

# Evaluation of targeted axillary dissection in node positive locally advanced breast cancer patients with complete pathological response to neoadjuvant chemotherapy

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## Background

This study aimed to evaluate targeted axillary dissection in node locally advanced breast cancer patients with complete pathological response to neoadjuvant chemotherapy.

## Patients and methods

This is a prospective cohort study including 25 females diagnosed with locally advanced breast cancer with proven lymph node involvement who had complete pathological response to the neoadjuvant chemotherapy regarding the clipped previously involved lymph node. Lymph node biopsy and frozen section of the clipped lymph node after wire localization and the sentinel lymph node after patent blue dye injection was done. This is followed by paraffin section examination of the lymph node biopsy and 6 months follow-up for the patients.

## Results

Twenty-four patients out of 25 patients had successful localization of the clipped and sentinel lymph node with no macrometastasis detected in frozen section. Twenty-two out of the 24 patients had no micrometastasis in paraffin section. Two of the 24 patients had micrometastasis on paraffin section and required axillary radiotherapy. One of the 25 patients failed localization of the clipped lymph node and received conventional axillary lymph node dissection. Two patients developed lymphedema, one of them after axillary radiotherapy, and the other one after axillary lymph node dissection.

## Conclusion

The combination of targeted axillary dissection and sentinel lymph node biopsy can replace axillary clearance in patients with node positive locally advanced breast cancer with complete pathological response to neoadjuvant chemotherapy.

## Keywords:

breast cancer, neoadjuvant chemotherapy, targeted axillary dissection

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## Introduction

Breast cancer is the most common malignancy in women worldwide with a rate of 2.26 million new cases and more than 684 thousand deaths in 2022 [1].

In Egypt, breast cancer is the most common malignancy in women. The incidence of recently diagnosed cases reached more than 22 thousand cases in 2020 [2].

Locally advanced breast cancer is defined as mass greater than 5 cm in diameter, inflammatory breast cancer, epidermis involvement, chest wall involvement, supraclavicular lymph node involvement, infraclavicular lymph node involvement, or combined axillary and inframammary lymph nodes involvement [3].

According to the American Joint Committee of Cancer Classification locally advanced breast cancer is stage III

with stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage IIIB (T4N0–2M0), and stage IIIC (TanyN3M0) [4].

Delayed screening in developing countries increases the incidence of the locally advanced breast cancer. In Egypt 33.4% of newly diagnosed cases have locally advanced breast cancer [5].

The one size fits all protocol is not valid for breast cancer patients. Each case needs to receive tailored therapy for a successful treatment. Breast cancer cases need a multidisciplinary team to decide on the optimal plan of management. It includes: breast surgeons,

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oncologists, pathologists, diagnostic and interventional radiologists, and specialized nurses [6].

The standard management of locally advanced breast cancer is neoadjuvant chemotherapy followed by re-evaluation and surgery then radiotherapy [7].

The affected lymph node can be clipped under ultrasound guidance before the neoadjuvant treatment with metallic clip, magnetic seed, radioiodine seed, or carbon tattooing [8].

The usual neoadjuvant chemotherapy regimen given for locally advanced breast cancer is anthracycline and taxane for six cycles. Pure Her2-neu positive patients who received a combination of pertuzumab (PERJETA), trastuzumab (Herceptin), docetaxel and carboplatin as neoadjuvant therapy, had the highest pathological complete response rate as shown in Neosphere trial [9].

In the second place comes the triple negative patients then the Her2-neu positive luminal B then lastly the pure luminal with the lowest pathological complete response rates [10].

In case of the partial or complete response of the tumor to chemotherapy, surgical treatment is planned.

The standard management is breast conservative surgery followed by whole breast radiotherapy.

The alternative to breast conservative surgery is simple mastectomy in patients having diffuse suspicious multicentric microcalcifications, multicentric lesions, diffuse positive margins [11].

Adjuvant therapy can continue if the patient did not complete the scheduled chemotherapy regimen before surgery.

Postoperative hormonal treatment is recommended for patients with hormone receptor-positive cancer. If the tumor is HER2-positive, complete course of trastuzumab therapy for up to a year. If necessary, permit radiation therapy alongside endocrine therapy and trastuzumab.

In the past radical axillary lymph node dissection was the standard of care in patients having locally advanced breast cancer with clinically positive lymph node. Axillary lymph node dissection is associated with high morbidity as arm edema, pain, sensory deficits, motor deficits, and frozen shoulder [12]. Therefore,

several trials assessed the safety and accuracy of de-escalation of the axillary lymph node dissection in these patients through sentinel lymph node biopsy. In 2013, Z1071 (Alliance) trial [13] showed false negative rates of 12.6%, while SENTINA trial showed a false negative rate of 14.2% [14]. The GANEA 2 study assessed the same procedure with false negative rate 11.9% [15]. In 2022, Kuemmel *et al.* [16] showed that the false negative rate of this operation is 4.2%.

