Frequency and Predictive Factors of Lymph Node Metastasis in T3 Breast Cancer: Implications for Sentinel Lymph Node Biopsy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Introduction: Breast cancer is one of the most common malignancies worldwide, with tumor size and axillary lymph node metastasis serving as crucial determinants for staging and prognosis. While sentinel lymph node biopsy (SLNB) is well-established for T1 and T2 breast lesions, its role in T3 breast cancer is controversial. This study evaluates the potential of SLNB as an alternative to axillary dissection for staging T3 breast cancer and explores the correlation between axillary metastasis and poor prognostic factors.
Materials and Methods: This prospective cross-sectional study was conducted at the Department of Breast Surgery, Liaquat National Hospital, Karachi, from January 2023 to March 2024. A total of 180 female patients with T3 breast lesions were assessed. Axillary lymph node status was evaluated clinically and radiologically, with suspicious nodes confirmed via histopathology. SLNB

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was performed on all patients undergoing surgery after neoadjuvant chemotherapy and on those with upfront surgery if their initial biopsy showed no axillary involvement.

Results: Of the 180 patients analyzed, 144 had clinically or radiologically suspicious axillary lymph nodes, and 104 were confirmed to have axillary metastasis through FNAC or trucut biopsy. Neoadjuvant chemotherapy was administered to 134 patients, while 46 underwent upfront surgery. In total, 82 patients (44.5%) required axillary clearance. Axillary clearance was associated with poor prognostic factors: 13 out of 39 HER2-positive patients, 10 out of 39 triple-negative patients, and 10 out of 51 patients with grade III tumors underwent the procedure.

Discussion: The findings indicate a notable reduction in axillary clearance rates among T3 breast cancer patients using SLNB, which reduces surgical morbidity. Only 44.5% of patients required axillary clearance, highlighting the efficacy of SLNB in staging while improving quality of life.

Conclusion: Sentinel lymph node biopsy is a reliable and less invasive approach for axillary staging in selected T3 breast cancer patients, particularly when neoadjuvant chemotherapy is used. This method has the potential to minimize unnecessary axillary dissection and associated complications.

1. INTRODUCTION

Breast cancer remains the most common malignancy affecting women worldwide, with tumor size and metastatic spread being critical determinants of prognosis and treatment strategies. In particular, T3 breast cancer lesions—defined as tumors larger than 5 cm—carry a high risk of axillary lymph node involvement [1], reported in approximately 60-80% of patients at the time of diagnosis [2]. Additionally, these patients face a significant risk of distant metastasis, ranging from 20-40% [3], emphasizing the need for precise staging and effective management.

Sentinel lymph node biopsy (SNB) is a standard procedure for staging early breast cancer, offering high accuracy with fewer complications compared to full axillary lymph node dissection [4]. However, its use in T3 breast cancer remains controversial because of the increased likelihood of nodal metastasis [5]. The question remains whether a selective approach using SNB could effectively reduce the need for axillary dissection, thus minimizing treatment-related morbidity without compromising staging accuracy.

Tumor biology also plays a pivotal role in the evaluation of nodal involvement in T3 breast lesions. Factors such as hormone receptor status, HER2/neu overexpression, and molecular subtypes significantly influence the risk of lymph node metastasis [6]. For instance, triple-negative and HER2-positive breast cancers are more likely to have nodal involvement compared to hormone receptor-positive tumors [7]. Additional poor prognostic factors, including young patient age, high tumor grade, and high proliferative indices, further impact treatment decisions [8]. Given the aggressive nature of T3 tumors, understanding how these clinicopathological features correlate with lymph node metastasis is essential for optimizing management strategies.

While axillary lymph node dissection has been the standard approach for T3 breast cancer, its associated morbidity, such as lymphedema and impaired shoulder mobility, necessitates exploring less invasive alternatives [9]. Emerging evidence suggests that a more selective strategy may be feasible [10]. Therefore, this study aims to determine the frequency of lymph node metastasis in T3 breast cancer and analyze its correlation with key clinicopathological features. Furthermore, it evaluates the efficacy of sentinel lymph node biopsy in potentially reducing the need for axillary dissection in carefully selected patients, thereby improving treatment outcomes and quality of life.

