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Original Article

Clinicopathological Features Associated with Sentinel Lymph Node Positivity In Early Breast Cancer Patients at a Tertiary Care Military Hospital

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ABSTRACT

Objective: To compare the positivity rates of sentinel lymph node biopsy (SLNB) in patients with breast cancer with various clinicopathological features

Study Design: Prospective analytical study

Place and Duration of Study: Breast Clinic, CMH Rawalpindi, Pakistan, from Jan to Aug 2024.

Methodology: All patients with early breast cancer having tumor size of cT1- cT3 with clinically node-negative (cN0) disease planned for SLNB. Dual tracer mapping was employed for identification, and histopathological evaluation of retrieved nodes was done. The final report of SLNB, along with the further plan of action regarding further axillary management, was recorded for data analysis.

Results: A total of 97 patients with early breast cancer fulfilling inclusion criteria were enrolled for the study, with a median age of 55 (IQR:65-43) years. The positivity rate in this study was 23.76%, mostly in the upfront setting, with only one case out of 21 post-chemo sentinels. In the data analysis, tumor size and upfront surgery were found to be associated with more cases of positive SLNB, with *p*-values of 0.02 and 0.002, respectively.

Conclusion: The study highlights the significant role of tumor size and upfront setting in predicting SLNB positivity, while other factors like tumor grade and receptor status were not statistically significant in this regard

Keywords: clinically node negative(cN0) breast cancer, early breast cancer, sentinel lymph node biopsy (SLNB)

How to Cite This Article: *Akram ZJ, Saleema A, Azam Z, Jan MM, Naqvi RQ, Akhund J. Clinicopathological Features Associated with Sentinel Lymph Node Positivity in Early Breast Cancer Patients at a Tertiary Care Military Hospital. Pak Armed Forces Med J 2026; 76(7): 943-948. DOI: https://doi.org/10.51253/pafmj.v76i7.12690*

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INTRODUCTION

Breast cancer is one of the most common malignancies, affecting one out of every nine women worldwide during their lifetime.[1] Advancements in technology, systemic regimens, and radiotherapy have completely revolutionized breast cancer diagnosis and treatment.[2] Better screening and effective treatments have reduced the extent of breast cancer surgery, with de-escalated procedures replacing traditional radical approaches.[3] In non-metastatic breast cancer, surgery helps determine the pathological stage in the breast and axilla and assess the effect of neoadjuvant therapy in post-chemo patients. This aids in planning adjuvant management. Achieving pathological complete response (pCR) is a key predictor of disease-free and overall survival.[4]

Formal axillary dissection, previously used for the axilla, resulted in high postoperative morbidity, including lymphedema (20-40% of patients), chronic neuropathy, numbness, and pain. As axillary clearance does not improve overall survival and systemic therapies have advanced, the trend is moving towards less invasive or non-invasive axillary evaluations.[5] Sentinel lymph node biopsy (SLNB) is a recognized method for staging the axilla in early breast cancer patients without clinically detectable lymphadenopathy (cN0).[6] It relies on the concept that tumors drain through the lymphatic system in an orderly manner, making the SLNs the first few nodes to be affected by metastasis.[7] A tumor-free SLN indicates a low likelihood of other nodes being affected.[8]

Preoperative sonography and/or MRI enhance clinical examination accuracy for cN0 labeling.[9] Any impalpable suspicious lymph node seen on imaging and biopsied negative for metastasis is also considered cN0.[10]

The rationale of this study is to examine factors affecting sentinel lymph node positivity, such as tumor size, location, focality, histology, grade, and receptors in an effort to identify potential candidates who could benefit from ALND right away, instead of SLNB.

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Received: 23 Sep 2024; revision received: 16 Dec 2024; accepted: 18 Dec 2024

METHODOLOGY

A prospective analytical study was conducted at Breast Clinic CMH Rawalpindi, Pakistan, from Jan to Aug 2024. Approval was obtained from the Ethical Committee/ Institutional Review Board, CMH Rawalpindi, at the start of the study (reference Ser No. 535; Dated: 01/01/2024). As there was a study limitation due to a small number of patients undergoing SLNB, we included all patients reporting during our study duration. Convenience sampling was done as the study was restricted to those who underwent the procedure during the pre-defined 8-month window.