These trials paved the way for a new procedure called the targetive axillary dissection. This involves biopsy of the clipped lymph node and the sentinel lymph nodes [17].

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## Patients and methods

### Patients

This study is a single-center, prospective cohort study conducted at Ain Shams University Hospitals on 25 female patients diagnosed with locally advanced node positive breast cancer with complete pathological response to neoadjuvant chemotherapy in the period from January 1, 2023 to July 30, 2023.

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

### Inclusion criteria

- (1) Females.
- (2) 18 years or older.
- (3) Locally advanced breast cancer.
- (4) Positive axillary lymph node additionally documented by FNAC.
- (5) TNM: T0N2M0; T1/2N2M0, T3N1/2M0, TanyN3M0, T4N $\geq$ 1M0.
- (6) Receiving neoadjuvant chemotherapy with complete pathological response as documented by absence of lymph node in clinical examination, computed tomography, or ultrasound.

### Exclusion criteria included

- (1) Males.
- (2) Distant metastasis.
- (3) No proven axillary lymph node metastasis.
- (4) Not receiving neoadjuvant chemotherapy.
- (5) Early-stage breast cancer.

All patients were subjected to triple assessment including history taking (past medical and surgical history, family history, contraceptive, and hormonal

therapy history) and clinical examination of both breasts and axilla, as well as, investigations including:

- (1) Baseline high-resolution sonomamography on both breasts and axillary lymph nodes or MRI if high-risk patient or dense breast.
- (2) Biopsy of the suspicious breast lesion and axillary lymph node: ultrasound guided Tru-cut biopsy.
- (3) Ultrasound-guided clipping of the affected axillary lymph nodes and tumor with metallic clips.
- (4) Immunohistochemistry staining on sampled obtained: ER, PR, HER-2-neu, Ki67.
- (5) Silver in-situ hybridization in case Her-2neu immunohistochemistry was equivocal.

### Neoadjuvant chemotherapy

The choice of chemotherapy protocols for subtypes of breast cancer depends on various factors such as the stage of cancer, the patient's health status, and the risk of recurrence. Breast cancer is typically categorized into four subtypes, luminal A, luminal B, triple negative, and Her2neu positive breast cancer. Luminal A patients usually receive cyclophosphamide, methotrexate, and 5-fluorouracil for six cycles. Luminal B patients are given 5-fluorouracil, epirubicin, and cyclophosphamide for six to eight cycles. Triple negative patients take anthracycline-based chemotherapy such as AC (doxorubicin/cyclophosphamide) followed by docetaxel or paclitaxel. Her2neu positive patients received

trastuzumab, doxorubicin, and cyclophosphamide (AC) followed by taxane-based chemotherapy such as paclitaxel or docetaxel.

It is important to note that chemotherapy protocols may vary depending on each individual patient in the study, and the decision on which protocol to use was made in consultation with an oncologist.

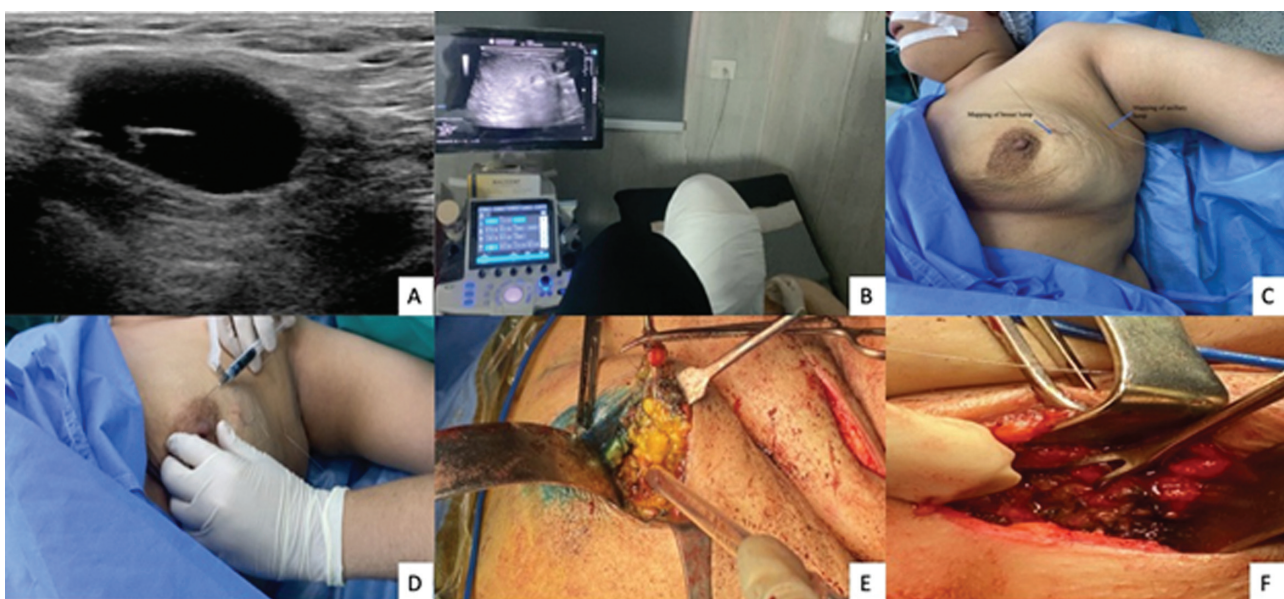
Postneoadjuvant chemotherapy, a high-resolution sonomamography or MRI were done on both breasts and axilla testing for response to neoadjuvant chemotherapy.

