Optimizing Surgical Management of the Axilla After Neoadjuvant Chemotherapy: An Evolving Story

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For patients with operable breast cancer and clinically negative axilla who undergo surgery first, sentinel lymph node biopsy (SLNB) has been established as the gold standard for pathologic evaluation of the axilla. When the SLN is negative, no further surgery in the axilla is required. Traditionally, intraoperative frozen section (FS) was used to assess SLN status. However, randomized clinical trials have shown that selected patients with clinically negative axilla and limited SLN involvement can be spared from completion axillary lymph node dissection (ALND).^{1,2} Therefore, intraoperative FS currently is reserved primarily for patients who do not meet criteria for inclusion or were underrepresented in those trials (e.g., patients undergoing mastectomy and those who have received neoadjuvant chemotherapy [NAC] before the SLNB).

During the past several years, use of NAC has expanded and currently is considered an alternative to adjuvant chemotherapy for selected patients with operable disease.³ Development of more active NAC regimens and improvements in patient selection for NAC have resulted in increasing rates of sterilization of subclinically or clinically involved axillary nodes, providing an opportunity to further de-escalate the surgical management of the axilla.³

For patients who undergo upfront SLNB, the volume of SLN involvement is an important predictor of the presence of non-SLN metastases^{2,4,5} but whether this is also the case for patients who undergo SLNB after NAC is not known. This question is clinically important as we continue to work on further de-escalation of axillary surgery for patients who have their involved axillary nodes

downstaged by NAC but are found to have small-volume disease in the SLN, either on intraoperative frozen section or on permanent pathologic evaluation.

In a recent issue of the *Annals of Surgical Oncology*, Moo et al.⁶ report on a large study from Memorial Sloan Kettering Cancer Center that aimed to determine the sensitivity of intraoperative SLN FS after NAC as well as the association between volume of disease in the SLN (by FS or permanent section) and probability of finding additional non-SLN involvement at completion ALND. During a 9-year period (2008–2017), 702 patients (711 cancers) who had SLNB after NAC were evaluated. All the patients had clinical stage 2 or 3 disease, and about half of the patients were clinically node-positive before NAC (> 80% of whom were histologically confirmed). All the patients were clinically node-negative by physical examination after NAC and underwent SLNB. For the patients who were clinically node-negative before NAC, SLN mapping was performed with single or dual tracers, at the surgeon's discretion, but the use of dual tracers was mandatory for the patients who were clinically node-positive before NAC.

Intraoperative FS examination was routinely performed, showing that 181 patients had metastases, and 530 were negative. Of the 530 node-negative cases, 33 were positive on the final pathology (false-negative rate of FS, 6.2%). Among the patients with a positive FS, 2% had isolated tumor cells (ITC) and no further disease at ALND, 23% had micrometastases, and 69% had macrometastases (6% did not undergo completion ALND). At ALND, 59% of the patients with micrometastases and 63% of those with macrometastases had at least one additional positive non-SLN. Among the 33 patients with a false-negative FS, 30% had ITC, 46% had micrometastases, and 24% had macrometastases. Of these patients, 17 had ALND, and 59% had at least one additional positive non-SLN.

Among all the patients with a positive SLN, irrespective of detection method, 17% of those with ITCs, 64% of those with micrometastases, and 62% of those with macrometastases had additional non-SLN metastases at ALND. More importantly, the extent of residual disease in the non-SLNs was substantial. Of the patients with SLN micrometastases, 34% had two or more positive non-SLNs, and one third of all the non-SLN metastases were macrometastases. The patients with SLN macrometastases had significantly greater numbers of additional positive non-SLNs (range, 1–15 vs. 1–8 for the patients with SLN micrometastases).

Based on the aforementioned findings, the authors concluded that low-volume SLN disease after NAC is not an indication for low risk of additional non-SLN involvement, but is an indication for ALND, even when SLN involvement is not detected on intraoperative FS.

The study by Moo et al. was a well-conducted study involving a large number of patients treated with NAC. The study population and SLNB method were typical for patients currently treated with NAC, making the study results generalizable. The rates of non-SLN positivity after NAC were similarly high for the patients with SLN involvement by micrometastases or micrometastases, but lower if the SLN was involved by ITCs. Similar results were reported in the sentinel node fine-needle aspiration cytology (SN FNAC) prospective, multi-centric trial evaluating SLNB followed by ALND for patients with biopsy-proven node-positive breast cancer.⁷ That trial showed no significant correlation between size of SLN metastases and rate of positive non-SLNs (57% for ypN0i+, 38% for ypN1mi, and 56% for ypN1; $p = 0.637$), but the number of patients with ypN0i+ ($n = 7$) and ypN1mi ($n = 8$) was small.⁷ In the study by Moo et al., 17% of the patients with ITCs in the SLN had positive non-SLNs, but the number of patients in this group also was small, preventing definitive conclusions. In both studies, the rates of non-SLN positivity for patients with micrometastases in the SLN after NAC are considerably higher than the 20% rate for patients with micrometastases found on upfront SLNB.⁴

