Evaluation of targeted axillary dissection following neoadjuvant therapy for a patient with node-positive breast cancer as initial experience in Ain Shams University Hospitals

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Received: 01 March 2022
Revised: 15 March 2022
Accepted: 20 March 2022
Published: 04 January 2023

The Egyptian Journal of Surgery 2023, 41:626–633

Introduction
Surgical treatment of the axilla in breast cancer shows a lot of advances over the past decade. Patients with clinically positive lymph node (LN) have a great chance to turn by neoadjuvant chemotherapy (NACT) to be negative clinically and radiologically, and so surgical management in those patients is still a field of research. Sentinel lymph node biopsy (SLNB) in such patients showed a high false-negative rate (FNR), which was decreased by the use of immunohistochemistry and if a clip was placed in the node with biopsy-confirmed metastases, with removal of that node with the SLNB which is called targeted axillary dissection (TAD).
Objectives
To determine the accuracy of TAD, ensuring that surgical removal of clipped nodes would improve accuracy of nodal staging in patients with initial positive LN.
Patients and methods
A prospective study including 30 patients with $cT_{1\_3(a\text{-}c)}$ $cN_{1\text{-}2,}$ M_0 breast cancer post-NACT, who had shown downstaging of their nodal status (N0) as proven by clinical examination and ultrasound assessment, who were recommended for TAD removing the clipped LN added to the SLNB at Ain Shams University Hospital, between March 2020 and March 2021.
Results
Out of the 29 patients, two patients showed residual disease in the clipped LN in a frozen section; one of them revealed positive SLN as well. Completion of axillary lymph node (ALN) dissection was done regardless of the frozen section results to detect any residual nodal disease, which revealed negative results in all cases and that indicate the success of TAD in removing the diseased LN and decreasing the FNR of SLN alone. Twenty-four patients with clipped ALNs were stained with patent blue dye while five patients with clipped ALNs were not stained by patent blue dye. Therefore, SLN was unable to detect clipped ALNs, which were previously positive in five patients, so there is a FNR of 17.2% if SLNB was done alone. So, with targeted procedure we can decrease the FNR of sentinel study and accurately assess the neoadjuvant effect on diseased LNs.
Conclusion
TAD is a feasible technique for axillary management in patients with clinically N1 breast cancer, who receive NACT and turned to N0. Preoperative clipped node guide wire localization significantly improves the identification rate of the clipped node and decreases the FNR of SLNB alone.

Keywords:
axillary dissection, breast cancer, sentinel lymph node, targeted axillary dissection

Egyptian J Surgery 2023, 41:626–633

1110-1121

Introduction

Breast cancer is the most commonly diagnosed malignancy and the second most common cause of cancer-related death in women worldwide [1]. Accurate staging and proper management of axillary lymph nodes (ALNs) are crucial for the treatment of breast cancer. Surgical management of the axilla in breast cancer has evolved greatly in the last 20 years. Sentinel lymph node biopsy (SLNB), which was first investigated in the early 1990s, has replaced axillary lymph node dissection (ALND) with its associated greater morbidity in early-stage node-negative patients. SLNB offers accurate assessment of nodal status and staging information [2].

In patients with early-stage clinically node-negative breast cancer, SLNB, as compared with ALND, has

achieved equivalent locoregional recurrence, disease-free survival, and overall survival results, without the added morbidity of ALND [3].

However, the role of SLNB management of the axilla in patients treated with neoadjuvant chemotherapy (NACT) is a matter of controversy. Although data on SLNB and NACT are accumulating, the value of SLNB in relation to long-term outcomes remains to be seen [2].

The presence of nodal metastases in breast cancer is an important prognostic factor that is used to guide locoregional and systemic treatment decision. Patients presenting with nodal metastases often receive NACT, which can eradicate nodal disease in 40–75% of patients [4].

Axillary lymphadenectomy (ALND) has been the standard surgical approach in clinically node-positive patients; however, this is associated with significant morbidity [5] with unclear benefit in those who achieve a nodal pathologic complete response with systemic therapy. Several trials have recently evaluated the use of sentinel lymph-node dissection (SLND) to stage the axilla after NACT) in patients initially presenting with node-positive disease [6,7].

One of this trial was the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, which enrolled patients with documented nodal metastases, who completed NCT followed by SLND and ALND to determine the false-negative rate (FNR) of SLND. Although the reported FNR of 12.6% exceeded the prespecified threshold of 10%, subgroup analysis showed a lower FNR if immunohistochemistry (IHC) was performed and if a clip was placed in the node with biopsy-confirmed metastases, with removal of that node as an SLN [5,8].

