International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 14, No. 2, February 2025 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_14.2.2025.115

Original Research

Role Of Sentinel Lymph Node Biopsy In Patients Treated With Neoadjuvant Chemotherapy For Breast Cancer And Its Implications Toward Axillary Dissection – A Prospective Study

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Received: 11December, 2024 Accepted: 29 January, 2025

ABSTRACT

Background: Breast cancer is the leading cancer among Indian women. Sentinel lymph node biopsy (SLNB) is the preferred method for axillary staging in early breast cancer with clinically negative nodes (cN0), reducing the need for axillary lymph node dissection (ALND). The role of SLNB and its implications post-neoadjuvant chemotherapy is unclear.

Objectives: To evaluate SLNB in post-neoadjuvant chemotherapy breast cancer patients, assess axillary metastases, residual disease, and cancer staging after chemotherapy.

Methods: This study (July 2022 - July 2024) assesses SLNB in 30 breast cancer patients post neoadjuvant chemotherapy and the correlation with ALND, along with the post NAC cancer status

Results: Post Neoadjuvant-chemotherapy, 26.7% of patients were down staged to T0, with significant improvements in nodal staging. The SLN identification rate was 90%, with SLNB accuracy at 83% and an 18.4% false-negative rate.

Conclusions: NACT is an effective way of downstaging LABC. SLNB using methylene blue dye is cost-effective, reliable, and accurate for lymph node mapping in post-NACT breast cancer patients.

Key words- locally advanced breast cancer, pathological complete response, NACT, SLNB, methylene blue, ALND.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and a leading cause of cancer-related mortality[2]. It is characterized by the uncontrolled growth of breast cells, often forming a tumor that can be detected via imaging or physical examination. The prognosis and treatment strategies depend on various factors, including tumor size, stage, and molecular characteristics.

In recent years breast cancer treatment has gradually shifted from aggressive surgical treatment to minimally invasive surgical procedures. The introduction of mass screening programs resulted in the earlier detection of breast cancers, which has brought about a change in stage distribution. These smaller breast lesions made room for less aggressive treatment options. Besides this rearrangement in stage distribution, the addition of neo-adjuvant and adjuvant chemotherapy, radiotherapy made less invasive treatment possible[3]. An excellent example of this shift in treatment is the sentinel node technique as an alternative for ALND for staging in breast cancer.

SLNB is based on the theory of stepwise dissemination. A node that receives lymph fluid directly from a tumour is most likely also the node that will be the first to contain metastatic disease if lymphatic dissemination occurs. This particular (first) node can be visualized with the aid of a radioactive tracer or blue dye and can then be harvested. Dependent on the tumor-status of the sentinel node, axillary lymph node dissection is performed. The sentinel node procedure thus serves two purposes. Firstly, to identify patients who do not have metastases in the axilla and can be spared axillary clearance. Secondly, to improve the accuracy of staging. Not only nodes in the axilla are evaluated, but

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also nodes that are located in the internal mammary chain or elsewhere. These nodes can be harvested, and appropriate treatment instituted if they are shown to be involved. Furthermore, a more thorough evaluation of the lymph nodes is possible without spending more time as only one or a few nodes are removed with sentinel node biopsy and not a major chunk. [4]

Introduced in the 1990s, SLNB has become a standard practice for staging early breast cancer, reducing the need for more invasive procedures like axillary lymph node dissection (ALND)making it a preferable choice for patients with clinically node-negative breast cancer.

Treatment

Neoadjuvant chemotherapy (NAC) refers to the administration of chemotherapy before surgical intervention. This approach aims to reduce tumor size, potentially allowing for less extensive surgery and improving surgical outcomes. NAC is particularly beneficial for patients with locally advanced breast cancer, as it can make inoperable tumors operable and provide early systemic therapy to address micrometastaticdisease. The response to NAC can also provide prognostic information and guide further treatment[5].

Nowadays, many patients with locally advanced breast cancer are planned to receive neoadjuvant chemotherapy (NAC) before surgery[6]. However, there is a large debate over the role of SLNB in patients, who have received NAC. Although small institutional studies have reported different false negative rates for SLNB after NAC, a recent meta-analysis has shown that SLNB can be considered as an accurate and reliable tool in order to make treatment decisions for patients, who have received 4 NAC[7]. As most of the published papers have included both clinically positive and negative axillary nodes (by ultrasonography and physical examination) in their studies, false negative rates of the SLNB following NAC might have been underestimated[8]. Some trials, however, have exclusively enrolled clinically node positive patients in their studies, which has resulted in higher false negative rates. Micro-metastasis, defined by the AJCC as metastatic foci under 2 mm in diameter, varies widely in detection rates (9-46%) across studies. Methods like serial sectioning and immunohistochemical staining improve detection, but the clinical impact of micro-metastasis is still uncertain. Some studies suggest a slight adverse effect on recurrence and survival, highlighting a need for further research on its prognostic significance, which could affect decisions on adjuvant therapy.

