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Original Research Article

Clinical predictors of axillary lymph node metastasis in early breast cancer in Indian patients

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ABSTRACT

Background: Surgical dissection is the accepted mode of staging the axilla in breast cancer. Proper prediction of axillary node positivity can help towards stratifying patients. The primary objective of the study was to assess the clinical factors influencing pathological axillary lymph node positivity in early carcinoma breast.
Methods: This was a retrospective study, conducted at a tertiary cancer centre. Case records of all the patients with invasive breast cancer which are clinical T1 and T2 and either N0 or NI, from January 2011 to October 2014 were analysed. Clinical profile of the patient including age, BMI, comorbid, menstrual history, family history, symptoms, site of the lesion, size, single or multi centric origin were analysed.
Results: Total of 608 patients of early breast cancer analysed of which 248 had pathological nodal positivity. The age group of 51 to 75 years, BMI ≥30, pre-menopausal patients had significant positive predictive value when compared to post-menopausal. Tumours in lower outer quadrant, central sector and multiple tumours also had positive predictive value. Clinical T2 when compared to clinical T1 stage and MRM when compared to BCS had significant positive predictive value.
Conclusions: To conclude in present study age of the patient and clinical location of the tumour and surgery performed emerged as significant independent predictive factors of positive lymph node. Prospective studies are required to further prove the significance of these factors.

Keywords: Axillary nodes, Breast cancer, Predictors, TNM staging

INTRODUCTION

Breast cancer is one of the leading causes of death among Indian women. Earlier cervical cancer was the most common cancer but over last ten years, breast cancer has been rising and at present, breast cancer is the most common cancer among Indian women. Overall incidence rate of breast cancer is 23.5/Lac among Indian women when compared to 90.7/Lac among western women. Early breast cancer constitutes only 30% of the breast cancer cases seen at regional cancer centre in India.[1] Whereas it constitutes 60-70% of cases in the developed world. Due to greater awareness and rising incidence in Urban Indian females, breast cancer is the commonest cancer and among rural Indian women, it is the second most common cancer after cervical cancer.[2]

Axillary lymph node metastasis is still considered the most important prognostic indicator for all invasive breast cancers, in spite of new tumour markers. Clinical examination of the axilla is not reliable and has poor specificity and sensitivity. Hence, axillary lymph nodal

dissection or sentinel node biopsy is considered to be the standard of care. Although the therapeutic role of axillary lymph nodal dissection is questionable, it is required for prognostication and planning adjuvant treatment.[3]

The mode of axillary lymph nodal involvement is not very clear. Several factors like multiple foci, higher grade, lateral and Retro-areolar location of the tumour, larger size of the tumour and presence of lympho-vascular invasion has been said to predict the lymph node metastasis.[4] The predictive role of age, histological subtype, ER/PR and HER-2 on axillary nodal status is controversial.[5] Many studies have shown that if we can exactly predict the axillary status in early breast cancer patients, we can plan the axillary surgery accordingly and there by prevents its complication.[6]

The main purpose of this study was to evaluate the predictive factors of axillary lymph nodal involvement based on demographic and clinical factors. Hence, by preoperatively predicting the axillary status, the patient care can be optimized by changing the extent of surgery.

METHODS

Case records of all the patients with invasive breast cancer which are clinical T1 and T2 and either N0 or NI, who were treated in this institute from January 2011 to October 2014 were analysed. The demographic features of the patients, clinical history, physical findings were noted. A lymph node lesion was recorded as palpable or non-palpable if it could be felt or not felt respectively by the examiner irrespective of either they were identified radiologically.

All early breast cancer cases who had undergone surgery were included in this analysis. Also 27 patients who had an excision biopsy in this institute for diagnosis were included.

Patients of all age groups, invasive early breast cancer (T1, T2, N0, N1) treated by upfront surgery, patients who are primarily treated in this institute, patients who have under gone BCS/MRM, patients who have complete axillary dissection (level I/level II/level III) were included. Male patients, those who have under gone excision biopsy outside, incomplete axillary dissection, received neo adjuvant therapy were excluded. The association between the characteristics of the patients and survival was evaluated with a Cox-model in univariate and multivariate analysis.

RESULTS

In this study, 608 patients of clinically T1, T2, N0, N1 carcinoma breast that were primarily treated in this institute from January 2011 to October 2014 were analysed. Of which 248 patients were found to have pathological nodal positivity (Table 1).

Table 1: Pathological nodal positivity.