Intuitively, specific evaluation of the LN proven to contain metastases at the time of diagnosis should improve the accuracy of nodal assessment after chemotherapy and is a logical addition to surgical staging.

Targeted axillary dissection (TAD) involves removing SLNs as well as removing the clipped LN by localization with a guide wire under ultrasound guidance. The ability to selectively remove clipped nodes in addition to SLNs has a significant clinical potential to improve the assessment for residual nodal disease after chemotherapy [9].

The aim of this study is to determine the accuracy of targeted axillary resection and ensuring surgical removal of clipped nodes would improve accuracy of nodal staging in those patients.

Patients and methods

This is a prospective study that was conducted on patients who underwent TAD after NACT at Al Demerdash Hospital, Faculty of Medicine, Ain Shams University, between March 2020 and March 2021.

We included 30 patients with $cT_{1\_3(a\text{-}c)}$ $cN_{1\text{-}2,}$ M_0 breast cancer post-NACT who had shown downstaging of their nodal status (N0) as proven by clinical examination and ultrasonographical assessment who were recommended for TAD after discussion by the multidisciplinary team.

This research was performed at the Department of General Surgery, Ain Shams University Hospitals. Ethical Committee approval and written, informed consent were obtained from all participants.

We excluded patients diagnosed with breast cancer with pregnancy, inflammatory breast cancer, and metastatic breast cancer. Any patient enrolled in the study and showed poor response to NAC as regards nodal status was excluded as well during the study.

Patients who presented to the Breast Surgery Unit or Medical Oncology Department at Ain Shams University Hospitals were properly examined. Proper history was taken from the patient in the form of present history, menstrual history, family history of previous breast diseases, history of any chronic diseases, and previous breast surgeries. Proper general and local examination was done; those presenting with suspicious masses, proceeded to further imaging procedures (mammography, ultrasonography, and MRI).

If a suspicious mass was found (BIRADS 4–5); an ultrasound-guided biopsy was taken for histopathological examination. Patients with a histopathological diagnosis of breast cancer underwent further metastatic workup according to the stage of presentation (computed tomography chest and abdomen in locally advanced cases), and IHC study of the tumor in the form of estrogen receptors, progesterone receptors, Her2 neu receptors, and proliferation index Ki67.

All the included cases were discussed at the multidisciplinary meeting with the attendance of a breast oncologist, breast surgeon, radiologist, and a pathologist on a weekly meeting for proper consultation about the management of patients.

Patients who were categorized as having clinically and pathologically positive LN were recommended to receive NACT (−/+) anti-Her2-targeted therapy whenever possible according to the molecular classification of breast cancer. NACT was then followed by surgery whether BCS or mastectomy plus TAD according to the clinical assessment post-NACT.

Technique

(1) All patients in our study performed Tru-cut ultrasound guided from the suspicious LN seen by us and underwent clip localization of this suspicious ALN depending on the radiological criteria of malignancy (if were multiple, we clipped the largest one).
(2) Clip localization was done for the breast mass, or else seeking conservative breast surgery according to chemotherapy response.
(3) Follow-up of the patient response for chemotherapy was done by clinical and radiological assessment.
(4) Cases with good response and candidate for TAD were counseled by the surgeon to explain the operative procedure and expected complications.

Operative details

Briefly, a guide wire was placed in the previously clipped node under ultrasound guidance at the day of surgery. The patent blue dye was injected subareolar before the start of surgery by 20 min.

During surgery

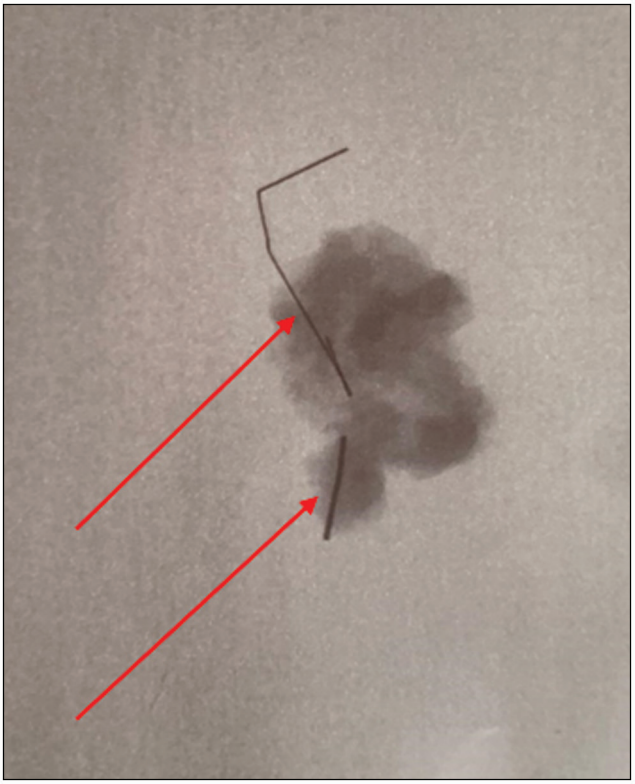
(1) Excision of the clipped LN guided by the wire was done (Fig. 1).
(2) Excision of the LNs stained by blue dye was done.

