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# Implementation of Targeted Axillary Node Assessment Following Neoadjuvant Therapy for Node-positive Breast Cancer Patients Improves Axillary Disease Detection

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Assessing the targeted node, a biopsy-proven metastatic node marked with a metallic clip before neoadjuvant chemotherapy along with sentinel node dissection improves the evaluation of pathological response in the axillary nodal basin after systemic treatment as compared to sentinel node dissection with dual tracer alone.
**Objectives:** The objective was to investigate the rate of the clipped node being a sentinel node and the sensitivity of targeted node dissection in detecting residual disease.

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**Methods:** A prospective study of biopsy-confirmed breast axillary nodal metastases with a metallic clip placed before initiating systemic therapy. After the therapy, the clip node was identified by ultrasound-guided needle localization and sentinel node biopsy by the dual tracer. At least 3 or more nodes were sent for biopsy. Nodal metastasis was confirmed by frozen section biopsy and complete axillary dissection was done even if micro-metastatic disease was detected.
**Results:** Of 120 patients enrolled in the study, 60(50%) patients had residual axillary nodal disease after neoadjuvant chemotherapy. Among 60 patients with positive residual disease clip node was positive for metastasis in all node-positive patients 60 (100%). Among these 60 patients with residual disease in 42 (70%) cases clipped nodes and sentinel nodes were alike/same, whereas the remaining 18 (30%) patients with residual disease clipped nodes were not sentinel nodes. In the 10/18 case, the sentinel node was also positive on biopsy or complete axillary clearance but in 8/18(13%) nodes that were clipped but not sentinel nodes clip node was only positive node, but the sentinel node was negative on frozen well as on complete axillary clearance. This emphasizes the importance of clipped node removal/assessment after neoadjuvant surgery without which we can miss about 13% of positive axillary disease.
**Conclusion:** Marking nodes (metallic clip) with biopsy-confirmed metastatic disease allows for selective removal and improves pathologic evaluation for the residual nodal disease after chemotherapy.

*Keywords: Targeted node; sentinel node; dual tracer; neo-adjuvant chemotherapy; axillary staging; chemotherapy; breast cancer.*

## 1. INTRODUCTION

Neoadjuvant chemotherapy implementation has improved pathological complete response (PCR) in up to 40-50% of cases of breast cancer and this rate is even higher in axillary nodes 40-74% [1]. Assessment of axillary nodal status is essential for staging purposes and the most significant prognostic marker for breast recurrence and overall survival [2].

In patients who have not received NAC, the size of the SLN metastasis is associated with the probability of the non-sentinel nodal metastasis, and low-volume SLN disease (that is, isolated tumor cells [pN0i+, <0.2 mm], and micro-metastasis [pN1mi, 0.2–2.0 mm] does not require completion ALND [3]. In the post, neoadjuvant setting presence of even isolated tumor cells (yp<0.2mm) is an indication of level II axillary dissection and has an impact on DFS and OS [4,5]. DFS was 51% versus 87%, respectively in patients who have a residual disease with metastasis on SLNB following Neoadjuvant chemotherapy (NAC) compared with those who had negative SLNB (p<0.001) [6]. Therefore, vigilant axillary assessment is essential before avoiding axillary clearance.

The conventional method of sentinel node biopsy in biopsy-proven node-positive cases has shown inconsistent false-negative and identification rates ranging from 10-30% [7] Sentinel node biopsy with single-agent alone has a high false-negative rate of 12.6% in the case of the downstaging of axillary disease [8,9,10]. With dual trace, it is 9% and this rate falls to 5% if the targeted clip node is also removed from the sentinel node [11] therefore it is valuable to remove the targeted node along with the sentinel node to have an accurate axillary assessment.

3 randomized control trials ACOSOG Z1071, SENTINA, and SN FNAC, demonstrated that, in patients who were initially node-positive and received NAC, an acceptable false-negative rate of 10 percent was achievable by removing at least three nodes and using dual tracer mapping of the sentinel lymph nodes [12,13,14].

In developing countries like ours, where the incidence of breast cancer is high (1:9 women) [15], most of the patients present late in stage II or III, and the younger age group in their forties [16]. Most of them are candidates for neoadjuvant chemotherapy and appropriate management of axilla is crucial. It would be interesting to see if in a post-NAC setting the clipped node is the same as the sentinel node an 113883d to see if that increases sensitivity in detecting residual axillary disease. Can only targeted clip node excision be enough to detect residual disease and decrease the financial burden on the patient for axillary assessment? There is no authentic data in this regard, this study will help us in the implementation of targeted clipped node assessment as a part and parcel of post-neoadjuvant axillary management

recommendation and for the axillary assessment in resource-constrained third-world countries.

