Frequency of lymph node metastasis in T3 breast cancer lesions and its correlation with clinicopathological features.

ABSTRACT

Introduction: Breast cancer is one of the most common malignancies worldwide with tumor size and axillary lymph node metastasis accounting for important staging and prognostic features. Sentinel lymph node biopsy is considered as standard practice for T1 and T2 breast lesions but is controversial for T3 breast Ca. This study assess applicability of sentinel lymph node biopsy in T3 breast Ca as a replacement for axillary dissection for staging purpose and association of poor prognostic factors with axillary metastasis in T3 breast lesion.

Materials and methods: This is the prospective cross sectional study of patients presented with T3 breast lesions at department of general surgery, LNH Karachi over the period of January 2023 to march 2024. Axillary lymph node status was assessed clinically and radiologically and all suspicious lymph nodes were confirmed via histopathological evaluation. Sentinel lymph node biopsy was done in all patients undergoing surgery after neoadjuvant chemotherapy and all patients with upfront surgery having negative axilla on initial biopsy. Axillary lymph node dissection was done in all patients with positive sentinel lymph node biopsy.

Results: Total 180 female patients above age of 18 years with T3 breast lesion were evaluated. Total 144 patients had suspicious axillary lymph node base on clinical and radiological evaluation among which 104 had axillary metastasis on initial FNAC or trucut biopsy. Out of 180 patients 134 had taken neoadjuvant chemotherapy and 46 had upfront surgery. Assessment of results showed axillary clearance in 82 patients out of 180 patients. Similar results were noted with association of poor prognostic features with axillary clearance. 13 out of 39 patients with her 2 positive disease and 10 out of 39 patients with triple negative disease and 10 out of 51 patients with grade III disease underwent axillary clearance.

Conclusion: Sentinel lymph node biopsy is as effective as axillary lymph node dissection in staging of patients with T3 breast lesions with 100% identification rate and markedly reduced morbidity This study shows high rate of axillary metastasis in T3 breast lesion with high rate of axillary lymph node tumor positivity in T3 breast lesions with poor prognostic factors as advanced age, her 2 positive disease, triple negative status and high grade of tumor but due to modified neoadjuvant treatment and its high efficacy on disease with positive poor prognostic factors, rate of axillary metastasis was noted to be significantly reduced and in case of axillary lymph node dissection, patients would have suffered with high morbidity.

Introduction

Breast cancer is one of the most common malignancies affecting women worldwide. Its prognosis and treatment are heavily influenced by the tumor size and the extent of metastasis. Tumor size is a critical determinant in the staging of breast cancer, with T3 lesions characterized by tumors larger than 5 cm in the greatest dimension. The frequency of metastasis in T3 breast cancer lesions is notably high, with significant implications for patient outcomes and treatment strategies. Lymph node involvement and tumor size are the most important factors in the prognosis of breast cancer and remain crucial for individual treatment decisions

Axillary lymph node involvement is a common occurrence in T3 breast cancer, with studies indicating that approximately 60-80% of patients present with lymph node metastasis at the time of diagnosis (1). The risk of

distant metastasis is also elevated in these patients, ranging from 20-40% (2). The high propensity for metastatic spread underscores the necessity for accurate staging and effective management strategies.

The sentinel node biopsy (SNB) has emerged as a pivotal procedure in the staging and management of breast cancer. This minimally invasive technique involves the identification and examination of the sentinel lymph node, the first node to which cancer cells are likely to spread from the primary tumor (3). The status of the sentinel node is a crucial prognostic indicator and influences subsequent treatment decisions. Studies have demonstrated that SNB has a high accuracy rate in detecting lymph node metastasis, providing reliable staging information with fewer complications compared to full axillary lymph node dissection (4).