The two specimens were sent to frozen section. In spite of whether the frozen section is negative or positive, all the included patients will undergo level I and level II axillary clearance in the same setting to assess the accuracy of TAD.

Then results of the clipped, SLNB, and the ALND were compared to detect false-negative results of the SLN in postneodjuvent setting.

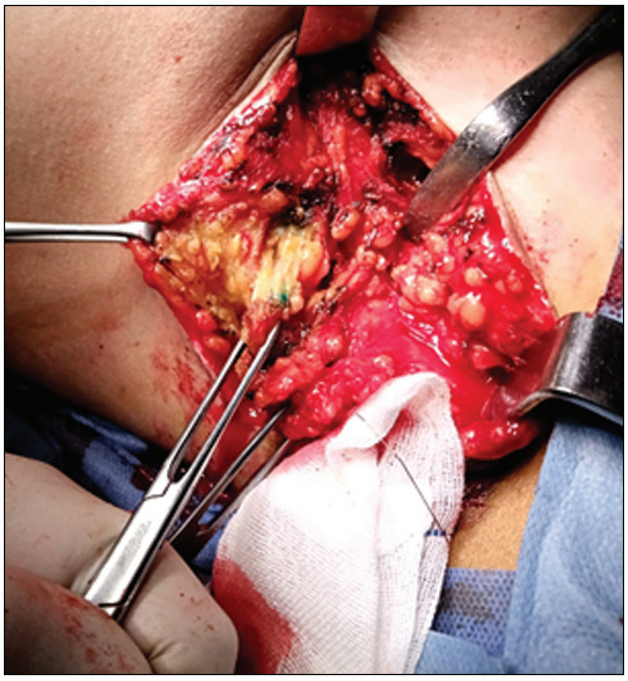
Detection of the clip inside the excised lymph node guided with the wire was done using intraoperative radiograph by the C-arm (Fig. 2).

Figure 1



Targeted axillary dissection was done guided with the wire to find the clipped axillary lymph node, which was previously positive and uptake the patent blue dye as well. LN, lymph node.

Figure 2



Arrows show: (a) guide wire and (b) clip inside the lymph node.

Results

The mean age of the included cases in our study was 43.3 ± 10.8 ranging from 27.0 to 66.0 years. Analysis of comorbidities of the included cases reveled that only two patients were hypertensive. Hypothyroidism was found in two (6.7%) cases, and only one (3.3%) patient was complaining of chronic liver disease (Table 1).

Table 1 Demographics and clinicopathological data

Characteristics	Mean±SD	Range
Age (years)	43.3± 10.8	27.0–66.0
	n (%)	
Comorbidity		
Hypertension	2 (6.7)	
Hypothyroidism	2 (6.7)	
Osteoarthritis	1 (3.3)	
Chronic liver disease	1 (3.3)	
Risk factors		
Family history	4 (13.3)	
Oral contraceptive pills	10 (33.3)	
Clinical assessment		
Side		
Right	17 (56.6)	
Left	13 (43.3)	
Number of lesions		
Single	11 (36.7)	
Multiple	19 (63.3)	
Axial LN		
Palpable	25 (73.3)	
Not palpable	5 (26.7)	
TNM classification		
T		
T1	4 (13.3)	
T2	10 (33.3)	
T3	16 (53.4)	
N		
N1	25 (83.3)	
N2	5 (16.7)	
M		
M0	30 (100.0)	
Histopathology		
Invasive ductal	25 (83.3)	
Invasive lobular	5 (16.7)	
Molecular classification	*n* (%)	
Luminal B	14 (46.7)	
Luminal A	13 (43.3)	
Triple negative	2 (6.7)	
HER2 neu over expression	1 (3.3)	
Type of surgery		
Modified radical mastectomy	19 (65.6)	
Breast conservative surgery	10 (34.4)	

LN, lymph node.

