Editorial Commentary

Two step procedures: sequels are never any good

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Several reports have been published since the initial use of targeted axillary dissection (TAD) after neoadjuvant systemic therapy (NST) in node positive breast cancer with different markers, identification rates (IRs) and false negative results (1-5). The use of TAD has shown to be a safe and accurate procedure for nodal staging reducing the rates of axillary lymph node dissection (ALND), and consequently the morbidity of the procedure while preserving oncologic outcomes, mainly in patients with an axillary pathologic complete response (3,6). The procedure is now widely used, although still very heterogeneous in the method and with technical challenges in the identification of the marked node.

In their comprehensive review, de Wild and colleagues examine the various techniques of TAD in node-positive breast cancer patients who have undergone NST (7). The authors provide valuable insights into the various markers and timing of placement used in TAD procedures, outlining the IRs and feasibility associated with different techniques. A systematic review of 51 studies, encompassing a total of 4,512 patients, reveals the considerable heterogeneity in TAD procedures. It also emphasizes that there is no single methodology that is demonstrably superior to another. These studies differ in the type of marker used [wire, ^{125}I-labelled seed, ^{99m}Tc, (electro)magnetic/radiofrequency marker, black ink or US-visible clip], the necessity for a second preoperative marking of the targeted lymph node (TLN) (two-step procedure) and the strategy chosen for surgical removal of the TLN. Nevertheless, the present study corroborates the efficacy of the TAD procedure, demonstrating an overall pooled IR of the TLN at the time of surgery to be 96–97%. The occasional mismatch between sentinel lymph node (SLN) and TLN may explain why TAD is able to decrease the false negative rate (FNR) below 13%, rate found in earlier trials exploring the accuracy of sentinel LN biopsy (SLNB) alone in node-positive breast cancer patients following NST (8).

The majority of the studies reported with the TAD procedure, particularly those at the outset, were based on the preoperative marking of the node by a wire or other marker (magnetic or radioactive seed, black ink, radar marker, etc.) of the node initially clipped with a marker before NST. The success of resecting the TLN was contingent upon the visibility of the clip inserted prior to NST. However, it should be noted that half of the studies included in the review (18 out of 41) excluded patients from the analysis in whom the TLN could not be located preoperatively by imaging. The range of TLN image identification values was found to be between 49% and 100%. This discrepancy is probably due to the use of different types of clips, some of them that cannot be found by ultrasound after NST. Exclusion of patients in whom the TLN was not visualized preoperatively may have contributed to the overestimation of the final IR of

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the TLN in cases where a second preoperative marking was required (two-step procedure). To enhance the IR of the TLN through imaging, the use of markers with a low risk of displacement and excellent long-term ultrasound visibility could be of value. The hydrophilic polymer gel-coated clip appears to be an optimal choice in this regard (9). Conversely, if a second marking is not necessary (one-step procedure), then, the number of procedures are reduced, improving patient's pathway.

It is shown that the IR of TLN at the time of surgery varies considerably, with rates ranging from 62% to 100% and 71% to 100%, depending on whether the one-step or two-step procedure is considered. This variation is likely due to the learning curve associated with the novel surgical technique, which often requires the collaboration of multiple specialists (surgeons, radiologists, nuclear medicine specialists). Nevertheless, there is still a paucity of well-designed prospective studies to assess whether both models (one-step *vs.* two-step) are comparable.

We agree with the authors that the use of wire localization is inexpensive and probably easier to radiologists/surgeons due to the experience in localization guided technique in the breast surgery. The wire has been shown to be uncomfortable to the patients and is clearly a second stage procedure. It also carries several weaknesses, including logistical difficulties due to the need of placement on the day of surgery and the potential for displacement (10). The introduction of intraoperative ultrasound (IOUS) and probe-guided technologies in breast guided surgery (11,12) have paved the way to its use for the TAD procedures. The replacement of wire localization by any of these techniques is needed as it will ease the breast cancer patient pathway through all the process of NST and surgery. IOUS has been shown benefits in breast conservative guided surgery compared to the use of wire localization. IOUS guided TAD is a one-stage procedure where an ultrasound visible clip is placed before NST, and the IOUS used to excised the clipped node. It has shown an IR of 96% and FNR of 7.0%, which decreased to 4.9% when a total of ≥3 or more nodes were removed (1,13).

Similar to the results from the systematic review by de Wild (7), with two-step TAD, the study by Munck *et al.* (14) shows that although re-marking of the clip is possible in approximately 80% of the patients, 1/10 of patients still have surgical non-detection of the twice marked lymph node, making these techniques the least appropriate for the procedure. Not detecting the marked node implies an indication for an ALND that will increase patient's morbidity. However, it is possible that in some patients the marker may continue to be absent on the ALND specimen. Failure to salvage the clip does not necessarily indicate that the initially metastatic node was not resected; it may be that the clip was extruded during the surgical procedure. There is a paucity of data to confirm the impact on the axillary relapse rate in this situation (15).