Eligible patients were those who had no clinical or radiological evidence of invasive cancer in the previously affected lymph nodes.

### Operative procedure

The clipped lymph node is marked by wire localization under ultrasound guidance as shown in Fig. 1a and b. The patient is placed under general anesthesia. The arm on the side of the affected breast is positioned away from the body to allow access to the axilla as shown in Fig. 1c. Injection of patent-blue dye into the breast tissue around the areola as shown in Fig. 1d. The dye travel through the lymphatic vessels to the sentinel lymph nodes, which are identified by their blue color. Identification and excision of the tumor from the breast with more than 0.8 cm safety margin is performed as in

Figure 1



(a) Clipped lymph node ultrasound. (b) Ultrasound-guided wire localization of the clipped lymph node. (c) Photograph of breast after wire localization of the clipped lymph node and breast mass. (d) Patent blue dye injection around the nipple-areola complex. (e) Excision of the peri-areolar tumor mass. (f) Excision of the sentinel lymph node.

Fig. 1e or simple mastectomy whenever indicated. Then, a small incision is made in the axilla to access the sentinel lymph nodes as in Fig. 1f. After that, the sentinel lymph nodes are removed for frozen section and examination under a microscope to determine if they contain macro-metastasis. Moreover, the clipped lymph node is localized through following the guide wire and excised for frozen section with the sentinel lymph node.

After the sentinel lymph node biopsy and/or targeted axillary dissection (TAD), if the frozen section biopsy was negative for residual metastasis, the incision is closed in layers with sutures.

If frozen section proved the presence of residual metastasis formal axillary clearance removing level 1 and 2 lymph nodes were performed then the incision is closed in layers with sutures.

## Results

This prospective cohort study involved 25 female patients with an average age of  $41.24 \pm 7.25$  years diagnosed with locally advanced breast cancer of average mass diameter  $4.74 \pm 0.86$  cm and axillary lymph node involvement with an average diameter of  $1.59 \pm 0.39$  cm. Included patients had complete pathological response to neoadjuvant chemotherapy regarding the lymph node and average tumor size postneoadjuvant chemotherapy of  $3.61 \pm 0.80$  cm. Table 1 shows the clinical findings among the patients participating in the study.

Twenty-one patients out of the 25 patients had expressed ER positive on immune histochemistry, 21 patients expressed PR positive, four patients were Her-2-neu positive including one patient who had equivocal immunohistochemistry and tested with silver in-situ hybridization technique. Six patients showed

**Table 1 The clinical characteristics of included patients**

	Mean±SD
Age	41.24±7.25
Mean tumor size before NACT	4.74±0.86
Mean tumor size post-NACT	3.60±0.80
Mean size of lymph node pre-NACT	1.59±0.39
Molecular subtype	n (%)
ER	21 (84)
PR	21 (84)
Her-2-Neu	4 (16)
Ki-67	6 (24)
Histological subtype	
Invasive ductal carcinoma	24 (96)
Invasive lobular carcinoma	1 (4)

**Table 2 The results of successful lymph node localization, frozen, and paraffin section results**

	n (%)
Targeted lymph node localization	
Failed	1 (4)
Successful	24 (96)
Clipped lymph node stained by dye	
No	20 (80)
Yes	5 (20)
Frozen section	
Negative	24 (100)
Positive	0
Paraffin section	
Negative	22 (91.67)
Positive	2 (8.33)

overexpression of Ki67 more than 20%. Most of the included patients had invasive ductal carcinoma grade I or II while only one out of the 25 patients had invasive lobular carcinoma. Table 2 shows the results of successful lymph node localization, frozen, and paraffin sections. Among patients who underwent targeted lymph node dissection 24 out of the 25 patients achieved successful localization of the clipped lymph node by guide wire under ultrasound guidance and confirmed by c-arm. Only one patient among the 25 patients who did the procedure had failed localization of the clipped lymph node. This patient had axillary clearance of levels 1 and 2 lymph nodes proven to be negative on histopathology later-on.