As regards the history of risk factors among the studied cases, only four cases out of the included cases had a positive family history of breast cancer and about 10 cases were on regular combined oral contraceptive pills.

Most of the included cases were presented with right breast cancer, which represents about 56.6% and the left side breast cancer represents about 43.3%.

Multicentric and multifocal breast cancer was seen in most of the included cases; about 19 patients were presented with multiple breast masses and only 11 patients were diagnosed with a single breast mass; however, all the cases were unilateral.

Table 2 Chemotherapy regimens among the studied cases

Findings	*n* (%)
3AC+12 weeks taxol	22 (73.3)
TCH	1 (3.33)
FEC+Taxotere 3	7 (23.3)

All were examined clinically for ALN and 25 patients were clinically positive for palpable LN. Other five patients were diagnosed by ultrasound to have radiologically suspicious LN. All had undergone LN biopsy under sonographic guidance and proved to be positive for metastatic cells.

Clinical and radiological staging of our cases showed that the majority of the cases were T3 and T2 representing 53.4 and 33.3%, respectively, as regards the tumor size. All the included cases were clinically and radiologically positive LN with about 83.3% being N1 and 16.7% being N2 (Table 1).

Tru-cut biopsy of the included cases revealed that invasive ductal carcinoma was much more common and represents 83.3% while invasive lobular carcinoma was 16.7%.

The molecular classification among the studied cases showed that 14 out of 30 patients were luminal B breast cancer, 13 out of 30 patients were luminal A breast cancer, two patients were triple negative breast cancer, and only one patient was HER2 neu overexpression.

All the cases were candidates for neoadjuvant therapy according to the nodal status and tumor size. Chemotherapy regimens vary among the studied cases, 22 patients received three cycles of adriamycin and cyclophosphamide plus 12 weeks taxol, and seven patients received three cycles of fluorouracil, epirubicin, cyclophosphamide plus three cycles taxotere. Only one case received taxotere carboplatin and three cycles Herceptin as it was HER2 neu overexpression (Table 2).

Assessment of ALN response after NCT was done for all cases by high-resolution ultrasound; all patients showed radiologically negative LN except for one case which was excluded from the study as it showed signs of malignancy and poor response to chemotherapy and not candidate for TAD (Table 3).

TAD was done for all the patients removing the clipped LN, which was positive previously (pre-NACT) and the SLNs were dyed with patent blue dye. All the removed LNs (clipped and sentinel) were assessed by the intraoperative frozen section, two out of 29 cases of clipped LNs were positive in the frozen

Table 3 Postchemotherapy assessment of axillary nodes by ultrasound

Findings	*n* (%)
Abnormal finding	1 (3.3)
Normal	29 (96.7)

Table 4 Pathological assessment axillary lymph node findings among the studied cases

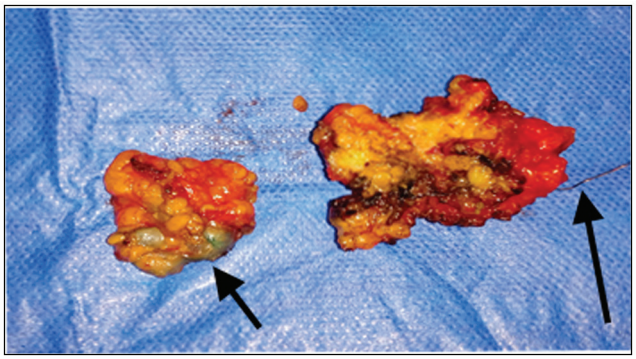
Groups	Findings	*n* (%)
Clipped	Positive	2 (6.9)
	Negative	27 (93.1)
Sentinel	Positive	1 (3.4)
	Negative	28 (96.6)
Axillary dissection	Positive	0
	Negative	29 (100.0)

Table 5 Differentiation characteristics of clipped technique in differentiating affected axillary lymph nodes

Characteristics	Value (%)	95% CI
Sensitivity	93.1	83.3–99.9
Specificity	100.0	88.1–100.0

CI, confidence interval.

Figure 3



Frozen specimen: the clipped axillary lymph node guided with the wire (not stained). Blue SLN which uptake the patent blue dye. SLN, sentinel lymph node.

section, and one of those two cases was positive in SLNs as well (Table 4).