False-negative rates in sentinel lymph node biopsy (SLNB) are a concern, historically ranging from 16% to 38%. Causes include variability in lymph flow, limitations in lymphoscintigraphy, and biological factors, with tumor cells potentially bypassing sentinel nodes. A learning curve exists for surgeons, where detection rates increase, and false-negative rates can drop to around 5%, considered acceptable by the oncology community. Despite promising applications, routine SLNB use requires experienced centers and further validation before widespread implementation.

METHODOLOGY

Study Design: This is a prospective study conducted on 30 patients

Study Design: Breast cancer is reported to be 34.4 per 100000 population in Bangalore. Prevalence of breast cancer is 0.034%. Considering 3% error sample needed to conduct this study is 15 cases. 30 cases will be selected.

Settings: Dept of General Surgery, JJMMC, Davanagere and its associated hospitals of Chigateri District hospital, DVG and Bapuji Hospital, DVG

Inclusion criteria:

- Patients in the age range of 20-80y of both sexes were included
- Patients with diagnosis of Ca Breast with clinical TNM staging up to cT1–4N0–2 (clinical stages 1–3) were included
- Patients who had completed 4 cycles of the AC regimen had also been included**.**
- Patients who had consented to the study procedures and protocols were included

Exclusion criteria:

- Women with recurrent cancer of the breast or patients with diagnosed inflammatory breast cancer were not included
- Patients who had undergone prior axillary surgery or neoadjuvant endocrine therapy were excluded from the study
- Patients with clinical symptoms and signs of systemic metastasis
- Patients with previous breast surgery
- Patients with previous radiotherapy and/or chemotherapy
- Patients who were allergic to methylene blue dye
- Women who did not consent to be part of the study were excluded

Method of data collection:

A Proforma containing relevant clinical information regarding diagnosis of breast cancer and the clinical staging, with Radiology, histopathology and laboratory reports were included along with consent from participating patients The prospective study identified 30 patients with a diagnosis of Breast Cancer up to cT1-4; cN0–2. The patients would then undergo 4 cycles of NAC of the AC regimen that includes – A combination of two chemotherapeutic agents, Doxorubicin (Weight based dosage of 60mg/m2 BSA) (Adriamycin) and Cyclophosphomide (Weight based dosage of 600mg/m2 BSA) given over slow IV infusion – This would be one cycle. This procedure would be repeated every 21 days,

DOI: 10.69605/ijlbpr_14.2.2025.115

constituting 4 cycles of the neoadjuvant chemotherapy.

Post 4 cycles of NAC, patients will undergo SLNB followed by breast surgery with completion axillary lymph node dissection

On the operative day, we used 1% methylene blue dye for axillary lymph node mapping. To do so, 3ml of methylene blue was injected Peri areolar followed by breast massage for 10 minutes. SLN was defined as a blue-stained lymph node. SLNs were separately submitted for pathological examination after surgery. After removing all SLNs, routine breast surgery and complete ALN dissection were performed. Lymph nodes were divided into two groups: the dye-stained lymph node as Sentinel Node and the rest of the lymph nodes removed by axillary clearance.