Nodes	Number	Percentage
Negative	360	59.2%
Positive	248	40.8%
Total	608	100%

Age distribution: the age distribution ranged from 27 to 80 years with an average age group of 51 years. When you combine the age group, 50.5% were found between 50-75 years of age. When age distribution and nodal positivity was correlated, node positive patients were common among the 5th decade of life with 88 patients (44.4%) being node positive. Nodal positive rate was 57.1% among the age group 20-35 years and 44.2% among 36-50 years and 36.8% among 51-75 years age group (Table 2).

Co-morbidities: overall around 60.9% had no comorbid, while 14.6% had multiple comorbid, 10.4% had hypertension and 8.6% had diabetes. Among the patients without comorbid, 156 (42.16%) were node positive, while 92/238 (38.7%) patients with comorbid were node positive.

BMI: overall 38.3% of the patients in this analysis were overweight and 21.7% were obese. 3.0% of the study population was under weight. Among the node positive patients 97/248 (39.1%) were with normal BMI when compared to 144/248 (58.06%) patients being either overweight or obese (Table 2).

Menstrual history: mean age of menarche was 14 years. 358 patients were post-menopausal, which included even surgical removal of uterus with average age of around 47 years. Among the post-menopausal patients 128 (51.61%) were node positive and among the pre-menopausal patients 120 (48%) were node positive.

Marital and parity: 600 patients were married and only 8 patients in this study were not married. 33 patients were nulliparous including 8 unmarried patients. 482 (79.2%) patients were multiparous with an average number of children being 2. All the 575 parous patients had breast fed their children for a minimum period of 1 to 2 months to a maximum period of 2 years. Total 11/33 (33.3%) among the nulliparous and 237/575 (41.12%) among the parous had positive nodes (Table 2).

Age of first child birth: the mean age of first child birth was 22 years. Number of patients having first child below 30 years were 535 among them 217 (37.39%) were node positive. Women with ≥30 years at first child birth were 40 patients, 20 (50%) among them were node positive (Table 2).

Family history: 70 patients were noted to have family history of cancer, 23 (32.85%) among them had nodal positive disease.

Clinical profile

Symptoms: all the 608 patients presented with symptoms and none of them were diagnosed incidentally. 590 patients had presented with history of lump, while 17 presented with nipple discharge and only one patient presented with fullness of the breast. Among the patients who presented with lump 241 had node positive and among the patients with nipple discharge 7 had nodal positive disease.

Table 2: Variables and nodal status.

Variables		Total no.	Node negative	Node positive
Age group	21-30	7	4 (57.14%)	3 (42.86%)
	31-40	92	48 (52.17%)	44 (47.83%)
	41-50	198	110 (55.56%)	88 (44.44%)
	51-60	186	108 (58.06%)	78 (41.94%)
	61-70	110	76 (69.09%)	34 (30.91%)
	71-80	15	14 (93.33%)	1 (6.67%)
Comorbids	None.	370	214 (57.83%)	156 (42.17%)
	Present.	238	146 (61.34%)	92 (38.66%)
BMI	<18.5	18	11 (61.11%)	7 (38.89%
	18.5-24.9	227	130 (57.26%)	97 (42.74%)
	25.0-29.9	231	143 (61.90%)	88 (38.1%)
	>=30.0	132	76 (57.57%)	56 (42.43%)
Menopausal status	Post	358	230 (64.24%)	128 (35.76%)
	Pre	250	130 (52%)	120 (48%)
Parity	Nulliparous	33	22 (66.66%)	11 (33.34%)
	Uniparous	93	48 (51.61%)	45 (48.39%)
	Multiparous	482	290 (60.16%)	192 (39.84%)
Age at FCB	<30	535	318 (59.43%)	217 (40.57%)
	>=30	40	20 (50%)	20 (50%)
Family history	Absent	538	313	225
	Present	70	47	23
Symptoms	Lump	590	349 (59.15%)	241 (40.85%)
	Nipple discharge	17	10 (58.82%)	7 (41.18%)
	Fullness of breast	1	1 (100%)	0 (0%)
Laterality	Right	296	166 (56.08%)	130 (43.92%)
	Left	312	194 (62.17%)	118 (37.83%)
Quadrant	UOQ	256	154 (60.15%)	102 (39.85%)
	UIQ	173	117 (67.63%)	56 (32.37%)
	LOQ	61	29 (47.54%)	32 (52.46%)
	LIQ	46	26 (56.62%)	20 (43.48%)
	CQ	44	22 (50%)	22 (50%)
	Multiple	28	12 (42.85%)	16 (57.15%)
Clinical T stage	T1	111	76 (68.46%)	35 (31.54%)
	T2	497	284 (57.14%)	213 (42.86%)
Surgery type	MRM	517	295 (57.05%)	222 (42.95%)
	BCS	91	65 (71.42%)	26 (28.58%)
Site	Single	559	340 (60.82%)	219 (39.18%)
	Multiple-multifocal	21	8 (38.09%)	13 (61.91%)
	Multiple-multicentric	28	12 (42.85%)	16 (57.15%)