The goal of this study is to determine after neoadjuvant therapy what percentage of sentinel nodes detected by radioactive and blue dye is the same as the targeted node detected by needle localization, and whether surgical removal of clipped nodes improves nodal staging.

## 2. MATERIALS AND METHODS

This study is a prospective interventional cohort study done in the Breast Surgery Department of Liaquat National Hospital and Medical College, Karachi, Pakistan from January 2019 to March 2021.

All patients above 18 years of age with biopsy-proven invasive breast carcinoma(T1-T4) with biopsy-proven axillary metastatic node (N1 -N2) marked with metallic clip referred to as targeted clipped node planned for neoadjuvant chemotherapy were included. Before starting systemic therapy ER, PR, Her2 neu, and KI67 were done on the biopsy and a complete workup was done to rule out metastasis. After neoadjuvant therapy, the patient's axillary radiological assessment by ultrasound was done to rule out any residual suspicious diseased node. Patients who had no radiologically evident axillary disease were planned for both sentinel node biopsy and targeted node (clipped node) removal with the help of ultrasound-guided wire localization just before surgery. Sentinel node identification was done by dual-trace (methylene blue dye and radioactive tracer) and at least 3 nodes were removed to reduce the false-negative rate.

Patients who were clinically and radiological node-negative (N0), no indication of neoadjuvant chemotherapy, failure to place a clip in biopsy-proven node or failure to localize clipped node after chemotherapy, clinically and radiological residual metastatic nodal disease in axilla after chemotherapy, and inflammatory breast cancer patients were excluded from the study.

All Clipped node localization was done under ultrasound guidance and confirmed by imaging of the node after removal to confirm the clip in it and sent separately for histopathology marked as a clipped node. Sentinel nodes were identified by either the blue color, increased radioactivity on the gamma probe, or both.

Nodal metastasis was confirmed by the on-table frozen section biopsy of the excised nodes. Nodes having residual macro-metastasis (yp>2mm), microscopic deposits (yp0.2-mm≤2mm), and even isolated tumor cells (yp<0.2mm) were considered positive and level II axillary clearance was done. No axillary clearance was done in the case of a negative biopsy.

### 2.1 Statistical Analysis

Patient data was compiled and analyzed through the Statistical Package for Social Sciences (SPSS) Version 25. Frequency and percentage were computed for qualitative variables. Mean ± SD was calculated for the quantitative variable. Chi-square or/and Fisher exact test was applied to see the association of all clinical factors with the axillary nodes. P-value ≤0.05 will be considered significant.

## 3. RESULTS

There were one hundred and twenty patients enrolled in our study. The mean age of the patients was 47.85±10.84 years. Their clinical tumor size was noted as 2(1.7%) had T1, 46(38.3%) had T2, 60(50%) had T3 and 12(10%) had T4. Most of the 106(88.3%) patients had a nodal stage N1 while only 14(11.7%) had nodal stage N2. The biomarkers status was observed as 15(12.5%) was Her2 positive, 30(25%) was luminal B Her 2positive, 8(6.7%) was Luminal A, 41(34.2%) were Luminal B and 26(21.7%) was Triple negative. Most patients 67(55.8%) were treated with the combination of AC + Paclitaxel neoadjuvant chemotherapy. All patients with triple-negative received AC + carboplatin along with Paclitaxel. Her 2 positive patients received Trastuzumab in all cases and Pertuzumab in affordable patients only. The post-chemo clinical tumor size was noted as 85(70.8%) had T0, 25(20.8%) had T1, 8(6.7%) had T2 and 2(1.7) had T3. The nodal stage after post-chemo was clinically and radiologically N0 in all cases. In 96(80.8%) cases axillary assessment was done by dual tracer radioactive isotope + methylene blue and needle localization followed by methylene blue+ needle localization in 24(20%) cases due to the unavailability of radioactive isotope during the covid pandemic. The clipped node was also radioactive and blue (sentinel node) in 87(72.5%) cases. All excised nodes minimum of 3 nodes were checked by the pathologist before calling it a negative for metastasis to reduce the false-negative rate. The detailed descriptive statistics are presented in Table 1.