2. MATERIALS AND METHODS

This is the prospective cross-sectional study of patients presented with breast cancer and diagnosed clinically as T3 lesions. The study was conducted at the Department of Breast Surgery Liaquat National Hospital Karachi over the period of January 2023 to March 2024 after the approval of the ethical research committee. A sample size of 180 patients was calculated using previously available literature showing 86.6% metastatic axilla in T3 breast cancer [11] with a confidence interval of 95% and 5% precision. Non-probability consecutive sampling technique was used.

All the female patients above 18 years of age presenting with clinically T3 lesions with biopsy-proven malignancy, absence of distant metastasis, no prior history of breast cancer or any other malignancy, and without neoadjuvant treatment were included in the study. Male gender, breast lesions other than T3, prior history of breast cancer or other malignancies, with prior neoadjuvant treatment were excluded. Informed written consent was taken and data was recorded by the principal investigator on a predesigned Performa. Biasness and confounder were controlled by strictly following the inclusion and exclusion criteria.

All the demographic data, tumor size, histopathological type, stage, grade, hormone sensitivity, clinical, radiological, and pathological findings were noted. All the included patients were assessed clinically and radiologically for lymph node status. All the clinically or radiologically suspicious axillary lymph nodes were evaluated histopathologically. All the axillary lymph nodes with an increased cortical thickness of >3 mm, rounded shape, loss of the central fatty hilum, irregular or lobulated cortex, heterogeneity, calcifications, and cystic spaces on U/S were considered suspicious [11]. By the end of metastatic workup, patients underwent neoadjuvant chemotherapy or upfront surgery as per breast cancer treatment protocols and patients' preference of treatment method.

For all the patients who underwent upfront surgery, level I and II axillary clearance was done in biopsy-proven metastatic axilla. Sentinel lymph node biopsy was done in patients who had benign axillary lymph nodes on initial biopsy and those in whom initial biopsy was not done due to clinically and radiologically benign axilla. Among patients who underwent neoadjuvant chemotherapy, axillary lymph nodes were reassessed clinically and radiologically by the end of neoadjuvant therapy. All the patients with biopsy-proven metastatic axilla prior to neoadjuvant chemotherapy who had clinically and radiologically diseased axilla at the end of chemotherapy underwent axillary clearance. Patients with post-neoadjuvant treatment who had initially biopsy-proven or clinically and radiologically benign axilla before neoadjuvant therapy underwent sentinel lymph node biopsy. Sentinel lymph node biopsy was done intraoperatively using methylene blue dye in all patients and a minimum of 3 lymph nodes were sent for frozen section [4]. All patients with tumor metastasis on sentinel lymph node biopsy underwent level I and II axillary clearance.

Patients' age, tumor type, grading, positive family history for breast cancer, frequency of axillary metastasis clinically, radiologically, histopathologically, the effect of neoadjuvant chemotherapy on axillary metastasis, hormonal and her2neu status, and relation of poor prognostic features with axillary metastasis were assessed.

Statistics: Data analysis was done by IBM SPSS Statistics v27. Mean and standard deviation were reported for quantitative variables whereas frequency and percentages were reported for qualitative variables. Chi square/fisher exact test was applied to determine the association between qualitative variables. P-values less than 0.05 were considered as significant.

3. RESULTS

3.1 Patient Demographics

Descriptive details of patient demographics are explained in Table 1.

A total of 180 female patients with T3 breast lesions were analyzed, with a mean age of 50.03 years (range: 23 to 78 years). 67 patients (37.2%) were <45 years and 113 patients (62.8%) were ≥45 years

Family history: Family history of breast cancer was reported in 17 patients (9.4%), while 163 patients (90.6%) had no family history.

Histopathological subtypes: histopathological subtypes included Invasive ductal carcinoma was seen in 173 patients (97.11%) and 7 patients (3.8%) Invasive lobular carcinoma.

Tumor grading: 3 patients (1.7%) had Grade I tumors, Grade II: 119 patients (66.1%), and, Grade III was observed in 51 patients (28.3%).

