

## **Implementation of Targeted Axillary node assessment Following Neoadjuvant Therapy for Node-Positive Breast cancer patients improves axillary disease detection**

### **Abstract:**

Assessing targeted node, biopsy-proven metastatic node marked with a metallic clip before neoadjuvant chemotherapy along with sentinel nodes dissection, improves evaluation of pathological response in the axillary nodal basin after systemic treatment as compared to sentinel node dissection with dual tracer alone. 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.

**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 along with 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 the 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 node and sentinel node were alike/same, whereas remaining 18 (30%) patients with residual disease clipped nodes were not sentinel node. In 10/18 cases sentinel node was also positive on biopsy or complete axillary clearance but 8/18 (44%) nodes which were clipped but not sentinel nodes clip node was only positive node, but 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.

**Key words:** Targeted node, sentinel node, Dual tracer, neo-adjuvant chemotherapy, axillary staging

### **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 cell ( $y_p < 0.2$  mm) 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 case of the down staging of axillary disease (8,9,10). With dual trace it is 9% and this rate falls to 5% if targeted clip node is also removed with sentinel node (11) therefore it is valuable to remove targeted node along with 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 the developing countries like ours, where the incidence of breast cancer is high (1:9 women) (15) and most of patients present late in stage II or III and at the younger age group in their forties (16). Most of them are a candidate 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 then does it increase 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 in the implementation of targeted clipped node assessment as a part and parcel of post neoadjuvant axillary management recommendation and for the for axillary assessment in the resource constrained third world countries.

The goal of this study is to determine that 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

**Operational definition:**

**Targeted node:** biopsy-proven axillary metastatic lymph node marked with the metallic clip before neoadjuvant chemotherapy in breast cancer patients

NAC: neoadjuvant chemotherapy,

**Dual tracer:** radioactive + methylene blue dye

**Study design:**

Interventional cohort study

### **Material and Methods:**

This study is a prospective interventional study done in the Breast surgery Unit of General 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 was done on the biopsy and 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 have no radiologically evident axillary disease were planned for both sentinel node biopsy and targeted node (clipped node) removal with the help of ultrasound-guided needle localization. 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 with clinically and radiological node-negative (N0), no indication of neoadjuvant chemotherapy, failure to place a clip in biopsy-proven node or failure to localize clip 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 node after removal to confirm clip in it and sent for separately for histopathology marked as a clipped node. Sentinel nodes were identified by either the blue color or increased radioactivity on the gamma probe or both.

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

## 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  $\pm$  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  $\leq$  0.05 will be considered significant.

## Results:

There were one hundred and twenty patients enrolled in our study. The mean age of the patients was  $47.85 \pm 10.84$  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 2 positive, 8(6.7%) was Luminal A, 41(34.2%) were Luminal B and 26(21.7%) was Triple negative. The majority of 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 Transtuzumab 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. 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 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-01.

We found statistically insignificant associate of axilla 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 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 node removed ( $p=0.001$ ). Positive axillary metastasis even after neoadjuvant chemotherapy was seen maximum in luminal B patients which showed poor response of chemotherapy in Luminal B cases and in 47% of them clipnode was same as sentinel node.

Overall, 50% of patients have post neoadjuvant positive metastatic axillary nodes and need 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 node was the same as the sentinel node. It showed in 18(30%) patients targeted node was positive but it was 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 positive node both on frozen section and even on complete axillary lymph node dissection. In node-negative cases, at least 3 sentinel node was assessed to decrease false-negative rates. The detailed descriptive statistics of axilla positive cases are presented in Table-02.

**Table 01: Clinical investigations of the population under study**  
n=120

	Frequency (%)
<b>Age</b>	47.85±10.84
<b>Clinical Tumor size (cT)</b>	
T1	2(1.7)
T2	46(38.3)
T3	60(50)

T4	12(10)
<b>Clinical Node stage (cN)</b>	
N1	106(88.3)
N2	14(11.7)
<b>Biomarkers</b>	
Her2	15(12.5)
B Her	30(25)
Luminal A	8(6.7)
Luminal B	41(34.2)
Triple-negative	26(21.7)
<b>Neoadjuvant Chemotherapy</b>	
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)
<b>Post Chemo size (yT)</b>	
T0	85(70.8)
T1	25(20.8)
T2	8(6.7)
T3	2(1.7)
<b>Post Chemo Node stage (yN)</b>	
N0	120(100)
<b>Lymph node mapping</b>	
Methylene blue+ needle localization	24(19.2)
Isotope+methylene blue+ needle localization	95(80.8)
<b>Node status</b>	
Blueand clip node	20(16.7)
Radioactiveand clip node	30(25)
Blue+Radioactive clip node	37(30.8)
Clip node other than blue or radioactive	33(27.5)
<b>Clip node same as sentinel node</b>	
Yes	87(72.5)

No	33(27.5)
<b>Axilla status</b>	
Positive	60(50)
Negative	60(50)

**Table 02: Nodal status findings in axilla positive cases n=60**

<b>Clip node same as sentinel node</b>	
Yes	42(70)
No	18(30)

### **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 deescalating 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 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 is one of important factors in the residual cancer burden calculator. By missing any residual axillary disease, we will underestimate the

original disease load and compromise adjuvant treatment applications as well as prognosis of patient (21).

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

As shown in our study results 13% of cases only the clipped node was positive, this means if one doesn't do 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 required. In our studies, all node clipping, and needle localization were done in ultrasound guidance. By this technique and vigilance, we can improve our post neoadjuvant axillary management and can provide breast cancer with the standard of care.

Another aspect of our study is in 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 it means assessment of pre-chemo axillary metastatic node is essential to avoid any false-negative result. 2ndly in 3<sup>rd</sup> world cost is a major concern, radioactive tracer is expensive and not readily available in every setup, needs special setup of gamma camera, our results can be a food for thought for local policies to do needle localization of clipped node for postneoadjuvant 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 were only clipped node but not blue or radioactive and 20 patients were clipped and blue nodes showing 53/out of 60 cases detection by only clip and methylene blue dye. But this needs more evidence from national and international data.

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 patient in higher proportion as compared to detect 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.

Conclusion:

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.

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