



Histopathological indicators of lymph node positivity in breast cancer patients: A Retrospective analysis

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Abstract

Objective: Since axillary lymph node involvement is the main cause of breast cancer surgical morbidity, identifying lymph node metastasis predictions might improve clinical outcomes. To predict the association of axillary lymph node positivity with involvement in breast cancer by using histopathological indicators.

Material and Methods: A retrospective study was performed on 50 breast cancer patients who had modified radical mastectomy at Pt. BDS Post-Graduate Institute of Medical Sciences, Rohtak, India from March, 2019 to March, 2021. Tumour size, histological type, grade, lympho-vascular invasion, hormonal and Her2/status, Ki67 index, and molecular

subtype were acquired from histopathological reports. The association between tumour features and lymph node status was assessed.

Results: Age at diagnosis, lymphovascular invasion, Her2/neu status, and Her2/neu-enriched molecular subtype were significantly associated ($p < 0.05$) with lymph node positive. Nodal metastases [54% (27/50)] and high Ki67 index [24% (12/50)] associated with lymph node positivity in total number of patients.

Conclusion: This study predicted breast cancer axillary lymph node involvement using lympho-vascular invasion, age at diagnosis, Her2/neu status, Her2/neu-enriched molecular subtype, and Ki67 index. This data may be utilized for breast cancer diagnosis and treatment.

Keywords: Breast carcinoma, Lympho-vascular invasion, Her2/neu status, Ki67 index, Axillary lymph node status

Introduction:

Breast cancer was the leading cause of global cancer incidence as in 2020, with an estimated 2.3 million cases, representing 11.7% breast cancer cases among all cancer cases. With around 685,000 deaths worldwide, it is the fifth leading cause of cancer mortality. It accounts for 1 in 4 cancer cases and for 1 in 6 cancer deaths among women, ranking first for incidence and for mortality in the vast majority of countries including India (1,2). Clinically imminent and prognostic indicators are essential for breast cancer therapy. Axillary lymph node involvement is the most important histological marker for predicting prognosis and is substantially related with disease-free and overall survival (3).

Women with breast cancer receive no benefit after the removal of non-involved axillary lymph nodes (4–6). Since many decades, axillary dissection has been used to identify women with metastatic nodes and choose adjuvant treatment since clinical examination poorly predicts node involvement (7).

Today, axillary dissection is less suited for treatment selection, because systemic therapy is increasingly being recommended in large proportions of women with node-negative breast cancer (8–10). Moreover, its significant contribution to the long-term morbidity by disrupting the anatomy and resulting in lymphedema, nerve injury, shoulder dysfunction, and other complications has therefore rendered it as overtreatment for many women (7,11–14). An oversight for methods that avert unnecessary axillary dissection are thus imperative for females with invasive breast carcinoma (7,15,16).

Predictive models for lymph node involvement may provide a way to guide the surgeon in treatment selection. A description of the associations of histopathological characteristics of primary tumour with lymph node status could provide clues regarding the biologic mechanisms underlying the behavioural variations of lymph node metastasis. The primary aim of this study was to determinate the predictive factors of axillary lymph node metastasis using histopathological information derived from mastectomy specimens of breast cancer patients.

Materials and Method:

A retrospective analysis was carried out in the General surgery department of Pt. BDS Post-Graduate Institute of Medial Sciences, Rohtak, India, during the period from March 2019 to March 2021. A total number of 50 patients, including one male patient, were diagnosed with

breast cancer in the outpatient clinic and were admitted for pre-operative investigations. All of them underwent modified radical mastectomy with axillary lymph node dissection and were considered for this study. Patients receiving neoadjuvant chemotherapy and those with recurrent disease were excluded in the study. The specimens retrieved were sliced at 1cm interval and overnight fixation was achieved by keeping them in 10% formalin solution. Following standard protocol gross examination was done. Enough blocks were prepared, ensuring adequate sampling. Staining of thin sections was done with routine Haematoxylin and Eosin stain.

