

Association of Level III Axillary Lymph Node Positivity with Clinicopathological Characteristics in Breast Cancer

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Abstract: Management of breast cancer has gradually shifted from era of radical surgery to present days of multi-modality management and conservatism. While complete axillary dissection is common for node-positive cases, less invasive approaches like sentinel node biopsy are often sufficient for clinically node-negative cases. However, these findings may not apply to all populations, particularly in India where advanced disease presentation is common. The objective of this study is to assess Level III Axillary Lymph Node Positivity with clinicopathological characteristics in Breast cancer.

This was a hospital based retrospective observational study on breast cancer patients conducted in single institute from 2016 to 2022. A total of 70 patients with operable breast cancers, who underwent primary tumour resection and complete axillary lymph node dissection, including level III were included in the study. Patients with inoperable and metastatic disease were excluded. Final histopathological examination data was collected and analysed.

Most patients (92.9%) underwent Modified Radical Mastectomy, with Infiltrating Ductal Carcinoma (IDC) being the most common histology (90%). Factors significantly associated with level III lymph node positivity included tumour size >4.5cm, nuclear grade III, pathological N3 stage and extra nodal extension. The study found no significant correlation with other factors like age, tumour laterality, location, hormone receptor status, HER2 status, or LVSI. These findings may help predict level III lymph node involvement in breast cancer patients. All these predictive factors should be considered during the axillary dissection.

Keywords: Axillary Lymph Nodes, Level III Lymph Node Dissection, Breast Cancer, ALND, level III, Mastectomy.

INTRODUCTION

Breast cancer is the most common cancer affecting women globally, accounting for 25.4% of all new cancer cases. It is the leading cause of cancer death in 103 countries including India [1]. Recent years has noted a trend of increasing incidence of young breast cancer in India and it accounts for 10-20 % of all breast cancers [2-4]. Surgery remains the cornerstone of treatment of non-metastatic breast cancer. In carefully selected patients, Modified Radical Mastectomy and Breast Conservation Surgery are proven to have analogous outcomes. For the planning of appropriate adjuvant therapy, it is necessary to adequately stage the axilla. In most of the node-positive cases, performing a complete axillary dissection is usually the norm. There is a significant possibility of a clinic-radiologically node negative axilla for harbouring occult metastatic disease, in up to 30 – 40% of the cases [5]. In clinically node-negative cases, instead of performing complete axillary dissection, low axillary sampling or a sentinel node biopsy is adequate to stage the axilla

[6,7]. In the event of negative axillary lymph nodes on sentinel node biopsy or low axillary sampling, one can waive off a complete axillary dissection, with an acceptable false-negative rate of 10% [8]. Morbidity in node-negative patients can be significantly reduced by limiting the extent of axillary dissection.⁵ In the scenario of presence of clinically positive axillary lymph nodes or positive nodes on sentinel node biopsy, completing axillary dissection is the current practice [9].

The dissection of level III ALNs, located between the costoclavicular ligament of Halsted and the medial border of pectoralis minor, is associated with a slightly longer surgical time and associated morbidity.⁹ There is no international consensus on how many anatomic levels of axilla need to be addressed as a part of routine axillary dissection. National Comprehensive Cancer Network (NCCN) guidelines recommend to clear level I and II of the axilla only [10].

The objective of this study was to determine the extent of level III ALN involvement, importance of level III ALND (Axillary Lymph node Dissection) and to study the relationship of apical (level III) lymph node positivity with different clinical and pathological characteristics of the primary tumour and level I and II axillary nodes.

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METHODS AND MATERIALS

The study was a hospital based retrospective observational study where a total of 70 Patients of biopsy proven operable breast cancers (early and locally advanced), up-front or post neo-adjuvant chemotherapy were included in the study. Patients with inoperable and metastatic disease were excluded.

A detailed history and physical examination were done for all the patients. All the information regarding demographics, clinical details and treatment details were recorded. After the complete preoperative work up and staging, all the patients underwent primary tumour resection, followed by complete axillary lymph node dissection. Level III lymph node dissection was done for all the patients. Inter-pectoral space was opened and dissection was done if any suspicious node present as a routine protocol. Level III lymph nodes and inter-pectoral nodes were marked separately, along with level I and II lymph nodes that goes with the primary specimen for final histopathological examination (HPE). Data was recorded and analyzed as per the aims and objectives of the study.

