



ORIGINAL ARTICLE

Diagnostic accuracy of sentinel lymph node biopsy in clinically node negative axilla after neo-adjuvant chemotherapy.

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ABSTRACT... Objective: To determine Diagnostic Accuracy of SLNB in a clinically node negative axilla after neo-adjuvant chemotherapy by taking ALND as gold standard. **Study Design:** Cross sectional study. **Setting:** Outpatient Department of Surgical Ward, Mayo Hospital Lahore. **Period:** 5th August 2020 to 5th March 2021. **Methods:** Including 43 patients with breast lump presenting in a six months duration after four cycles of neo-adjuvant therapy, restaging was done and primary surgery was performed along with SLNB followed by ALND. The hottest and blue nodes along with stained lymphatic were collected and sent for histopathology. **Results:** In this study sensitivity came out to be 94.6%, specificity 63%, positive predictive value of 97% and negative predictive value of 71%. Our diagnostic accuracy came out to be 93%. **Conclusion:** Based on the results of this study it can be concluded that SLNB should be done in all patients presenting with breast carcinoma and clinically node negative axilla to stage the axilla. It can prevent undue ALND.

Key words: Sentinel Lymph Node Biopsy, Axillary Lymph Node Dissection, Clinically Node Negative Axilla, Diagnostic Accuracy, Neo-adjuvant Chemotherapy.

INTRODUCTION

Breast carcinoma is commonest carcinoma among females in the whole world and is one of the prime causes of mortality among them and the incidence is increasing day by day.¹ It stands fifth in the commonest causes of cancer causing mortality in the whole world.² The incidence and death rates of breast cancer in Pakistan are five times and three times higher, respectively, as compared to the rates in other Asian countries.⁴

The treatment options for breast cancer are chemotherapy, operation, radiation to breast, targeted therapy and hormonal therapy. Breast conservation surgery is currently famous outlook in the management of locally spreading breast carcinoma. In the locally spreading breast carcinoma neo-adjuvant chemotherapy go in advance of BCS or mastectomy. To lessen the risk of metastasis and for complete recovery of patient, adjuvant radiotherapy plays a chief role.⁵ Axillary staging in Breast carcinoma is

done either clinically (Physical Examination, USG, Mammogram, MRI) to label as N0, N1, N2 and N3 or pathologically (USG guided FNAC/ Tru-cut biopsy, SLNB or resected specimen histopathology).

ALND role in patients with axilla having no positive nodes has been noted, as 70%–80% have come out to be pathologically free nodes (pN0).⁶ If we will go for ALND in these type of patients, this will expose most of them to unjustified morbid conditions after operation of axilla such as lymphedema of ipsilateral arm, axillary numbness as well as shoulder abduction deficit.⁷ No one can doubt the prognostic importance of the positivity of tumor in axilla and extent of involvement of lymph nodes of axilla at the time of making diagnosis and staging tumor, but most women having early stage breast carcinoma can and should undergo for evaluation of the status of axilla for positive lymph nodes by sentinel node sampling, this avoids the need for dissection of

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axilla in case of negative SLN.

The standard protocol for initial management of carcinoma of breast that is locally advanced and in those where we suppose the reduction in breast tumor size leading to breast conservation is neo-adjuvant chemotherapy (NACT). This neo-adjuvant chemotherapy demands professional close collaboration between oncological surgeons, medical oncologists, radiologists and pathologists.⁸

When discussing neo-adjuvant setting, clinical physical examination of axilla and its assessment is not that promising. Assessment of axilla by physically examining the patient has shown up to 45% false negative rates (FNR). Imaging techniques are used such as ultrasound imaging of both breasts and axilla, MRI, and PET/CT have proved to be of comparatively low significance in staging of cN0 axillary region.² In a previous study, the sensitivity value and the specificity value, false-negative rate, false-positive rate, positive-predictive value, negative-predictive value, and overall accuracy of PET/CT to detect metastasis in axilla were 73%, 78%, 27%, 22%, 89%, 54%, and 74%, respectively.⁹ In another study false negative rate of ultrasound and ultrasound guided FNAC was 38% and 17% respectively.¹⁰ While discussing core needle biopsy, sensitivity value, specificity value, positive-predictive value, negative-predictive value, and accuracy came out to be 87%, 100%, 100%, 93% and 95%.¹¹ The only gold standard method was the assessment of surgical staging of axilla in such patient group.