Tumor biology also plays a significant role in nodal evaluation in T3 breast lesions. Factors such as hormone receptor status, HER2/neu overexpression, and molecular subtypes of breast cancer can influence the likelihood of lymph node involvement and metastasis (5). For instance, triple-negative and HER2-positive breast cancers are often associated with higher rates of lymph node metastasis compared to hormone receptor-positive subtypes (6). Understanding the biological characteristics of the tumor can aid in predicting the extent of nodal involvement and tailoring appropriate treatment strategies. Overall, young patients, high-grade tumors, and high proliferative indices are considered bad prognostic factors. Considering the large tumor size T3, which is itself a higher stage, it is important to note whether there is any correlation with these known clinic pathological markers

Given the high frequency of metastasis in T3 breast cancer lesions and the critical role of sentinel node biopsy in managing this disease, it is essential to investigate these aspects further to improve patient outcomes. This study aims to evaluate the frequency of nodal metastasis in T3 breast cancer lesions, the influence of known adverse prognostic markers, and tumor biology on nodal metastasis evaluation. It would be important to know the impact of sentinel node biopsy on treatment planning and prognosis, in this subgroup of patients.

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 Department of General surgery Liaquat National Hospital Karachi over the period of January 2023 to march 2024 after the approval of ethical research committee. Sample size of 180 patients was calculated using previously available literature showing 86.6% metastatic axilla in T3 breast cancer (20) with 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 and confidentiality was preserved. 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, 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 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 . 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

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 prior to neoadjuvant therapy underwent sentinel lymph node biopsy. Sentinel lymph node biopsy was done intraoperative using methylene blue dye in all patients and minimum of 3 lymph nodes were sent for frozen section. 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, 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 association between qualitative variables. P-value less than 0.05 were considered as significant.

Results

Total 180 female patients with mean age of 50.03 years having T3 breast lesions on clinical examination were analyzed. Upon physical assessment smallest tumor size included 5.5*5.5 cm and largest tumor size included 15*11 cm. 17 (9.4%) out of 180 patients had positive family history of breast cancer. All of the patients underwent radiological and histopathological evaluation of the breast lumps. All patients had radiologically suspicious breast lesions confirmed pathologically via trucut biopsy, along with biomarkers identification. Pathologically tumor characteristics included 173 (97.11%) invasive ductal carcinoma and 7 (3.8%) invasive lobular carcinoma. Most tumors were Nottingham histological grade II accounting for 70% cases**.** Biomarkers evaluation showed 113 (73.3%) ER positive, 118 (65.6%) PR positive, 39 (21.6%) Her2Neu positive and 39 (21.6%) triple negative patients.

Based on age, 67 (37.2%) patients were <45 years and 113 (62.7%) patients were >45 years of age. 31 out of 67 patients in age group <45 years had axillary clearance and 51 out of 113 patients with age > 45 years had axillary clearance. Among 180 patients 17 (9.4%) had positive family history of breast cancer including 8 with biopsy proven metastatic axilla, 6 biopsy proven and 3 patients with clinically and radiologically benign axilla, out of which 7 patients underwent axillary clearance.

Assessment of surgical procedure showed 39 modified radical mastectomy, 91 mastectomy and sentinel lymph node biopsy among which 33 had axillary clearance, 50 breast conserving surgery and sentinel lymph node biopsy among which 10 had axillary clearance. Post operatively 123 patients had undergone radiotherapy and 129 patients had taken hormonal therapy (table 1).

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

Axilla were evaluated clinically and radiologically via U/S in all patients. Among 180 patients, 65 (36.1%) had clinically palpable and 144 (80%) had radiologically suspicious axillary lymph nodes. All the clinically palpable lymph nodes were radiologically suspicious except 1 patient having clinically palpable but radiologically benign axillary lymph nodes. 32 (17.7%) patients had clinically as well as radiologically benign axilla**.** All patients with clinically palpable lymph nodes underwent FNAC and those with radiologically suspicious lymph nodes underwent U/S guided trucut biopsy. Among 144 patients who underwent histopathological evaluation of axillary lymph nodes, 104 (57.8%) came out positive for tumor metastasis to axilla**.** Metastatic workup done in all patients was negative for any distant tumor spread.

