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Original Article

Oncology Section

Tumour Characteristics Predicting Axillary Nodal Metastasis in Early Breast Cancers- A Study from Southern India

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ABSTRACT

Introduction: Breast cancer is the commonest cancer among women in India and the leading cause of cancer related deaths. In patients with invasive breast cancer, axillary nodal metastasis remains as the most important predictive factor for recurrence and survival, despite progression made in molecular and genetic characterisation of these cancers.

Aim: To know the nodal positivity rate and pathologic predictive factors of nodal positivity in early breast cancer in Indian patients, which may help in predicting the axillary status pre-operatively.

Materials and Methods: This study was retrospective review of patients treated in Cancer Institute, Chennai, Tamil Nadu, India between January 2011 to October 2014 for invasive breast cancer which were clinical T1 and T2 and either N0 or N1. Pathologic characteristics of the primary tumour such as size, centricity, histological type, nuclear grade, and Lympho Vascular Invasion (LVSI), Estrogen receptor (ER) and Progesterone Receptor (PR) Status, Human Epidermal growth factor Rector 2 (HER-2)/*neu* and Ki-67 were analysed and correlated to nodal positivity using univariate and multivariate analysis.

Results: In the univariate analysis using chi-square test, Pathological T stage, number of tumours, LVSI, ER and PR status emerged as significant variables. Variables like pT2 (p-0.032), multiple tumours (p-0.007), LVI (p<0.0001), ER positive (p-0.002) and PR positive (p-0.001) and HER2 -2+ (p-0.040) was found to have positive predictive value with statistical significance. On multivariate analysis, LVSI proved to be a highly significant predictor of positive nodes.

Conclusion: Although variables such as pT2, multiple tumours, LVSI, ER positive, PR positive and HER2+ was found to have positive predictive value with statistical significance, only LVSI emerged as significant independent predictive factors of positive lymph node.

Keywords: Lymphovascular space invasion, Predictive factors, Sentinel node

INTRODUCTION

Breast cancer is one of the leading causes of death among Indian women. As per WHO for the year 2018, there were 1,62,468, new cases of breast cancer and about 87,090 women in India died of the disease [1]. Overall incidence rate of breast cancer is 25.8/Lac among Indian women when compared to 95/Lac among women in UK [2]. In western countries majority of breast cancer present in stage I and II, however in India, about 45.7% present in advanced stages [3]. Due to greater awareness and rising incidence due to westernised lifestyle in urban women, breast cancer is the commonest cancer and, among rural women, it is the second most common cancer after cervical cancer [4]. With increase in mammographic screening, the breast tumours are detected in smaller size with lower incidence of nodal metastasis. This has led to a more conservative approach to addressing the axilla.

Axillary node metastasis is considered the most important prognostic indicator for all invasive breast cancers and axillary lymph nodal dissection has been considered to be the standard of care, as clinical examination has poor sensitivity and specificity. It is essential for prognostication and planning further treatment. Axillary dissection is associated with complications like, shoulder stiffness, lymphedema. In order to reduce these complications Sentinel Lymph Node Biopsy (SLNB) had been introduced for T1 and T2 tumours with clinically no palpable lymph nodes.

Many factors like multifocality, increased grade, tumour location, tumour size, presence or absence of LVSI, have all been implicated in predicting lymph nodal metastasis [5]. The contribution of age, histology, hormonal receptor status, HER-2 on lymph nodal metastasis is controversial [6].

The use of predictive factors as alternate to axillary surgery to estimate nodal metastatic risk can be applied to patients with carcinoma breast with a very low risk of nodal involvement and who can be spared of the axillary surgery. These factors along with gene expression and clinicopathologic models have been studied [7].

We had earlier analysed the clinical factors which can be used as predictive factors in same population of early breast cancers and concluded, age of patient, tumour location and nature of surgery performed as significant predictive factors for axillary nodal metastasis [8].

The purpose of this study was to evaluate the relation between pathologic factors of carcinoma breast and axillary lymph nodal involvement. Hence these data can be used to preoperatively predict who are likely to be node-negative and thus most likely to benefit from SLNB.

MATERIALS AND METHODS

It was a retrospective study done in Cancer Institute, Chennai, a tertiary teaching hospital, in Chennai, Tamil Nadu, India where all clinical early breast cancers treated from January 2011 to October 2014 were analysed, after Institute ethical committee approval and patients consent.

All the patients with invasive breast cancer which were clinical T1 and T2 and either N0 or N1 were reviewed for present study. The demographic features of the patients, clinical history, physical findings and pathological features of the biopsy as well as prognostic markers were looked upon.