The topic of management of axilla surgically in carcinoma of breast has always been an interesting topic. SLNB has proved itself the less invasive surgical approach for accurately staging the axilla as ALND is now confined to a limited group of locally advanced breast cancer patients.³ Thus we can now say SLNB has replaced ALND in patients with clinically negative axilla (cN0). Many previous studies have shown SLN identification rate (IR) of 72% to 100% and FNR up to 33% after neo-adjuvant chemotherapy.¹²

Initially, there was a concern that high FNR (which

are unacceptable) for SLNB after undergoing neo-adjuvant therapy are because of lymphatic vessels fibrosis as tumor emboli that responded to chemotherapy would affect lymphatic drainage in the breast. Previous studies showed identification rates of SLNB following Neo-adjuvant chemotherapy ranging from 63% to 100% while FNRs of 0% to 33%.¹³ SLN presence in breast was shown by Krag et al. and Kett et al. They used two distinct injection techniques. In another study, the sensitivity value, specificity value, positive and negative predictive values, false-negative and false-positive rates came out to be 81.25%, 97.44%, 92.86%, 92.73%, 18.75% and 2.56% respectively.¹⁴

In literature review, chemotherapy has proven to cause fibrosis that induces deposition of emboli and debris in lymphatic channels that can alter lymphatic mapping and decrease Identification Rate. Van der Heiden-van der Loo et al. showed that statistically there was no difference between IR of SLN prior to or afterwards NAC. However, it seems that identification rate in upfront SLNB is higher than in IR of SLNB after NAC. To standardize the management clinically node negative axilla in breast carcinoma patients after neo-adjuvant therapy in our setup, we conducted a study as no such type of previous study was available in our setup. It also helped in preventing undue axillary dissection and associated morbidity of ALND in neo-adjuvant setting.

METHODS

After approval from the ethical review board on 29-07-2020 and approval of grant of research project, we included 43 patients fulfilling inclusion criteria from the outdoor department of surgery in mayo hospital Lahore (MHL) after complete workup.²⁴ Written consent was taken before including the patients in study. All patients were discussed in breast MDT for final plan. Patients who required Neo adjuvant chemotherapy as decided in MDT were sent for Neo-adjuvant chemotherapy.

Our regimen for Neo-adjuvant chemotherapy included Adriamycin with cyclophosphamide (four cycles) followed by taxanes (four cycles) each after three weeks interval. Upon completion

of the neo adjuvant therapy, all patients were restaged. Primary surgery such as mastectomy or lumpectomy was performed and axillary staging (SLNB along with ALND) was performed in all the patients as mentioned in operational definitions after 3 to 4 weeks. Surgical intervention was done in all patients under general anesthesia.

For Sentinel node biopsy, a radioactive chemical was injected near the tumor one night before surgery. During operation blue dye injected in retroareolar area and gamma probe was used to detect lymph node/nodes that contained the radioactive substance or LN that were stained with the blue dye were seen. The nodes with highest radioactive count (hottest) SLN were excised along with all nodes whose count was 10% or more of the hottest node ("10% rule"). The blue nodes or nodes contiguous with blue-stained lymphatic were excised as well. After removal of the Sentinel node, it was sent for the histo-pathology to check for the presence of cancerous cells.

Axillary lymph node dissection (ALND) was done in all the patients after SLNB, Dissection was done up to the apex to involve the nodes that lie medial to the pectoralis minor (Berg level III). The fat and nodes were finally separated from the axillary tail of the breast for excision. Around 20 lymph nodes were excised.

The main outcome variable findings on SLNB in evaluation of Axillary lymph nodes (yes/no) presented as diagnostic accuracy and calculated by taking sensitivity, specificity, positive-predictive values, negative predictive-values, true-positive, true-negative, false-positive and false-negative results. Axillary Lymph Node Dissection specimen was taken as gold standard.