Among 180 patients included in the study, 134 (74.4%) had taken neoadjuvant chemotherapy followed by surgical intervention at the completion of chemotherapy and 46 (25.5%) patients underwent upfront surgery. Descriptive details are explained in **table 2.** Among 134 patients receiving neoadjuvant chemotherapy, 80 patients had pathologically proven metastatic axilla, 38 patients had biopsy proven benign axilla and 16 patients had clinically and radiologically benign axilla. Among 80 patients with metastatic axilla, 13 had radiologically suspicious lymph nodes at the end of chemotherapy so underwent modified radical mastectomy. 34 patients had positive sentinel lymph node and 33 patients had negative sentinel lymph node on frozen section. Among 38 patients with biopsy proven benign axilla prior to neoadjuvant chemotherapy, 2 came out positive for tumor metastasis and 1 patient out of 16 with clinically and radiologically benign axilla had metastatic axilla on sentinel lymph node biopsy making it a total of 50 patients with metastatic axilla among neoadjuvant group. All the patients with metastatic axilla on frozen section underwent level I and II axillary clearance. Analysis showed decrease in frequency of metastatic axilla from 44.4% prior to chemotherapy to 27.7% after neoadjuvant treatment. Among 46 patients who underwent upfront surgery, 24 had biopsy proven metastatic axilla so underwent modified radical mastectomy. 10 patients had biopsy proven benign axilla, among which 6 patients had positive sentinel lymph nodes on frozen section and underwent axillary clearance. 12 patients among upfront surgery group had clinically and radiologically benign axilla, among which 2 came out positive for axillary metastasis on sentinel lymph node biopsy, making it total of 32 patients who underwent axillary clearance among upfront surgery group.

Table 2. Summary of lymph node metastasis SLNBx 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

Descriptive details of association of poor prognostic features with lymph node positivity are explained in **table 3.** Assessment of axillary status in relation to hormonal status showed, 39 (21.6 %) patients were her2 neu positive and 39 (21.6%) patients were triple negative.

Triple negative: Among triple negative patients, 25 had biopsy proven metastatic axilla among which 4 underwent upfront surgery (MRM), 21 patients post neoadjuvant chemotherapy had sentinel lymph node biopsy among which 6 came out positive for metastasis and underwent axillary clearance. 12 patient with triple negative biology had biopsy proven and 2 had clinically and radiologically benign axilla. All these patients had taken neoadjuvant therapy and all of them had negative sentinel lymph nodes later on at the time of surgery. Total of 10 (5.5%) patients with triple negative disease had axillary clearance.

Her 2 positivity: 39 (21.6%) patients had her2neu positive disease. Among these 21 (11.6%) had biopsy proven metastatic axilla, 12 had biopsy proven benign and 6 had clinically and radiologically benign axilla. Among biopsy proven metastatic axilla group, 3 underwent upfront surgery (MRM), 18 had neoadjuvant chemotherapy out of which 8 patients had positive sentinel lymph node later on. Among biopsy proven benign group 1 patient had upfront surgery with positive sentinel lymph node, 11 patients underwent neoadjuvant therapy following which all had negative sentinel lymph nodes. Among 6 patients with clinically and radiologically benign axilla, 3 had upfront surgery, among which 1 had positive sentinel lymph node making it a total of 13 (7.2%) her2neu positive patients with axillary clearance.

