Mans. Med. J. *Vol. 51. Issue 4*, 2022, Pages 246-257

Mansoura Medical Journal

(Official Journal of Mansoura Faculty of Medicine)

pISSN: 1110-211X; **eISSN:** 2735-3990

Targeted Axillary Dissection In Breast Cancer Patients After Neoadjuvant Therapy

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DOI: 10.21608/mjmu.2022.129215.1088

Submit Date: 23 March 2022
Accept Date: 17 October 2022
Available online: 01 Dec. 2022

Keywords

- Breast cancer,
- sentinel lymph node
- targeted axillary dissection
- neo-adjuvant chemotherapy

Abstract

In the last 20 years, axillary surgery for breast cancer has changed dramatically. In clinically node-positive patients, ALND is the conventional procedure. With the development of efficient neo-adjuvant chemotherapy (NACT), there is a shift toward less aggressive operation in patients who have clinical signs of excellent response and disease shrinkage. Therefore, SLN biopsy (SLNB), which offers an accurate, less morbid staging procedure that prevents complications of ALND has become the standard technique in node negative early breast cancer. In these patients, However, there has been a reluctance to perform (SLNB) after completion of NACT in patients with histologically proven axillary metastases because of false-negative rates (FNRs) greater than 10%. To deal with this problem, a new and promising technique called targeted axillary dissection (TAD) has been developed for determining axillary status in post-neoadjuvant chemotherapy (NACT) node-positive breast cancer patients. It includes removal of the SLN as well as the pathologically proven positive nodes which have to be marked before starting the NACT. TAD can be considered a practical, reproducible, and valid method for ruling out metastatic axillary involvement in patients with breast cancer who have had a favourable response to NACT

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Introduction

Over the previous couple of decades, there has been a trend towards decrease of surgical management of the axilla. Despite this, axillary lymph node dissection (ALND) is commonly performed in patients with clinically node-positive (cN+) illness to guide loco-regional and systemic therapy decisions. In nodal metastases, According to studies, a pathological complete response (PCR) in the axilla is possible in up to 40% of clinically node-positive patients who undergo neoadjuvant treatment [1,2]. Furthermore, the axillary PCR rate in the human epidermal growth factor receptor 2+ (HER 2+) illness subgroup can reach 74% [3].

Several studies have addressed the viability of doing SLNB in individuals who had positive axillary nodes but had an outstanding response to NACT and had good accuracy [4-6].

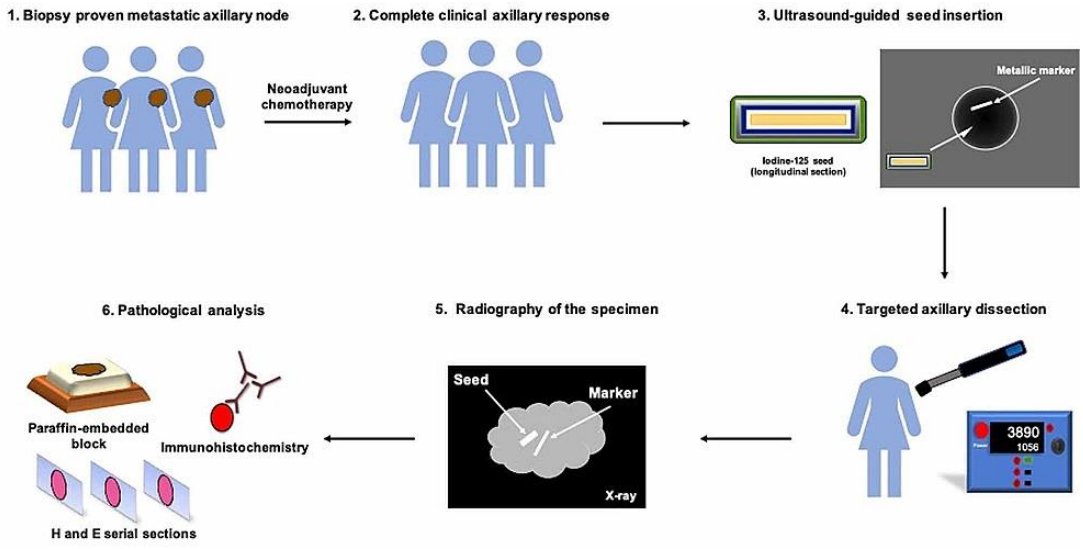
As a result, it may no longer be necessary to commit all node-positive patients to ALND in order to appropriately stage the axilla. In addition, ALND is linked to higher rates of morbidity, lymphedema, paresthesia, sensory loss in the arm, and shoulder function impairment [7].