Completion of ALN dissection was done regardless of the frozen section results to assess the sensitivity of the technique by the paraffin section that revealed negative results, which indicate the success of TAD in removing the diseased LN and decreasing the FNR of SLN alone (Table 4).

The clipped technique had high characteristics in differentiating affected ALNs: sensitivity (96.8%) and specificity (100.0%) (Table 5).

In all, 24 patients with clipped ALNs were stained with patent blue dye and five patients with clipped ALNs were not stained by patent blue dye (Fig. 3). Therefore, SLNB was unable to detect five clipped ALNs in five patients, so there is a FNR of 17.2%. Therefore, with the targeted procedure we can decrease the FNR of sentinel nodes (Table 6).

Table 6 Categorization of clipped lymph nodes in all the cases in our study

	n (%)
Clipped node	24 (stained) (82.7)
	5 (not stained) (17.3)

Discussion

Surgical treatment of the axilla has undergone an evolution. Since the 1800s, a complete axillary dissection was considered a staging technique and locoregional disease control. Positive LN required more aggressive systemic therapies and axillary/chest wall radiation to improve survival and reduce the risk of local recurrence. Around 10–40 LNs were typically removed en bloc with an increased risk of complications such as lymphedema, limited shoulder motion, and neuropathic pain [10].

In modern practice, the role and benefits of axillary dissection have been influenced by many trails.

The National Surgical Adjuvant Breast Project (NSABP) B-04 trial raised the question of the diagnostic and therapeutic values of the procedure in patients with no clinical evidence of metastasis to the axilla, which concluded that axillary dissection has no effect on the overall survival; however, it is an important prognostic and locoregional control tool. However, even after publication of the B-04 results, ALND remained the standard of care in axillary staging because it provided excellent regional disease control and prognostic information, and helped identify candidates for adjuvant chemotherapy and radiotherapy [11].

The AMAROS trial, presented at the Annual Meeting of American Society of Clinical Oncology, compared the use of axillary radiotherapy with axillary clearance in patients who had a positive sentinel node and found no significant difference in disease-free or overall survival, but reduced lymphedema rates in the radiation group [12].

Results from the Z0011 trial reported patients without clinical or radiological evidence of axillary metastases undergoing breast-conserving surgery having whole-breast radiotherapy, with positive sentinel nodes, did not achieve any further oncological benefit by having axillary clearance [13].

Most of all the trials that changed the concept of axillary dissection were conducted on clinically negative ALN and those trials result in considering the SLN as a standard of care for those patients.

However, patients with clinically positive LN is still a field of research with the advances in NACT; there is about 40–60% of those patients who turn out to be of negative LN clinically and radiologically. So there is a need to investigate that if we can omit cLNAD in those who turned out to be of negative axilla.

Although it is unlikely that performing extensive axillary surgery on patients without residual nodal disease confers oncologic benefit, identifying patients who may not require ALND has been problematic [8].

This is because we depend mainly on the radiological assessment with ultrasound and clinical assessment which is operator dependent and its accuracy cannot be assessed.

The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, which enrolled patients with documented nodal metastases who completed NCT reported an FNR of 12.6% on using SLNB in patients with ex-positive ALNs.

This was decreased by the use of IHC and if a clip was placed in the node with biopsy-confirmed metastases before NACT with removal of that node with the SLN (FNR 7–4%) [8].

In our study, we tried to assess the efficacy of TAD in the removal of the biopsy-confirmed metastatic LN combined with the SLNB and then we performed axillary dissection to level 1 and 2 LN to exclude any residual nodal disease.

The pathologic findings in the clipped node and SLNB were compared with the remaining axillary nodes to determine the FNR.

We found that 24 patients with clipped ALNs were stained with patent blue dye and five patients with clipped ALNs were not stained by the patent blue dye. Therefore, SLNB was unable to detect five clipped ALNs, which were previously positive LNs in five patients so that it is a FNR of about 17.2% if we use SLNB alone; however, this FNR is not a true false negative as only two from those five patients were positive for malignancy, which indicates poor response to NAC.

So, the importance of removing the clipped LN which was positive before NAC is to assess the response to NAC, which reflect the prognosis.

Less data are currently available regarding the FNR of TAD, which adds the assessment of SLNs to the clipped node. Diego and colleagues reported no false-negative results in 11 patients. That is comparable with our study as if we compare the pathological data of the clipped node and SLNB with the remaining ALN. We found that there is no residual nodal disease in the removed ALN; so in our study, the TAD procedure decreased the FNR of the sentinel study alone from 17.2 to 0%. This could have been caused by the limited number of the included cases in our study and the Diego *et al*. [14] study as both are considered pilot studies.

