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EDITORIAL – BREAST ONCOLOGY

Sentinel Node Biopsy After Neoadjuvant Systemic Therapy for Breast Cancer: The Method Matters

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The transition from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) has been a major advance over the past 30 years, leading to decreased morbidity of breast cancer treatment.[1,2] Similarly, demonstrations that neoadjuvant systemic therapy (NST) is equivalent to adjuvant therapy have paved the way to de-escalation of local and regional therapies, despite some concerns about possible increased risk of local recurrence in the breast.[3–8] For example, now NST often is used to avoid total mastectomy, to reduce the magnitude of partial mastectomies and potentially to avoid ALND and/or regional nodal irradiation, even in patients with clinically positive nodes at the time of diagnosis.[6,9,10] The use of SLNB in place of ALND after NST has been widely accepted for patients with clinically negative nodes at presentation, but the same approach has been more controversial for patients with clinically and pathologically proven positive nodes. Current NCCN guidelines regarding surgical lymph node staging after NST state that if axillary node imaging or needle biopsy is negative, then SLN should preferably be performed after NST.[11] It also notes that NST "may allow SLNB alone if a positive axilla is cleared with therapy." ASCO guidelines from 2016 suggest that SLNB may be offered to patients who receive NST but suggest caution for patients with large or bulky metastatic axillary nodes.[12] Conversion of positive to negative nodes is more likely to occur with triple negative or HER-2$^+$ breast cancers, and multiple studies have shown that neoadjuvant chemotherapy results in a fairly consistent conversion rate from clinically positive nodes to pathologically negative nodes in the range of 40%.[10,13–17]

The main concerns regarding the use of SLN for patients who present with positive nodes and then receive NST have been whether the identification rate is adequate and whether the false-negative rate (FNR) is sufficiently low. The failure to map is not as big an issue as the FNR, as the fallback position from failure to identify a SLN would be to proceed with ALND in patients with positive nodes prior to NST. False-negative SLN (i.e., histologically negative SLN despite residual cancer in other axillary nodes), on the other hand, has significant potential consequences. These include misrepresentation of the prognosis for these patients, especially for TNBC and HER-2$^+$ cancers, for whom the absence of a pathologic complete response, especially residual cancer in lymph nodes, signifies a higher likelihood of subsequent recurrence and death.[3,18,19] Residual disease in axillary nodes has become even more significant since recent reports, such as the CREATE-X and Katherine trials, have shown that adjuvant treatment for patients with residual cancer after NST reduces the risk of recurrence for TNBC or HER-2$^+$ cancers, respectively.[20,21] Similarly, conversion of positive nodes to negative may be a basis for omitting regional nodal irradiation, depending on the results of trials like NSABP B-51.[22]

Previous studies of the identification rates and accuracy of SLN biopsy, including meta-analyses, have been interpreted in varying ways. Multiple retrospective studies and meta-analyses of SLN biopsy performed with ALND have been consistent in finding FNR in the range of 7–13%.[13,23–26] The prospective Z1071 trial found that the false-negative rate overall for patients with clinical N1 disease and two or more SLN found was 12%, a bit higher than the target rate of 10%.[14] Patients with clinical N2 nodal disease (fixed or matted nodes) were included in the

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study but were not analyzed as part of the primary endpoint. A number of controllable aspects of the method were associated with lower FNR, including using dual tracer techniques (radioactive and color) and confirmation of removal of the initially biopsied positive node by placing a clip and confirming retrieval of the clipped node at the time of the SLNB. More recently, techniques for marking the needle biopsy-positive nodes and verification that they are removed, combined with SLN mapping and removal, can reduce the FNR to as low as 2%.[27–31] These methods have included placing a clip in the node at the time of biopsy, identification of the clip by intraoperative ultrasound and specimen radiograph, ^{125}I seeds placed at the time of biopsy or before surgery, or tattooing positive nodes with India ink.[27,28,32] Nonradioactive marker options, such as using magnetic, radiofrequency, or radar technology markers, are additional options. The importance of this is highlighted by the fact that 20% or more of marked positive nodes are *not* among the nodes identified by mapping, even with use of dual tracers.[27,30,31,33] For us, this means that SLN is generally reserved for patients with no more than two to three abnormal nodes on imaging, because biopsy and marking more than this is not generally feasible. A more recent study suggests that ALND is actually associated with improved survival in patients presenting with N2-3 disease.[16]

In this issue of the *Annals of Surgical Oncology*, So-Youn et al. reported a small, randomized trial of SLN mapping after NST with radioisotope (RI) alone versus a dual method (DM) with radioactive tracer plus a fluorescent dye, indocyanine green (ICGF).[34] They found that the rate of SLN identification was equal in both groups (93.8% with RI alone vs. 98.3% with DM), and they claim that the identification rate with ICGF alone "exceeded" that for RI alone (94.7 vs. 93.8%). Neither of these differences are statistically or clinically significant, and the sample size was predicated on the assumption that the identification rate with RI alone would be only 80%. Both rates are similar to the identification rate in the Z1071 trial (92.7%, including the N2 patients). Although a second SLN was found more often with ICGF than with RI, this was based on only 30 patients and was not statistically significant. Because they did not actually test ICGF alone versus RI alone, their conclusion that we could switch to ICGF alone seems premature. While the ICGF technique does avoid the logistic hurdles of using radioactive tracer, using ICGF would require many hospitals to buy new equipment to perform the procedure.

Most importantly, what they cannot tell us from this study is the FNR for the dual method versus ICGF alone. This is particularly concerning in a small series that included 45.9% of subjects with N2 or N3 disease, which some would consider unsuitable for SLNB in the first place. Conversely, in contrast to the Z1071 patients, not all of the patients had biopsy-proven nodal metastases, and the primary group also included 9 cN0 patients, all of whom were randomized to the RI alone group. Compared with the Z1071 study, which showed that dual mapping techniques reduced the FNR to more acceptable levels, and studies showing that 20% or more of marked positive nodes are not identified as SLN by mapping, switching to a single method of mapping could lead to unacceptable FNRs. Optimizing the technique of SLN biopsy is important for any patients in whom nodal status may impact subsequent treatment, particularly for patients with positive nodes who receive NST. While simplification also is worthwhile, the primary goal should be accurate staging and optimizing therapy. Currently, it appears that best practice is to consider SLNB after NST for patients who present with cN1 disease and convert to cN0 by imaging. SLN mapping with two dyes plus marking positive nodes with a method that facilitates detection and confirmation of their removal is the safest option. Whether ALND should be performed if a marked positive node is not found is an unsettled question, as is whether completion ALND is required if any SLN or marked nodes are still positive. The latter question is being addressed by the ongoing Alliance for Clinical Trials in Oncology A11202 trial, a randomized phase III trial evaluating the role of axillary lymph node dissection in breast cancer patients (cT1-3 N1) who have positive sentinel lymph node disease after neoadjuvant chemotherapy (NCT01901094).[35]

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