Previous research has shown that SLND has difficulties in properly identifying patients with residual lymph node disease after chemotherapy [8-12]. The false-negative rate (FNR) of SLND post-chemotherapy was 13% in the ACOSOG Z1071 trial in patients with stage T0-4, N1-2 M0 breast cancer [8].In the SENTINA research, high FNRs were also discovered, limiting the use of standard SLND in individuals who were changed to clinically node-negative condition after chemotherapy [9].

In these trials, the utilization of a dual-tracer method (each blue dye and a radioisotope) resulted in higher rates of sentinel lymph node identification [12]. Lower FNRs were accomplished when at least two nodes have been retrieved [9-11]. And when a metal marker was used to retrieve the biopsy-proven positive node, the FNR decreased. [8,11]. However, there has been a reluctance to perform (SLNB) after neoadjuvant therapy in patients with histologically proven axillary metastases due to higher false negative rates (FNRs) of more than 10%, also when dual localization techniques and more than two sentinel nodes are resected [8].

A unique technique to deal with this problem has now been developed by Several units in the United States and Europe which established the concept of "targeted excision" of suspicious axillary lymph nodes. Patients who are scheduled to get neoadjuvant therapy undergo axillary staging using ultrasonic imaging during this procedure (Figure 1) [13].

TAD is a viable option that, in comparison to SLNB after NACT in clinically node-positive patients, may be a more accurate method to stage the axilla. Additionally, compared to ALND, a more limited axilla technique is associated with reduced morbidity and a lower likelihood of arm lymphedema [14].



(Figure 1) Steps of TAD [25].