Inclusion Criteria: Female patients, aged 25 to 65 years, with early breast cancer, having cT1- cT3 with cN0 disease, and patients with DCIS undergoing mastectomy with SLNB were included. Diagnosed cancer patients were offered SLNB, either in an upfront or post-chemotherapy setting, according to the MDT plan. Patients undergoing SLNB in the post-chemotherapy setting were reconfirmed for negative axilla at the end of systemic therapy (yN0) before going for surgery.

Exclusion Criteria: All patients with cT4 and cN1 or above status were excluded.

A total of 97 patients meeting the inclusion criteria, planned for SLNB, during the study period were included after informed consent. To Increase Identification Rates (IR) and Decrease False Negative Rates (FNR) of SLNB, at least 2-5 nodes were identified using a dual-tracer technique based on radiolabelled technetium and patent blue dye. Retrieved lymph nodes were assessed by histopathology along with immunohistochemistry (IHC). Patients' final histopathology reports were collected at the time of follow-up.

Data were analysed using Statistical Package for Social Sciences version 27. Age was not normally distributed and represented by Median (IQR). Qualitative data was represented by using percentage and frequency.Chi-square was applied to evaluate predictors of positive Sentinel lymph node biopsy and p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

A total of 97 patients with early breast cancer fulfilling the inclusion criteria were recruited for the study, with a median age of 55 (IQR:65-43) years (Figure-1).There was no obvious side predilection, with 51.5% of cases in the left and 48.5% in the right breast. Two of the patients had bilateral early breast cancer and underwent SLNB on both sides.

There were 74 patients in the upfront setting, and 23 patients underwent post-chemo SLNB according to the initial MDT plan. In three patients undergoing the upfront setting, there was failure to identify sentinel lymph nodes (SLNs) in the axilla, and the plan was converted into Axillary Lymph Node Dissection (ALND) peroperatively. In our study, the failure rate of SLN was 3.07 %. In the remaining 94 cases, 4.3 ± 1.75 SLNs were retrieved in each case, using dual tracer mapping. Only one patient underwent SLNB with single method i-e radiolabelled technetium, due to her ongoing pregnancy. (Figure 2).

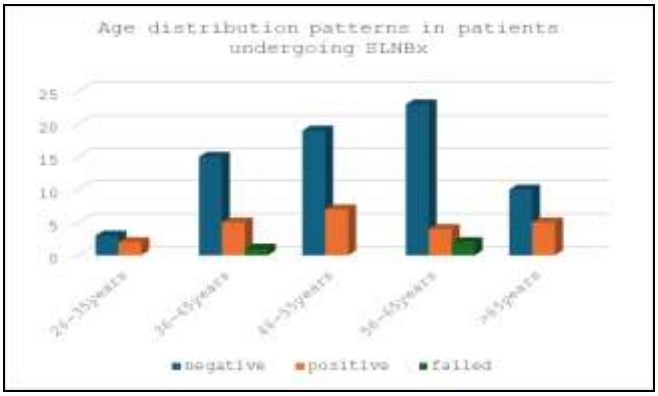


Figure-1: Age-Wise Sentinel Lymph Node Biopsy (Slnb) Positivity Trends

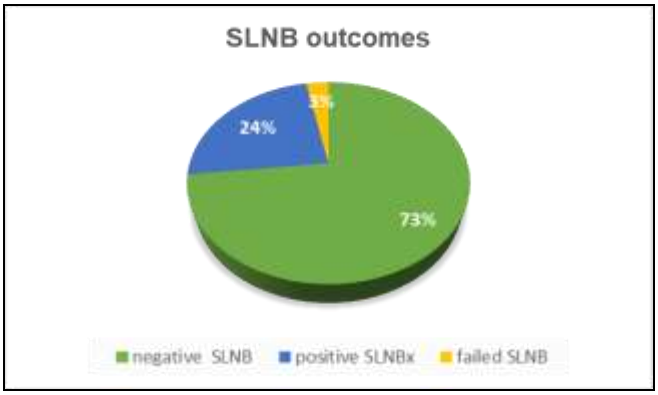


Figure-2: Sentinel Lymph Node Identification, Positivity and Failure Rates

Of 94 patients, 71 had a negative SLNB report and were spared further axillary management (surgery or radiation). Twenty-three patients had positive SLNB, giving a positivity rate of 23.7%. Out of these 23 positive cases, 4 patients required completion ALND; 19 patients underwent post-SLNB axillary radiation (XRT) (Figure-3).