**Table 1. Clinical investigations of the population under study n=120**

| | Frequency (%) |
|---|---|
| **Age** | 47.85±10.84 |
| **Clinical Tumor size (CT)** | |
| T1 | 2(1.7) |
| T2 | 46(38.3) |
| T3 | 60(50) |
| T4 | 12(10) |
| **Clinical Node stage (cN)** | |
| N1 | 106(88.3) |
| N2 | 14(11.7) |
| **Biomarkers** | |
| Her2 | 15(12.5) |
| B Her | 30(25) |
| Luminal A | 8(6.7) |
| Luminal B | 41(34.2) |
| Triple-negative | 26(21.7) |
| **Neoadjuvant Chemotherapy** | |
| AC+Paclitaxel | 67(55.8) |
| AC+Paclitaxel+Carboplatin | 19(15.8) |
| AC+Paclitaxel+Herceptin | 10(8.3) |
| AC+Paclitaxel+Herceptin+Perjeta | 21(17.5) |
| Paclitaxel+Herceptin+Perjeta | 3(2.5) |
| **Post Chemo size (yT)** | |
| T0 | 85(70.8) |
| T1 | 25(20.8) |
| T2 | 8(6.7) |
| T3 | 2(1.7) |
| **Post Chemo Node stage (yN)** | |
| N0 | 120(100) |
| **Lymph node mapping** | |
| Methylene blue+ needle localization | 24(19.2) |
| Isotope +methylene blue+ needle localization | 95(80.8) |
| **Node status** | |
| Blue and clip node | 20(16.7) |
| Radioactive and clip node | 30(25) |
| Blue + Radioactive clip node | 37(30.8) |
| Clip nodes other than blue or radioactive | 33(27.5) |
| **Clip node same as sentinel node** | |
| Yes | 87(72.5) |
| No | 33(27.5) |
| **Axilla status** | |
| Positive | 60(50) |
| Negative | 60(50) |

**Table 2. Nodal status findings in axilla-positive cases n=60**

| **Clip node same as sentinel node** | |
|---|---|
| Yes | 42(70) |
| No | 18(30) |

We found a statistically insignificant association of axillary status with the clinical tumor size (p=0.766), clinical nodal stage (p=0.570), lymph node mapping (p=0.062), and clip node which is the same as sentinel node (p=0.683). The statistically significant association of axilla status was found with the help of biomarkers (p=0.001), neoadjuvant chemotherapy (p=0.001), post-chemo tumor size (p=0.047), node status (p=0.027), and number of nodes removed

(p0.001). Positive axillary metastasis even after neoadjuvant chemotherapy was seen maximum in luminal B patients which showed poor response to chemotherapy in Luminal B cases and 47% of the clip node was the same as the sentinel node.

Overall, 50% of patients had post-neoadjuvant residual positive metastatic axillary nodes and needed level II axillary dissection, and the targeted node was positive in all 60 (100%) cases. In all axilla-positive cases, we observed about 42(70%) targeted nodes were the same as the sentinel node. In 18(30%) patients, the targeted node was positive but not a sentinel node showing high reliability to the targeted node dissection. Among 18 cases 10 cases have both clipped and sentinel node-positive in frozen section or level II axillary clearance, however in 8 cases (13.5%) clip node was only a positive node both on frozen section and even on complete axillary lymph node dissection. In node-negative cases, at least 3 sentinel nodes were assessed to decrease false-negative rates. The detailed descriptive statistics of axilla-positive cases are presented in Table 2.

## 4. DISCUSSION

Axillary management is part and parcel of breast cancer management and a most powerful prognostic indicator of breast cancer disease [17,18]. Neoadjuvant chemotherapy recently became the mainstay of treatment in locally advanced breast cancer and in aggressive biological disease to downstage disease and de-escalating surgery.

Targeted axillary dissection was first described by Caudle and colleagues in 2016 and involves radiological clipping of the metastatic node at diagnosis and subsequent removal of the sentinel nodes as well as the clip node identified preoperatively by localization of the clipped node [19]. This technique can result in a reduction in the axillary false-negative rate from 10 to 2.4 percent.

Currently in the setting of neoadjuvant chemotherapy presence of residual axillary disease even in the form of isolated tumor cells needs complete axillary dissection and has a poor prognostic marker. The residual cancer burden is an important prognostic index to detect poor prognosis disease cases and help in further adjuvant treatment decision-making to improve DFS and overall survival [20]. Axillary nodal disease, number of lymph nodes involved, and size of tumor nodal metastatic deposits are some of the important factors in the residual cancer burden calculator. By missing any residual axillary disease, we will underestimate the original disease load and compromise the adjuvant treatment application as well as the prognosis of the patient [21].

