Intraoperative Pathologic Evaluation with Targeted Axillary Dissection

Editorial for “Intraoperative Touch Imprint Cytology in Targeted Axillary Dissection After Neoadjuvant Chemotherapy Among Breast Cancer Patients with Initial Axillary Metastasis”

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The management of axillary disease in breast cancer patients is constantly evolving; however, the practice of routine axillary clearance for clinically node-positive patients has recently been questioned. With the increased use of neoadjuvant chemotherapy (NAC), as well as increasing efficacy of systemic therapy, a substantial proportion of clinically node-positive patients may achieve a nodal pathologic complete response (pCR) with chemotherapy. Several recent studies have explored minimally invasive techniques to identify those patients who may not benefit from extensive axillary surgery.^{1–4} One such approach is targeted axillary dissection (TAD).^{4,5} With this technique, lymph nodes with biopsy-confirmed metastases are marked with a clip prior to initiating NAC. TAD involves selective localization and removal of the clip, in addition to removal of the sentinel nodes for axillary staging. Wu et al. report their results of using TAD and the use of intraoperative touch imprint cytology to evaluate the excised lymph nodes. They prospectively enrolled patients with biopsy-confirmed nodal metastases who underwent NAC followed by TAD and completion axillary lymph node dissection (ALND). They used intraoperative touch imprint cytology to assess nodes removed by TAD and compared this with the final pathologic results, finding a sensitivity of 87.9% and specificity of 94.9%. The authors

found that a false negative result for intraoperative analysis was more likely when only micrometastatic disease remained.

The authors should be congratulated for this contribution to the field. While the use of intraoperative analysis of sentinel lymph nodes (SLNs) has been found to be an accurate, cost-effective approach in treatment-naïve patients,^{7,8} we cannot assume that the evaluation will be as accurate after therapy. Luckily, the authors of that article show that touch imprint cytology correctly identified the presence of metastases in 33 of the 37 cases with confirmed residual disease. A recent study from Memorial Sloan Kettering evaluating frozen section analysis of SLNs after NAC also found that this approach to intraoperative evaluation was beneficial, finding a false negative rate (FNR) of only 6.2%.⁹ These studies support the use of intraoperative analysis in this setting as the decision to proceed with ALND can be made in a single operative setting. This spares patients the anxiety and risks associated with multiple operations, as well as the delays in starting adjuvant radiation.

The authors describe the limitations of intraoperative assessment. First, small-volume disease such as micrometastases and isolated tumor cells (ITCs) may be missed. In their report, all false negative (FN) results for touch imprint cytology were due to the small volume of residual disease. This was also seen in the article by Moo et al.⁹ in which 30% of the 33 false negative results had ITCs on final pathology and 46% had micrometastasis. There is growing recognition that this small-volume disease is relevant in patients after NAC. The American College of Surgeons Oncology Group (ACOSOG) Z1017 trial and the Sentinel Node Biopsy Following Neoadjuvant

Chemotherapy (SN FNAC) trial showed that the use of immunohistochemistry reduces the FNR of SLN dissection (SLND).^{2,10} One concern is that the authors reported three false positive results, of which two occurred due to misclassification of macrophages and lymphocytes as tumor cells, and one was due to treatment effect seen in the node. Treatment effect can result in fibrosis, mucin, or groups of foamy histiocytes, which makes evaluation of nodes after NAC more challenging than when nodes are retrieved prior to therapy.¹¹ Pathologists and surgeons must discuss the intraoperative findings and place them in clinical context. If the diagnosis of a positive node is in doubt, the decision on whether to perform a completion ALND should be based on clinical judgment, or deferred until final pathology is available.