Information was collected from the histopathological reports concerning tumor size (the largest dimension of the gross specimen), histological subtype, grade, lymphovascular invasion (LVI) by tumor emboli, status of estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2/neu) status, Ki67 index and the molecular subtype. The tumor size was classified into three categories based on the T stage: 2 cm or less, 2-5 cm and more than 5 cm. As per the demographic details, the age of the patient at the time of diagnosis was also included as a parameter in this study. The relationship between tumor characteristics and lymph node status was evaluated (Table 1).

Table 1: Association of various parameters with Lymph node metastasis.

Parameters	Positive Lymph Nodes		p value
	Yes (n = 27)	No (n = 23)	
Age			0.048
21-30 Years	2 (66.7%)	1 (33.3%)	
31-40 Years	5 (100.0%)	0 (0.0%)	
41-50 Years	11 (68.8%)	5 (31.2%)	
51-60 Years	6 (46.2%)	7 (53.8%)	
61-70 Years	1 (16.7%)	5 (83.3%)	
71-80 Years	2 (33.3%)	4 (66.7%)	
81-90 Years	0 (0.0%)	1 (100.0%)	
LVI present	17 (81.0%)	4 (19.0%)	0.001
HER2neu			0.034
Negative	10 (38.5%)	16 (61.5%)	
2+	6 (66.7%)	3 (33.3%)	
3+	9 (81.8%)	2 (18.2%)	
Ki67			0.041
<15%	4 (33.3%)	8 (66.7%)	
>15%	9 (75.0%)	3 (25.0%)	
Molecular Subtype			0.042
Luminal A	2 (33.3%)	4 (66.7%)	
Luminal B	6 (66.7%)	3 (33.3%)	
HER2Neu Enriched	10 (83.3%)	2 (16.7%)	
Basal	7 (36.8%)	12 (63.2%)	

Statistical Analysis:

Data were coded and recorded in Microsoft Excel spreadsheet program. SPSS v23 (IBM Corp.) was used for data analysis. Statistics were expressed in form of Means ± Standard deviation for continuous variables and percentage for categorical variables. Fisher’s exact test and Chi-square test were performed to compare the rates of axillary lymph node positivity between various study groups. Spearman’s correlation and Pearson’s correlation were used to analyse the association of two continuous variables. Univariate and Multivariate

binary logistic regression analysis were carried out to evaluate different risk factors associated with axillary lymph node involvement and to determine the odds ratio (OR) and 95% confidence intervals (CI) for likelihood of axillary lymph node metastasis. All p-values lesser than 0.05 were regarded as statistically significant.

Results:

Out of total 50 cases included in this study, axillary lymph nodes were isolated in all of them and in more than half of the investigated cases (n = 27) histological confirmation of metastasis was found. The range of involved lymph nodes was between 1 and 16.

The age range observed in our patients was from 28 to 81 years, with mean age being 53.62 ± 13.86 years. A total of sixteen cases (32%) were observed in the age group of 41-50 years and represented the majority group, followed by the age group of 51-60 years which had thirteen cases (26%). Study showed significant association between different ages at breast cancer diagnosis and lymph node metastases with largest positivity seen in the 31-40 years age group as mentioned in Figure 1 & 2. Among all the histological types of breast carcinoma, the most commonly diagnosed was invasive ductal carcinoma - no special type i.e., 39 cases (81.2%), followed by Medullary carcinoma (12%) and Papillary carcinoma, Metaplastic carcinoma and invasive lobular carcinoma - classic type (1 case each). The most common histological grade observed was grade II (44.4%) followed by grade III (33.3%) and grade I (22.2%) tumours. There was no significant association between histology and grade as stated in Figure 3 & 4. LVI was observed in 21 cases (48.8%). 81% of cases with presence of LVI had metastatic lymph nodes and thus showing a strong positive association was seen demonstrated in Figure 5.

