Long-Term Follow-Up Confirms the Oncologic Safety of Sentinel Node Biopsy Without Axillary Dissection in Node-Negative Breast Cancer Patients

Armando E. Giuliano, MD, and Alice P. Chung, MD

The sentinel node biopsy (SNB) technique for breast cancer was introduced in the early 1990s as a less invasive means of axillary staging than standard axillary dissection (ALND). There have been a multitude of studies performed to evaluate the accuracy of SNB, and a recent meta-analysis demonstrated that the status of the sentinel lymph node (SLN) can accurately predict the status of the axillary basin with an average false-negative rate of 7.3%. Experienced surgeons achieve even lower false-negative rates, ranging from 0% to 5%. Before definitive evidence from randomized controlled trials was available to demonstrate its long-term safety, SNB was rapidly accepted by the surgical and oncological communities. This occurred because the procedure proved to be an accurate diagnostic test to assess the axillary lymph nodes. Each surgeon could determine his or her own accuracy by performing SNB and comparing the results to ALND in the same patient. A randomized trial is not necessary to test the accuracy of a diagnostic test, and SNB has now replaced ALND as the standard of care for axillary staging in patients with early breast cancer. A randomized trial is necessary to determine the safety and therapeutic implications of a new procedure.

A number of randomized trials specifically addressed short- and long-term morbidity of SNB compared with ALND. These trials showed that the morbidity of SNB is less than that of ALND. However, there are only a few studies that report data on the long-term outcome of SNB, and the follow-up in these reports is limited. In this issue of Annals of Surgery the study by the excellent group led by Veronesi, is the first randomized trial to report 10-year follow-up for SNB with or without routine completion ALND.

The trial was a single institution study involving 516 patients with breast tumors of 2 cm or less in size, who were randomly assigned to either SNB followed by ALND or SNB with ALND only if the SLN contained metastatic disease. The initial results from this trial were published in 2003, where the efficacy and safety of the SNB procedure were validated. In their earlier report, they demonstrated the false-negative rate of the SNB procedure to be 8.8%, with an overall accuracy of 96.9%. They found that there was less pain and greater arm mobility in patients who had SNB alone compared with those who had ALND. These results are similar to the findings reported from other randomized trials that specifically evaluated efficacy and side effects. With a mean follow-up of 46 months, the 2003 report demonstrated that short-term survival was not compromised in those who had a negative SNB without ALND.

The authors then provided an update on this trial in 2006, where after a median follow-up of 79 months, there were 34 breast cancer-related events, 16 in the SNB arm with one axillary recurrence and 18 in the ALND arm with no axillary recurrences (P = 0.6). The 5-year overall survival was 98.4% in the SNB group and 96.4% in the ALND group. These findings are similar to results of the other randomized trials with shorter follow-up that evaluated the disease-free and overall survival of SNB with and without ALND. Zavagno et al conducted a multicenter trial of 697 patients with tumors less than or equal to 3 cm in diameter. After a mean of 56 months of follow-up, there were 29 locoregional events in the SNB group and 22 events in the ALND group. They found no difference between the 2 groups with respect to disease-free or overall survival. Canavese et al compared SNB with and without ALND in a much smaller cohort of 115 patients followed up for a median of 66 months. There were 12 events in the ALND arm with one axillary recurrence and 10 events in the SNB arm with no axillary recurrences. The authors did not demonstrate a difference in disease-free or overall survival between the 2 groups.

In the current report by Veronesi et al, an update of their randomized trial is provided with a median follow-up of 102 months. There were a total of 49 breast cancer-related events, 23 in the SNB arm and 26 in the ALND arm (P = 0.52). There was no difference between the 2 groups with respect to disease-free survival (89.9% in the SNB arm vs. 88.8% in the ALND arm).
arm); the overall survival was slightly greater in the SNB arm, 93.5%, compared with the ALND arm, 89.7%, but this was not statistically significant ($P = 0.15$).