Tumor size (p = 0.002) and upfront setting (p = 0.02) showed significant associations with SLNB positivity, while other factors such as menopausal status, tumor location, grade, focality, receptor status, and tumor type did not show statistically significant correlations, as shown:

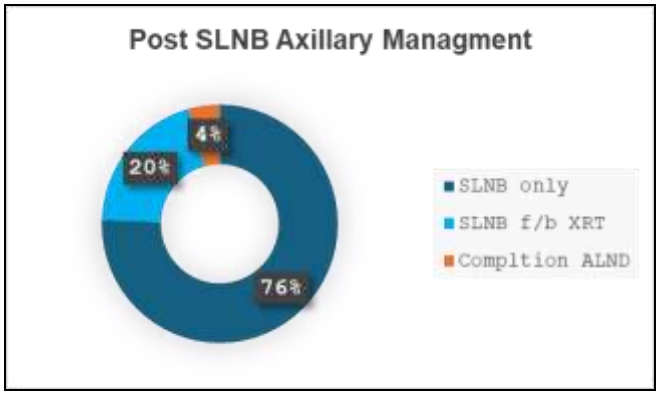


Figure-3: Number of Patients Undergoing Various Axillary Management Steps As Per Initial Slnb

SLNB positivity differed markedly between the upfront and post-chemotherapy settings. In the upfront setting, 30.9% were SLNB positive, a difference that was statistically significant (p = 0.02). This indicates a strong association between the upfront setting and SLNB positivity. In contrast, in the post-chemotherapy group, SLNB positivity was observed in only 4.3%. This highlights a markedly lower rate of SLNB positivity in post-chemotherapy cases compared to upfront cases. Tumor size also showed a significant association with SLNB positivity (p = 0.002), with higher positivity rates observed in larger tumors, with cT2 at 36.8% and cT3 at 62.5%.

Tumor grade analysis showed that most SLNB-positive cases were associated with Grade II tumors, accounting for 31.8% of positive cases. In comparison, Grade III tumors had a lower SLNB positivity rate of 9.5%. Although Grade II tumors were more frequently linked to positive SLNs, the difference was borderline, with a p-value of 0.08. Similarly, luminal tumors were the most common type compared with TNBC and HER2-enriched tumors, but the difference was not statistically significant, with a p-value of 0.14.

Different histological approaches, such as IBCA NST, ILCA, mucinous carcinoma, IBCA with apocrine features, and others, including medullary carcinoma, solid papillary carcinoma, and IBCA with metaplastic and micropapillary features, were observed. However, for the other histologic types, the number of patients was too small to comment on the statistical significance of a positive SLNB associated with them. All 3 failed sentinel cases were Grade II IBCA NST, with characteristics like multifocality, unusual lymph node involvement, and specific tumor locations.

DISCUSSION

The findings of the present study revealed a positive association between tumor size, surgical setting, and sentinel lymph node metastasis among patients with early-stage breast cancer. Sentinel lymph node biopsy, in place of axillary lymph node dissection, is an appropriate technique for early-stage breast cancer. Sentinel lymph node biopsy decreases the risk of upper-limb lymphedema and chronic neuropathic pain associated with formal axillary dissection.[11] Thorough preoperative assessment with axillary US coupled with FNAC can identify patients with significant axillary burden and could be an important tool to initially evaluate patients and avoid unnecessary SLNB surgeries.[12]

According to Qiao *et al.,* although the combination of blue dye and radioisotope outperformed radioisotope alone in SLN detection, the superiority of dual tracers may be limited for patients with positive lymphoscintigraphy or for those after neoadjuvant chemotherapy.[13] In upfront cases, a single tracing modality may underestimate the positive SLN numbers compared to a dual tracing modality, as shown by Chen *et al*.[14] Different tracing modalities of SLNB will significantly affect Axillary management, referring to Z0011 trial criteria. Guiliano *et al.,* concluded that the combined technique remains the most accurate and effective technique for SLNB.[15] Similarly, in our study, dual tracer mapping was used to identify sentinel lymph nodes based on radiolabelled Tc and patent blue dye. An average of four sentinel lymph nodes were identified per patient, demonstrating that the dual technique with radiolabelled technetium and patent blue dye is a reliable and effective method. The identification rate in our study was 96.9% which was equivalent to international figures reported by Boniface *et al.,* thereby giving a failure rate of sentinel rate of 3.7%.[16]