RESULTS

Among different age groups, majority of the patients (more than 20%) fall in category aged 31 to 35, as shown below in Figure-1. Out of 43 female patients, 24 underwent BCS followed by SLNB and ALND while 19 patients underwent mastectomy followed by SLNB and ALND. More than 60% of the tumors lie in the upper outer

quadrant of breast, as shown in the Figure-2. Before neoadjuvant chemotherapy (NACT), 14% of the tumors were less than or equal to 2cm T1 (Stage I) category, 84% % of the lumps were greater than 2cm but less than 5cm, and hence were categorized as T2N0M0 (Stage IIA) and 2% of the lump were greater than 5cm and fall in T3N0M0 category (Stage IIB). After NACT, 30% of the tumors were less than or equal to 2cm (T1) (stage I), 67% of the lumps were greater than 2cm but less than 5cm, and hence were categorized as T2N0M0 (stage IIA). Only 2% of the tumors fall in T3N0M0 category that is greater than 5cm (stage IIB) as shown in Figure-3. The 100% of our patients had clinically negative axilla pre and post neoadjuvant chemotherapy having no distant metastasis. Out of 43 sentinels, 36 (84%) came out to be positive; while out of 43, 37 axillary dissection lymph nodes came out to be positive (86%). Below shown is the table demonstrating cross tabulation between SLNB and ALND results. (Table-I). As shown in the Table-I, 35 cases were true positive; 2 cases were false negative; 1 case was false positive and 5 cases were true negative. The sensitivity of SLNB came out to be 94.6%. The specificity of SLNB came out to be 83%. This test has the positive and negative predictive values of 97% and 71% respectively. All these results show an excellent sensitivity and specificity of SLNB with an accuracy of 93%. It shows the significance of SLNB in early stage of breast cancer in a clinically node negative axilla after neo adjuvant chemotherapy.

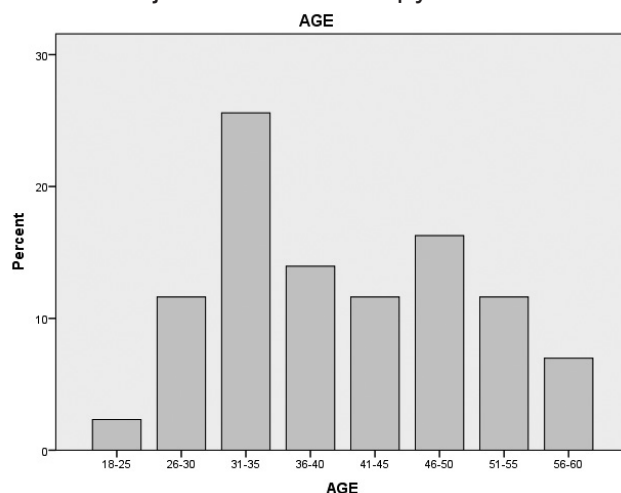


Figure-1. Bar chart showing frequency distribution of breast cancer among different age groups

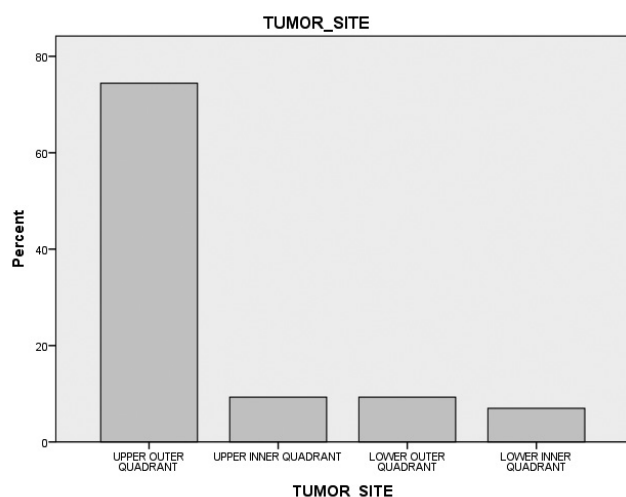


Figure-2. Bar chart showing quadrant involvement

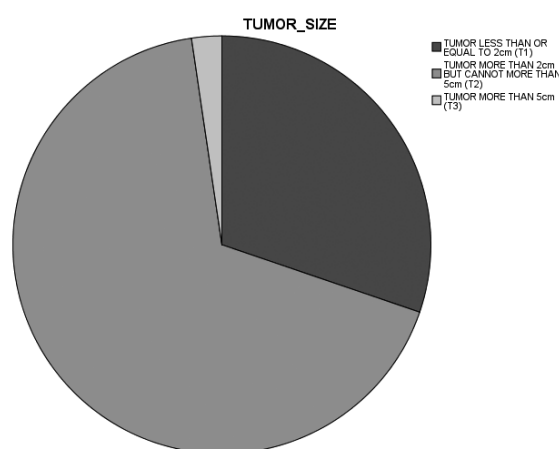


Figure-3. Bar chart showing size distribution of tumor

	Positive Result On SLNB	Negative Result On SLNB
Positive on ALND	35(True-Positive)	2(False-Negative)
Negative on ALND	1(False-Positive)	5(True-Negative)