The collected data were analyzed with IBM.SPSS statistics software version 25.0. To describe about the data, descriptive statistics were used. Frequency analysis and percentage analysis were used for categorical variables and Mean & Standard Deviation (S.D) were used for continuous variables. To find the significant difference between the bi-variate samples in independent groups, Unpaired sample t-test was used.

The probability value 0.05 is considered as significant level.

RESULTS

A total of 70 biopsy proven breast cancer patients were included in the study with a median age of 52 years. The tumours were predominantly located in the outer quadrant in 45 patients. The minimum tumour size was 2cm and maximum tumour size was 11cm, with a mean of 4cm. A total of 25 (35.7%) patients had received neo-adjuvant chemotherapy. 65 patients underwent Modified Radical Mastectomy (MRM) and 5 patients underwent Breast Conservation Surgery (BCS). On Post Operative HPE, IDC was the most Common histological type (90%). A total of 52 patients were Hormone receptor (Oestrogen and/or Progesterone receptor) positive and 18 patients were HeR2 positive. Tumor characteristics and Surgery details are given in Table 1.

The number of axillary lymph nodes harvested from level I and level II to axilla ranged from 9 to 31 lymph nodes, with a mean of 16.4 lymph nodes, out of which metastatic deposits were seen at least in one lymph node in 34 patients. 22 out of these 34 patients with positive axillary lymph nodes had extra nodal extension.

Total number of apical lymph nodes (level III) harvested ranged from 0 to 11, with a mean of 2.91 lymph nodes, out of which metastatic deposits were positive at least in one apical node in 13 patients. None of the patients had skip metastases to apical (level III) nodes. Inter-pectoral lymph node dissection was

Table 1: Tumour and Treatment Characteristics (N: Number)

Tumor characteristics	Variable	N	Percentage
Tumor Location	Central	13	18.60%
	Lower Inner	3	4.30%
	Lower Outer	9	12.90%
	Upper Inner	6	8.60%
	Upper Outer	39	55.70%
HR Status	Negative	18	25.70%
	Positive	52	74.30%
HER2 Status	Negative	57	81.40%
	Positive	13	18.60%
Treatment-Surgery	BCS	5	7.10%
	MRM	65	92.90%
Total		70	100%

carried out in 43 out of 70 patients (61.4%). Out of the 43 patients, at least one lymph node was identified in 12 patients. Out of the 12 patients, only one patient had metastatic deposits in the inter-pectoral nodes.

On comparing tumour grade, pathological tumour size (pT), pathological nodal involvement (pN) and ENE (Extra-nodal Extension) with Apical Lymph node Positivity (APLN), grade III tumours (92.3%), pT2-T3, pN3, and ENE had high APLN which was statistically significant (Table 2).

On univariate analysis (χ^2 test), tumour size greater than 4.5cm (p=.0005), presence of histologic nuclear grade III (p=.001), pathological N3 stage (p=.0005), presence of extra nodal extension (ENE; p=.0005) and presence of more than 6 metastatic axillary (level I and II) lymph nodes were significantly associated with level III (apical) lymph node metastases.

On comparing Tumour location and hormonal status with the APLN, outer quadrant tumours had high chance of apical lymph node positivity (61.5%) and Hormone positive and Her2 Negative tumours had high chance of APLN. However, these results were statistically not significant (Table 2). Age, tumour laterality, tumour location, hormone receptor status, HER2 receptor status and presence of lymphovascular space invasion (LVSI) did not correlate significantly with level III involvement (Table 3).