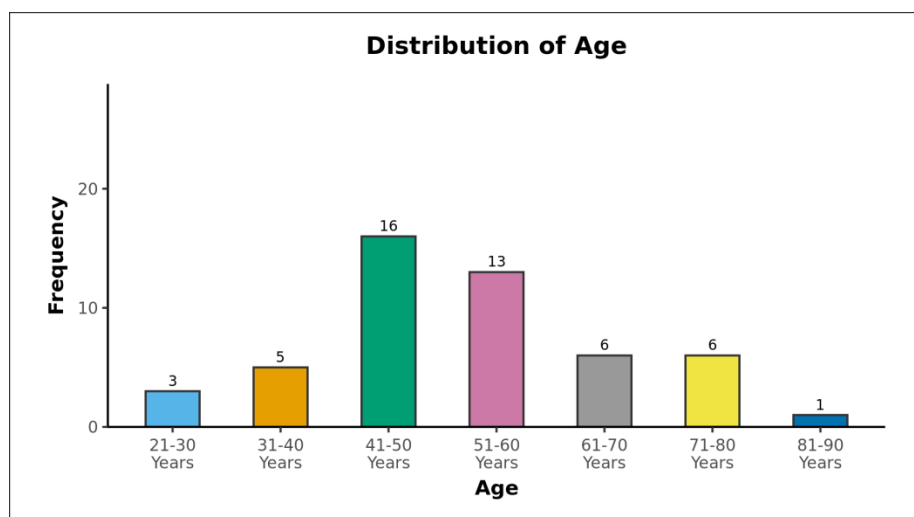


Figure 1: Age distribution with Lymph node metastasis

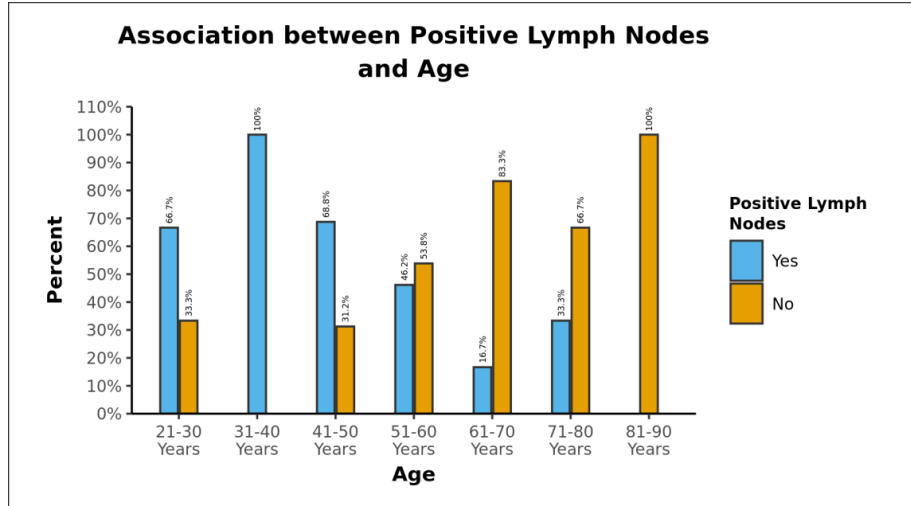


Figure 2: Association of Age with Lymph node metastasis

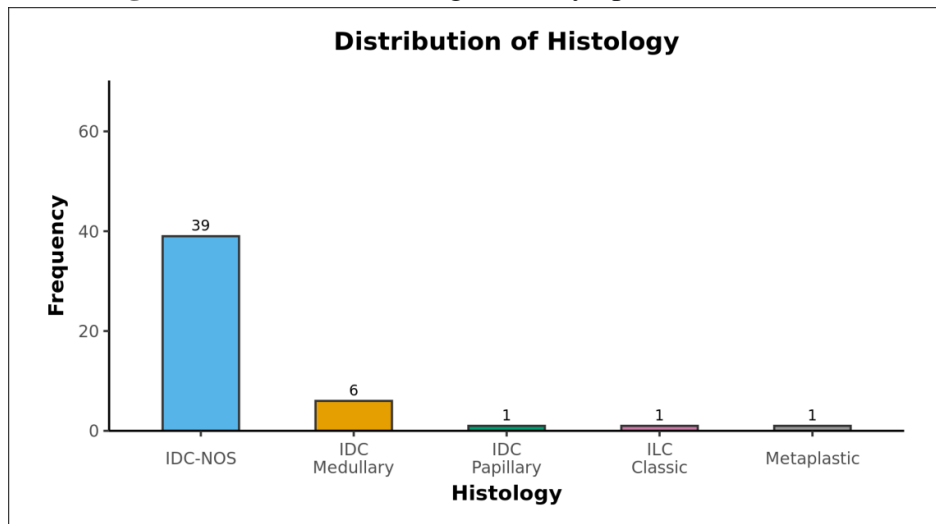


Figure 3: Distribution of various histological types

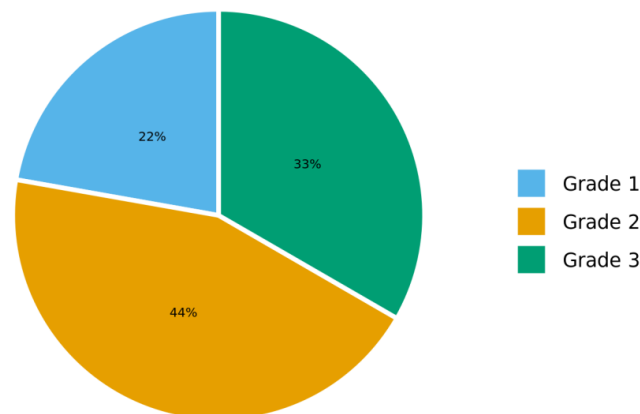


Figure 4: Distribution of various grades

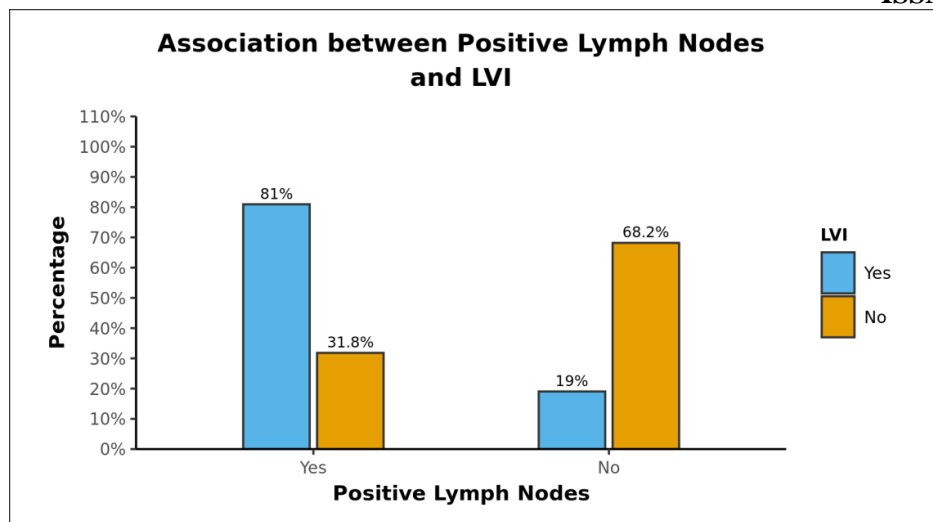


Figure 5: Association of LVI with Lymph node metastasis.

This study demonstrated that most common pathological T stage was T2 (56.2%, n=27) stage followed by T1 (25%, n=12), T3 (12.5%, n=6) and T4 (6.3%, n=3). In this study there was no significant association of tumor size and axillary lymph node metastasis. The overall positivity for ER was observed in 30.4% of cases and that for PR was found to be in 26.1% of cases. Lymph node metastasis was not related to hormone receptor status.