Table-I. Cross tabulation between SLNB and ALND with results

DISCUSSION

Carcinoma of breast is rising and continuously increasing health issue and was ranked among the three most common malignant conditions worldwide in year 2012. It is the commonest carcinoma in females with an incidence of 25% of all carcinomas in women. It ranks 5th among the most common causes of death while discussing

carcinoma-related death globally. Currently, almost 90% diagnosed breast carcinoma patients have survival rate up to 5 years, the survival depends strongly on the stage of the cancer at time of diagnosis.²

Maguire et al. says that the clinical trials done recently have made us clear that axillary lymph node dissection has no significance and benefit on the outcome of cN0 patients having limited involvement of sentinel lymph nodes, who are treated with a amalgam of BCS, radiation therapy to whole breast and chemotherapy. This has improved the clinical treatment plan of the axilla.¹⁵

Ye J-M et al. have also shown advantages of sentinel lymph node biopsy as compared to ALND. Commonly used methods for mapping in SLNB include blue dye, radioisotopes, their combination and fluorescence imaging.¹⁶ ALND must be avoided in patients in early stages of breast carcinoma having limited involvement of sentinel lymph nodes, this leads to decreased post-surgical complications of axilla without any adverse effect on the survival of patient.¹⁷

In our study sensitivity came out to be 94.6%, specificity 63%, positive predictive value of 97% and negative predictive of 71%. Our diagnostic accuracy came out to be 93%. Pusina et al. performed similar surgery with comparable results. They had sensitivity of 68%, specificity of 98%, positive-predictive value of 67% and negative-predictive value of 96% and diagnostic accuracy of 98% in post neoadjuvant setting. Both of these results are comparable with the results shown by oncological centers deal in breast cancer. These centers allow introducing sentinel lymph node biopsy in routine practice as a substitute for ALND breast carcinoma for Stage I and Stage II.¹⁸

Okur et al. studied 230 clinically node negative preoperatively and undergone sentinel lymph node biopsy. 36% of the patients were having positive sentinel lymph nodes and underwent ALND. Among them 51.8% of the patients came out positive for tumor.¹⁹ Geng et al included a total of 1,456 patients. Total 16 studies were reviewed in

their study. He showed 96% pooled identification rate for sentinel lymph node biopsy. The pooled sensitivity was 94%, negative predictive value was 94% accuracy rate of 98%.²⁰

Veronesi et al. compared two groups. In the axillary dissection group, the diagnostic accuracy of the sentinel-node biopsy came out to be 96.9 percent, sensitivity of 91.2 percent and specificity of 100 percent. These results are comparable with our study.²¹ Canavese et al. studied one hundred and fifteen patients in ALND group and 110 in SLNB group. In the ALND group, 27 patients came out to be positive. A positive SLN was found in 27 patients in the ALND group. Overall accuracy of SLNB came out to be 93.0%. Sensitivity and negative-predictive values came out to be 77.1% and 91.1%, respectively.²²

Fayyaz et al. showed that mean age was 46.61 ± 8.75 years. In 67 FNAC positive patients, 61 were True Positive and 06 were False Positive. Among, 93 FNAC negative patients, 18 were False Negative whereas 75 were True Negative. Overall sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy of US guided FNAC of suspicious axilla nodes in patent with primary breast carcinoma was 77.22%, 92.59%, 80.65%, 91.04% and 85.0% respectively.²³

CONCLUSION

Based on the results of this study it can be concluded that SLNB should be done in all patients presenting with breast carcinoma and clinically node negative axilla in pre neoadjuvant setting to stage the axilla. It can prevent undue ALND.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

1	Ahmad Afnan Ali: Data collection.
2	Ali Akbar: Supervision.
3	Sana Afroze: Data collection.
4	Hamna Khan: Data analysis.
5	Jamal Anwar: Writing.
6	Shabeeh Ahmed: Analysis.
7	Ameer Afzal: Discussion writing.
8	Khalid Masood Gondal: Proof reading.