Laterality and quadrant: of the 608 patients 312 patients had left sided tumour and 296 had right sided tumour. 43.9% on the right side had positive nodes when compared to left side which was 37.8%. Clinically tumour was found to be most common in UOQ (256), followed by UIQ (173). Patients with LOQ tumour and LIQ were found to be 61 and 46 respectively. 44 patients were found to have central compartment tumours. 28

patients were found to have multiple tumours. Among them multiple tumours had higher percentage of nodal positivity (57.1%), followed by central quadrant tumours with 50% when compared to the other sites (Table 2).

Clinical Tumour and Nodal stage: clinically major bulk of the disease was of T2 comprising of 497 (81.7%) when compared to 111 (18.3%) of T1. All the patients with palpable nodal disease were included in the study with clinical node positive cases being 528/608. 213/497 (42.9%) patients were node positive among cT2 tumours when compared to 35/111 (31.5%).

Clinical stage: in this study clinical T3 tumours and N2 were excluded. Clinical T2N1 comprising of 445 (73.2%) patients was the major group when compared to T1No, T1N1, T2No comprising of 28 (4.6%), 83 (13.7%), 52 (8.6%) respectively (Table 3).

Table 3: Clinical stage distribution.

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

Type of surgery: 517 patients (85%) underwent MRM and only 15% of the patients underwent BCS. Among the MRM patients 42.9% had nodal positivity when compared to 28.6% positivity of BCS patients.

DISCUSSION

The assessment of correlation between various clinical factors and lymph node metastases was done to have a better insight into the prognostication of breast cancer, understanding that nodal metastases is the best single prognostic indicator in breast cancer.

Nodal positive rate: it is well known that a manual clinical examination of the axilla has poor sensitivity and specificity. In this study, 248/608 patients were found to have pathological nodes, amounting to 40.78%, even though clinically 528/608 was found to have clinically palpable axillary nodes. The mean number of lymph nodes being evaluated was 16.48 lymph nodes per patient being examined.

In study of early breast cancer by Lee JH in Korean patients, positive axillary nodes were detected in 104 patients for an overall incidence of 28.8% the mean number of lymph nodes examined per patient was 15.4.[7] Of the 380 subjects studied by the Tan LG among early breast cancer of Singapore, 136 (35.8%) were found to be node positive. The median number of nodes examined was 14.[8]

Age distribution: in Asia, breast cancer incidence peaks among women in their forties, whereas in the United States and Europe, it peaks in their sixties.[9] The median age in this study was 51 years with age range between 27-80 years, this is almost similar to the study by Raina V et al, in whom the median age was 47 years (range 23-82 years).[10] The age in Korean patients with early breast cancer by Lee JH ranged from 28 to 79 years with a median age of 48.0 years.[7] In study by Tan LG, among Singapore patients, the median age was 52 years with a range from 24 to 87 years.[8]

Age in relation to nodal positivity: in this study from 0 to 50 years, 45.45% (135) were found to have positive nodes. Patients with age >50 years had 36.33% (113) nodal positivity. In the study on the Korean patients of early breast carcinoma, nodal positivity in <50 years was 55.6% and in patients with age >50 years the positive rate was 44.4%.[7] Similarly in the study by AL-Qaisy JK who noticed that 45% were node positive in the age group of 28-50 yrs and 31.3% were positive in the 50-72 age group.[11]

In this study, when author categorize the age group it's seen that the nodal positivity was more among the younger age group than the older age group. On Chi-square test overall age was found to be a significant factor of axillary nodal predictive factor but on analyzing the unadjusted odds ratio with 95% CI, it was found that when compared to age group 0-35 years the odds ratio for 36-50 was 0.595 which was not significant and for 51-75 it was 0.437 and it was significant with 95% CI. It implies that the older age group has lesser chance of nodal positivity. Although overall age group was found to be significant, only the age group of 51-75 yrs had significant lesser chance of nodal positivity in this study but on multivariate analysis age did not prove to be significant predictive factor (Table 4 and 5).

