Editorial Commentary

Axillary surgical staging after neoadjuvant chemotherapy: does technical accuracy matter?

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Comment on: Pantiora E, Eriksson S, Wärnberg F, *et al*. Magnetically guided surgery after primary systemic therapy for breast cancer: implications for enhanced axillary mapping. Br J Surg 2024;111:znae008.

Keywords: Sentinel lymph node biopsy (SLNB); targeted axillary dissection (TAD); neoadjuvant chemotherapy (NACT)

Submitted May 21, 2024. Accepted for publication Jul 17, 2024. Published online Aug 21, 2024.
doi: 10.21037/gs-24-183
View this article at: https://dx.doi.org/10.21037/gs-24-183

Optimal surgical staging, and subsequent surgical management of the axilla in patients with breast cancer, have been topics of controversy for the last 20-plus years. The general trend has been towards de-escalating axillary surgery [i.e., replacing axillary lymph node dissection (ALND) with sentinel lymph node biopsy (SLNB)] whenever possible due to the significant morbidities associated with ALND. This has been made increasingly possible by the widespread use of neoadjuvant chemotherapy (NACT). In patients with initially node-negative (cN0) disease who receive NACT, like upfront surgery patients, SLNB has largely replaced ALND. However, the story is less straight forward for patients initially presenting with node-positive disease (cN+, defined as cN1–3), specifically those who convert to node-negative after NACT (ycN0). NACT can lead to a nodal pathologic complete response (pCR, ypN0) in >40% of cN+ patients, with the highest responses seen in patients with HER2-positive and triple-negative disease; however, among those with residual nodal disease after NACT the accuracy of SLNB is a topic of major debate (1,2).

In a prospective institutional cohort study of 113 ycN0 patients (33 of which were initially cN1) undergoing SLNB or targeted axillary dissection (TAD) after NACT, Pantiora *et al.* investigated the utility of superparamagnetic iron nanoparticles (SPIO) as a tracer for mapping to axillary sentinel lymph nodes (SLNs) (3). Patients received radioisotope on the day of surgery, and SPIO injections at a median of 3 (range, 0–248) days before surgery, with 18.6% receiving SPIO before the start of NACT. Authors found that SPIO performed comparably to radioisotope, and that timing of SPIO administration had no significant effect on concordance with radioisotope. This is interesting for a few reasons. First, the ability to administer a tracer prior to the day of surgery is beneficial from an operational logistics standpoint, e.g., fewer procedures to coordinate on or immediately before the day of surgery. Additionally, as a proportion of patients in this study received SPIO prior to NACT, this suggests that SPIO may allow for more accurate axillary staging (i.e., mapping the axilla before chemotherapy-induced fibrosis and remodeling) (4). However, these conclusions must be interpreted cautiously, as they were based on a very small sample size, only 18.6% (n=21) of all patients in this study received SPIO before the start of NACT and only 29% (n=33) were cN1 at presentation.

Pantiora *et al.* also found that SPIO detected more SLNs

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than radioisotope (median of 3 versus 2 SLNs respectively, P<0.001), and that in ypN+ patients, SPIO identified more metastatic SLNs than radioisotope; however, this too was based on a very small sample size (n=19) (3). Furthermore, in the 33 patients who presented with cN+ disease, converted to ycN0, and underwent TAD, the specifically targeted lymph node (LN) was SPIO-positive in 94% of patients versus radioisotope positive in 67% (P<0.001), again suggesting that SPIO may be more accurate in mapping the axilla before NACT (3).

It is important to note that while all these findings are interesting and certainly hypothesis-generating, authors provide very little detail around the patient population, including outcomes by tumor subtype. Also notably lacking are details about the methods of assessing presenting axillary LN status and nodal response to NACT, i.e., whether the patients were considered cN+ based on physical exam alone, or by axillary imaging with or without percutaneous LN biopsy proving nodal metastases. This lack of granularity makes the findings difficult to apply broadly, but still this study highlights an important debate when it comes to the use of SLNB in cN+ patients after NACT: how important is the technical accuracy of axillary surgical staging? Is nodal clipping and localization necessary?

