Debate Over Sentinel Node Biopsy Continues

By Charles Bankhead

Three decades after urologist Ramon Cabanas, M.D., made the first published reference to the “so-called sentinel lymph node,” the role and utility of sentinel lymph node (SLN) evaluation in cancer continues to provide fuel for debate. In particular, oncologists are still arguing the clinical significance of micrometastases in sentinel nodes of breast cancer patients.

Removing the lymph nodes under the arm, called axillary lymph node dissection (ALND), has been the traditional approach to breast cancer staging. Unquestionably accurate for determining whether breast cancer has spread to the lymph nodes, ALND can result in substantial long-term problems, including loss of arm sensation and movement. Since the early 1990s, SLN biopsy has emerged as a less invasive approach to determine whether cancer has spread to the lymph nodes. However, questions have persisted about SLN biopsy’s relative accuracy compared to ALND.

The American Society of Clinical Oncology has issued clinical guidelines that recognize SLN biopsy as an appropriate alternative to ALND for patients with early-stage breast cancer and whose axillary lymph nodes show no clinical signs of disease. When an SLN biopsy detects metastasis, ALND remains the standard of care for staging, according to the guideline.

Two ongoing National Cancer Institute–sponsored clinical trials aim to further clarify the role of SLN biopsy in breast cancer staging. One trial is examining the prognostic value of SLN biopsy and bone marrow micrometastases in women with early-stage breast cancer. The other is comparing SLN biopsy followed by ALND versus SLN biopsy and observation.

Despite continuing uncertainties, SLN biopsy clearly has affected breast cancer management. “The sentinel lymph node is here to stay,” Dutch cancer surgeon Emiel Rutgers, M.D., said during a presentation at the San Antonio Breast Cancer Symposium in December. “It is the standard of care for clinically node-negative disease. The clinical false-negative rate is less than 0.5% after 3–4 years. Examination of sentinel lymph nodes prevents unnecessary axillary lymph node dissection.”

Omgo Nieweg, M.D., Ph.D., a colleague of Rutgers at the Netherlands Cancer Institute in Amsterdam, reviewed 25 studies comprising 8,687 breast cancer patients who had negative SLN biopsies. During 3–4 years of follow-up, the risk of the cancer growing in the lymph nodes under the arm because of a false-negative SLN reading, called axillary relapse, was just 0.36%. That finding compares favorably with reported rates of relapse after ALND, ranging between 0.8% and 2.3%, Rutgers said.

Microscopic Questions

Still, questions persist about the implications of micrometastases (0.2–2.0 mm) in SLNs. Should every immunohistochemistry (IHC)-positive cell in the node be considered a viable cancer cell? Does the presence of micrometastases have prognostic value? Does one micrometastasis predict the presence of others? Do multistep pathologic sectioning of biopsy specimens and IHC influence staging or treatment?

The first question was examined in a recent report in the Journal of Clinical Oncology by investigators at Mount Sinai School of Medicine in New York, who described 25 cases involving IHC-positive epithelial cells in SLNs of breast cancer patients, normally an indication that the cancer has spread to the lymph nodes. In all cases the cells appeared benign, and in 22 of the 25 cases the cells had features similar to small, noncancerous tumors called intraductal papillomas often found in needle biopsy cores or surgical biopsies. According to the authors, the most likely explanation for the findings was that the biopsy itself helped the migration of benign breast epithelial cells into axillary lymph nodes, an observation that has been reported by other researchers. The authors also concluded that IHC-positive cells in SLNs do not automatically indicate the spread of cancer to the lymph nodes.

The available evidence suggests that micrometastases and isolated tumor cells in SLNs have no prognostic value. Rutgers cited two large retrospective studies of patients found to have micrometastases after ALND. Neither demonstrated an association with survival. A prospective evaluation of 3,047 patients who underwent SLN biopsy produced similar results. The study, reported at the 2005 San Antonio Breast Cancer Symposium by researchers at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, showed that the presence of isolated tumor cells in SLNs had no association with survival but did identify patients who required more extensive evaluation by ALND. If SLN biopsy revealed no additional disease, patients with isolated tumor cells or micrometastases survived at the
same rate as those with node-negative disease.