Comorbidities: overall around 60.9% of patients did not have any comorbid condition in this study, while 14.6% had multiple comorbid. Comorbidities did not have any predictive value in this study.

BMI: It was observed that urban women were more obese and had relatively larger body size in the early years of life. A positive association was observed between breast cancer risk and augmented anthropometric factors for both pre- and post-menopausal rural and urban women. The study supports the hypotheses that increased anthropometric measures are important determinants of breast cancer in India, although they do not appear to contribute appreciably to the urban-rural breast cancer differences. Similar to other demographic profiles BMI did not have any correlation to nodal positivity, even though when compared to patients with normal BMI others had decreased rate of nodal positivity which was not significant.

Menstrual history: in India premenopausal patients constitute about 50% of all patients. The risk of breast cancer was more for women who had menopause after 50 years compared to women who had menopause before 45 years of age.[12]

In this study, mean age of menarche was 14 years, 358 (58.8%) patients were post-menopausal with average age of around 47 years, pre-menopausal were 250 (41.1%). The study distribution was similar to that of the patient population of Singapore, studied by Tan LG with pre-menopausal being 41.4% and post-menopausal being 58.6 %.[8]

On univariate analysis premenopausal patients had higher chances of nodal positivity when compared to post-menopausal patients and it was highly significant in this study with an odds ratio of 1.659 with 95% CI that means when compared to post-menopausal patient's premenopausal patients had 65% chances of increased nodal positivity and it was statistically significant but on multivariate analysis even though the pre-menopausal showed increased risk it was not statistically significant (Table 4 and 5).

Marital history and parity: nulliparous women were at higher risk of breast cancer than parous women. The risk decreases as parity increases. A case-control study carried out in Mumbai showed that single women compared to married women had 4-5-fold higher risk for development of breast cancer in the age group of 40-54 years and above.[13] In this study, parous patients had higher chances of nodal positivity when compared to nulliparous but statistically it was not significant. Tan LG in their study on early breast cancer also noticed 26.2% of nulliparous and 39% of multiparous had node positive.[8]

Age of first child birth: women who have their first full-term pregnancy at an early age have a decreased risk of developing breast cancer later in life. Even though patients age more than 30 years at the time of their first child birth had 50.0% chances of having nodal positive when compared 40.65% among the patients who have their first child birth before 30 years, it was found to be not significant.

Family history: on statistical analysis there was no significant correlation between family history and nodal positivity. Similar to this study, the study of Tan LG et al, the nodal positive disease was 29.1% and 36.5% in patients with and without family history respectively.[8]

Clinical profile

Symptoms: all the 608 patients presented with symptoms and none of them were diagnosed incidentally, mainly due to lack of screening programme. 590 patients of this analysis presented with history of lump. This is in contrast to the study by Lee JH et al, where 174/361 patients were detected without palpable breast tumour.[7]

Symptoms did not correlate statistically with nodal positivity but patients with nipple discharge had higher trend of nodal positivity when compared to patients presenting with lump. Laterality and quadrant of tumour: of the 608 patients 312 patients had left side tumour and 296 patients had right sided tumour. There was 33% less chance of left breast having nodal positive when compared to right breast, though it was not significant.

When UIQ tumours were taken as baseline it was found that LOQ, central quadrant and multiple tumours had higher rate of having nodal positivity and was statistically significant both by Chi-square analysis as well as with unadjusted ODDS ratio of 95% CI but on multivariate analysis it was found to be not significant (Table 4 and 5). Site of tumour was found to have a predictive value even in the study by Yoshihara E, where the laterally situated tumours had increased nodal positivity when compared to the tumours situated medially.[14]

Clinical stage: in this study, clinical T3 tumours and N2 were excluded. Clinical T2N1 comprising of 445 (73.2%) patients was the major group when compared to T1N0, T1N1, T2N0 comprising of 28 (4.6%), 83 (13.7%), 52 (8.6%) respectively.

On Chi-square analysis, clinically T2 patients were found to have significant nodal positivity, when compared to clinical T1. Even the unadjusted odds ratio was 1.629 with 95% CI that means T2 tumours was found to have 62% higher chance of having nodal positivity when compared to T1 tumours and it was also statistically significant but on multivariate analysis it was not found significant (Table 4 and 5).