All early breast cancers had pathological confirmation either by fine needle aspiration cytology or core biopsy. Patients who had undergone either Modified radical mastectomy or breast conservative surgery with complete axillary dissection, including level 3 lymph nodes were included in analysis. A total of 27 patients who had an excision biopsy for diagnosis were also included. There were a total of 608 patients eligible for study.

Clinical tumours more than five cm (T3), male patients, patients who have undergone excision biopsy elsewhere, who have had incomplete axillary dissection or received neo adjuvant therapy were excluded. A lymph node status was recorded as palpable or non-palpable if it could be felt or not felt respectively by the examiner irrespective of whether, they were identified radiologically.

Pathologic characteristics of the primary tumour considered were size, single or multicentric origin, histological type, nuclear grade, and lymphatic/vascular invasion, ER and PR status and HER-2/*neu* and Ki-67 were analysed. Number of axillary lymph nodes dissected and number of nodes being positive for metastatic deposits were also noted. Size of the tumours was categorised using the TNM system of the American Joint Committee on Cancer 8th edition. Invasive carcinomas were classified using the largest dimension of the invasive component to size: T1a-5 mm or less; T1b- 6-10 mm; T1c-11-20 mm; T2- 2-5 cm [9].

The axillary contents and all identified lymph nodes were dissected and sectioned through the hilum and examined histologically. Histological type of the lesion, histological grade of the tumour, and lymphatic and vascular invasion which were evaluated on routine haematoxylin and eosin slides was noted. The ER and PR analyses were based on an IHC assay. IHC analysis was performed on the formalin-fixed, paraffin embedded breast cancer tissue specimens. Any nuclear staining of invasive tumour cells was considered as positive, for ER and PR. HER2 status was also evaluated by IHC. IHC was performed as per the standard methodology using primary antibodies; clone ID5-ER (DAKO, Glostrup, Denmark), clone PgR636-PR (DAKO, Carpinteria-CA), clone HER2/*neu* (c-erbB2). Ki-67is a proliferative biomarker and is considered to be prognostic factor for breast cancer. Ki-67 expression is measured as the percentage of tumour cells positively stained by the antibody, with nuclear staining being the most common criterion for the positivity. A cut-off point of 14% was considered as distinction between low and high proliferative tumours [10].

STATISTICAL ANALYSIS

The association between the characteristics of the patients and survival was evaluated with a univariate and multivariate analysis. The adjusted OR's, 95% CI's and p-values <0.05 were considered to be significant. Statistical analysis was performed using SPSS software (IBM SPSS Statistics Version 17; Chicago IL). Multivariate logistic regression analysis was done to assess the relationship between the nodal status and pathologic variables, adjusting for other factors.

RESULTS

In this study 608 patients of Clinically T1, T2, N0, N1 carcinoma breast that were treated, were analysed. There were 248 patients with pathologically positive nodes [Table/Fig-1].

Clinical	Number	Percentage
T1N0	28	4.6%
T1N1	83	13.7%
T2N0	52	8.6%
T2N1	445	73.2%
Total	608	100.0%

[Table/Fig-1]: Clinical distribution.

The minimum age of the patient was 27 years and the maximum age was 80 years with an average of 51 years. Most patients were within the age group of 41 to 50 years comprising of 198 patients, 32.6% of the study group. Next common age group was between 51-60 years. When we combined the age group, 307 (50.5%) were found between 50-75 years of age.

Pathological variables, stratified with axillary nodal status are presented in [Table/Fig-2].

		Node status		Total
Variables	Grades	Negative	Positive	
pT size	0-1.0 (2.79%)	12	5	17
	1.1-2.0 (30.26%)	120	64	184
	2.1-3.0 (45.23%)	161	114	275
	3.1-4.0 (16.11%)	55	43	98
	4.1-5.0 (3.45%)	8	13	21
	>5 (2.13%)	4	9	13
Tumour origin	Single (91.94%)	340	219	559
	Multiple (8.05%)	20	29	49
Multiple tumours	Multifocal (3.45%)	8	13	21
	Multicentric (4.6%)	12	16	28
Grade	I (0.49%)	2	1	3
	II (15.46%)	59	35	94
	III (84.04%)	299	212	511
Histology	IDC (96.05%)	343	241	584
	ILC (1.64%)	5	5	10
	Papillary (0.16%)	1	0	1
	Mucinous (1.15%)	7	0	7
	Medullary (0.98%)	4	2	6
LVSI	Absent (80.01%)	341	146	487
	Present (19.9%)	19	102	121
ER	Positive (74.34%)	251	201	452
	Negative (25.65%)	109	47	156
PR	Positive (61.34%)	201	172	373
	Negative (38.65%)	159	76	235
HER -2	1+ (24.83%)	100	51	151
	2+ (36.67%)	124	99	223
	3+ (38.48%)	136	98	234
Ki-67	0-14 (3.28%)	13	7	20
	>14 (96.71%)	347	241	588