Moreover, 20% of the patients had the clipped lymph node stained with patent blue dye as sentinel lymph node indicating that sentinel lymph node biopsy alone is not an alternative to TAD and removal of the clipped lymph node. None of the patients had positive frozen section results, and only two patients had positive histopathology in paraffin section. These patients received axillary radiotherapy later and had no recurrence within the 6 months follow-up period of the study. Only two patients developed grade one lymphedema including the patient who did the conventional lymph node dissection and the patient who received the postoperative axillary radiotherapy.

## Discussion

The study included 25 patients mean age was  $41.25 \pm 7.25$  years, while in a study published by Pinto *et al.* [18] included 37 patients the age range was 35–78 years old while Kanesalingam *et al.* [19] included 37 patients with a median age of 49 years. Beniey *et al.* [20] conducted a similar study on 35 patients with an age

range of 29–76 years. This comparison showed that the average age of breast cancer is lower in Egypt than the global values that may be due to genetic causes or the recent screening program campaign conducted by the ministry of health and population encouraging early diagnosis.

This study also included only patients with locally advanced breast cancer so the TNM staging showed 15 out of the 25 patients were classified as T2 while 10 were classified as T3. Similarly, a study by Kanesalingam *et al.* [19] conducted in 2019 also included only locally advanced breast cancer patients classified as 29 patients T2, five patients T3, and three patients T4. In comparison, Beniey *et al.* [20] study had five patients classified as T1, 21 patients as T2, seven patients as T3, and one patient as T4 highlighting a diverse range of tumor population with the sample of Baniey's study and further reinforcing the feasibility of TAD operation among different stages of breast cancer. Moreover, Hartman study published in 2018 also showed wide sample including nine patients classified as T1, 20 patients classified as T2, and one patient classified as T3 [21]. A comprehensive analysis of the molecular subtypes of breast cancer cases included in the study showed that 21 out of the 25 patients had expressed ER positive on immune histochemistry with less response to NACT which agrees with the study published by Sharma *et al.* [22] about locally advanced breast cancer. Six patients showed overexpression of Ki67 and there was significant direct correlation between the overexpression of Ki67 and the tumor response to neoadjuvant chemotherapy. This was also the same in a study published by Pistelli *et al.* [23]. Regarding the proper localization of the clipped lymph node it was achieved successfully in 96% of cases involved in this study. Similarly, in Beniey *et al.* [20] study, successful localization was achieved in 97% of cases, while in previous studies the success rate was as low as 78% in Kanesalingam *et al.*'s [19] study and 83.3% in Hartmann's study published in 2018 [21]. This indicates that the accurate localization of the clipped lymph node has become a more feasible and precise procedure across time. Although, Pinto *et al.* [18] published a study with the success rate of 81% in localization of the clipped node, which is much lower than this study and Baniey study, several factors may have contributed to this difference including the study objectives, patient's population and variations in the employed techniques of lymph node localization. The correlation between the clipped lymph node and the sentinel lymph node has varied across different studies. In some studies the clipped

lymph node was the same as the sentinel lymph node in up to 76% of cases in Kanesalingam *et al.* [19] study, while in Hartmann study in 2018 only 35.7% of cases had the clipped lymph node same as the sentinel lymph node [21] and in this study only 20% of cases had the clipped node as a sentinel lymph node. The relatively low concordance rates shown in this study and in Kanesalingam study emphasizes the importance of clipped lymph node localization and frozen section as an addition to the traditional sentinel lymph node biopsy.

Lymphedema was significantly reduced among patients who undergone the TAD at a rate of 8% in this study compared to the higher percentage of lymphedema among patients who undergone axillary lymph node clearance of levels 1 and 2 lymph nodes which was 24.6% in Yuki's study in 2022 [24].

There was no significant difference in the disease-free survival or overall survival rates among patients who undergone TAD compared to axillary lymph node clearance of levels 1 and 2 lymphatics as stated by study published by Kuemmel *et al.* [25]. These findings mark the TAD as a safe and feasible alternative to axillary clearance of levels 1 and 2 lymph nodes in patients with node positive locally advanced breast cancer who had complete pathological response to neoadjuvant chemotherapy reducing the morbidity associated with the postoperative lymphedema due to conventional axillary clearance.

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## Conclusion

Targeted lymph node localization is considered a feasible and accurate technique for lymph node management in patients with clipped lymph nodes who achieved a complete pathological response to neoadjuvant chemotherapy. This reduces the morbidities associated with the typical axillary clearance of levels 1 and 2 including lymphedema. Further research and larger-scale studies are warranted to validate these findings and explore the long-term implications of this technique.

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## Conflicts of interest

There are no conflicts of interest.

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