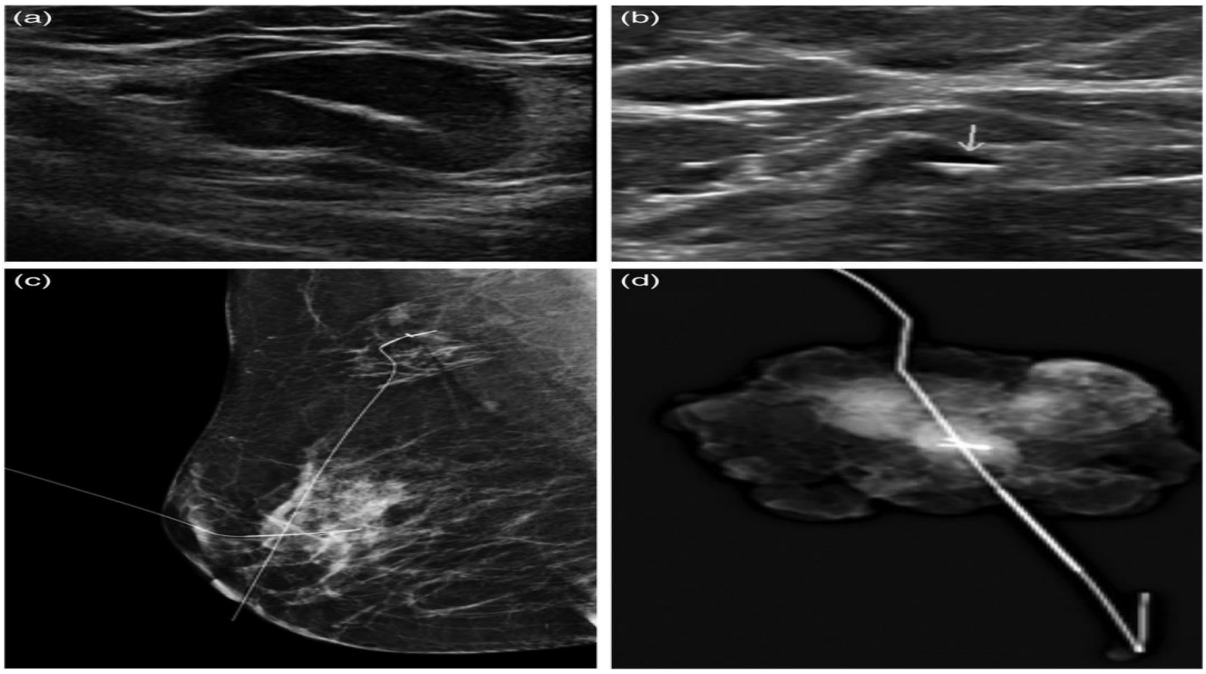
Technique of TAD

Targeted Axillary Dissection (TAD) is a novel surgical approach that combines sentinel lymph node dissection (SLND) with selective localization and excision of clipped nodes to reduce (FNR) when compared to SLND [15-17]. Patients had ultrasound-guided FNA after abnormal axillary lymph nodes were identified. When immediate cytological evaluation revealed metastasis, a clip marker was put within the cortex of the sampled node under ultrasound guidance [15-17].

Before surgery the clipped node was re-identified using grayscale ultrasound. Targeting the clipped node with a standard radioactive I125 titanium seed or a hook wire was confirmed on post-procedural mammograms. The I125 seed has a half-life of sixty days and was implanted five days before the scheduled surgery [17].

Prior to or during surgery, mapping agents such as radioisotope (technetium-99m sulphur colloid) and/or blue dye were injected. During surgery, a gamma probe on the iodine-125 setting was used to identify the seed-containing node, and a technetium-99m probe on the iodine-125 setting was used to identify the SLNs. All nodes with blue dye, radioactivity, or palpability were excised and identified as SLNs. Intra-operative x-ray proven that the resected node contained the clip and seed. In individuals who had wire localization, the

lymph node was excised separately and x-rayed to check it contained the clip (Figure 2) [17].



(Figure 2) TAD: (a) placed a clip into the biopsy node that was positive. (b) Follow-up ultrasonography after NACT, revealing satisfactory response to systemic treatment and the presence of a marker clip (white arrow) within the lymph node. (c) Lesion of the breast and clipped axillary node after post-localization mammography. (d) An intraoperative radiograph of a clipped node excision specimen. [18].

Evolution of the technique & previous trials

In 2016, TAD was established by surgeons at The University of Texas MD Anderson Cancer Center to further minimize the FNR of SLND and enhance the accuracy of axillary staging and a disease assessment in clinically node-positive breast cancer and avoid the necessity for more aggressive treatment with associated consequences [17].

A study published in January 2016 found that Radioactive Seed Localization (RSL)/SLNB is a useful method for staging the axilla after NACT in patients whose condition becomes clinically node-negative (cN0). The state of the biopsy-proven positive lymph node (BxLN) after NACT expected nodal status, implying that localization of the BxLN may be more reliable than SLNB alone for axillary staging in the cN0 patient after NACT [19].

Boughey and colleagues' study published in April 2016 found that clipping a node at the time of diagnosis of node-positive disease and then removing the clipped node during SLN surgery reduces the FNR of SLN surgery following NACT [11].

A Korean study published in August 2017 found that cytology-confirmed metastatic ALN can be tattooed with charcoal upon presentation and that it has no effect on SLNB following NACT. The tattooing process is useful for enhancing SLNB diagnostic performance in this setting because it does not require any further preoperative localization [16].

In January 2018, a retrospective study in Czechia showed that targeted axillary dissection (TAD) may be indicated if axillary lymphadenopathy regresses during neoadjuvant treatment. It is likely that this procedure carries a lower risk of false negativity than the sentinel biopsy alone [20].

In January 2019, a study in Greece found that axillary lymph node tattooing is a viable, effective,

and low-cost strategy of marking positive lymph nodes in individuals with cN+ prior to NACT. Surgeons can easily identify tattooed lymph nodes during surgery, therefore no other invasive techniques or costly instruments are required (Figure 3) [21].

In June 2019 a study in the Netherlands demonstrated that a greater rate of identifying and improving the detection of residual axillary disease was achieved by removal of pretreatment positively marked LN with SLNs in patients with clinical node-positive diseases following the neoadjuvant systemic treatment [22].

According to the first Australian study on the viability of TAD, published in December 2019, the total identification rate of the clipped node was 78%, with a 100% identification rate if the clipped node was localised pre - operatively, and a substantially lower than 68% identification rate in individuals who did not have the clipped node localized [18].

