Editorial Commentary

Navigating axillary staging post-neoadjuvant systemic therapy: innovations, efficacy, and oncologic safety

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Targeted axillary dissection (TAD), comprising marked lymph node biopsy (MLNB) and sentinel lymph node biopsy (SLNB), is increasingly recognised for its effectiveness in reducing false negative rate (FNR) in node positive early breast cancer patients receiving neoadjuvant systemic therapy (NST) (1). The MLNB refers to the retrieval of the biopsy-proven lymph node that has been tagged with a marker.

In a pooled analysis of 13 studies spanning 521 patients, we previously reported that TAD was associated with an FNR of 5.2% compared to axillary lymph node dissection (ALND). This FNR falls well below the accepted threshold of 10% for the safe omission of ALND (1).

Recent advances in systemic therapy have increased pathological complete response (pCR) rates, underscoring the imperative need for precise axillary staging post-NST (2). In addition to providing important prognostic information, precise determination of pCR is critical particularly in patients with high-risk HER2-positive or triple negative breast cancer (TNBC) in whom the finding of residual disease would guide recommendations related to adjuvant systemic therapy (3). Furthermore, the axillary status post-NST in initially node positive patients plays a critical role in tailoring regional nodal irradiation (RNI) (4).

The biopsy-proven target lymph node was traditionally marked using various inactive markers made of stainless steel, titanium, polyglycolic acid, carbon particles or black ink tattooing deployed during ultrasound-guided needle biopsy (1). While tattooed nodes can be directly visualized during surgery, other inactive markers require a separate localisation procedure before surgery, and identifying them accurately with ultrasonography can be challenging when pathological nodes normalize in response to NST (1). Moreover, limitations such as potential pigment migration and the need for wider surgical dissection exist with the technique of carbon or black ink tattooing (1). These challenges have spurred the development of wire-free technologies, including radioactive iodine (^{125}I) seeds, magnetic seeds (Magseed®), electromagnetic reflectors (Savi Scout), and radio-frequency identification (RFID) tags (LOCalizer) (1,5). All four methods allow for the preoperative localisation using active markers thus reducing the need for scheduling coordination, and enable single stage marking and localisation at the time of biopsy. The single stage approach is more precise and cost-effective compared to the two-stage localisation method (1,5).

Radioactive iodine seed localisation (RSL), also known as the Marking the Axilla with Radioactive Iodine seeds (MARI) procedure has demonstrated an excellent clinical performance in TAD in a multi-centre prospective trial

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with an FNR of 2.5% (6). However, the complex radiation safety regulations required present a significant limitation to its widespread adoption. Furthermore, the time limitation for implantation of the radioactive iodine seeds in certain jurisdictions represent a significant disadvantage.

The efficacy of magnetic seeds in TAD has been explored in several small studies, showing them to be reliable and safe (7). In our recent pooled analysis of 9 studies involving 497 Magseed procedures, we reported a 94.2% successful localisation rate, a 98.8% retrieval rate, and a 68.8% concordance rate between MLNB and SLNB. pCR was observed in 47.9% with an FNR of 4.2% for MLNB and 17.6% for SLNB (P=0.0013) (7). However, there is a tendency for the magnetic seeds to be found outside the targeted lymph node into neighboring axillary soft tissue when inserted post-completion of NST compared to deployment at diagnosis before initiating NST. One primary concern with magnetic seeds is the creation of large MRI artefacts (4–5 cm), potentially impacting the interpretation of surveillance imaging to evaluate the response to NST. Additionally, all metallic instruments must be removed from the surgical field during dissection and the Sentimag requires frequent recalibration (7).

The excellent efficacy of the Savi Scout system in TAD was recently demonstrated in a pooled analysis spanning 252 procedures (8). The authors reported a 99.6% successful localisation rate and 100% retrieval rate. The average interval from reflector placement to surgical retrieval was 52 days (range, 1–202 days) and pCR was observed in 42% of cases, with no significant migration or complications reported. The concordance rate between the MLNB and SLNB was found to be 81% (95% CI: 76–86%). Omitting MLNB or SLNB would have under-staged the axilla in 9.7% or 3.4% (P=0.03) of cases, respectively.