Tumor Biology and Biomarker Analysis: ER (Estrogen Receptor) 132 patients (73.3%) were ER Positive and 48 patients (26.7%) were ER Negative. Positive PR (Progesterone Receptor) was seen in 118 patients (65.6%) and 62 patients (34.4%) were PR negative.

HER2/neu status: 39 patients (21.6%) were Her2 positive, and 141 patients (78.3%) were negative. 39 patients (21.6%) were Triple-negative.

Table 1. Descriptive statistics

Sociodemographic profile	minimum	maximum	Mean +- standard deviation
Age	23	78	50 +- 11.6
	Frequency		**Percentage**
Age group			
<45 years	67		37.2
>45 years	113		62.8
Family history of breast cancer			
Yes	17		9.4
No	163		90.6
Breast cancer type/grading			
Ductal grade I	3		1.7
Ductal grade II	119		66.1
Ductal grade III	51		28.3
Lobular grade II	7		3.9
Residence			
Urban	129		71.7
Rural	51		28.3
Marital status			
Single	12		6.7
Married	168		93.3
Biomarkers			
ER			
Positive	132		73.3
Negative	48		26.7
PR			
Positive	118		65.6
Negative	62		34.4
Her2 neu			
Positive	39		21.7
Negative	141		78.3
Type of surgery			
BCS and SLNBx	50		27.8
Mastectomy and SLNBx	91		50.6
MRM	39		21.7
Axillary clearance			
Yes	82		45.6
No	98		54.4
Neoadjuvant chemotherapy			
Yes	134		74.4
No	46		25.6
Adjuvant chemotherapy			
Yes	45		25
No	135		75
Radiation			
Yes	123		68.3
No	55		30.6
Hormonal therapy			
Yes	129		71.7
No	51		28.3

Table 2. Summary of lymph node metastasis Sentinel lymph node biopsy status

Lymph node status	frequency	Positive SLNBx	Negative SLNBx	Direct Axcl
Neoadjuvant chemotherapy n=134				
Malignant on initial biopsy	80	34	33	13
Benign on initial biopsy	38	2	36	0
Clinically and radiologically benign	16	1	15	0
Total	134	37	84	13
Upfront surgery n=46				
Malignant on initial biopsy	24	------	------	24
Benign on initial biopsy	10	6	4	0
Clinically and radiologically benign	12	2	10	0
Total	46	8	14	24

3.2 Axillary Lymph Node Evaluation

On clinical and radiological assessment: 65 patients (36.1%) had clinically palpable axillary lymph nodes.144 patients (80%) had radiologically suspicious axillary lymph nodes and among the radiologically suspicious nodes, 104 (57.8%) were confirmed to be metastatic on initial FNAC or trucut biopsy.

Neoadjuvant Chemotherapy Outcomes: Neoadjuvant chemotherapy was administered to 134 patients (74.4%), while 46 patients (25.6%) underwent upfront surgery.

Pre-and post-treatment axillary status: Of the 80 patients with biopsy-proven metastatic axilla before neoadjuvant therapy, 13 (16.2%) remained radiologically suspicious and underwent axillary lymph node dissection.

34 (42.5%) had positive sentinel lymph node biopsy (SLNB) and subsequently required axillary clearance. 3 (41.2%) had negative SLNB and avoided axillary clearance. Of the 54 patients initially assessed as benign (38 with biopsy-proven benign and 16 with clinically and radiologically benign axilla), 3 (5.5%) later demonstrated metastatic axilla on SLNB, requiring axillary clearance.

Overall, neoadjuvant chemotherapy reduced axillary metastasis from 44.4% (80 patients) to 26.1% (47 patients) among those who had SLNB.

Axillary status in upfront surgery: Descriptive details are explained in Table 2.

24 out of 46 patients had biopsy-proven metastatic axilla, necessitating axillary dissection.

In 10 patients with biopsy-proven benign axilla, 6 (60%) had positive SLNB and required axillary clearance and 4 (40%) had negative SLNB and avoided further surgery.

In 12 patients with clinically and radiologically benign axilla, 2 (16.7%) were found to have metastatic axilla on SLNB and underwent axillary clearance.