In February 2020, a Spanish study showed that the placement of iodine-125 seeds is a feasible technique for intra-operative localization of the positive biopsied lymph node in conjunction with SLNB in NACT-treated patients with breast cancer, The histopathological result of the combined procedure of SLNB and lymph node marked with an iodine-125 seed can determine axillary lymph node status post-NACT [23].

Another Korean study published in October 2020 proposed the concept of targeted axillary node biopsy combined with preoperative US-guided tattooing for the most accurate axillary staging in early breast cancer patients [24].

In April 2021, a new study found that TAD is effective in 97 percent of patients and that ALND can be prevented in 50 percent of patients [25].

Another study in Spain published in July 2021 found that 71.7 percent of patients had a full clinical lymph node response to NACT, with no constraints or complications in clipping procedure. And confirmed our previous finding that TAD is viable and accurate for ruling out axillary metastatic involvement in patients with cN1 breast cancer who respond to NACT [26].

Several studies have examined the use of TAD and came to similar conclusions, but they did not prepare to evaluate the FNR because no axilla dissection was performed [27-28]. Identification rates, FNR, and negative predictive values were compared across all trials in a meta-analysis of Twenty studies investigating the diagnostic accuracy of various surgical methods for staging of axilla after NACT in breast cancer patients with biopsy-proven node-positive. The authors found that completing each SLNB and removing the pre-treatment indicated positive node provided the most accurate axillary staging after neoadjuvant therapy [1].

Figure 3) Tattooed/SLN Identification During Surgery [21].

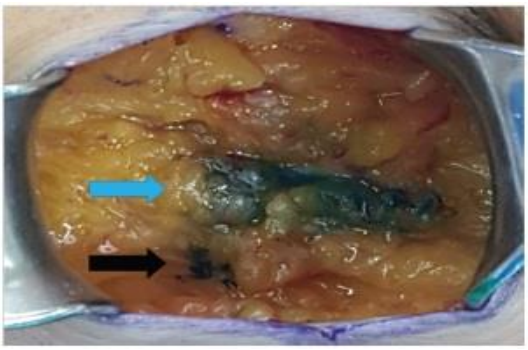
Identification and Clipping of metastatic LNs

Positive lymph nodes are identified under local anesthetic before NACT. Under US direction, a marker clip (UltraClip II Tissue Marker) was implanted in biopsy-proven metastatic axillary nodes [17]. Furthermore, Wire localization of pre-NACT clipped nodes was highly useful than SLN in accurately identifying lymph nodes [29].

Several approaches using various materials have been published in previous research to identify positive nodes before NACT [30-32]. Besides the clip and guidewire, Activated charcoal [16,31], radioactive seeds [30,33,34], and carbon microparticles [32] were utilised to identify clipped nodes for post-NACT surgery.

Choy et al. showed that tattooing clipped nodes with high-purity carbon ink just at time of node biopsy resulted in 100% eradication at the time of SLNB after NACT in a group of Twelve patients [35].

In a group of 20 patients, Park et al. tattooed the metastatic node with charcoal just at time of diagnosis and biopsy. After NACT, SLNB was conducted with dual tracers, and the tattooed node was found in 100% of the patients (Figure 4) [16].



(Figure 4) Charcoal tattoo (black arrow) and blue dye (blue arrow) tracks during surgery [16].