Several prospective trials have investigated the accuracy of SLNB in patients who present with cN+ disease but who convert to cN0 after receiving NACT, including NSABP B-27 (5), GANEA 1 (6), ACOSOG Z1071 (7), SENTINA (8), and SN FNAC (9). These studies reported variable SLN identification rates ranging from 80% to 93% and false negative rates (FNRs) from 8.6% to 15% (5-9). Because a threshold of 10% was chosen as the maximal acceptable FNR (albeit somewhat arbitrarily, presumably based on cooperative group clinical trialist input, patient advocate input, and data from patients undergoing upfront surgery in the NSABP B-32 trial) (10), these SLNB accuracy trials were effectively "negative" as the majority exceeded the pre-specified 10% target. This sparked a body of literature focusing on the technical aspects of SLNB to increase its accuracy, including dual-tracer mapping, identification of ≥3 SLNs, routine use of immunohistochemistry (IHC), and placing a clip in the biopsied node (7-9,11,12). In the SN FNAC trial, the only trial that actually met the 10% threshold at 9.6% overall, IHC was used routinely in addition to standard hematoxylin and eosin staining (9). Although the overall FNR in ACOSOG Z1071 was 12.2%, when analyses were restricted to patients with ≥3 SLNs identified, FNR was 9.1% (7). Subsequent subgroup analyses of ACOSOG Z1071 revealed that using dual tracers reduced the FNR of the SLNB to 6.2% (11). These findings were similarly shown in SENTINA, where overall FNR was 14.2%, but when 3 SLNs were identified, FNR dropped to 7.3%, and when dual tracer was used FNR was 8.6% (8). Furthermore, in a subset of ACOSOG Z1071 patients who had a clip placed in the pre-NACT biopsy-proven metastatic LN, removal of the clipped node during SLNB reduced the FNR to 6.8% (12). This is how TAD—a SLNB with dual tracer in addition to specific pre-operative localization of the clipped, biopsy-proven metastatic LN—was born.

In a single-institution study of 118 patients with biopsy-proven and clipped cN1 disease who received NACT, FNR of SLNB alone was 10.1%; however, retrospective review of adding evaluation of the clipped node reduced the FNR to 1.4% (13). In the same study, when TAD was performed prospectively (using radioactive seed localization), FNR was 2%. Around the same time that TAD came into use, a similar procedure to identify the biopsy-proven metastatic LN was developed: marking the axilla with radioactive iodine seeds (MARI) alone (14). Instead of a clip, the MARI procedure involved placing a radioactive iodine seed at the time of initial pre-treatment LN biopsy. Then, at the time of surgery, this biopsy-proven malignant and radioactive lymph node (the MARI node) was resected. In a single-institution study of 95 cN+ patients who underwent the MARI procedure followed by ALND; removal of the MARI node was associated with a 7% FNR (15).

This body of work was followed by a surge of descriptive single-institution series focusing on localization of clipped nodes after NACT, just a few of which are described here. A retrospective review of 91 patients with biopsy-proven and clipped metastatic LNs who underwent NACT found that pre-operative wire-localization led to successful removal of the clipped node in 97% of patients, which was significantly higher than when no wire was used (83.3%, P=0.04) (16). Another trial found that pre-operative localization of the clipped metastatic LN could successfully be accomplished using magnetic seeds, as opposed to wires. In this prospective trial of 50 patients with cN+ disease undergoing TAD after NACT, the clip and magnetic seed were retrieved from the same LN in 98% of patients (17). Finally, a pilot study of a radar reflector, SAVI SCOUT® (South Jordan, Utah, USA), found that placement of the reflector in the clipped node pre-NACT was a feasible method to localize the node after treatment (18). Although axillary surgery was performed >4 months after SAVI

placement, the reflector was successfully retrieved in all 25 patients. This line of work focusing on optimal methods to identify metastatic nodes after NACT persists today, as evidenced by the current referenced study by Pantiora *et al.*

Investigators have certainly proved that a SLNB can be accurate for patients with cN1 disease who convert to ycN0 after NACT, and a TAD even more so. But does this matter? Several studies have been published with considerable variability in approach to SLNB and criteria for omission of ALND. Collectively they found that the incidence of axillary nodal recurrence was very low among patients who were initially cN+ but converted to ycN0 after NACT and experienced an axillary pCR as evidenced by SLNB alone (19-22). For example, Barrio *et al.* included a standardized approach with all patients receiving dual-tracer mapping and retrieval of ≥3 negative SLNs (19). At a median follow-up of 40 months, there was only one axillary recurrence and it was synchronous with local recurrence in a patient who refused post-operative radiation. Kahler-Ribeiro-Fontana *et al.* used a single tracer (99 technetium labeled radiocolloid) and had no requirements for number of SLNs retrieved (20); in fact, about 75% of the patients included in their series had less than three LNs retrieved, and 50% had just one LN retrieved. With 10 years of follow-up, axillary recurrence among initially cN+ patients that converted to ycN0 was <2% (20). Compelling data from the recently published study by Montagna *et al.* showed that SLNB alone was comparable to TAD alone for every oncologic outcome, including axillary recurrence at median 3.5 years follow-up (21). In this study of 1,144 patients with cN+ disease who underwent NACT and achieved nodal pCR, the 3-year axillary recurrence rate of the entire cohort was 0.65%, with no significant difference between SLNB and TAD groups. There were also no significant differences in 3-year rates of locoregional recurrences or invasive recurrences between SLNB and TAD (21). Similar to the study by Barrio *et al.*, all 666 patients who had SLNB alone had a standardized approach with dual-tracer mapping and an average retrieval of four SLNs (19,21). Finally, in 2023, the experts at St Gallen came down against nodal clipping—noting that nodal recurrence rates are low among patients who are cN1 at presentation, convert to ycN0 after NACT, and are then pathologically node-negative with at least three sentinel nodes retrieved, without nodal clipping (23).