So a false-negative event in TAD can be defined as a case where the specified node (either the clipped node or the SLN) did not show metastasis; however, there is residual disease seen in other axillary nodes.

Data from the ACOSOG Z1071 trial also indicated that removal of the clipped node could lower the FNR for SLND. In that study, 170 patients had a clip placed in the LN containing metastases at the time of initial biopsy. Among the 107 patients for whom the clipped node was retrieved as an SLN, the FNR was 6.8% [8].

Caudle *et al*. [9] showed in their study that evaluation of the clipped node, marked at the time of initial needle biopsy, is associated with an FNR of 4.2%. In contrast, the FNR for SLND alone was 10.1%, while removing the clipped node in addition to removal of SLNs (TAD procedure) resulted in an FNR of 2.0%.

These data are in line with our findings that pathologic evaluation of the positive node before chemotherapy and marking it as useful. This is further reflected in the National Comprehensive Cancer Network guidelines, which recommend consideration of clip placement to ensure removal of the clipped node at the time of surgery [15].

The pitfall of TAD is the fact that the clipped node might not be identified as an SLN with traditional mapping techniques, as seen in five (17.3%) cases in our study population. The Z1071 trial had similar results, with the clipped node seen in the axillary contents (not the SLN) in 20% (34 of 170) of cases; however, unlike our data, the clip location was unknown in 17% (29 of 170) of cases [8].

Caudle and colleagues showed that among the 134 patients who underwent SLND, the clipped node was not identified as an SLN in 23% (31 of 134) of patients.

This arises the need to develop a technique to localize the clipped node as part of the TAD procedure.

In our study, we used a guide wire preoperatively to guide us to the clipped LN and a radiograph using the C-arm was done before sending the specimen to the frozen section that helps in identification of the clipped LN (clip identification rate was 100% in our study, but Kavitha Kanesalingam *et al*. IR was 68%) [16].

According to Kavitha Kanesalingam *et al*. [16] showed in four (14%) patients that the clipped node was not the sentinel node and identification rate. The median number of nodes removed was four (2–17). The clipped node was retrieved in 29 of 37 patients resulting in an overall IR of 78%. Eleven patients had the clipped node localized with a wire on the day of surgery and one patient had the clipped node localized with I-seed. The clipped node was successfully retrieved in all 12 patients who had preoperative localization (IR 100%). The clipped node was not localized in 25 patients, and it was in this group that the clipped node was not successfully retrieved in eight patients resulting in a reduced IR of 68%.

A similar technique for the localization of LNs has been reported from the Netherlands. The MARI (marking the ALN with radioactive seed) procedure involves placing the iodine-125 seed at the time of diagnostic biopsy. It is left in place throughout NACT. In their first 100 patients, the marked node was identified successfully in 97% of cases, with an FNR of 7%. They did not use SLND, a component that we believe is important in complete nodal evaluation. In addition, leaving the radioactive seed in place throughout chemotherapy is not in line with current US regulations [17].

Recent studies have introduced the tattooing of positive nodes with a sterile black carbon suspension at the time of biopsy. This technique has the advantage that no radioactive materials are used, which might be a promising and more applicable technique for some centers.

TAD technique, a procedure that involves SLND with removal of the clipped node identified positive metastatic disease pre NAC, is an evolving technique that may change the practice of ALN in clinically positive LN toward de-escalation of aggressive axillary dissection. Our study support the efficacy of TAD in accurate assessment of ALN post-NAC as the FNR for TAD was dropped to 0 versus 17.3% for SLND alone. Although limited sample size may affect the statistical analysis, this pilot study is promising for further multicentric long-term studies to be done exploring other methods of LN marking.

Conclusion

TAD is a feasible technique for axillary management in patients with clinically N1 breast cancer who receive NACT and turned to N0. Preoperative clipped node guide wire localization significantly improves the identification rate of the clipped node and decreases the FNR of SLNB alone.

Limitations

This study is considered as an initial experience of our institute detecting feasibility of applying such technique and the oncological safety of it; however, it was done at the era of COVID-19 which affects the number of cases included in the study. We need further multicenter studies with a larger sample size with the introduction of new techniques of localization which are less expensive and demanding.

Financial support and sponsorship

Nil.

Conflicts of interest

No conflict of interest.

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