HER-2/neu overexpression was seen in 43.5% of the cases in the present study. 75% of cases with HER-2/neu overexpression showed lymph node positivity confirming a strong association as shown in Figure 6. Based on collective expression of ER, PR and HER2/neu molecules, 19 of the cases were categorized as triple negative/basal types, while luminal type A, luminal type B and HER2-neu enriched type were documented in 6, 9 and 12 cases, respectively. Among the 9 luminal type B cases, 1 of them was luminal/HER2-negative and 8 were luminal/HER2-positive cases (Figure 7).

Although, data collection for the information on Ki67 index was done in only 24 cases, and this analysis suggested a strong association between high Ki67 and lymph node positivity, with 75% cases with high Ki67 showing lymph node metastasis.

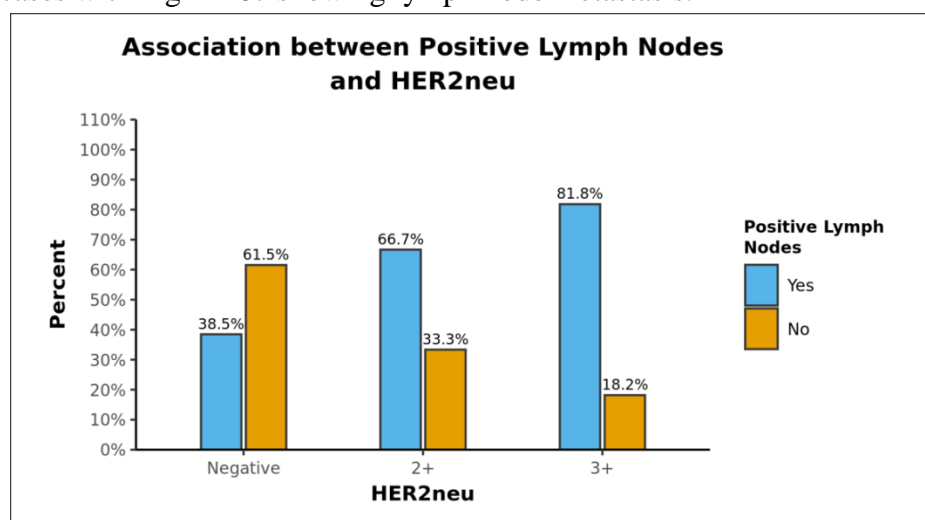


Figure 6: Association of Her2/neu expression with Lymph node metastasis.

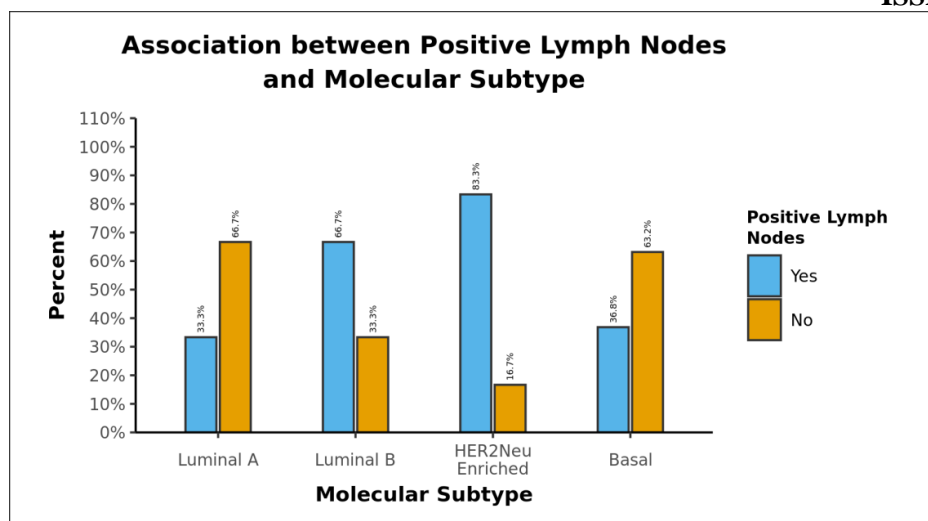


Figure 7: Association of Molecular subtypes with Lymph node metastasis.