Grading: Based on Nottingham histological grading, 3 (1.66%) patients had grade I, 126 (70%) Grade II, 51 (28.3%) had grade III disease. Among grade I 1 patient had clinically and radiologically benign disease, 2 had biopsy proven negative axilla, sentinel lymph node biopsy after neoadjuvant chemotherapy showed benign axilla in all 3 patients. Among grade II, 73 patients had biopsy proven metastatic axilla, 30 patients had biopsy proven and 23 patients had clinically and radiologically benign axilla. 92 patients underwent neoadjuvant chemotherapy and 36 patients later on had axillary clearance. 34 patients underwent upfront surgery out of which 22 had axillary clearance making it a total of 58 (32.2%) patients with axillary clearance**.** Total 47 patients with grade II disease had axillary clearance. Among grade III patients, 31 had metastatic axilla on initial biopsy, 16 had biopsy proven and 4 had clinically and radiologically benign axilla. 39 patients underwent neoadjuvant chemotherapy out of which 14 had axillary clearance later on and 12 had upfront surgery out of which 10 had axillary clearance making it a total of 24 (13.3%) patients with axillary clearance.

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 negative 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

Analysis of poor prognostic features with sentinel lymph node positivity showed statistical significance of triple negative disease with axillary metastasis. Though high rate of axillary lymph node metastasis was noted yet no statistical significance was seen related to age, positive family history, high tumor grade and her 2 neu positive disease **(table 4)**

Table 4 : Prognostic features with sentinel lymph node positivity

Table 4.	**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)	

Discussion

Breast cancer is the most common cancer among females with tumor size and nodal involvement being the most important factors in the prognosis of breast cancer and remain crucial for individual treatment decision (10). In relation to tumor size, axillary lymph node involvement is more likely in tumor >5 cm with up to 80% lymph node positivity rate in T3 breast cancer (2). Axillary lymph node dissection determines the accurate lymph node stage as well as can be beneficial in loco regional control but is associated with significant morbidity in up to 9% of patients (8). Over the last few years and with the advent of newer treatment modalities including neoadjuvant chemotherapy, radiation, hormonal therapy, the surgical approach to breast cancer has become less aggressive (11) as the concept of sentinel lymph node biopsy has emerged and has been determined as the high accuracy method for determining the axillary status (12). Some articles also show that 32.5% of T3 and T4b patients had pathologically negative sentinel lymph node biopsy and if direct axillary clearance would have been achieved, they would have suffered from over treatment (23)

Nodal recurrence becomes controversial when sentinel lymph node biopsy is performed without axillary clearance in patients who had positive axilla before chemotherapy however post neoadjuvant therapy axillary lymph nodes become negative. (15-18). National comprehensive cancer network guidelines allow sentinel lymph node biopsy rather than axillary clearance for the staging of patients whose clinically nodal status has changed from positive to negative after neoadjuvant therapy. Studies including NSABP B18 AND B27 shows low loco regional recurrence rate in patients with ypN0 after neoadjuvant chemotherapy. (19)

In our study we have assessed frequency of tumor positive axillary lymph nodes clinically, radiologically and pathologically both before and after neoadjuvant chemotherapy and association of poor prognostic factors with lymph node status. Axillary lymph node status was assessed in 180 patients, all having T3 breast lesions. Effect of poor prognostic factors such as age, her2 positivity, and triple negative status, high tumor grade, positive family history of breast cancer on axillary metastasis was assessed. Among 180 patients with T3 breast lesions 80% had clinically and radiologically suspicious axillary lymph nodes among which only 57.8% came out positive for tumor metastasis on FNAC/trucut biopsy, which is similar with the results shown by Takei et al, which showed axillary metastasis in 59.3% cases (26). Among patients who underwent neoadjuvant chemotherapy, 80 patients (44.44%) had metastatic axilla which after neoadjuvant chemotherapy decreased to 47 patients on sentinel lymph node biopsy accounting for 27.7% patients with positive axillary lymph nodes for tumor metastasis. Among patients whose initial biopsy was negative and underwent neoadjuvant chemotherapy, 3 patients later on came out to be

positive for tumor metastasis. Among 46 patients who underwent upfront surgery, 32 had metastatic axilla, making it a total of 45.5% patients who needed axillary clearance. These results are consistent with uyan M (31) which showed statistically significant difference in axillary lymph node metastasis between neoadjuvant and non neoadjuvant therapy group.