Specific examination of nodes that had biopsy-confirmed metastases at the time of diagnosis is a logical addition to staging of the axilla after NAC. In the ACOSOG Z1071 trial, the FNR of SLN was 6.8% if the clipped node was retrieved as an SLN.^{1,12} In a study from our institution, the FNR of evaluating the clipped node alone was 4.2%, which dropped to 2% when TAD was performed.⁴ Recognizing the advantage of this, the current National Comprehensive Cancer Network (NCCN) guidelines recommend routine clipping of nodes with biopsy-confirmed disease, with removal at the time of surgery.¹³ A recent survey of members of the American Society of Breast surgeons revealed that 67% now place clips in nodes at the time of biopsy, and 71% of those localize them either with a wire (73%), seed (13%), or other technique (14%). In those who do not localize the clipped node, 82% perform an X-ray to confirm that the clipped node was removed for evaluation.¹⁴

The benefit of localizing the clipped node is that it is not always retrieved as an SLN. Thus, relying on SLN alone in these cases would miss evaluation of the node known to have cancer prior to NAC. Wu et al.⁶ report that this was the case in 67% of their patients. In the ACOSOG Z1071 trial, the clipped node was an SLN in 63% of cases, and was definitely not an SLN in 20% of cases.¹² In the remaining 20%, it is unknown whether the SLN specimens contained the clipped node or not. This was also seen in our data where the clipped node was not an SLN in 23% of cases.⁴ Similarly, a study from the University of Pittsburgh reported a rate of 27%.¹⁵

Several institutions have published on their experience with localizing clipped nodes.^{15–19} One group from Spain reports an FNR for evaluation of the clipped node alone of 4.1%, similar to our institution's observed FNR of 4.2%.^{4,18} A group from The Netherlands has reported an FNR of 7% for their marking the axillary lymph node with radioactive seed (MARI) procedure, where the seed is placed at the time of the original biopsy and left in place

through NAC.¹⁷ Less data are currently available regarding the FNR of TAD, which adds the assessment of SLNs to the clipped node. Diego et al. reported no false negative results in 11 patients.¹⁵ We anticipate that the group from the Mayo Clinic, which has reported the technical results of their first experiences with the technique, will report their outcomes in the future,¹⁹ as will the Dutch group, which is currently conducting a prospective trial.²⁰ The authors in this paper report an FNR of 10.8%, which is higher than our initial experience with this technique.⁴ While the authors do not elaborate on this group, we have identified factors that contribute to increased FNRs that could have been in play.¹⁵ First, similar to ACOSOG Z1071, SENTINA, and SN FNAC, we also found that the use of the dual tracer technique impacts accuracy.^{1–3} In data presented at the Society of Surgical Oncology (SSO) annual meeting,²¹ use of the single tracer technique resulted in an FNR of 5.6% (95% confidence interval [CI] 0.7–13), compared with 1.1% (95% CI 0.03–6) with dual tracers. The second factor that might contribute is the number of abnormal nodes seen on initial imaging. In the same SSO presentation, we reported that the FNR was 1.1% (95% CI 0.03–5.9) if less than four abnormal nodes were seen on the first ultrasound, compared with 5.7% (95% CI 0.7–19.2) if four or more nodes were seen. As this practice increases, more reports should be available describing other institutions' experience with TAD, which will allow us to assess the technique in a variety of settings.

Adding intraoperative evaluation of nodes retrieved in TAD has the potential to benefit patients if it is reliable, which this article supports. Omission of ALND if no residual metastasis is seen is somewhat controversial since data reporting oncologic outcomes when completion ALND is not performed are not currently available. However, 85% of respondents in the American Society of Breast Surgeons' survey said they offer SLND to at least some of their patients, suggesting that many surgeons are beginning to change their practice.¹⁴ The ability to assess nodal response intraoperatively will help in this transition as, in the current guidelines, patients with a positive node after chemotherapy require axillary clearance. The Alliance A011202 trial, which randomizes clinically node-positive patients who have a positive SLN after chemotherapy to ALND with nodal radiation versus nodal radiation alone, is currently in accrual and may affect this paradigm in the future.

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