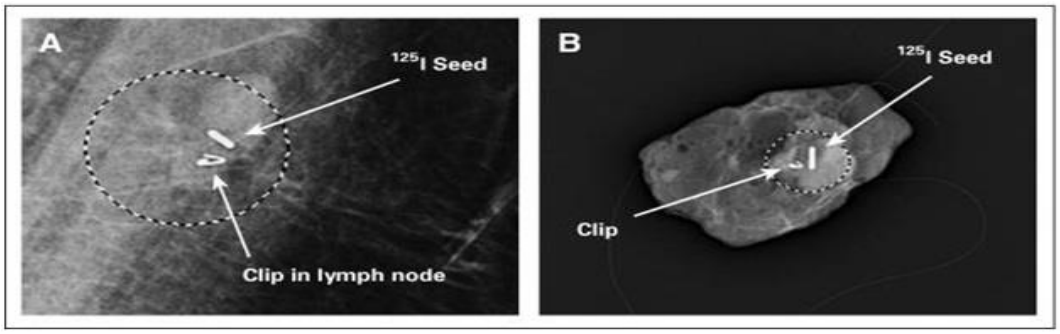
Localization Methods for Clipped Nodes

First attempts were undertaken with the traditional hook wire to locate the clipped node following the NACT(Figure5) [18,27-29,36]. However, this approach still exists today, but it has several drawbacks: the requirement to insert it within the axilla on the same day as surgery, probable displacement, or relocation following placement, patient irritation and vascular damage during installation. The attention has therefore turned to the use of different localisation methods [27,28].One of the most widely utilised localization techniques is radioactive seed localization (RSL). It's well-known for identifying non-palpable breast lesions and It can be used as both a method of identifying the clipped node [19,22,33,34] and as the clip itself (MARI procedure) [15,37,38] . The benefits of using a radioactive seed for localization include that the seed is usually put one to five days before surgery, is extra satisfied for the patient, and uses the same equipment as SLNB (Figure 6) [19].

Some centres have used non-radioactive methods of localisation because of the regulatory problems surrounding the use of RSL. During axillary surgery, the ILINA method uses intraoperative ultrasonography to locate the clipped node. While this method has a 97.1 % accuracy rate and a 4.1 % FNR, it does necessitate the surgeon's expertise

in the use of axillary ultrasound [39]. Ultrasonography is also used in the "SMART" procedure to record the radiologist's placement of the clipped node on the skin on operation day, as well as the surgeon's insertion of a needle to guide the excision of a 1-cm region in the axilla [40].

(Figure 5) Wire-localisation of the clipped node on intra-operative radiography [27].



(Figure 6) The excision of clipped axillary lymph nodes was localised using iodine-125 seeding. TAD includes not only removing all sentinel nodes, but also locating and removing clipped nodes selectively. (A) A breast radiologist places an iodine-125 seed within the clipped node under ultrasound guidance one to five days prior to surgery. The clip and the seed are seen within the node on a mammogram taken after seed insertion. (B) A specimen radiograph is taken after the localised node has been removed to check that the clip and seed have been resected [33].

Future methods of Clipped Node Localization

Device implantation during core needle biopsy is a new approach. During SLNB after NACT, In 19 patients, Taback et al. was using a non-radioactive infrared-activated fiducial reflector (SAVI ScoutTM) to locate the clipped node; the clipped node was collected in 100% of cases, comparing to 47.3 percent in a control group [41].

Greenwood et al. have reported a 97 % effective retrieval rate in 35 patients utilising a magnetised stainless steel seed (MagseedTM) [42]. While these approaches bypass RSL restrictions and reduce the number of operations required by the patient, they do necessitate specialised instruments and are associated with greater institutional expenses.

Drawbacks

In many regions, there are concerns about the processing and disposal of radioactive particles associated with the usage of iodine-125 seeds, TAD may be difficult to achieve. The traditional wire used for non-palpable breast cancer localisation is such possible widely available alternative [29]. Of course, this would necessitate inserting the wire on the day of the procedure, restricting the flexibility of using iodine-125 seeds. This dilemma may be addressed in the future by the development of alternative radioisotope-independent new procedures [43].

Patients with persistent axillary involvement after NACT are heterogeneous; those with oestrogen receptor/progesterone receptor-negative disease will not receive additional systemic therapy,

whereas those with (HER 2+) tumours, as well as those with oestrogen receptor positive cancer, will receive additional systemic therapy. In addition, the node clipping procedure's outcomes must be quantified [13].

Nobody knows for sure what clip is best for LN localization, which nodes are clippable and which aren't (for example, the size of the metastasis, the number of involved nodes, and the location of the node), or what percentage of clips loosen following NACT. TAD is an uncomplicated treatment that requires more research in certain patient subgroups after NACT to ensure that it is performed in the proper individuals with minimal axillary morbidity and no adverse effects on cancer-related outcomes [13].

Conclusion

To summarise, Targeted Axillary Dissection can be considered a practical, reproducible, and valid approach for excluding metastatic axillary involvement in patients of breast cancer who responded well to NACT in a select group of node-positive patients. It avoids the drawbacks of ALND as well as the deficiencies in SLNB in this category of patients.

Acknowledgment

The authors would like to thank the MMPME for funding this work and the valuable assistance throughout its conduct.

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