[Table/Fig-2]: Patient characteristics.
IDC: Infiltrating ductal carcinoma; ILC: Invasive lobular carcinoma; pT: Pathological T stage

In this study, majority were T2 lesions, which were similar in distribution as that of clinical size. Pathologically, 13 cases were found to be T3 lesions even though clinically T3 lesions were not included. In this study, there was an increasing trend towards the nodal positivity rate as the size of the tumour increases, but was found to be insignificant on multivariate analysis [Table/Fig-3,4].

A total of 248 (40.78%) patients were found to have pathological nodes, even-though 528 patients were found to have clinically palpable axillary nodes. The mean number of lymph nodes being evaluated was 16.48 nodes per patient. In this study, 25 patients were found to have pathological N3 disease as shown in [Table/Fig-5].

While clinically, 28 patients had multiple tumours, on final HPE, 49 patients had multiple tumours. Among the multiple tumours patients with positive nodes, 13 patients had multifocal disease and 16 patients had multicentric disease. Grade III lesions were 511 (84%), with 212 (41.48%), having node positive disease. Even though there was increased node positive rate as the grade increased, it was not found to be significant in present study.

Infiltrating Ductal Carcinoma (IDC) was the most common being 95.9%, and Invasive Lobular Carcinoma (ILC) being only 1.7%. IDC had 41.3% Positive nodes; ILC had 50% positive nodes. Mucinous and papillary did not have any positive nodes while medullary tumour had 33.3% positive nodes and histological type of tumour had no significant relation to nodal positivity. 19.9% (121) patients had LVSI and among them 102 (84.29%) patients had positive lymph nodes.

Variables in the equation					
		Unadjusted odds ratio	95% C.I.		
			Lower	Upper	p-value
p T size (0-1.0 cm) vs. Others	0-1.0				**0.041**
	1.1-2.0	1.280	0.432	3.794	0.656
	2.1-3.0	1.699	0.583	4.957	0.332
	3.1-4.0	1.876	0.614	5.733	0.269
	4.1-5.0	3.900	0.996	15.276	0.051
	>5	5.400	1.120	26.044	**0.036**
pT1 vs. Others	T1				0.049
	T2	1.472	1.033	2.096	**0.032**
	T3	2.868	0.783	10.509	0.112
Single Tumour vs. Multiple Tumour	Multiple	2.251	1.242	4.079	**0.007**
Grade III vs. Others	Grade III				0.718
	Grade I	0.705	0.064	7.827	0.776
	Grade II	0.837	0.532	1.317	0.441
Types IDC vs. Others	IDC				0.977
	ILC	1.423	0.408	4.970	0.580
	Papillary	0.000	0.000		1.000
	Mucinous	0.000	0.000		0.999
	Medullary	0.712	0.129	3.916	0.696
LVI Absent vs. Present	Present	12.539	7.405	21.232	**<0.0001**
ER Negative vs. Positive	Positive	1.857	1.259	2.741	**0.002**
PR Negative vs. Positive	Positive	1.790	1.273	2.517	**0.001**
HER2 Negative vs. Positive	HER2 1+				0.113
	HER2 2+	1.565	1.020	2.403	**0.040**
	HER2 3+	1.413	0.923	2.163	0.111
KI671 Low vs. High	High	1.290	0.507	3.280	0.593

[Table/Fig-3]: Univariate analysis-unadjusted odds ratio.

Variables in the equation					
		Adjusted odds ratio	95% C.I.		
			Lower	Upper	p-value
pT size (0-1.0 cm) vs. Others	0-1.0				0.126
	1.1-2.0	0.770	0.208	2.846	0.695
	2.1-3.0	0.999	0.267	3.738	0.999
	3.1-4.0	1.210	0.306	4.785	0.786
	4.1-5.0	3.073	0.597	15.826	0.179
	>5	2.551	0.391	16.656	0.328
Single vs. Multiple	Multiple	2.113	0.902	4.947	0.085
LVI Absent vs. Present	Present	13.673	7.755	24.106	**<0.0001**
ER Negative vs. Positive	Positive	1.563	0.850	2.875	0.151
PR Negative vs. Positive	Positive	1.291	0.752	2.217	0.355
HER2 Negative vs. Positive	HER2 1+				0.384
	HER2 2+	1.427	0.858	2.374	0.171
	HER2 3+	1.298	0.781	2.158	0.314

[Table/Fig-4]: Adjusted odds ratio: multivariate analysis.

pN Stage	Number	Percentage	Number
N0	360	59.2%	
N1	180	29.6%	1 node-95 2 nodes-54 3 nodes-31
N2	43	7.1%	
N3	25	4.1%	
Total	608		

[Table/Fig-5]: Pathological nodal distribution.

