Commentary

Can a seed-sized tool from Texas spare clinically node positive breast cancer patients from a complete axillary dissection?

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Axillary lymph node status guides both treatment course and prognosis in patients with breast cancer. When patients receiving neoadjuvant chemotherapy (NAC) are excluded, NCCN guidelines call for a sentinel node (SN) biopsy in clinically node negative stage I and II patients, followed by complete axillary lymph node dissection (ALND) only if there is a SN metastasis and the patient does not meet eligibility criteria for the ACOSOG Z0011 trial (1). In the remainder, ALND can be omitted. Testing whether this concept can be extended to patients diagnosed pre-operatively as both node positive and scheduled to receive NAC has been the subject of multiple investigations; their impetus being the desire to reduce ALND and its attendant morbidity (2-6). Avoiding ALND in patients identified as node positive pre-operatively by needle biopsy requires evidence that a negative SN biopsy after NAC is an adequate proxy for the status of the axilla; i.e., the false negative rate (FNR) is low. The FNR for SN biopsy in patients undergoing surgery as their first cancer treatment has consistently been shown to be less than 5–10%. Whether this low FNR can be replicated in the post-NAC setting was recently reported by investigators from the MD Anderson Cancer Center in the *Journal of Clinical Oncology* (April 2016) (7). Building on prior trials that measured both the SN identification rate and the FNR after NAC (2-6), a novel approach termed targeted axillary dissection (TAD) was developed to compare its efficacy to accurately stage the axilla compared to SN biopsy alone. TAD presupposes that the patient's SN status after NAC potentially differs from the status of the node found to be positive pre-NAC; thus if both are removed, the FNR may be improved. With TAD, the node found to be positive preoperatively is marked with a clip during the time of needle biopsy, then later removed after NAC using a radioactive seed localization technique. TAD combines a standard two dye SN biopsy technique with removal of the clipped node found to be positive on pre-NAC needle biopsy.

In the MD Anderson report, Caudle and colleagues prospectively audited patients with Stage I–III breast cancer with needle biopsy-proven nodal disease on initial evaluation who were later found to be clinically node negative following NAC (7). FNR was calculated across several categories. Of 208 enrolled patients, 85 underwent TAD, with an FNR of 2.0%. SN biopsy alone in this group resulted in a FNR of 10.6% (P=0.13). A total of 191 patients underwent ALND with retrieval of the clipped node, whether as part of TAD or otherwise. The FNR of the clipped node in this group was 4.2%. Finally, 118 patients underwent ALND, SN biopsy, and evaluation of the clipped node, though not necessarily as part of a formal TAD. In this subset of patients, SN biopsy alone resulted in an FNR of 10.1%, while SN biopsy and evaluation of the clipped node produced an FNR of 1.4% (P=0.03). Addressing one of the authors' stated objectives, they found that the clipped node was not the SN in 23% of cases. The authors concluded that routine use of TAD may reliably spare appropriate patients from ALND, lessening their risk of lymphedema. In summary, the investigators found (I) TAD is technically feasible; (II) removal of the pre-operative clipped positive node by itself has a FNR <5%; (III) TAD has a lower FNR than SN or clipped node removal alone; (IV) the node found to be positive pre-operatively is not necessarily the SN; (V) identification and removal of clipped nodes is not a technically "perfect" procedure; even

in experienced hands, a clipped node could not be found in 5 of 96 patients.

Although Caudle *et al*. are the first to report TAD, several previous studies examined the use of SN biopsy in women who converted from clinically node positive to node negative disease during NAC (2-6). The SENTINA trial [2013] found an overall FNR of 14.2% (5). In the trial, FNR was associated with the number of SN identified and dye technique. With dual tracer and >2 nodes removed, the FNR was <10%. Based on their findings, the authors concluded that sparing a patient an ALND based on the post-NAC SN biopsy should be restricted to patients undergoing a dual dye technique and excision of >2 SN. The ACOSOG Z1071 trial investigators also reported an overall high FNR of 12.6% (2-4). However, when dual mapping agents were used and >2 SNs and the clipped node were removed, the FNR was less than 10%. For 107 (75.9%) patients in whom the clipped node was within the SLN specimen, the FNR was 6.8%. In another study, the FNAC group [2014] added routine use of immunohistochemistry (IHC) of the SN to the recipe, reporting an FNR of 8.4% (6). Given the results from all these trials, NCCN Guidelines currently state that SN biopsy is an option for patients who convert from clinically node positive to node negative after NAC, but they also note that the FNR is greater than 10%.

Since the authors' FNR after TAD is so low, surgeons ought to ask themselves whether implementing TAD into their practice tomorrow makes sense. To inform this decision, a few details of the study should be noted.

First, the study surgeons are practicing in a high volume institution with years of successful experience with radioactive seed localization techniques. Secondly, these surgeons are afforded the opportunity to work with breast specialty imagers, also highly experienced in targeting techniques. Outside of this framework, TAD may not be immediately generalizable to all practice types.

Additionally, there are still some unanswered questions regarding TAD as well as the topic of post-NAC SN biopsy.

Are the authors comfortable with other institutions adopting TAD "off protocol"?

What is the role of IHC of SNs after NAC? Routine use could reduce the FNR at the expense of increasing the ALND rate. Clinically, what is the best approach? Some trials used IHC (SN FNAC), some did not (ACOSOG Z1071 and SENTINA) and at MD Anderson, it was optional (per pathologist).

What is the difference in local regional recurrence with TAD compared to full axillary dissection? The answer to this question will require long term follow-up and a large sample size because contemporary recurrence rates are very low, mostly less than 1% per year and in some studies as low as 0.5% per year (8).

Do the authors include a statement in their informed consent discussion with the patient about the unknown risk of local recurrence with TAD compared to ALND?

What if there are two or more nodes confirmed positive on initial needle biopsy? Should all be clipped and excised post NAC?

For institutions without resources for seed localization, can wire localization works as well as seeds?

Given the nuclear medicine regulatory requirements too burdensome to be met by some institutions, can newer localization methods, such as electromagnetic wave technology (9) be substituted for seeds, with equal success to TAD?

What if there are fewer than two nodes removed with TAD? Would the FNR still be low or would it be >10%, as identified in ACOSOG 1071?

What if the clipped (seed localized) node or the SN cannot be found? Should the default plan be to perform an ALND in all these patients?

What if the patient does not tolerate the full course of planned NAC, but still has converted to a clinically node negative status? Can TAD still be offered?

Can we extend the ACOSOG Z0011 eligibility criteria to NAC patients who undergo TAD, to further reduce the number of patients subjected to ALND? Is it ethical to do this outside of a randomized controlled trial?

We applaud the MD Anderson team for their innovative development of this novel technique, high success rate and the clear description of their findings. This is yet another major contribution from these authors and this center. This study is in alignment with many others during the last century that result in a surgical conceptual drift, moving from more to less radical techniques, limiting the patient's burden of post-operative morbidity. For those centers electing to adopt this technique, we recommend they audit their FNR. We recommend their FNR targets be at least <10% and hopefully, will be found to be <5%. Until further corroborating studies are published, surgeons considering use of TAD should ensure that their patients fully understand the benefits, risks, and some uncertainties of this approach. Based on the strength of this study, we recommend other institutions consider implementation of TAD into their practice. If they do so, we urge them to

maintain a database to study their outcomes.

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Footnote

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