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 alongwith sentinel nodes dissection, improves evaluation of pathological response in the axillary nodal basin after systemic treatment as compared to sentinel node dissection with dual traceralone.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 3or 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 hadthe 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 60patients with residual disease in42 (70%) cases clipped node and sentinel node were alike/same, whereas remaining 18 (30%) patients with residual disease clippednodes were not sentinel node. In 10/18case sentinel node was also positive on biopsy or complete axillary clearance but 8/18(13%) 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 afterneoadjuvant 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 upto 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 (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 onSLNB following Neoadjuvant chemotherapy (NAC) compared with those who had negative SLNB (p<0.001) [6].Therefor 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 rateof 12.6% in case of the down staging of axillary disease(8,9,10) .With dual trace it is 9% and this rate fallsto 5% if targeted clipnodeis also removed with sentinel node(11) therefore it is valuableto remove targeted node along with sentinel node to have an accurate axillary assessment.

3 randomized control trialsACOSOG 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 patientspresent late in stage II or III andatthe 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 ina post-NAC setting the clippednodeis the same as thesentinel node then does it increase sensitivity in detecting residual axillary disease. Can only targeted clip node excision be enough to detect residual disease and decreasethe financial burden on the patient for axillary assessment. There is no authentic data in this regard,this study will help usin 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 resourceconstrained 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

Comment [l1]: references

Operational definition:

Targeted node: biopsy-proven axillary metastatic lymphnode 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

Comment [I2]: deleted

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, PakistanfromJanuary 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 referredto 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'saxillary radiological assessment by ultrasound was done to rule out any residual suspicious diseased node. patients who have no radiologicallyevident 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 atleast 3 nodes were removed to reducethe false-negative rate.

Patients with clinically and radiological node-negative (N0), noindication 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 onthe gamma probe or both.

Nodal metastasis was confirmed by on table frozen section biopsy of the excised nodes. Nodes having residual macro-metastasis (yp>2mm), microscopic deposits (yp0.2-mm≤2mm) and even with isolated tumor cells (yp<0.2mm)wereconsidered 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± 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≤0.05willbeconsidered significant.

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. 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 andPertuzumab 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 3nodes werechecked by the pathologist before calling it a negative for metastasisto 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 (p0.001). 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 reliabilitytothe 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, atleast 3 sentinel node was assessed to decrease false-negative rates.The detailed descriptive statistics of axilla positive casesare presented in Table-02.

Table 01: 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	
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)
Clip node same as sentinel node	
Yes	87(72.5)

No	33(27.5)
Axilla status	
Positive	60(50)
Negative	60(50)

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

Clip node same as sentinel node	
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 lymphnodes involved, and size of tumor nodal metastatic deposits is one of important factors inthe residual cancer burden calculator.By missing any residual axillary disease, we will underestimate the

original disease load and compromise adjuvant treatment applicationas 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 emphasis 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, itrequires atechnically sound surgeon and atrained 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. Bythis 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 mean assessment of pre-chemo axillary metastatic node is essential to avoid any false-negative result 2ndly in 3rd 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 be 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.

Reference

1Mougalian SS, Hernandez M, Lei X, et al. Ten-Year Outcomes of Patients With Breast Cancer With Cytologically Confirmed Axillary Lymph Node Metastases and Pathologic Complete Response After Primary Systemic Chemotherapy. JAMA Oncol 2016;2:508-16.

2 Tonellotto F, Bergmann A, de Souza Abrahão K, de Aguiar SS, Bello MA, Thuler LCS. Impact of the number of positive lymph nodes and lymph node ratio on survival of women with node-positive breast cancer. *Eur J Breast Health.* 2019;15:76–84.

3)Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (ibcsg 23–01): A phase 3 randomized controlled trial. *The Lancet Oncology.* 2013;14:297–305.

4) Symmans F, PS, Lester S, Kulka J. Post-therapy effects. In: Lakhani SR, EI Schnitt SJ, Tan PH, de van Vijver MJ, editors. *World Health Organization classification of tumors of the breast.* 4th. Lyons: IARC; 2012. pp. 24–26

5) Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015;33:258–264.

6) Kuerer HM, Sahin AA, Hunt KK, Newman LA, Breslin TM, Ames FC, Ross MI, Buzdar AU, Hortobagyi GN, Singletary SE. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg.* 1999; 230:72–78. DOI: 10.1097/00000658-199907000-00011.

7) Takahashi M, Jinno H, Hayashida T, Sakata M, Asakura K, Kitagawa Y. Correlation between clinical nodal status and sentinel lymph node biopsy false-negative rate after neoadjuvant chemotherapy. *World J Surg.* 2012; 36:2847–2852. DOI: 10.1007/s00268-012-1704-z

8) Tee SR, Devane LA, Evoy D, Rothwell J, Geraghty J, Prichard RS, McDermott EW. Meta-analysis of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial biopsy-proven node-positive breast cancer. *Br J Surg.* 2018;105:1541–1552. DOI: 10.1002/bjs.10986.

9) Kelly AM, Dwamena B, Cronin P, Carlos RC. Breast cancer sentinel node identification and classification after neoadjuvant chemotherapy – a systematic review and meta-analysis. *AcadRadiol.* 2009;16:551–563.

10). van Deurzen CH, Vriens BE, Tjan-Heijnen VC, et al. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: a systematic review. *Eur J Cancer.* 2009;45:3124–3130

11) Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, Lebeau A, Liedtke C, von Minckwitz G, Nekljudova V, Schmatloch S, Schrenk P, Staebler A, Untch M. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013;14:609–618. doi: 10.1016/S1470-2045(13)70166-9.

12) Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA.* 2013;310:1455–1461.

13) Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013;14:609–618.

14) Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L, Meterissian S, Arnaout A, Brackstone M, McCready DR, Karp SE, Trop I, Lisbona A, Wright FC, Younan RJ, Provencher L, Patocskai E, Omeroglu A, Robidoux A. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015; 33:258–264.
DOI: 10.1200/JCO.2014.55.7827.

15) Sohail S, Alam SN. Breast cancer in Pakistan - awareness and early detection. J Coll Physicians Surg Pak. 2007;17(12):711–2.

16)Rufina Soomro.Age and stage of breast cancer in Pakistan: An experience at a tertiary care center, J of Pak Med Assoc. 2018 Nov;68(11):1682-1685.

17) Shen SD, Zhong SZ, Wang CZ, Huang WH. Correlation of lymph vascular invasion with clinicopathological factors in invasive breast cancer: a meta-analysis. *Int J Clin Exp Med.* 2015;8(10):17789–95.

18) Wu J-L, Tseng H-S, Yang L-H, Wu H-K, et al. Prediction of axillary lymph node metastases in breast cancer patients based on pathologic information of the primary tumour. *Med Sci Monit.* 2014;20:577–81.

19) Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection,J Clin Oncol, 2016 Apr 1;34(10):1072-8. doi:10.1200/JCO.2015.64.0094. Epub 2016 Jan 25.

20) Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007;25:4414–4422.

21) Sheri A, Smith IE, Johnston SR, et al. Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. *Ann Oncol.* 2015;26:75–80.

22)M R Boland, Z Al-Hilli. Management of the axilla after neoadjuvant chemotherapy in breast cancer patients. BrJ Surg.2021 Jul 23;108(7):748-749. doi: 10.1093/bjs/znab137.