Of note, there were only 2 (0.39%) axillary recurrences in this study, both of which occurred in the SNB-only group (0.77%). A very low rate of axillary relapse was also observed in other randomized trials with shorter follow-up. Zavagno et al. found only one (0.002%) axillary recurrence among 697 patients. This recurrence was in the SNB-only arm (0.29%). Canavese et al. found 1 (0.87%) axillary relapse in the ALND arm, with no axillary recurrences in the SNB arm. The American College of Surgeons Oncology Group (ACOSOG) Z0010 trial was one of the largest trials of SNB in clinically node-negative breast cancer, which included over 5000 patients. With a median follow-up of 31 months, only 0.2% of the SLN-negative patients were found to have an axillary recurrence. In the current study, among patients in the SNB arm who did not have ALND, a lower than expected number developed overt axillary metastases. The authors theorize that the lower rate of axillary relapse may be due to the presence of non-stem cancer cells within the lymph node, which do not have the capacity to establish viable metastatic foci that would later present as an axillary recurrence. Another potential explanation for fewer axillary relapses is that the axillary nodes may have incidentally received radiation therapy during whole-breast irradiation, with opposing tangential fields. It is also possible that adjuvant chemotherapy or hormonal therapy may have an effect on metastatic foci in the lymph nodes, preventing or prolonging time to axillary relapse.

In this study, axillary dissection did not result in an increase in survival, confirming the findings from the NSABP-B04 trial performed decades ago. However, one of the strongest criticisms of the B-04 trial, which included over 1000 study participants, was that it was underpowered to demonstrate a survival difference between the treatment arms. While the Veronesi trial included a moderate sample size and was executed with excellent quality control and patient care, it is still underpowered to make any definitive conclusions about the overall survival following SNB alone. The NSABP B-32 trial, which randomized 5611 patients with clinically negative lymph nodes in a similar design, only recently reported the results of morbidity and it will be several years before the outcome data with 10 years of follow-up are available. Due to the low number of patients with axillary metastases, it is possible that even this trial may be underpowered to determine the effect of SNB on survival, since there is little risk associated with omitting ALND in SNL-negative patients.

Since over 95% of SLN-negative patients are truly node-negative, it is unlikely that ALND will benefit the node-negative patient. Based on the Veronesi study and the B32 trial, the potential benefit of ALND would most likely apply only to the false-negative SLN group of patients since the true-negative SLN cases are highly unlikely to benefit from ALND. Among the SLN-negative patients, 341 were randomized to ALND (n = 174) or no ALND (n = 167). In the group that had ALND, 23 (8.9%) false-negative SLNs were identified, and this number represents the subgroup of patients that may benefit from ALND. It is impossible to draw any meaningful conclusion regarding the advantage of ALND from such a small sample size. The NSABP-B04 trial (2002) demonstrated no difference in overall survival between the group that had ALND compared with those treated with radiation or no axillary treatment. In this trial, there were 586 patients with positive nodes and none of these patients received adjuvant systemic therapy. The ACOSOG Z0011 trial examines only SLN-positive patients to address this question. This trial randomized over 900 SLN-positive patients to ALND or no further treatment. This study also may have been underpowered. Due to a lower accrual and event rate than anticipated, the study was closed.

The authors also report that 60/175 (34%) of the node-positive cases contained only micrometastases. After 10-years of follow-up, they found that patients with micrometastases had a lower rate of distant metastases than those with macrometastases. These results confirm the findings in several retrospective analyses investigating the prognostic significance of micrometastases. De Boer et al. compared outcomes in 856 patients with micrometastases and/or isolated tumor cells who did not receive adjuvant therapy with 955 similar patients who received adjuvant therapy. With a median follow-up of 5.1 years, they found that there was a difference in disease-free survival between patients with isolated tumor cells or micrometastases compared with node-negative patients only among those who did not receive adjuvant systemic therapy. This difference was not seen in distant disease-free survival but only in locoregional or contralateral disease.

In a recent publication by our group, the presence of isolated tumor cells or micro metastasis in the SLN did not affect survival compared with those who were node-negative after 8 years of follow-up. Clearly, the controversy regarding the prognostic significance of occult metastases still exists. In addition, the findings raise the question of whether completion ALND would even benefit those with SN micrometastasis. The authors are currently participating in the IBCSG 23–01 trial to compare ALND with no ALND in patients with SLN micrometastases. This trial has a similar design to the ACOSOG Z0011 trial, but only includes patients with SLN involved with micrometastases or isolated tumor cells. If the IBCSG trial is able to recruit an adequate number of study participants, we may finally have the data to appropriately address the value of completion ALND in patients with occult lymph node involvement.

We applaud professor Veronesi’s group for providing randomized data showing that SNB is as safe as ALND, and the risk of axillary recurrence in SLN-negative patients who do not undergo ALND is extremely low. This randomized trial is a well-designed study with the longest follow-up reported, and shows that ALND does not benefit SNL-negative patients and omission of ALND in these patients does not decrease locoregional control or overall survival.

REFERENCES

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