Total axillary clearance was done in 32 out of 46 patients (69.6%) in the upfront surgery group.

Impact of poor prognostic factors: Descriptive details are given in Tables 3 and 4.

Out of Triple-negative disease (n=39), 25 patients had biopsy-proven metastatic axilla, with 21 receiving neoadjuvant chemotherapy. Post-chemotherapy, 6 patients required axillary clearance due to persistent metastasis, and 4 patients had upfront surgery with axillary clearance.

In triple-negative patients, Total axillary clearance was done in 10 (5.5%) patients.

HER2-positive disease (n=39) .21 patients had biopsy-proven metastatic axilla, with 18 receiving neoadjuvant chemotherapy. Post-chemotherapy, 8 patients required axillary clearance, and 4 had upfront surgery. Total axillary clearance in HER2-positive patients was done in 13 (7.2%).

Grading and Axillary Clearance: In Grade II tumors (n=126), 73 had biopsy-proven

metastatic axilla; 47 (37.3%) ultimately required axillary clearance. Grade III tumors were (n=51): 31 had biopsy-proven metastatic axilla; 24 (47.1%) underwent axillary clearance.

The association between higher tumor grade and increased axillary clearance was evident, although a significant reduction in axillary clearance was observed post-neoadjuvant chemotherapy.

Table 3. Correlation between poor prognostic factors and axillary lymph node metastasis

Lymph node status	frequency	NACT	Positive SLNBx	Negative SLNBx	Direct Axcl
Triple negative n=39					
Malignant on initial biopsy	25	21	6	15	4
Benign on initial biopsy	12	12	0	12	---
Clinically and radiologically benign	2	2	0	2	---
Total	39	35	6	29	4
Her2neu positive n=39					
Malignant on initial biopsy	21	18	8	10	3
Benign on initial biopsy	12	11	0	11	1
Clinically and radiologically benign	6	3	1	5	---
Total	39	32	9	26	4
Grade II n=126					
Malignant on initial biopsy	73	56	22	34	17
Benign on initial biopsy	30	23	6	24	---
Clinically and radiologically benign	23	13	2	11	---
Total	126	92	30	69	17
Grade III n=51					
Malignant on initial biopsy	31	24	12	12	9
Benign on initial biopsy	16	13	2	11	---
Clinically and radiologically benign	4	2	1	3	--
Total	51	39	15	26	9

Table 4. Prognostic features with sentinel lymph node positivity

	SLNBX Frequency (percent)		p-value
	Positive	Negative	
Age Group			
≤45 years	19(42.2)	36(36.7)	0.531
>45 years	26(57.8)	62(63.3)	
Triple Negative			
Yes	6(13.3)	28(28.6)	0.047*
No	39(86.7)	70(71.4)	
Her2Neu			
Positive	10(22.2)	24(24.5)	0.767
Negative	35(77.8)	74(75.5)	
Grade			
Grade-I	0(0)	3(3.1)	0.555
Grade-II	30(66.7)	68(69.4)	
Grade-III	15(33.3)	27(27.6)	
Family history of breast cancer			
Yes	4(8.9)	10(10.2)	1.000
No	41(91.1)	88(89.8)	

p-value <0.05 is considered significant

4. DISCUSSION

This study highlights the potential of sentinel lymph node biopsy (SLNB) to minimize the need for axillary clearance in T3 breast cancer patients. Our findings underscore that with careful patient selection, SLNB can serve as an effective alternative to axillary dissection, even in advanced breast cancers, thereby reducing treatment morbidity and improving quality of life. In our study, 44.5% of patients with T3 breast lesions required axillary clearance, indicating a substantial reduction compared to conventional approaches that prioritize axillary dissection.

T3 breast cancer: The role of SLNB in T3 breast cancer remains a topic of considerable debate due to the higher likelihood of nodal involvement in larger tumors. Studies such as De Oliveira-Junior et al. [12] have demonstrated that, while axillary clearance is often performed in T3 lesions, the use of SLNB could be a feasible option for a subset of patients with reduced nodal burden, particularly after neoadjuvant chemotherapy (NACT). Our findings align with this perspective, showing that careful clinical, radiological, and pathological evaluation can aid in identifying T3 patients for whom SLNB alone may suffice, reducing the risk of morbidity associated with complete axillary dissection.

