Appropriate Role for Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Patients With Early-Stage Breast Cancer

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Few areas of modern medicine have captured the imagination more than the rapid and groundbreaking progress that has been observed in the treatment of patients with early-stage breast cancer (ESBC). It is perhaps because of such dramatic advances that some investigators, not unlike those who take pride in the progress against childhood leukemia, have been asking whether the same or even better results could be obtained with less invasive approaches. In addition to breast-conserving surgery and the increasing role of more targeted and less toxic treatments, we now have less invasive surgical procedures for both achieving adequate margins and for the assessment of the axillary lymph node status.

No one doubts the major prognostic importance of the presence and extent of axillary nodal involvement at the time of diagnosis, but most women with ESBC can and should have the axillary lymph node status assessed using lymphatic mapping and sentinel node sampling, which avoids the need for completion lymph node dissection (CND) when no disease is identified. Lymphatic mapping and sentinel node sampling techniques were originally developed for patients with malignant melanoma and were most extensively studied in patients with ESBC; breast cancer surgeons have now been widely trained in these techniques, and the technology to perform them is available in virtually all academic and major nonacademic centers. When the original American Society of Clinical Oncology (ASCO) guidelines for the use of sentinel node biopsy (SNB) in patients with ESBC were made available in 2005, randomized controlled trials had been initiated but were not yet completed. Evidence available to the 2005 Guideline Panel was derived from a variety of published sources, including a meta-analysis of 69 cohorts that included more than 8,000 patients with ESBC who underwent both SNB and CND. Although the overall identification rate of 96% and false-negative rate (FNR) of 7.3% were encouraging, large variation across reported studies was observed, with more than one third of cohorts experiencing an FNR of over 10%. Since then, a number of randomized controlled trials have been published, leading to an update of the ASCO SNB guideline in 2014. Important modifications in the original recommendations included revision of the role for SNB in many patients with one or two positive sentinel nodes on the basis of the results of ACOSOG (American College of Surgeons Oncology Group) trial Z0011.

During the time period between these published guidelines, the role of neoadjuvant (preoperative) chemotherapy (NAC) has changed. Originally providing a surgical option for women with large, unresectable tumors, NAC now plays a number of additional important roles: it presents an extended opportunity for breast-conserving surgery; improves cosmesis; enables assessment of systemic therapy response; allows for downstaging of the axilla; and provides research opportunities to better understand the biology of the disease. To this list we can now add that NAC presents an opportunity for newly developed agents to potentially gain accelerated approval by the US Food and Drug Administration, given that NAC has demonstrated an impact on pathologic complete remission (pCR), which has been proposed as a possible surrogate for therapeutic benefit.

The role and timing of SNB in patients receiving NAC continues to be a topic of some discussion. Although there are a number of theoretical advantages when the SNB occurs after NAC (eg, the overall chemosensitivity of NAC can be assessed and an additional surgical procedure before NAC can be avoided), prognostic information that is relevant to locoregional and systemic treatment decision making may be lost. Largely on the basis of results from an unplanned retrospective analysis of a subgroup of patients undergoing SNB after NAC in NSABP (National Surgical Adjuvant Breast and Bowel Project) study B-27, the use of SNB in this setting (after NAC) was not recommended in the 2005 ASCO Guideline. Therefore, the panel encouraged its use before NAC. Since that time, a number of prospective clinical studies have been published that have attempted to address the role of SNB after NAC, particularly in patients with clinically or biopsy-proven lymph node involvement before NAC.

Among 649 evaluable patients who were enrolled onto the ACOSOG Z1071 (Alliance) trial with biopsy-proven (cN1) disease, no sentinel lymph node (SLN) was identified in 7% and only one SLN in 12% after NAC. The observed FNR was 31.5% when only one SLN was resected and 12.6% when two or more were examined, prompting the investigators to conclude that greater sensitivity would be necessary to support the use of SNB in this setting. In another recent study (SENTINA [Sentinel Neoadjuvant]) from Germany, among patients with clinically node-positive disease on the basis of examination or ultrasound who were found to have clinically negative nodes after...
recurrence and the impact on disease-free or overall survival in this high-risk setting.

As highlighted in the 2014 ASCO SNB guideline, in the absence of evidence for axillary nodal disease, clinicians may offer women with operable breast cancer SNB either before or after planned NAC; CND represents the standard of care when nodal metastases are found after systemic therapy. However, as demonstrated by the results of SN FNAC, as well as by ACOSOG Z1071 and SENTINA, the risk for positive nonsentinel nodes is high in patients with clinically or biopsy-proven nodal disease before NAC, potentially resulting in understaging and inappropriate treatment. SNB performed after NAC is associated with a relatively low identification rate and an unacceptably high FNR in patients with two or fewer identified SLNs. Proposed strategies for improving the evaluation of the axilla after NAC need to be addressed in adequately powered, prospective trials with longer follow-up, and need to address issues not only related to SNB but also the role of subsequent radiation and systemic therapies. The hypotheses raised by the SN FNAC (and other recent trials of post-NAC SNB) that relate to extending the definition of positive nodes, the use of clips, and the use of dual-agent mapping also warrant further evaluation in prospective studies. Trials such as Alliance A011202 (NCT01901904) are ongoing to further address the need for CND in patients with SNB-positive disease after NAC. Until more data from ongoing and future trials are available on the safety and appropriate use of SNB after NAC, we must maintain a cautious and evidence-based approach to the management of patients with known or suspected nodal metastases.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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