In the literature, Kocaoz *et al.,* reported that the positive rate of SLNs in cN0-stage patients who undergo SLNB ranges from 20.5% to 25.5%; the positive SLNB results in our study were comparable, at 23.7%.[17] Out of these, only one patient had a positive SLNB in the post-chemotherapy setting and underwent completion axillary dissection. Among

positive upfront cases,[19] patients met the criteria for omission of axillary dissection and received axillary radiotherapy instead of re-surgery, according to Z0011, AMAROS, and SENOMAC trials. Three upfront cases had a larger T size of T3, more than 2 positive SLNs and/or ENE, and underwent surgery for completion ALND at the end of adjuvant systemic therapy, as reported by Corona *et al*.[18] Accordingly, 90 out of 97 patients (92.78%) in our study were spared formal axillary dissection.

Table-I: SLNB-based Clinicopathological Characteristics of Early Breast Cancer Patients

Variables	SLNB positive n(%)	SLNB negative n(%)	Total	*p*-Value
Upfront	22(23.4%)	49(52.1%)	71(75.5%)	0.02
Post chemo	1(1.06%)	22(23.4%)	23(24.4%)	
Menopausal Status				
Premenopausal	8(8.5%)	22(23.4%)	30(31.9%)	0.931
Postmenopausal	15(15.9%)	49(52.1%)	64(68%)	
Site of Tumour				
Upper outer Quadrant	8(8.5%)	29(30.8%)	37(39.3)	0.768
Lower outer Quadrant	2(2.1%)	13(13.8%)	15(15.9%)	
Central/Retinular	6(6.3%)	10(10.6%)	16(17.0%)	
Upper inner Quadrant	5(5.3%)	13(13.8%)	18(19.1%)	
Lower inner Quadrant	2(2.1%)	6(6.3%)	8(8.5%)	
Tumour Focality				
Unifocal	18(19.1%)	58(60.6%)	76(79.7%)	0.933
Multifocal	5(5.3%)	13(13.8%)	18(19.1%)	
Tumour Size				
cT1	3(3.1%)	22(23.4%)	25(26.5%)	0.002
cT2	14(14.9%)	24(25.5%)	38(40.4%)	
cT3	5(5.3%)	3(3.2%)	8(8.5%)	
ypT	1(1.06)	22(23.4%)	23(24.5%)	
Tumour Grade				
Grade I	0(0%)	7(7.4%)	7(7.4%)	0.087
Grade II	21(22.3%)	45(47.8%)	66(70.2%)	
Grade III	2(2.1%)	19(20.2%)	21(22.3%)	
Receptors				
Luminal type	22(23.4%)	50(53.1%)	72(76.6%)	0.144
TNBC	1(1.1%)	14(14.9%)	15(15.9%)	
HER2 Enriched	0(0.0%)	7(7.4%)	7(7.4%)	
Tumour Type				
IBCA NST	19(20.2%)	58(61.7%)	77(81.9%)	0.967
ILCA	2(2.1%)	6(6.4%)	8(8.5%)	
Mucinous carcinoma	0(0%)	3(3.2%)	3(3.2%)	
IBCA with apocrine features	1(1.1%)	1(1.1%)	2(2.1%)	
Others	1(1.1%)	3(3.2%)	4(4.3%)	

**cT1 tumor size < 2 cm, cT2 tumor size> 2 cm- 5 cm, cT3> 5 cm, ypT post-chemo residual tumor, TNBC Triple Negative Breast Cancer, IBCA NST Invasive Breast Cancer, no special type, ILCA Invasive Lobular Carcinoma*

