Researchers Embrace Sentinel Lymph Node Biopsy

BY BRUCE JANCIN
Denver Bureau

San Antonio — Sentinel lymph node biopsy is as accurate as the traditional surgical practice of dissecting the entire axillary lymph node chain in women with breast cancer but inflicts far less nerve damage and fewer other complications, Mark Kissin, M.Chir., reported during a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

The results of the first large-scale randomized trial of sentinel lymph node biopsy in breast cancer patients featuring comprehensive functional and quality of life assessment are so compelling that British health officials who have seen the data have directed that all U.K. surgeons undergo formal training in the technique, according to Dr. Kissin.

'There shouldn't really be a choice anymore.' Sentinel biopsy 'should be the standard of care.'

DR. KISSIN

"There shouldn't really be a choice anymore. Sentinel node biopsy, for the patient, should be the standard of care," he declared.

Dr. Kissin was a coinvestigator in the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, a multicenter U.K. study in which 1,031 women with clinically node-negative breast cancer were randomized to sentinel lymph node biopsy (SLNB) or to the traditional surgical practice of dissecting the entire axillary lymph node chain. Surgeons who participated in the trial were required to have undergone systematic training in SLNB with demonstrated technical competence in its performance.

ALMANAC featured both patient assessments of functional status and quality of life as well as objective measurements of arm and shoulder morbidity, anxiety, and resource utilization at 1, 3, 6, 12, and 18 months. The 6-month follow-up data were the focus of presentations at the San Antonio meeting, although the 18-month data are being processed and should be available soon.

Only one-quarter of patients assigned to SLNB proved SLN-positive.

That means three-quarters of women who undergo routine axillary node clearance needlessly experience the considerable associated morbidity that was documented in ALMANAC, Dr. Kissin, who is a surgeon at Royal Surrey County Hospital in Guildford, England, explained at the meeting.

During the first 3 months of follow-up, 83% of women who received standard axillary node dissection experienced at least one arm problem—lymphedema, shoulder stiffness and loss of range of motion, and/or sensory deficits; for 79%, the problem remained at 18 months.

For example, at 1 month, 62% of women randomized to axillary node clearance experienced sensory loss secondary to damage to the intercostal-brachial nerve, as did 43% at 6 months. In contrast, this was the case at 1 month in only 18% assigned to SLNB, and at 6 months in 16%.

It is worth emphasizing that ALMANAC employed an intent-to-treat analysis. Since all patients with a positive SLNB subsequently underwent full axillary clearance, and the associated morbidity was recorded on the SLNB side of the ledger, the study greatly underestimated the true benefits of having a negative SLNB.

At 6 months, 3% of women in the axillary clearance group had moderate to severe lymphedema, a rate that was sixfold greater than that of the patients in the SLNB group.

The SLNB group had lower infection rates and operating time and shorter hospital stays.

DR. MANSEL

ALMANAC principal investigator Robert E. Mansel, M.D., reported that the SLNB group had significantly lower infection rates and operating times and shorter hospital stays.

There was no difference between the two study arms in anxiety levels as measured by the Spielberger State-Trait Anxiety Inventory.

That's an important finding, noted Dr. Mansel, who is professor of surgery at the University of Wales, Cardiff.

Had patients undergoing SLNB experienced increased anxiety, Dr. Mansel said, it might have cancelled out many of the other observed benefits.

ALMANAC isn't powered to reach definitive conclusions regarding breast cancer recurrence and survival. It's unlikely substantial differences exist in these end points between patients undergoing SLNB compared with routine axillary clearance, since patients with clinically node-negative disease enjoy a generally favorable long-term prognosis.

For most candidates, the substantial quality of life advantages and reduced morbidity entailed by SLNB will be the decisive factor.

For recurrence and survival data, oncologists will look to the results of the National Surgical Adjuvant Breast and Bowel Project B-32 trial, the largest-ever randomized prospective trial evaluating SLNB in clinically node-negative patients.

Thomas B. Julian, M.D., presented preliminary technical results from the phase III trial in which 5,210 participants were randomized to SLNB with or without immediate conventional axillary dissection.

A total of 26% of patients in both the SLNB and conventional axillary dissection groups proved SLN-positive.