The notably higher FNR of the SLNB in comparison with the MLNB highlighted in the mentioned pooled analyses (7,8) underscores the need to incorporate the MLNB in axillary staging post-NST in patients undergoing NST for node-positive breast cancer. This is aligned with the current National Comprehensive Cancer Network (NCCN) guidelines (7).

Savi Scout, unlike RSL, is radiation-free and lacks significant MRI void signals, making it preferable to Magseed in the context of TAD.

At present, there's currently limited data on the performance of RFID tags in TAD, with only 40 procedures reported, showing a 2.5% failed localisation rate (9). However, the wide bore of the introducer needle, the glass casing of the radio-frequency tag, which could lead to migration and fracture, along with MRI artefacts (about 2 cm), likely pose inherent limitations that hinder optimal performance as a single-stage procedure in TAD (10).

As emerging technologies validate accurate identification of axillary pCR post-NST, the pivotal question arises: is TAD without ALND oncologically safe for those achieving axillary pCR?

Throughout the world, practices in axillary staging post-NST for clinically node positive disease vary, influenced by tumour biology (11). There is a growing body of evidence that supports safe de-escalation of axillary treatment in excellent responders to NST. The SenTa study compared TAD alone *vs.* TAD with ALND, suggesting similar recurrence rates (12). However, its observational design and limited follow-up are limitations. TAD demonstrates low FNR and locoregional failure rates, but its suitability for extensive pre-NST axillary disease is uncertain. Wu *et al.* reported on TAD outcomes, showing no significant difference in nodal recurrence rates between TAD alone and ALND (13).

The latest 5-year data from the NSABP B-51 trial confirms the oncological safety of reducing axillary treatment for pCR patients (4). According to the findings of the NRG Oncology/NSABP B-51/RTOG 1304 study, it appears safe to omit RNI for patients transitioning from cN1 to ypN0 status via SLNB post-NST, providing additional support for the de-escalation of radiation therapy thus reducing arm morbidity and improving quality of life without compromising oncological outcomes.

Further evidence regarding the oncological safety of TAD and SLNB following NST was provided by a recent multicenter retrospective cohort study involving 1,144 patients with consecutive stage II to III biopsy-proven node-positive breast cancer (14). The 5-year rates of any axillary, locoregional, and any invasive recurrence in the entire cohort were 1.0%, 2.7%, and 10% respectively.

Future research should focus on identifying the most effective localisation approach by conducting head-to-head comparisons between emerging novel wire-free and tattoo free technologies and the accuracy of TAD in patients with significant initial lymph node involvement (≥3 clinically suspicious lymph nodes) or residual axillary disease after NST.

Determining the best axillary treatment in patients with positive axillary staging after NST is currently the focus of clinical trials. The ALLIANCE-A011202 Phase III Trial (15) evaluates the effectiveness of radiation to the

undissected axilla and regional lymph nodes versus ALND plus radiation to regional lymph nodes (excluding the dissected axilla) on the recurrence-free interval of invasive breast cancer in patients with positive SLNB after NST.

Other current clinical trials, such as AXSANA (NCT04373655) and MINIMAX (NCT04486495), are enrolling all patients irrespective of their axillary response following NST (16,17). The MARI trial involves patients with clinically involved axillary lymph nodes (cALN) less than 4 who receive adjuvant axillary radiotherapy and those with cALN 4 or more who undergo ALND. The reported 3-year axillary recurrence-free survival rate was 98.2%, with all axillary relapses occurring in patients with fewer than 4 cALNs, leading to a 3-year axillary recurrence rate of 3.4% (18).

Embracing a risk-adapted tailored treatment optimisation is poised to become the cornerstone of future advancements in breast cancer management.

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