Taken together, these studies suggest that increasing the technical accuracy of SLNBs (e.g., FNR) does not translate into improved oncologic outcomes in these patients. Perhaps there are other reasons to subject patients to additional, potentially unnecessary, procedures?

Currently, the presence of residual disease in the breast or LNs after NACT is used to guide adjuvant systemic. For example, the KATHERINE trial demonstrated that for patients with HER2-positive breast cancer with residual invasive disease after NACT, adjuvant trastuzumab emtansine (T-DM1) is superior to trastuzumab alone (24). Similarly, but for patients with HER2-negative breast cancer and residual invasive disease after NACT, the Create-X trial established the benefit of adding adjuvant capecitabine to standard therapy (25). There are ongoing escalation trials like these, such as CompassHER2 RD (NCT04457596) which is randomizing patients with residual HER2+ disease to T-DM1 +/– tucatinib. There are also de-escalation trials, like OptimICE-pCR (NCT05812807) which is randomizing triple-negative breast cancer patients who experience a pCR after chemo-immunotherapy to finishing out their year of pembrolizumab versus observation alone. Common amongst all these trials is a dependence on surgical pathology, and thus surgical intervention and perhaps accuracy. At first glance, the detection of residual nodal disease is important to select the appropriate post-NACT adjuvant systemic therapy. However, it is a rare event that a patient has residual nodal disease without disease in the breast. For example, patients who present with cN0 HER2-positive or triple negative disease and experience a breast pCR after NACT have a 0–4% chance of pathologic nodal disease (26,27). In other words, it would be very unlikely that a patient's LNs would have disease when their breast does not, and less likely still that small differences in SLNB technique and FNR would lead to a different treatment decision, and subsequently any worse oncologic outcomes. So, again, these technical factors may not matter.

The last horizon where technical factors and the FNR of SLNB may matter is making radiation therapy decisions, now that NSABP B51/RTOG 1304 has resulted (28). This phase III trial showed that among 1,602 patients with a nodal pCR, with or without breast pCR, randomized to +/– adjuvant regional nodal irradiation (RNI), omission of RNI led to equivalent oncologic outcomes. At a median follow-up of 5 years, there was no significant difference in invasive recurrence-free interval nor local recurrence-free interval between groups (28). Similarly, there was no difference in distant recurrence-free interval, disease-free survival, or overall survival. Therefore, in patients with initially cN+ disease who convert to ypN0 after NACT, RNI can be safely omitted without adversely affecting oncologic outcomes. In this one scenario, accuracy of SLNB may matter. If nodal

disease is missed, and if RNI is not administered based on a falsely presumed nodal pCR, we might potentially see an increase in axillary recurrences—but this is unlikely in our opinion. Nodal clipping and specific localization of the clipped node among patients with cN+ converted to ycN0 disease may represent unnecessary healthcare dollar expenditures and a burden to patients, but it will likely persist. As such, future studies expanding on the findings from Pantiora *et al.* may be warranted; however, so too are more outcomes studies in which nodal clipping is abandoned.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-183/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-183/coif). K.G. received honoraria for a lecture on 2023 San Antonio Updates for radiation oncology at an Empire State Hematology Oncology Society Meeting and serves as the co-chair for the Survivorship Committee of National Consortium of Breast Centers (unpaid position). A.W. reports Sponsored Research Agreement with Institution from Myriad Laboratories, Inc.; consulting fees from Merck and Myriad Laboratories, Inc.; Honoraria from Society of Breast Imaging, MJH Lifesciences, and Breast Cancer Foundation New Zealand; Food and beverage from Endomag; and he is the advisory board member at Merck and Myriad Laboratories, Inc. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Marin C, Gergelis K, Weiss A. Axillary surgical staging after neoadjuvant chemotherapy: does technical accuracy matter? Gland Surg 2024;13(8):1353-1357. doi: 10.21037/gs-24-183