Adachi *et al*., found that premenopausal women with breast cancer had a significantly higher rate of axillary lymph node metastasis compared to postmenopausal women, which they attributed to larger tumor size, higher grade, and more aggressive histology in premenopausal patients.[19] However, in our study, about two-thirds of the patients were postmenopausal, and sentinel lymph node positivity was similar between premenopausal and postmenopausal groups (p = 0.931). According to Chand *et al*., there is a higher incidence of lymph node positivity with increasing size of breast tumour, shorter tumour-nipple distance, and for tumors located at the upper outer quadrant of the breast.[20] In comparison, our study showed tumour size was one of the most powerful predictors of sentinel lymph node positivity. Larger tumor size, particularly cT3, was significantly associated with a positive sentinel lymph node biopsy (SLNB), with a p-value of 0.002. While most patients had tumors located in the upper outer quadrant, 42.1% of patients with retroareolar tumors had a positive SLNB. Although this association was statistically insignificant (p = 0.76), patients with retroareolar tumors showed a higher likelihood of having positive sentinel lymph nodes.

Sentinel lymph node biopsy (SLNB) is well-established for managing small, unifocal breast cancers, but its role in multifocal and multicentric cancers has been debated. Recent literature reviews report a false-negative rate for SLNB in MF and MC cancers of less than 10%, with low axillary recurrence rates, and SLNB is routinely performed with careful technical processes.[21] While multifocality in breast cancer is linked to a higher likelihood of metastasis, our study found no statistically significant association between tumor multifocality and positive SLNB (p = 0.93). Although Elleson *et al*., showed strong associations of positive SLNB with higher tumor grade, in our study, most cases of positive sentinel lymph nodes were from grade 2 tumors, with only a few grade 3 tumors showing a positive result. None of the grade 1 tumors gave a positive sentinel lymph node report.[22]

Malter *et al*., found that luminal breast cancer subtypes have a higher rate of lymph node (LN) involvement at diagnosis compared to triple-negative subtypes. It was also noted that LN involvement is an inherent characteristic of the molecular subtype of breast cancer, with triple-positive tumors showing the highest and triple-negative tumors the lowest likelihood of LN involvement.[23] In contrast, our study showed that most patients with hormone receptor-positive tumors underwent upfront sentinel lymph node biopsy, while triple-negative and HER2-positive

patients typically had post-chemotherapy SLNB. Notably, 95.6% of positive sentinel lymph nodes were found in hormone receptor-positive tumors, with only one positive SLNB in triple-negative cases. Furthermore, patients with triple-negative and HER2-positive breast cancer who underwent post-chemotherapy SLNB showed good response to treatment, with ypN0 results indicating no axillary metastasis. Corona et al., showed that ILC cases have more non-SLN metastases than IDC cases in SLN-positive patients. The option of omitting ALND in patients with ILC with 1–2 positive SLNs still requires further investigation.[18] Later, Adachi *et al.*, concluded ILC histology is not associated with higher risk of further metastasis at ALND.19 However, surgical management decisions should be taken considering tumor histotype, biology, and expected sensitivity to adjuvant therapies. We encountered six patients with invasive lobular carcinoma; of these, two had bilateral disease, and sentinel lymph node biopsy was done on both sides. There were 83 IBCa NST; SLNB positivity was almost equal in both histologies. Other distinct histologies encountered were mucinous carcinoma, metaplastic carcinoma, medullary carcinoma, invasive breast carcinoma with apocrine differentiation, and micropapillary features. One of the two patients with IBCA with apocrine differentiation, and the only patient with micropapillary features, had a positive SLNB.

It is also noteworthy that we could not obtain information on certain factors such as lymphovascular invasion and ki 67 proliferative index in all cases, which have been associated with lymph node metastasis in previous studies.

CONCLUSION

To conclude, this study highlighted a positive correlation of tumor size and surgical setting with sentinel lymph node metastasis in early breast cancer patients. These findings may play a role in guiding regional management considerations if confirmed in further studies. Additional predictive factors identified in this study, as well as other studies, such as tumor site, grade, patient age, tumor location, and multifocality, should help guide management in these patients.

ACKNOWLEDGEMENT

This work was backed in part by all colleagues at the Breast Surgery Department, CMH Rawalpindi, and unwavering family support.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ZJA & AS: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZA & MMJ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RQN & JA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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