In about 75 percent of patients, the clipped node is one of the sentinel nodes [22]. This is evident from our study, 70% of cases of clipped nodes were sentinel nodes too but 30% of cases of clipped nodes were though positive but not sentinel nodes, this assured the need for axillary clipped node assessment to avoid misreading of axillary residual disease.

As shown in our study results, in 13% of cases only the clipped node was positive, this means if one doesn't do a clipped node assessment, we can miss residual axillary disease which is a significant number. This emphasizes the role of targeted node dissection in axillary nodal staging and prognosis after neoadjuvant treatment.

Axillary assessment by a core biopsy and axillary clipping as well as post NAC needle localization of clipped node is a feasible and affordable procedure, it requires a technically sound surgeon and a trained radiologist with a simple ultrasound machine and metallic clips. No special equipment is required. In our study, all node clipping, and needle localization were done under ultrasound guidance. With this technique and vigilance, we can improve our post-neoadjuvant axillary management and provide breast cancer with a standard of care.

Another aspect of our study is that out of 120 patients, 60 patients had no residual axillary disease which showed 50% axillary surgery downstaging which is matching to international data [22]. Despite the improvement in PCR rates in breast cancer with the development of novel therapies, ALND is still considered a gold standard in most patients. Accurately identifying the subgroup of patients in whom ALND can be avoided remains a clinical challenge. In 60 axillary residual disease patients clipped node was positive in all 60 cases which means assessment of pre-chemo axillary metastatic node is essential to avoid any false-negative result. 2ndly in 3$^{rd}$ world cost is a major concern and a radioactive tracer is expensive and not readily available in every hospital and needs a special setup of the gamma camera, our results

can be food for thought for local policies to do needle localization of clipped node for post neoadjuvant axillary staging along with affordable and easily available methylene blue dye with at least 3 nodes removal to reduce false-negative rate. As in our 60 patients of positive axillary metastatic disease after NAC, 3 patients had only clipped nodes but not blue or radioactive, and 20 patients had clipped and blue nodes showing 53/out of 60 cases detected by only clip and methylene blue dye. In the review article published by the London Breast Institute, a total of 9 studies evaluated the pooled FNR of Marked Lymph node ( MLNB) alone which was 6.28% (95% CI: 3.98–9.43), the addition of SLNB to MLNB (TAD) was associated with false negative rate ( FNR) of 5.18% (95% CI: 3.41–7.54), which was not significantly different from that of MLNB alone (p = 0.48) [23]. The SLNB adds minimal new information and therefore can be safely omitted from TAD. The only concern is the identification and retrieval of marked nodes. The success rate in the above-pooled analysis study was reported as 90.0% (95% CI: 85.1–95.1), though we have only included in our study the patients where we were able to retrieve the clipped node, our success rate was comparable. These results demonstrate that the FNR associated with MLNB alone or combined with SLNB is acceptably low and both approaches are highly accurate in staging the axilla in patients with node-positive breast cancer after NACT.

Targeted node dissection helps us to confidently select patients in whom ALND may be avoided post-NAC. Our data demonstrate that ALND can be avoided in 50% of patients who are node-positive before neoadjuvant chemotherapy but downstage to node-negative disease after treatment and confirmed by sentinel as well as by targeted node dissection. This is a significant proportion of patients in whom the additional morbidity associated with ALND can be avoided. Correspondingly, targeted node dissection helps us to miss disease in residual node-positive disease patients in higher proportion as compared to detection by simple radioactive or methylene blue method as shown by our 13% higher detection rate.

We believe that targeted axillary dissection is a safe and acceptable procedure that should be offered to all neoadjuvant biopsy-proven metastatic node-positive patients. The insertion of a clip to mark the biopsy-proven metastatic node is an essential step for the accuracy of the technique. The long-term effect of ALND omission on patients' prognosis is under study. With vigilant assessment and staging of disease, it will be possible to determine how to best identify the subgroup of patients with residual disease who will benefit from adjuvant treatment and, who will not benefit from a subsequent ALND.

## 5. CONCLUSION

Sentinel node biopsy along with removal of the clipped node after neoadjuvant chemotherapy, an affordable and practically possible procedure, improves residual axillary disease burden detection and decreases false-negative results.

## CONSENT

Informed consent was taken from the patients and patient identification was kept confidential.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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