Table 5 Systemic review regarding association of T3 breast cancer with axillary metastasis.

Table 5. Study	T stage	No of cases	Positive SLNBX N (%)
De Oliveira et al (10)	T3	38	17 (44.7)
Takei et al (26)	T3	91	54 (59.3)
Wong SL et al (32)	T3	31	23 (74.2)
Bedrosian et al (33)	T3	20	16 (80)
Greer et al (34)	T3	30	16 (53)
Coros et al (35)	T3	135	117 (86.6)
Bernardi et al (25)	T3	16	9 (56.3)
Okamoto et al (36)	T3	20	7 (35)

Assessment of poor prognostic factors: Some studies state that neoadjuvant chemotherapy and with increased effectiveness of systemic therapy showing a good response especially in aggressive tumor features as triple negative and her2 positive, the approach to the direct axillary clearance needs to be modified (14). Triple negative disease is an important poor prognostic factor associated with 10-15% of invasive breast cancer and presents with high grading and frequent metastasis (28). In our study association of triple negative disease with axillary metastasis showed that 39 patients (21.6%) had triple negative disease among which 25 patients had axillary metastasis on initial biopsy which decreased to 10 patients after neoadjuvant treatment who had to undergo axillary clearance in comparison to 43.8% (29) and 64% (30) patients with axillary metastasis in triple negative disease in previous studies. Her 2 neu positivity, another poor prognostic factor overexpressed in 20% of breast cancer (24). In our study 39 patients (21.6%) had her 2 positive disease which is similar with results depicted by Englander K et al (22) as per which 33.3% of patients with T3 and her2 positive disease were noted to have axillary metastasis, however in our study only 7.2% underwent axillary clearance by the time of surgery at the end of neoadjuvant treatment. Similarly association of axillary metastasis with grade II and III shows positive rate of 40.5% and 17.2% respectively which is similar to the results of venketash PM (27) post neoadjuvant shows decrease in axillary metastasis and axillary lymph node dissection to 32.2 and 13.3 % in grade II and grade III respectively. Similar results are noted in considering association of positive family history and advanced age with axillary metastasis.

Some studies have shown a false negative rate of up to 10% in sentinel lymph node biopsy with nodal tumor positivity later on paraffin studies (7). Some studies show identification rate of sentinel lymph node biopsy was 100% (10). Another study shows T3 breast cancer patients who underwent axillary clearance after sentinel lymph node biopsy show 3% false negative rate with accuracy of 98% (13). This study shows high rate of axillary metastasis in T3 breast lesion with high rate of axillary lymph node tumor positivity in T3 breast lesions with poor prognostic factors as advanced age, her 2 positive disease, triple negative status and high grade of tumor but due to modified neoadjuvant treatment and its high efficacy on disease with positive poor prognostic factors, rate of axillary metastasis was noted to be significantly reduced and axillary lymph node dissection in such cases as preferable to sentinel lymph node biopsy would have been associated with significant increase in morbidity and overtreatment. In our study identification rate of sentinel lymph node biopsy was 100% with no evidence of false negative or false positive results.

Strengths of study

- Prospective study.
- Depicts frequency of axillary lymph node metastasis both before and after neoadjuvant chemotherapy.
- Depicts frequency of axillary lymph node metastasis in patients with poor prognostic factors.

Limitations

- Single center study.
- This study does not follow patients on long term basis so cannot assess recurrence in patients who underwent sentinel lymph node biopsy only as compared to patients who had axillary clearance.
- Other factors prognostic for axillary metastasis such as tumor location not explained.

Conclusion

Sentinel lymph node biopsy is as effective as axillary lymph node dissection in staging of patients with T3 breast lesions with markedly reduced morbidity.

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