Hormonal receptor status is mentioned in [Table/Fig-6]. Similar to LVSI, ER positive patients had higher nodal positivity rate in 201 patients (44.5%), when compared to ER negative of 47 patients (30.1%), which was highly significant on univariate analysis but not on multivariate analysis. PR positive tumours had higher nodal positivity when compared to PR negative tumours and were statistically significant on univariate analysis but again similar to ER status; on multivariate analysis it was found to be not significant. Among the nodal positive cases 169 were ER and PR positive, while 44 patients were ER and PR negative.

	PR				
ER	Positive	(%)	Negative	(%)	Total
Positive	365	60.03 (%)	87	14.30 (%)	452
Negative	8	1.31 (%)	148	24.34 (%)	156
Total	373		235		608
Nodal positivity					
	PR				
ER	Positive	(%)	Negative	(%)	Total
Positive	169	68.14 (%)	32	12.90 (%)	201
Negative	3	1.20 (%)	44	17.74 (%)	47
Total	172		76		248

[Table/Fig-6]: Both estrogen and progesterone receptors distribution.

A total of 98 (41.8%) out of 234 HER-2 positive tumours had node positive disease. HER-2 was negative in 151 patients and 51 (33.3%) among them being node positive. On univariate analysis it was found that HER-2 Positive cases had higher rate of nodal positivity compared to HER-2 negative tumours. But it was not statistically significant.

In this study 588 patients had high Ki-67 value, compared to only 20 patients with low value of 0-14. Among them, 241 in the higher group and 7 from the lower group had nodal positive disease.

DISCUSSION

Axillary dissection remains the gold standard in prognostication, planning further therapy. With mammographic screening becoming prevalent, more tumours are detected at smaller size with lower incidence of axillary nodal metastasis [11]. These patients may not benefit from axillary dissection, and suffer from its complications. This had led to study of factors predicting axillary nodal metastasis in addition to sentinel node biopsies. Factors predicting axillary nodal metastasis, may not predict sentinel node metastasis with similar sensitivity and specificity.

The incidence of breast cancer in Asian women peaks in their forties, whereas among European and American women, it peaks in their sixties [12]. The median age in present study was 51 years with age range between 27-80 years; this was similar to the study by Raina V et al., among Indian patients in whom the median age was 47 years (range 23-82 years) [13]. In study by Tan LGL et al., among Singapore patients, the median age of the subjects was 52 years, with a range from 24 to 87 years [14].

Pathological T Stage

Both in node positive and node negative cases T2 lesion was more common. In the study by Tan LGL et al., among Singapore T2 lesions were 41.1%, whereas in study by Lee JH et al., among Korean population, the T2 lesions comprised of 45.7% [14,15].

The relation of the tumour size and axillary lymph nodal positive rate is evident in multiple other studies also [Table/Fig-7] [14-17]. But this proportional relationship may not be very reliable, as cases with small primary with extensive nodal metastasis have been reported, with an aggressive clinical course [18].

Study (reference)	Tumour size (mm)				
	≤5	6~10	11~20	21~30	31~50
Tan LGL et al., [14]	2/40 (5%)	5/46 (9.2%)	24/110 (21.8%)	73/165 (44.2%)	
Lee LH et al., [15]	23/380 (6.3%)	37/380 (9.6%)	163/380 (43.0%)	157/380 (41.1%)	
Orang E et al., [16]	33/789 (4.18%)		127/789 (18.81%)	164/789 (24.29%)	216/789 (27.37%)
Silverstein MJ et al., [17]	3/45 (7%)	37/166 (22%)	171/541 (32%)	262/525 (50%)	
Present study	5/17 (29.4%)		64/184 (34.7%)	114/275 (41.4%)	56/119 (47%)

[Table/Fig-7]: Tumour size with relation to positive nodes [14-17].

Pathological N Stage

It is well known that a manual clinical examination of the axilla has poor sensitivity and specificity. In present study, although 86.8% had clinically positive node, only 40.78 had pathological nodal positivity. In the study, by Lee JH et al., positive axillary lymph nodes were detected in 104 patients for an overall incidence of 28.8% in early breast cancer, with mean number of lymph nodes of 15.4±5.2 [15]. Of the 380 subjects, studied by Tan LGL et al., 136 (35.8%) were found to be node positive. The median number of nodes examined was 14 (±6.81), with a range of 1-41 [14].