Discussion:

The presence of axillary lymph node involvement seen in our study of 50 breast tumors (54%) is more than the incidence scale described in literature (33.2% - 39%) (17). In our study, age seemed to be negatively related to lymph node involvement and this data showed compatibility to previous studies (18). On univariate and multivariate regression analysis, age had a fairly weak relationship with lymph node involvement (OR per 10-year increase 0.93 in univariate and 0.92 in multivariate with 95% CI). In the study by Wildiers et al. (19) after the age of 70 years, increasing age positively affected the risk of lymph node involvement and this was weakly concordant with our study where 33.3% of patients in the age group of 71-80 years showed lymph node involvement. The outcome of age on lymph node involvement by age was found to be nonlinear. Studies conducted by Barth A et al (20) and Ravdin et al (21) shows tumour grade and histology have been described to have a pivotal role in lymph node metastasis, but we did not find a significant association between them.

The most significant characteristic of primary tumours related to nodal involvement in our study was observed to be the presence of LVI. In a study by Rezaianzadeh et al (22), the prognostic role of LVI was notably associated with involvement of axillary lymph nodes. LVI has been frequently shown to be a predictor of lymph node metastasis in many studies (22)(23,24). In multivariate analysis, LVI was consistently the most significant variable associated with nodal disease with an OR of 6.62 at 95% CI. Hence it may be regarded as the precursor of nodal involvement and can be used as a decision-making tool in the therapeutic protocol of breast cancer patients. Olivotto et al (25) reported a close relationship between axillary lymph node metastasis and primary tumour size. The chances of involved nodes were seen to increase with increasing tumour size in many other studies (20,26), but in this study, there was no significant association concurring with data of previous studies.

There was a significant association between various molecular subtype groups and axillary lymph node metastasis with HER2/neu-enriched molecular subtype showing the highest risk of lymph node metastasis (83.3%). Ahmed AR et al showed that HER-2/neu overexpression served as a strong independent predictor for lymph node metastasis in breast cancer patients (27). This study shows a strong association of HER2/neu overexpression and lymph node involvement. On Univariate regression analysis, Her2/neu-enriched subtype was seen to be a

strong predictor for lymph node metastasis (OR=10 with 95% CI), thus confirming the importance of Her2/neu overexpression in assessing the metastatic potential of breast cancer. The predictive role of ER and PR status in past studies has been debatable, with some studies concluding their negative correlation with lymph node involvement (17,18). Concordant to their findings, in this study also we could not establish any relationship between both hormone receptor status and lymph node metastasis. We defined 'high Ki67' based on St. Gallen Consensus on the primary therapy of early breast cancer and set it to $\geq 15\%$ (28-51). The study was concurrent with findings of study conducted by Yin Y. et al which suggested that Ki-67 positivity has value both as a prognostic and predictive biomarker in breast cancer (28)..

Conclusion:

The analysis of various primary tumour features like LVI, Her2/neu status, molecular subtype and Ki67 index, will enable surgeons to separate breast carcinoma patients into separate groups as far as management of axillary lymph node is concerned. This Study concludes LVI, Her2/neu overexpression, Her2/neu-enriched molecular subtype and high Ki67 as best predictive variables for axillary lymph node metastasis and age is independently associated with axillary lymph node involvement. Despite few limitations like small sample size and retrospective nature, the current data may provide an insight towards tailoring the management protocol of breast cancer patients and avoid long term morbidity in them.

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Conflict of interest: No conflict of interest.

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