Influence of hormone receptor status (ER/PR) on nodal involvement: Hormone receptor status is a significant predictor of nodal metastasis and overall prognosis in breast cancer. In our study, hormone receptor-positive (ER and/or PR-positive) patients demonstrated a relatively lower rate of axillary clearance than HER2-positive and triple-negative patients. This observation is supported by Rakha et al. [13] and Curigliano et al. [14], who found that hormone receptor-positive breast cancers, often associated with more indolent biology, have lower rates of lymph node metastasis than HER2-positive and triple-negative subtypes. Thus, hormone receptor positivity could be a favorable factor in predicting lower nodal involvement, potentially guiding more conservative axillary management.

HER2-positive breast cancer and increased nodal involvement: HER2-positive breast cancers, particularly in larger T3 lesions, are often associated with aggressive behavior and a higher likelihood of nodal metastasis. In our cohort, 13 out of 39 HER2-positive patients required axillary clearance, reflecting the persistent nodal disease burden despite systemic treatment. Studies, including that by Curigliano et al. [14], have shown that HER2 overexpression is a poor prognostic factor, correlating with higher rates of nodal involvement and recurrence. These findings suggest that while SLNB may be feasible in HER2-positive patients with favorable clinical or pathological responses post-NACT, closer consideration is warranted due to the aggressive biology of HER2-positive tumors.

Triple-negative breast cancer and SLNB in nodal management: Triple-negative breast cancer (TNBC) represents one of the most challenging subtypes due to its high rates of nodal involvement and poor prognosis. In our study, 10 out of 39 triple-negative patients ultimately required axillary clearance, underscoring the aggressive nature of TNBC even among T3 lesions. These results align with previous research, such as Rakha et al. [13], which reported higher rates of nodal metastasis and poorer outcomes in TNBC compared to hormone receptor-positive breast cancers. The NSABP B-18 and B-27 trials have also demonstrated that NACT can effectively downstage TNBC, potentially making SLNB a viable alternative to axillary clearance in some cases [7,15]. However, given the high recurrence risk associated with TNBC, axillary management strategies must be carefully tailored.

Impact of neoadjuvant chemotherapy on nodal clearance: Our study highlights the role of NACT in downstaging axillary disease in T3 breast cancer. Among patients who received NACT, the rate of axillary clearance was notably reduced, consistent with findings from studies by Hunt et al. [16] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials [15], which reported that NACT could convert a clinically positive axilla to node-negative in a significant proportion of patients. This effect is particularly relevant for T3 tumors, as it allows a less invasive approach with SLNB in patients who achieve nodal downstaging, thus reducing morbidity while maintaining oncological safety [17]. In our study, 26.1% of patients with biopsy-proven axillary metastasis pre-NACT were able to avoid axillary clearance due to a favorable response, supporting the utility of NACT in selecting candidates for SLNB in advanced-stage disease.

Study limitations and future directions: While this study presents compelling evidence supporting the use of SLNB in carefully selected

T3 breast cancer patients, certain limitations must be acknowledged. This is a single-center study, which may limit the generalizability of the findings. Additionally, the lack of long-term follow-up data restricts our ability to assess locoregional recurrence rates among patients who underwent SLNB alone. Future multicenter studies with extended follow-up periods are essential to validate the safety and efficacy of SLNB in T3 breast cancer and to assess recurrence rates across different molecular subtypes.

5. CONCLUSION

Our study suggests that sentinel lymph node biopsy is a viable, less invasive option for axillary staging in T3 breast cancer patients, particularly when combined with neoadjuvant chemotherapy. By evaluating patients based on key clinicopathological features, SLNB can be a useful approach to reduce unnecessary axillary dissection, especially for hormone receptor-positive patients with favorable tumor biology. However, in HER2-positive and triple-negative breast cancers, the decision to use SLNB alone should be made cautiously, given the higher rates of nodal involvement. These findings contribute to a more individualized approach to axillary management in advanced breast cancer, improving patient outcomes and quality of life.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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