Number of Tumour

In the study by Yoshihara E et al., 87.22% of the patients had unifocal tumour and 12.78% had multifocal tumour. In present review 8% patients had multiple tumours on pathological examination. There was two-fold increased chance of multiple tumours being node positive when compared to single tumour with an odds ratio of 2.251 with a 95% CI, and it was found to have statistically significant. But again in multivariate analysis it was not found to be significant [19].

Grade

Even though there was increased node positive rate as the grade increased, being 33%, 37% and 41% for Grade I, II, III tumours respectively, it was not found to be significant in present study. Similarly, in the study by Lee JH et al., the nodal positive rate among Grade I, Grade II, Grade III was 4 (3.8%), 28 (26.9%), and 35 (33.7%), respectively and in the study by Tan LGL et al., the nodal positive rate for grade I, II, and III was 21.0%, 34.3% and 50.5% respectively [14,15].

Histological Type

In present study even though ILC had 50% rate of nodal positivity when compared to IDC with a positivity rate of 41.3%, it was not significant, and may be due to the less number of patients. In the study by Lee JH et al.,, IDC was the predominant histological type seen in 315 patients (87%), followed by medullary carcinoma in 20 patients (5%). There was no difference in the distribution of axillary lymph nodal metastasis among the different histological types [15]. In the study by Tan LGL et al., IDC were 84.5% and ILC 3.4% and others being 12.1%. Nodal positive rate was 39.6% for IDC and 30.8% for ILC and 10.9% for others [14]. In the study by Yoshihara E et al., also the Ductal carcinoma constituted 91.39% and Lobular 10.99% [19].

LVSI of the Tumour

The presence of LVSI is a well-known risk factor for nodal metastasis. Chakraborty A et al., in his review of 426 patients in eastern India had similar results, in patients who had no LVI, 38.97% had axillary node metastases, compared with 76.81% where LVI was present [20]. Tumour with LVI had the highest chance of nodal positivity rate more than 12.5 times the tumour without LVI and it had high statistical significance both in univariate analysis and also on multivariate analysis. Similar results with relation to LVSI and axillary lymph nodes were seen in other studies too. In the study by Tan LGL et al., 75.4% patients were node positive among the patients with LVI [14]. In study by Sandoughdaran S et al., among Iranian population, LVSI emerged as the most powerful independent predictor of axillary nodal metastasis [21].

Hormonal Receptor Status

As in present study, other studies have showed that nodal positivity was more among the patient with ER positivity and or PR positivity [Table/Fig-4]. Recent data have shown incidence of breast cancer increasing in India and Pakistan, particularly ER, PR negative cancers. Only 20-45% of Indian patients were detected to have ER, PR positive tumours. In comparison to western population, Indian patients have been shown to have lower ER positivity. In study by TMH, Mumbai, tumours expressing ER and/or PR comprised 51.2% of which 73.4% expressed both ER and PR [22]. In series by He ZY et al., he noted, that PR concentrations were independently associated with increased risk of axillary nodal metastasis [23].

KI67

Ki-67 proliferative index has been shown to have a significant relation to lymph nodal positivity. In the study by Ivkovic-Kapicl T et al., 43% of patients with high Ki-67 had node positivity, in contrast only 14% of low Ki-67 proliferative index were node positive [24]. In present study also tumours with higher Ki-67 had higher chances of nodal positivity but it was not found to be statistically significant.

In patients considered for breast reconstruction, risk of nodal involvement may influence the timing of reconstruction. Patients with low risk of nodal metastasis can be offered primary reconstruction, and in patients with high risk of nodal disease, delayed reconstruction can be considered. Also, patients with high risk of nodal metastasis may still be candidates for sentinel node biopsy, as a subgroup of them, can avoid axillary dissection.

Limitation(s)

Present main limitation is the retrospective nature of study and being conducted in a single institution.

CONCLUSION(S)

Our study was aimed at knowing the nodal positivity rate in early breast cancer patients and pathologic predictive factors of nodal positivity in early breast cancer in Indian patients, which may help in predicting the axillary status pre operatively. Although variables such as pT2, multiple tumours, LVSI, ER positive, PR positive and HER2+ was found to have positive predictive value with statistical significance, only LVSI proved to be a highly significant predictor of positive nodes in present study and LVSI emerged as significant independent predictive factors of positive lymph node. These data can be used to tailor treatment protocols for effective diagnosis and treatment, improving the quality of life. Prospective studies are required to further prove the significance of these factors.

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