Site of tumour origin: on correlating with the site of origin and nodal positive rate it was found that 39.17% of the single lesions were node positive while 59.18% of the patients with multiple tumours were node positive. Even in the study by Yoshihara E, 87.22% of the patients had unifocal tumour and 12.78% had multifocal tumour.[14] Multiple tumours had almost two-fold increased chances of getting nodal positive disease on odds ratio with 2.251 with a 95% CI when compared to a single tumour and it was found to have statistically significant but again in multivariate analysis it was not found to be significant (Table 4 and 5).

Type of surgery: 517 patients (85%) underwent MRM and only 15% of the patients underwent BCS.

MRM formed the major treatment component of this study with 42.9% nodal positive among them when compared to 28.6% nodal positive among the BCS group and it was statistically significant on univariate analysis and even on multivariate analysis also this was found to be significant factor with an odds ratio of 0.545 with 95% CI. That means patients undergoing MRM had higher chance of being nodal positive than the patients undergoing BCS. This could be explained by the fact that

tumour with larger size and not suitable for BCS was taken up for MRM and this may be the reason for MRM being more node positive and also multi-centrality and multifocality is a contra indication for BCS. The mode of treatment emerged as a significant variable even after multivariate analysis (Table 4 and 5).

Table 4: Univariate analysis (Unadjusted odds ratio).

Variables		p-value	Unadjusted odds ratio	95% C.I.	
				Lower	Upper
Age	0-35	0.098			
	36-50	0.196	0.595	0.271	1.306
	51-75	0.038	0.437	0.200	0.956
	76-80	0.999	0.000	0.000	
Comorbidities: with vs without	With	0.391	0.864	0.620	1.206
BMI: normal vs. abnormal	18.5-24.9	0.748			
	<18.5	0.751	0.853	0.319	2.280
	25.0-29.9	0.312	0.825	0.568	1.198
	>=30	0.029	0.746		
Postmenopausal vs. premenopausal	Premenopausal	0.003	1.659	1.194	2.305
Nulliparous vs. parous	Nulliparous	0.208			
	Uniparous	0.138	1.875	0.817	4.301
	Multiparous	0.461	1.324	0.628	2.793
Age of first child birth: <30 vs >=30	>=30	0.244	1.465	0.770	2.789
Family history: without vs with	With	0.153	0.681	0.402	1.153
Symptoms: lump vs others	Lump	1.000			
	Nipple discharge	0.978	1.014	0.381	2.700
	Fullness of breast	1.000	0.000	0.000	
Side: right vs left	Left	0.126	0.777	0.562	1.074
Quadrants: UIQ vs. Others	UIQ	0.022			
	UOQ	0.116	1.384	0.923	2.075
	LOQ	0.006	2.305	1.272	4.179
	LIQ	0.162	1.607	0.827	3.123
	CQ	0.031	2.089	1.068	4.088
	Multiple	0.014	2.786	1.235	6.283
cT1 vscT2	T2	0.029	1.629	1.051	2.524
BCS vs. MRM	MRM	0.011	1.881	1.156	3.062
Tumour: single vs multiple	Multiple	0.007	2.251	1.242	4.079

Table 5: Multivariate analysis (adjusted odds ratio).

Variables		P value	Adjusted odds ratio	95% CI	
				Lower	Upper
Age	0-35	0.124			
	36-50	0.044	0.375	0.144	0.972
	51-75	0.368	0.591	0.188	1.858
	76-80	0.999	0.000	0.000	-
Postmenopausal vs premenopausal	Premenopausal	0.126	1.682	0.864	3.276
Quadrants: UIQ vs others	UIQ	0.088			
	UOQ	0.790	1.067	0.663	1.717
	LOQ	0.024	2.193	1.106	4.348
	LIQ	0.036	2.211	1.053	4.643
	CQ	0.215	1.664	0.744	3.722
	Multiple	0.841	1.123	0.360	3.503
cT1 vs cT2	T2	0.405	1.269	0.724	2.224
Single vs multiple	Multiple	0.085	2.113	0.902	4.947
BCS vs MRM	MRM	0.050	1.833	1.000	3.361

CONCLUSION

Present study was aimed at knowing the Nodal positivity rate in early breast cancer patients and predictive factors of nodal positivity in early breast cancer in Indian patients, which may help in predicting the axillary status pre-operatively.

To conclude in this study, age of the patient and clinical location of the tumour and surgery performed emerged as significant independent predictive factors of positive lymph node. Prospective studies are required to further prove the significance of these factors.

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