DISCUSSION

Surgical management of breast cancer has seen a gradual and significant transition from radical mastectomy to breast conservation therapy. In a similar manner, surgical management of the axilla has also seen a parallel shift from complete axillary dissection to sentinel lymph node biopsy [3]. A mathematical model was constructed in Milan using data of 1,446 patients,

Table 2: Comparison of pT, N, ENE and Grade with APLN. p<0.05 Statistically Significant

Variable			APLN		Total	p-value
			Present	Absent		
Grade	I	n	0	1	1	0.001
		%	0.00%	1.80%	1.40%	
	II	n	1	36	37	
		%	7.70%	63.20%	52.90%	
	III	n	12	20	32	
		%	92.30%	35.10%	45.70%	
pT size (cm)	T1	n	0	6	6	0.033
		%	0.00%	10.50%	8.60%	
	T2	n	9	47	56	
		%	69.20%	82.50%	80.00%	
	T3	n	4	4	8	
		%	30.80%	7.00%	11.40%	
pN	N0	n	0	36	36	0.0005
		%	0.00%	63.20%	51.40%	
	N1	n	0	11	11	
		%	0.00%	19.30%	15.70%	
	N2	n	2	9	11	
		%	15.40%	15.80%	15.70%	
N3	n	11	1	12		
	%	84.60%	1.80%	17.10%		
Extra nodal Extension	Absent	n	0	48	48	0.0005
		%	0.00%	84.20%	68.60%	
	Present	n	13	9	22	
		%	100.00%	15.80%	31.40%	

Table 3: Comparison of Tumour Location, Grade, Hormone Receptor (HR) Status and LVSI with APLN. p<0.05 Statistically Significant. (n: number, %: Percentage)

Variable			APLN		Total	p-value		
			Present	Absent				
Tumour Location	Central	n	3	10	13	0.861		
		%	23.10%	17.50%	18.60%			
	Lower Inner	n	0	3	3			
		%	0.00%	5.30%	4.30%			
	Lower Outer	n	1	8	9			
		%	7.70%	14.00%	12.90%			
	Upper Inner	n	1	5	6			
		%	7.70%	8.80%	8.60%			
	Upper Outer	n	8	31	39			
		%	61.50%	54.40%	55.70%			
	HR Status	Negative	n	3	15		18	1.000
			%	23.10%	26.30%		25.70%	
Positive		n	10	42	52			
		%	76.90%	73.70%	74.30%			
HER2 Status	Negative	n	11	46	57	0.743		
		%	84.60%	80.70%	81.40%			
	Positive	n	2	11	13			
		%	15.40%	19.30%	18.60%			
LVSI	Absent	n	1	14	15	0.272		
		%	7.70%	24.60%	21.40%			
	Present	n	12	43	55			
		%	92.30%	75.40%	78.60%			
Total		n	13	57	70			
		%	100.00%	100.00%	100.00%			

which predicted that a minimum of 10 axillary lymph nodes(ALN) had to be dissected to not leave behind any residual disease in 90% of patients [11]. Hence, for accurate staging of axilla, as per the TNM staging, it is believed that harvesting a minimum of 10 ALNs is essential.

Clinical examination of the axilla is infamously inaccurate for staging, with a false-positive rate of 30% and a false-negative rate of 45% [12]. Dodging complete axillary dissection is now an accepted standard of care in case of absence of metastases in a or low axillary sampling or sentinel lymph node biopsy. There are significantly higher adverse effects encountered with complete axillary dissection, as compared with sentinel lymph node biopsy in a node-negative axilla [9]. The universally widely accepted false-negative rate of 10% was not found to be inimical

in overall survival as studied in multiple randomized controlled trials [10].

As shown in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 study, albeit the absolute numbers being small, it should be noted that the number of axillary recurrences doubled in the no axillary dissection arm [6]. Low axillary sampling is a routinely followed procedure, in node-negative axilla, which is similar in principle to sentinel lymph node biopsy, with a comparable false-negative rate, proven by adequate evidence [5].

Axillary lymph node metastasis is considered to be the most important prognostic factor for early breast cancer, and as the number of positive lymph nodes increases, the prognosis worsens. The role of axillary dissection in the therapeutic grounds has been questioned by many. It has been labelled only as a

staging procedure for the mere purpose of planning of appropriate adjuvant therapy and prognostication [11.] No survival advantage was reported with axillary dissection for the first time in a landmark randomized trial NSABP B-04 [13]. However, in the no axillary treatment arm, the axillary recurrence rate was 19%. But, a number of other studies have advocated better local control with complete axillary lymph node dissection, which measures up to an improvement in survival [14]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has reported that for every four local recurrences avoided, one life can be saved [15]. The therapeutic advantage of complete axillary lymph node dissection in breast cancer has been proven for patients with positive lymph nodes. Prophylactic axillary node dissection had an average overall survival benefit of 5.4% (2.7% to 8.0%; probability of survival benefit. 99.5%, 95% CI) in a Bayesian meta-analysis of six randomized controlled trials [14].