In 61.5% of SLN-positive patients, the sentinel node was the only positive node.

The overall accuracy of SLNB was 97.2%, with a negative predictive value of 96.1% and a false-negative rate—"the number you've all been waiting for," Dr. Julian said—a less than stellar 9.7%.

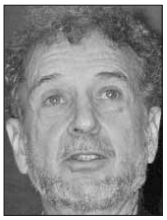
The false-negative rate was not affected by a surgeon's case experience, but it was influenced by the biopsy method employed. The highest false-negative rate—15.2%—occurred with excisional biopsy, for reasons not yet clear, according to Dr. Julian of NSABP headquarters in Pittsburgh.

Surgeons participating in NSABP B-32 had to complete a training protocol that included manualized instruction, a site visit, and performance of qualifying cases. ■

Refined Chemo Benefits ER-Negative Patients

BY BRUCE JANCIN
Denver Bureau

San Antonio — Twenty years of refinements in adjuvant chemotherapy have brought dramatically improved outcomes in lymph node–positive breast cancer patients, but the benefit has been confined to those with estrogen receptor–negative tumors, Donald A. Berry, Ph.D., said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.



Gains for ER-negative patients are 'enormously greater' than in ER-positive women.

DR. BERRY

In patients with node-positive, estrogen receptor–positive breast cancer, hormone therapy—first with tamoxifen, now increasingly with aromatase inhibitors—has resulted in better outcomes over the past 2 decades. There are no comparable treatments specifically targeting ER-negative tumors. But the benefits of chemotherapy in node-positive patients with ER-negative disease are "enormously greater" than in ER-positive women, according to Dr. Berry, professor and chair of the department of biostatistics and applied math at M.D. Anderson Cancer Center, Houston.

He illustrated his point via a review of the three most recent Cancer and Leukemia Group B (CALGB) randomized trials of various chemotherapy regimens in women with node-positive breast cancer. The three studies collectively included 6,644 patients, of whom 2,537 were ER negative. The first of the studies, CALGB 8541, began accruing patients 20 years ago. The most recent, CALGB 9741, started enrollment in the late 1990s.

Each trial randomized patients to lower-dose, less intensive chemotherapy regimens or higher-dose, more aggressive ones. In each study, patients with ER-negative disease who were assigned to the more intensive regimens had significantly greater improvements in disease-free and overall survival than women on conservative, lower-dose chemotherapy. And in each study, the benefits of more modern, aggressive chemotherapy didn't come close to achieving significance in patients with ER-positive breast cancer who were on adjuvant tamoxifen.

The relative reductions in relapse risk in ER-negative patients assigned to high-dose, as compared with low-dose chemotherapy in the three trials were 23%-36%. Similarly, patients on high-dose chemotherapy had relative reductions in all-cause mortality of 22%-29%.

Just how far chemotherapy has come in the past 20 years was best illustrated by a comparison of outcomes between ER-negative participants in CALGB 8541 who were on the standard adjuvant chemotherapy regimen of 20 years ago—low-dose cyclophosphamide, doxorubicin, and fluorouracil—and patients in CALGB 9741 on a much more contemporary regimen of concurrent high-dose doxorubicin and cyclophosphamide followed by paclitaxel with dosing every 2 weeks. Patients on the contemporary regimen had relative risk reductions of 63% for recurrence and 59% for death.

Analyzing the data from the trials on a year-by-year basis, it's apparent that the real benefit of chemotherapy is seen in the first several years of follow-up.

"There's an enormous hazard in the early part of follow-up. Those cancers that are aggressive recur early and are removed from the at-risk set. In the later period in every trial, the risk from about 5 years on out is only 2%-3% per year. That's comparable with what's seen in node-negative disease. This is important to tell your patients: If you're able to get over this hump and get out to 4 or 5 years, your risk is essentially the same as that of a node-negative patient. Roughly speaking, any risk factor is trumped by being able to get to this" period, Dr. Berry said.

Why were there no improved outcomes in ER-positive patients who receive the same chemotherapy regimens so successful in ER-negative patients? "Tamoxifen so lowers their risk that it's difficult to see any benefit for chemotherapy. The number of events in the first few years of follow-up, where chemotherapy is doing its work, is so small that we can't see a statistically significant benefit," he said. ■