One possible explanation for the high rates of non-SLN positivity in the aforementioned studies is that about 40% of the patients in the Moo et al. study and all the patients in the SN FNAC trial had documented axillary involvement before NAC. The study by Moo et al. did not report separately on the rates of non-SLN involvement in the patients with positive SLNs who presented with clinically negative versus clinically positive axilla. Such information could be clinically helpful for axillary management after NAC when the axilla is clinically negative at presentation but the SLN is positive after NAC.

In the study by Moo et al., determination of clinically negative nodal status after NAC was by physical examination. The study did not report on the use of axillary ultrasound after NAC or how such use may have affected the frequency and/or the burden of non-SLN metastases.

In the ACOSOG Z1071 trial evaluating SLNB in patients who presented with documented SLN involvement and had clinically negative axilla after NAC. Negative axillary ultrasound (by central review) was associated with lower burden of disease in the axilla when the SLN remained involved.⁸ Patients with a suspicious axillary ultrasound after NAC were significantly more likely to be SLN-positive at surgery (71.8%) than those with a normal axillary ultrasound (56.5%). Furthermore, patients with suspicious nodes by axillary ultrasound had a greater number of positive nodes and larger metastases ($p < 0.001$).⁸

Among the patients with positive SLNs at surgery after a normal axillary ultrasound, 63% had no additional positive nodes in the ALND specimen. These findings indicate that the use axillary ultrasound can be helpful in identifying patients who despite a positive SLN after NAC have lower residual tumor burden in non-SLNs. Such patients are currently candidates for the Alliance A11202 trial, which randomizes patients with documented involvement of the axilla before NAC and positive SLNs after NAC to completion ALND rather than no ALND under the premise that those patients will receive adjuvant radiation (<https://clinicaltrials.gov/ct2/show/NCT01901094>).

In the study by Moo et al., immunohistochemistry (IHC) in the SLN was not used (except for selected cases, such as those with a few suspicious cells, treatment effect, or crush/processing artifact). Recent reports from studies that examined the SLNs by IHC either prospectively (SN FNAC) or retrospectively (ACOSOG Z1071) in patients who presented with documented involvement of the axilla, who became clinically node-negative with NAC, and who underwent SLNB plus ALND have shown a decrease in the false-negative rate of SLNB, with low rates of unnecessary ALND (where no additional positive non-SLNs are found).^{7,9} These results indirectly support the Moo et al. findings of high rates of non-SLN positivity after NAC when the SLN is minimally involved. It is possible that if SLN evaluation by IHC had been routinely used in the study by Moo et al. for patients presenting with axillary involvement before NAC, additional patients with SLN and non-SLN involvement could have been identified. However, optimal locoregional management of such patients (i.e., with more surgery plus radiation vs. radiation alone) remains to be determined.

From a biologic standpoint, persistent disease in the SLN after NAC represents a population of tumor cells resistant to chemotherapy. Whether low-volume disease in

the SLN represents a small amount of disease unresponsive to NAC or a larger volume of disease reduced to low volume by NAC, the expected prognosis for such patients would be worse than for patients with low-volume disease in the SLN with upfront surgery.

In the NSABP B-18 trial that compared neoadjuvant versus adjuvant chemotherapy with doxorubicin/cyclophosphamide, the outcomes for the patients with micrometastases (< 2 mm) or mini-micrometastases (< 1 mm, detected by IHC) at ALND were similar to those for the node-negative patients in the group that received surgery first. However, the outcomes for the patients with micrometastases or mini-micrometastases in the group that received NAC were similar to those for the node-positive patients with macrometastases and significantly worse than those for node-negative patients.¹⁰ Thus, identifying minimally residual disease in the axilla after NAC and recognizing its adverse impact on prognosis provides the opportunity to consider additional adjuvant therapy interventions (either established or novel) as part of clinical trials to improve the outcomes for these patients.

The results of the study by Moo et al. continue to support ALND as the standard of care for patients who have any size involvement in the SLN after NAC, whether such involvement is identified intraoperatively by FS or postoperatively on permanent pathology. Until results from randomized trials such as the Alliance A11202 study show that completion ALND does not significantly improve outcomes for these patients, this practice should continue. Intraoperative examination of the SLN by FS can identify nodal metastases at the time of surgery and help avoid a return trip to the operating room for the majority of patients.

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