Is there a need for TAD procedures after NST or is it enough with SLN to stage the axilla? Reported studies from different institutions have shown that SLNB technique could be equivalent to TAD following specific requirements (16,17). By using a dual tracer and removing at least 3 nodes, one could assume that the TLN would be highly likely to be among the SLNs, and if not, it seems that not removing the TLN would not increase the risk of developing axillary recurrence. The first study describing the TAD technique did not find any predictors of concordance between SLN and TLN, including the initial number of suspicious nodes, the number of SLNs resected, the SLN localization technique, or the presence of residual disease (5). Previous studies of SLN after NST have shown that retrieval of three or more SNs occurred only in 34–56% of patients (18,19), so ensuring that at least 3 nodes are resected may involve an undesirable random sampling of nodes.

There have been controversies regarding how many positive nodes may be marked. In the majority of studies, a single node is marked, similar to the first publication on TAD (2,5). Other authors propose marking all suspicious nodes, which would reduce the FNR and make it possible to avoid SLN biopsy. However, this approach would increase the cost, the risk of leaving a marked node unresected and the risk of resecting a larger number of nodes, thus increasing morbidity on the arm (20). The idea that there is a heterogeneous response of nodes to NST, which could result in a higher risk of false negatives, has not been proven to be true or at least, have not been shown to increase rates of FN.

An attempt has been made to assess the role of positron emission tomography/computed tomography (PET/CT) in defining the extent of lymph node disease initially, in assessing the response to NST and evaluating the need of a completion ALND depending on response (21). Combining PET/CT before NST and the MARI (marking axillary lymph nodes with radioactive iodine seeds) procedure after NST has the potential for avoiding unnecessary ALND (22). A low 3-year axillary relapse rate (1.8%) is achieved by applying an ALND de-escalation strategy based on the initial axillary disease burden as determined by PET/CT

(≤4 *vs.* ≥4 nodes). ALND was only performed in case of ≥4 suspicious nodes by initial PET/CT and residual disease in TLN. This strategy resulted in the avoidance of ALND in 80% of initially node-positive patients. However, of the five recorded axillary relapses, all had <4 nodes initially by PET/CT and persistent disease in the TLN. In all cases, ALND was omitted in favour of axillary radiotherapy. The use of PET/CT in this setting has not gained further adepts, mainly due to its expense in the majority of countries.

Those patients who may potentially benefit from the TAD procedure are those who experience a good response in the axilla. Data from retrospective studies appear to indicate that the omission of ALND in cases of axillary pathologic complete response provides good disease control, with axillary relapse rates as low as 0.4–2.3% (23,24). Ongoing trials as the AXSANA (NCT04373655), an international prospective cohort study that evaluates data on axillary staging after neoadjuvant chemotherapy comparing different techniques may contribute to defining the optimal axillary staging procedure to achieve oncological safety and improved quality of life. In those patients with residual disease in the SLN, Moo *et al.* demonstrated that the presence of micrometastases or macrometastases in the SLN is associated with a higher probability of finding positive non-sentinel nodes in the axilla. This probability was found to be 64% and 62%, respectively (25) and irrespective of biological subtype. Other ongoing trials such as Alliance A011202, and ADARNAT (NCT01901094 and NCT04889924, respectively) will provide further evidence on the most appropriate management of patients with persistent axillary disease (ypN+) based on long-term outcomes of different treatment strategies.

In terms of quality of life, rates of lymphedema after TAD procedures remain to be elucidated. The biggest fear of axillary surgery is the development of arm lymphedema. We know that the extent of axillary surgery is directly proportional to the risk of developing lymphedema. The 5-year risk of lymphedema after SLN biopsy is estimated to be 5%, whereas after ALND ranges from 15–31%, depending on whether ALND is followed by radiation therapy to the lymph nodes (6). The ultimate goal of TAD is to reduce damage to the axillary lymphatic drainage as opposed to ALND.

The TAD procedure represents a novel surgical technique that necessitates the use of additional resources. The specific nature of these resources will depend on the technique employed, with instances requiring, in-house markers, consoles for the detection of this marker, and ultrasound devices. This presents a significant challenge for low- and middle-income countries potentially depriving women in these countries of important surgical de-escalation strategies such as TAD. To address this, an easy, reproducible, low-cost technique that relies on the fewest number of procedures and practitioners required should be offered, and IOUS may be one option.

TAD technique should be chosen taking into account the resources, the breast surgeon experience, but mainly the one that preserves and eases breast cancer patient's pathway. Data is still lacking in assessing which TAD procedure is better in terms of their benefits in streamlining pathways from radiology to NST to surgery, rather than only focusing on IRs in which they are unlikely to advance more in the current practice

To improve patient experience and operating room workflow, a one-step procedure would be preferable. Depending on the material resources and safety regulations of each institution, there will be a greater or lesser number of options to choose from. As we continue to navigate the evolving landscape of breast cancer management, it is imperative that we remain attuned to the ongoing advances and evidence-based insights that will shape the future of TAD, positive axilla management and its impact on patient quality of life.

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