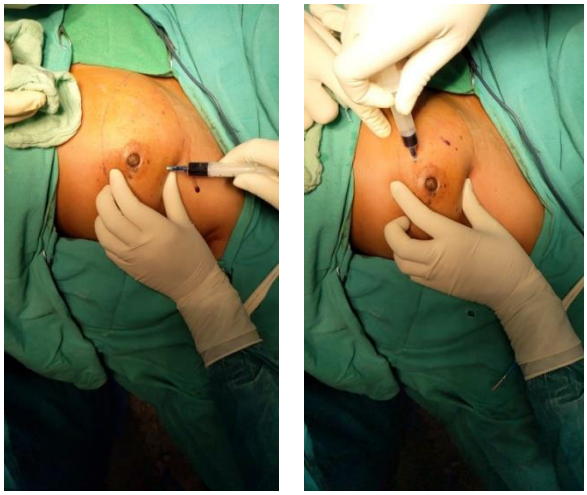

Fig. 1 – Methylene blue dye injection

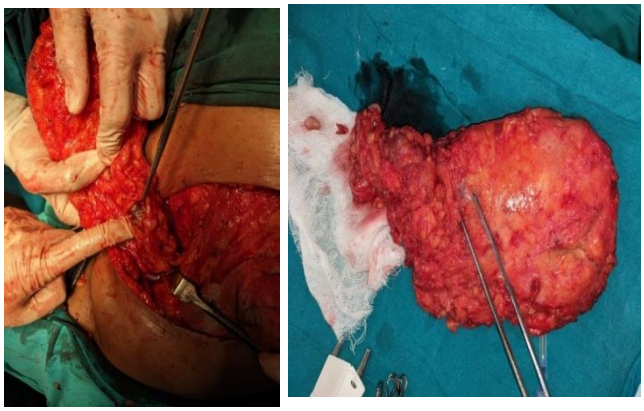

Fig 2. Sentinel Lymph node identification

The specimen after surgery was done was labelled as the Tumor, Axillary lymph nodes specimen and the sentinel lymph node, all labelled separately and submitted to the Dept. Of Pathology for further evaluation. The biopsy reports were then analyzed.

The above-mentioned procedures adhered to the ethical standards laid down by ICMR's Ethical guidelines for biomedical research on human participants (2017)

Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software and Epi-info version 7.2.1 (CDC Atlanta) software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation.

Kappa Statistics: Agreement between two or more observers/ between two or more methods or instruments and equipment's was assessed by using Kappa statistics.

RESULTS

A total of 30 patients with the age range of 22-76y were included in the study. The majority of the subjects (43.3%) were in the age group of 41 to 50 years, followed by 30.0% in the 51 to 60 years group. Only 13.3% of the participants were under 40 years or over 60 years of age. The mean age of the subjects was 50.17 ± 10.083 years. This distribution suggests that the study primarily involved middle-aged adults,

DOI: 10.69605/ijlbpr_14.2.2025.115

with a relatively balanced representation across the age spectrum from 40 to 60 years.

Table 1: TNM Staging Before NAC and after NAC

	Number of Subjects Clinical Staged Before NAC		Number of Subjects Staged After NAC and Surgery		P value
	Count	%	Count	%	
T staging					
T0	0	0%	8	26.7%	<0.001*
T1	1	3.3%	10	33.3%	
T2	14	46.7%	11	36.7%	
T3	12	40%	0	0%	
T4	3	10%	1	3.3%	
N Staging					
N0	4	13.3%	19	63.3%	<0.001*
N1	13	43.3%	10	33.3%	
N2	13	43.3%	1	3.3%	
N3	0	0%	0	0%	
Complete Pathological Response					
Yes			8	26.7%	-
No			22	73.3%	

In the present study, a significant shift in tumor staging (T stage) was observed after neoadjuvant chemotherapy (NACT). Initially, no subjects were staged as T0, but post-NACT, 26.7% of the subjects were down staged to T0 ($p < 0.001$). The proportion of T1 cases increased from 3.3% to 33.3%, while T2 cases remained relatively stable, decreasing slightly from 46.7% to 36.7%. Notably, T3 cases, which constituted 40% of the subjects before NACT, were completely eliminated post-NACT, highlighting the effectiveness of the treatment. T4 cases reduced slightly from 10% to 3.3% after NACT.

In terms of nodal staging (N stage), the proportion of N0 cases increased markedly from 13.3% before NACT to 63.3% after NACT, demonstrating a significant reduction in lymph node involvement ($p < 0.001$). The percentage of N1 cases decreased from 43.3% to 33.3%, and N2 cases showed a substantial decrease from 43.3% to 3.3%. No subjects were staged as N3 either before or after NACT. Additionally, a complete pathological response was achieved in 26.7% of the subjects, indicating no residual disease, while the remaining 73.3% had some form of residual disease.

Table 2: Identification rate

Variable (n = 30)		Identification rate
SLNB detected	27	90%
SLNB Not detected	3	10%

In the study, sentinel lymph node biopsy (SLNB) was successfully detected in 90% of the subjects (n=27. This high identification rate indicates that SLNB is a feasible and reliable technique for identifying sentinel lymph nodes in this patient population.

Table 3: Relationship of sentinel lymph node biopsy and axillary status

		Non-Sentinel Lymph node (Axillary lymph node)				Total
		Positive (With Metastasis)		Negative (without Metastasis)		
		Count	%	Count	%	
Sentinel Lymph node	Positive	9	81.8%	3	15.8%	12
	Negative	2	18.2%	16	84.2%	18
	Total	11	100%	19	100%	

The study also examined the relationship between sentinel lymph node biopsy (SLNB) results and axillary lymph node status. A significant association was found, with a chi-square test yielding a p-value of <0.001. Among the subjects with positive SLNB, 81.8% also had positive axillary lymph nodes, while 84.2% of those with negative SLNB had negative axillary nodes. The sensitivity of SLNB for detecting axillary metastasis was 81.82%, and the specificity was 84.21%. The positive predictive value (PPV) was 75%, and the negative predictive value (NPV) was 88.89%, with an overall diagnostic accuracy of