Seemingly contradictory results emerged from a retrospective analysis of 702 Italian breast cancer patients who had nanometastases (≤0.2 mm) or micrometastases in SLNs. Nanometastases predicted worse survival than that of patients with negative nodes, but the presence of the larger micrometastases did not influence survival. In an update of the Italian study, reported at the San Antonio meeting, the disparate findings relative to the clinical significance of nanometastases versus micrometastases persisted. When the microscopic and submicroscopic disease categories were combined, disease-free survival did not differ from that of patients who had node-negative disease. The risk of distant metastasis was increased when the two categories were considered together.

“Nanometastases are a strong risk factor for all adverse events and for disease relapse. The lack of a size threshold indicates that lymph node deposits are bona fide metastases at very early stages of disease. The constant risk of relapse over time supports an unvaried capacity to metastasize over the years.”

Hungarian investigators performed a meta-analysis of 25 studies in an attempt to quantify the likelihood that cancer would be found in a non-SLN after the discovery of micrometastases or isolated tumor cells in SLNs. The analysis revealed non-SLN involvement in about 20% of cases. If SLN involvement was detected by IHC alone, the incidence of non-SLN involvement was about 9%.

Researchers at the European Institute of Oncology in Milan, Italy, examined the association between positive SLNs and additional axillary metastases in 3,600 breast cancer patients, 1,228 of whom had node-positive disease. The presence of micrometastases in 318 patients’ SLNs predicted additional axillary involvement in 68 cases (21.4%). Isolated tumor cells were identified in 116 patients, 17 (14.7%) of whom had other axillary metastases.

Because of the mixed findings, Rutgers said pathologists should be asked to look only for disease that has known clinical relevance. If ALND in patients with micrometastases fails to identify involvement beyond the SLN, the disease should be considered node negative, and adjuvant therapy should be based on the primary tumor’s prognostic features.

“The prognostic significance of micrometastases for survival is unclear and at most limited,” Rutgers said. “The primary tumor characteristics, such as size and grade, are the most important prognostic factors.”
Guiding Staging

Even though the debate is still raging, physicians use the presence of microscopic metastases to influence treatment. Netherlands Cancer Institute investigators in Amsterdam examined micrometastases’ ability to predict non-SLN involvement and influence clinical management. They reviewed data on 2,150 patients, 650 (30%) of whom had positive SLNs, including 254 (12%) patients who had micrometastases or isolated tumor cells. This finding resulted in a difference in staging in 15% of cases involving micrometastases, and treatment was altered in 7%. The presence of isolated tumor cells led to a change in stage in 4% of cases, and no patient’s treatment was affected. This finding is important because a change in stage can affect how the cancer is treated.

Staging influences another important part of the SLN debate: the degree of side effects with the different surgeries. A randomized trial comparing SLN biopsy alone and SLN biopsy followed by routine ALND corroborated previous evidence that SLN biopsy alone is associated with fewer problems. However, the results did not answer the question of whether the risk of cancer recurrence differs between the two techniques.

The study involved 1,088 patients in Australia and New Zealand who had single tumors less than 3 cm in size and clinically negative axillary lymph nodes, said P. Grantley Gill, M.D., head of breast, endocrine, and surgical oncology at the Royal Adelaide Hospital in Australia. At the first follow-up, more patients in the routine axillary clearance group had infections (14% versus 9% with biopsy) and seromas (36% versus 17%), and arm swelling was more pronounced in the routine axillary clearance patients than that in the biopsy group. The proportion of patients with a more than 15% increase in arm volume was 7.1% with routine axillary clearance and 4.2% with SLN biopsy.

“Sentinel node biopsy leads to substantially less morbidity than axillary clearance based on both objective clinicians’ measurements and subjective patient-rated outcome measures,” Gill said. “Differences in arm mobility diminished over time. Differences in arm swelling increased over time.” Definitive answers about cancer recurrence associated with biopsy versus routine axillary clearance require a comprehensive meta-analysis of all randomized trials, he concluded.