In patients with a positive sentinel lymph node, the American Society of Clinical Oncology (ASCO) does recommend a complete axillary node dissection. The NCCN (National Comprehensive Cancer Network) recommends routine clearance of level I lymph nodes and palpation for presence of nodes in level II and III [9]. In a Cochrane review done recently, treatment with limited axillary surgery (axillary sampling or sentinel lymph node biopsy) reduced the overall survival when compared to complete axillary node dissection (HR, 1.09, 1.01 to 1.17; 95% CI ;18 studies; 6,478 patients) [16]. The conclusion of this review was that limited axillary clearance is acceptable only in proven cases of pathologically node-negative axilla.

In our analysis, we found a high incidence of level III ALN involvement (ie, 18.57% of total patients and 38.23% of all node-positive patients). The probability of level III axillary lymph node positivity was as high as 56.5% when four or more lymph nodes were positive in level I and II of axilla ($p = .0005$). Hence, more than 50% of patients with high level I and II axillary nodal burden carry the risk of having residual disease in the axilla, if level III is not addressed during surgical clearance. In a similar study done at Turkey, 31% of patients had positive level III axillary lymph nodes among the 86 patients undergoing a mastectomy. Other similar studies done in 1987 and 2011 have found level III axillary lymph node positivity ranging from 15% to 59% [17,18]. Documented incidence of skip metastases to level III ALNs range from 0% to 15% of patients; but we found the rate of level III lymph node skip metastases to be 0% [17,19].

In our study, tumour size greater than 4.5cm, presence of poor histologic nuclear grade, pathological N3 stage, presence of extra nodal extension and presence of more than 6 metastatic axillary (level I and II) lymph nodes were significantly associated with level III (apical) lymph node positivity. Few other studies have tried to demonstrate the correlation between some other clinicopathologic factors and level III lymph node positivity. In a study by Chua *et al.* 320 patients were analyzed. Involvement of level III lymph nodes was observed in 7% of patients (22 patients), and 16% patients (51 patients) had four or more positive nodes. In the above study, palpability of axillary nodes, pathologic tumour size, and Lymphovascular space invasion, presence of four or more positive nodes were significantly associated with involvement of level III axillary nodes by univariate and multivariate analyses [20]. Up to 42% of patients in this study had level III axillary node involvement when four or more ALNs were positive, similar to the 56.52% seen in our study.

Khafagy *et al.* reported that 53.5% of patients with nodal metastases in lower axillary levels had level III axillary nodal involvement. Veronesi *et al.* also reported that, as the number of positive lymph nodes in lower levels increase, there will be an incremental risk of level III axillary node involvement [17]. In another study by Fan *et al.* from China, even after stage I and II breast cancer patients receiving preoperative neoadjuvant chemotherapy, 47 out of 521 patients (9%) had residual positive nodal disease. These patients showed a significantly worse distant disease-free survival when level III axillary nodes were involved (84.9% and 91.6% in level III node positive and negative groups, respectively; $p = .011$) [21].

We found overall inter-pectoral node positivity to be 8.3% in our study. If an inter-pectoral node was found on histopathology, it was positive 22.2% of the time. Other studies have shown range of inter-pectoral node positivity between 0.1% to 14% [22,23]

Our study is one of the few prospective series addressing separate level III axillary lymph node dissection. However, as this is an observational study, done for a relatively short period, one of the main shortcomings of our study is to not be able to study the impact of level III dissection and level III lymph node positivity on survival. Alongside the relatively small sample size, also mention clearly that the lack of survival data and long-term follow-up are key limitations of this study.

CONCLUSION

In our study, the factors determining the possibility of axillary level III lymph node positivity are large tumours size, poor histologic nuclear grade, presence of extra nodal extension, metastatic level I and II axillary nodes. It is reasonable to consider level III clearance according to these risk factors, but its impact on survival still needs further investigation.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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