is unnecessary about 50% of the time.

In September, researchers published a controversial prospective study suggesting that ALND doesn't improve outcomes in some sentinel node–positive patients. Led by Armando Giuliano, M.D., from the John Wayne Cancer Institute in Santa Monica, Calif., the study found that after 6 years' follow-up, SNB alone and SNB followed by ALND produced similar survival outcomes, as well as comparable regional and local tumor control among node-positive women treated with lumpectomy and whole-breast irradiation. The American College of Surgeons Oncology Group (ACOSOG) sponsored the study, which appeared in the *Annals of Surgery*.

In another study, Min Yi, M.D., and colleagues from the M. D. Anderson Cancer Center in Houston reviewed case histories from nearly 27,000 node-positive patients in the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database. Published last October in *Annals of Surgical Oncology*, the study found that patients who undergo SNB and ALND combined have worse disease-specific survival than those who have SNB alone. But that's probably because patients subjected to both procedures also have more advanced disease, as indicated by larger tumors and negative estrogen receptor status, the authors wrote. Among patients with fewer micrometastases—smaller than 2 mm—disease-specific survival was the same for both SNB only and ALND plus SNB. Yi and her colleagues concluded that the benefits of avoiding the ALND must be weighed against potential risks of harboring undetected axillary metastases.

## Deciding Against ALND

Citing ACOSOG's results, many surgical oncology programs are now abandoning ALND for SLN-positive patients, Newman said. But some experts question whether that's appropriate, given that the study never reached its accrual target of 1,900 patients. After launching the trial in May 1999, ACOSOG had to close accrual in December 2004, with only 446 patients enrolled in the SNB-only arm and 445 patients in the SNB-plus-ALND arm. According to David Krag, M.D., an oncologist at the Vermont Cancer Center in Burlington, accrual stopped prematurely because too many doctors worried that patients randomized to the SNB-only group faced unacceptable risks if the rest of their nodes were actually positive.

Krag argues that with its limited accrual, the study was statistically underpowered to detect a meaningful difference between the arms, which throws the findings into question. "The authors claim no difference, but in my view, they don't have enough statistical confidence to confirm the accuracy of their results," Krag said. Another drawback, Newman points out, is that all the patients received whole-breast irradiation, so some axillary nodes could have been treated incidentally. "That could help to explain why significant differences weren't detected," she said.

Lisa Jacobs, M.D.

Lisa Jacobs, M.D., an associate professor of surgery at Johns Hopkins University who chairs ACOSOG's audit committee, said that her group interprets the ACOSOG study cautiously. "We bring each node-positive case to our tumor board for discussion," Jacobs said. "And we make sure that everyone agrees that the ALND isn't necessary before we decide not to do it." ALND deferral is warranted, Jacobs said, only for node-positive patients who have the same characteristics as the patients

in the ACOSOG study: small (T1 or T2), low-grade, estrogen receptor–positive tumors, found in at most three sentinel nodes, in women scheduled for lumpectomy and whole-breast irradiation. "These decisions have to be made on an individual basis," Jacobs said. Newman also recommended a conservative approach.

### Fine-Needle Aspiration

Meanwhile, a more recent staging process—axillary ultrasound and fine-needle aspiration (FNA) of the axillary lymph nodes—is also generating some interest. Like SNB, FNA is a response to the era of early breast cancer detection and growing numbers of women being diagnosed with node-negative disease for whom ALND is excessive. Most clinicians agree that a positive finding on axillary FNA removes the need for SNB, and many of these patients go directly to ALND during breast surgery. That's because FNA's positive predictive value—the likelihood of nodal involvement when the FNA reveals tumor cells—is high.

Negative FNA findings are more problematic. According to Newman, FNA misses up to 20% of axillary metastases, especially if they're smaller than 5–7 mm. Because of that, negative FNA findings are almost invariably followed by SNB for confirmation, she said.

Most clinicians today limit FNA to nodes deemed suspicious on the basis of ultrasound. But according to Jacobs, even nodes that look normal on ultrasound can harbor metastatic cells. "So we tend to aspirate any node that can be aspirated," she said. Doing so adds to the cost of staging, she conceded, and it's a burden to patients because FNA is painful. Still, a positive finding on FNA saves patients from undergoing an SNB.

Moreover, FNA's costs are balanced by the savings incurred by avoiding SNB among patients found to be node positive, according to a study led by Judy Boughey, M.D., from the Mayo Clinic in Rochester, Minn., and published in April in *Annals of Surgical Oncology*. Newman said that the method also has other advantages: positive findings on FNA, for instance, can be followed immediately by neoadjuvant chemotherapy, which can shrink tumors and make women better candidates for lumpectomy. "That's the real benefit of the FNA," Jacob said. "Patients have a better idea of staging before

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going to surgery, and if they're on the fence about breast surgery, we can try to shrink the tumor first so we get a better cosmetic result."

Could avoiding ALND be possible, even with a positive FNA? According to Newman, no data currently support that position. SNB will clear the axilla of metastases in a substantial fraction of patients, she said, but FNA-positive cases still retain metastatic nodes.

In fact, only when the SNB tests are negative can doctors avoid ALND with confidence, Krag said. Deciding against ALND in sentinel node-negative cases has been standard practice for years. However, it's only recently that this approach has been experimentally validated. Krag was principal investigator on a decade-long phase III clinical trial, published by *Lancet Oncology* in September, showing that among women with a negative SNB, ALND produced no benefits for survival or regional cancer control. Sponsored by the National Surgical Adjuvant Breast and Bowel Project (NSABP), the study involved 5,611 patients treated at 80 institutions in the United States, Canada, and Puerto Rico. "So the ALND can't be justified when the SNB is negative," Krag said. "That issue is now closed."

As to quandaries posed by the ACOSOG data on patients with positive sentinel nodes, the question is far from settled, even for patients similar to those included in the trial. "It's going to take interpretation by the community at large to determine how to handle it," Jacobs said. "But in the meantime, I don't think it's a good idea to extrapolate results beyond the study's inclusion criteria."

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