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86.33%. The false positive rate (FPR) was 15.79%, and the false negative rate was 18.4%. Cohen's kappa, a measure of agreement between SLNB and axillary status, was 0.6479, indicating substantial agreement $\chi 2 = 12.656$, df =1, $p < 0.001$* **[Chi-square test]**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity or TFR	81.82%	52.3, 94.86
Specificity or TNR	84.21%	62.43, 94.48
Positive Predictive Value	75%	46.77, 91.11
Negative Predictive Value	88.89%	67.2, 96.9
Diagnostic Accuracy	86.33%	66.44, 92.66
False Positive Rate	15.79%	
False Negative Rate	18.4%	
Cohen's kappa (Unweighted)	0.6479	0.2909 - 1.005

True Positive Rate (TPR), True Negative Rate (TNR)

TABLE COMPARING OUR STUDY TO SIMILAR SINGLE CENTER STUDIES

Author	Age Range (Mean)	Median TNM Stage Evaluated	Lymphatic Mapping Method	Identification Rate (%)	Node Positive (Total Patients)	False Negative Rate (%)
Chintamani et al	32-85 (47.3)	T3N2	Methylene blue	100	13 (30)	13.3
Ravi Arjun et al	26-63 (45.18)	T3N1	Dual Mapping	67 (Methylene Blue), 100 (Dual)	28 (44)	21.4
Haid et al	31-77 (53.4)	T2N1	Dual Mapping	88	18 (33)	0
Breslin et al	25-68 (45)	T2N1	Dual Mapping	84.3	25 (51)	12
Stearns et al	29-79 (46)	T3N2	Methylene blue	85.3	13 (34)	14.3
Our Study	**22-76 (50.1)**	**T2N1, T2N2**	**Methylene blue**	**90**	**12 (30)**	**18.4**

DISCUSSION

Following NACT, traditionally ALND is performed as a part of optimum breast surgery. This however is associated with considerable morbidity. A less aggressive approach is therefore sought for, making SLNB after NACT an attractive strategy as the axilla is downstaged to N0 in several patients (20-40%). Thus, considerable number of patients could be spared the morbidity of ALND, once the SLNB gets established as a standard of care in patients with LABC after NACT. The safety of the same has been established in many trials

Comparative analysis of age demographics and TNM staging across studies assessing sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NACT) reveals key differences in patient profiles and disease progression. Chintamani et al. reported the broadest age range (32-85 years) with a mean age of 47.3 years, while our study spanned an age range of 22-76 years with a higher mean age of 50.1 years, highlighting an inclusive age diversity. Median ages across studies remain close, supporting comparability of results.

The age distribution could influence outcomes, as younger patients generally face a poorer prognosis, while older patients have higher breast cancer incidence rates. In TNM staging, Chintamani et al. and Stearns et al. focused on advanced stages with significant nodal involvement, while others addressed larger tumors with varying nodal spread. Our study encompassed T2N1 and T2N2 stages, providing insights into a broader spectrum of tumor sizes and nodal involvement, enhancing generalizability and bridging gaps between early and advanced cases.

SLNB success rates vary across mapping techniques, with dual mapping showing high identification rates, achieving 100% in Ravi Arjun et al.'s study. Methylene blue alone, used by Chintamani et al. and Stearns et al., had lower rates, 85.3-100%, while our study achieved a reliable 90% using methylene blue, underscoring its efficacy as a cost-effective option. Node-positive and false-negative rates also varied, with our study reporting a node-positive count of 12 and a false-negative rate of 18.4%, comparable to other studies despite procedural complexities post-NACT. Larger studies in high-volume centers, such as Haid et al., show minimal false-negative rates, demonstrating the impact of procedural experience.

Notably, NACT led to a substantial downstaging, with N0 cases rising from 13.3% pre-NACT to 63.3% post-

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NACT and a complete pathological response in 26.7% of cases. These findings support SLNB's inclusion in treatment protocols, even considering theoretical limitations, such as lymphatic fibrosis from NACT affecting drainage and node involvement. In line with international trials, such as SENTINA, which reported false-negative rates of 18.5% with two-node resection, our study's 18.4% rate is within acceptable limits, supporting SLNB accuracy.

Our findings reinforce SLNB's role in reducing the need for axillary lymph node dissection (ALND) and associated lymphedema, especially as many locally advanced cases will require radiotherapy. The primary limitation of our study is a small sample size, lack of a comparative arm, and absence of long-term follow-up. However, the study's strengths include a standardized lymphatic mapping and SLN assessment procedure by a single investigator, offering robust methodology and reliability in real-world settings.

Financial support
All finances were borne by the author and no external sponsor was present

Competing interests
The authors declare that they have no conflicts of interests

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