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Predicting Axillary Nodal Positivity in Patients with Breast Carcinoma Treated at Vajira Hospital

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Abstract

Background: **The single most significant predictive factor of survival in patients with breast cancer is the absolute number of lymph nodes involved with metastases. The purpose of this study was to estimate the likelihood of axillary lymph node involvement base on a variety of clinical and pathologic factors and determined the nodal positivity, survival and other prognostic factors.**

Methods: **All patients with breast cancer treated at Breast Clinic, Vajira Hospital from January 1994 through December 2001 who underwent modified radical mastectomy or axillary lymph node dissection as part of their treatment were evaluated.**

Results: **Of 204 breast cancer patients the axillary node metastases is 86 (42.2%). The axillary node metastases in nonpalpable tumor is 5 of 40 (12.5%) and palpable tumor is 81 of 164 (49.4%). The nonpalpable tumors have smaller size than palpable tumors, they are less likely to have positive axillary nodes (p 0.000) and less likely to have lymphatic vascular invasion (p 0.05). Nonpalpable tumors have a better survival than palpable tumor (p 0.0217).**

Conclusions: **For the breast cancer patients, the axillary lymph node metastases are positively correlated with tumor size, the axillary nodal status is the most significant predictive factor of survival. Nonpalpable tumors are more likely to be smaller and their nodal positivity is lower.**

Carcinoma of the breast is the most common site-specific cancer in women and is the leading cause of death from cancer for females during the fourth to sixth decades of life.[5,12] Worldwide, breast carcinoma represents an epidemiologic problem. The causes of carcinoma of the breast is unknown but there are several predisposing factors. Most breast carcinomas presented as palpable, visibly obvious masses. With the development and utilization of high quality mammography and ultrasonography, approximately 30% to 50% of all newly diagnosed breast carcinoma cases from centers utilizing these techniques are nonpalpable at diagnosis.[7,8,16,18]

Metastatic disease of the breast occurs predominately by routes that are extensive and arborize in multiple directions through skin and mesenchymal

lymphatics especially lymphatic flow toward the axilla.[3,4] Two accessory directions for lymphatic flow from breast parenchyma to nodes of the apex of the axilla include the transpectoral and retropectoral routes. Interpectoral (Rotter's) nodes, between the pectolaris major and minor, receive lymph that terminates in the apical (level III) group. Accessory pathways provide major lymphatic drainage by way of the external mammary and central axillary node groups (Levels I and II). Internal mammary lymphatic trunks eventually terminate in subclavian node groups.

Greater than 75 percent of lymph from the breast passes to the axillary lymph nodes ; the remainder of lymph flows into parasternal lymphatics.[1,11]

There are several prognostic variables for breast carcinoma that determine recurrence and overall survival such as Tumor size, Nodal status, Estrogen-progesterone receptor, Histologic type, Proliferative rate, Growth factors and chromosomal / oncogene abnormality. Axillary lymph node status continues to be the single most important prognostic variable for breast cancer survival.[1,10]

The T category of the TNM staging system divides primary tumors into a number of subgroups. Tis is used for all noninvasive breast carcinomas or any ductal carcinoma in situ ; T1a, Tumor ≤ 0.5 cm ; T1b, Tumor > 0.5 ≤ 1.0 cm ; T1c, Tumor > 1.0 ≤ 2.0 cm ; T2, Tumor more than 2 cm but not more than 5 cm in its greatest dimension ; T3, Tumor more than 5 cm in its greatest dimension ; T4, Tumor of any size with direct extension to chest wall or skin.

The probability of axillary metastases increases with increasing tumor size ; and with in a given T category the probability of nodal positivity may range widely. An 1 cm lesion is less likely to reveal axillary involvement than a 3 cm lesion.

If axillary lymph node status could be accurately predicted prior to axillary dissection, selected patients with an acceptably low probability of axillary metastases might avoid axillary dissection and its associated morbidity.

The purpose of this study was to estimate the likelihood of axillary lymph node involvement based on a variety of clinical and pathologic factors and to analyze lesions by T category and method of diagnosis (nonpalpable versus palpable) to determine if there were differences in nodal positivity, survival, and other prognostic factors. With improved accuracy in the preoperative prediction of axillary status, modification of both surgical and chemotherapeutic treatment strategies will optimize patient care.

Materials and Methods

All patients with breast cancer treated at Breast Clinic, Vajira Hospital from January 1994 through December 2001 who underwent Modified radical mastectomy or axillary lymph node dissection as part of their treatment are included.

A lesion was recorded as palpable if it could be felt obviously as a mass by an examiner prior to radiographic identification ; it was recorded as nonpalpable if it was discovered by mammography or the physical examination was recorded as ill defined or nonpalpation.

Palpable lesions were measured and tumor size was recorded to the centimeter. If a clinically nonpalpable lesion could be visualized or felt after excision, it was measured to the centimeter but did not change its preoperative clinically nonpalpable status. If a nonpalpable lesion was neither visualized nor palpable, size was determined by microscopic measurement.

Tumor were categorized by T category using the TNM system of the American Joint Committee on cancer : Tis, any ductal carcinoma in situ, regardless of size ; T1a, 0.11-0.5 cm ; T1b, 0.51-1.0 cm ; T1c, 1.01-2.0 cm ; T2, 2.01-5.0 cm ; T3, 5.01 cm or more ; T4, chest wall or skin fixation, skin edema or ulceration, inflammatory carcinoma.

Interrelations between clinical and pathologic characteristics and T categories were determined by contingency table analysis or the t-test. Life tables were computed using the Kaplan-Meier method ; comparisons of the groups were made with the log-rank test. Program computer using SPSS for Windows Version 10.0, p-value ≤ 0.05 is significant.

Results

In our study of a total of 204 patients shows statistically significant increased nodal positivity as the T category increased in T1c, T2 and T3 subgroups. (Table 1).

Figure 1 shows relationship between tumor size and potential for node metastasis. Table 2 shows the difference in nodal positivity is statistically different for nonpalpable versus palpable lesions in the total number

of patients (p value is 0.000), even in the subgroup of patients shows none of the differences were statistically significant.

Table 3 compares the average maximum diameter for nonpalpable and palpable lesions by T categories T1a through T2. For T1b through T2 categories, the average palpable lesion is larger than the average nonpalpable lesion. The differences are significant (p value is 0.000).

Table 4 shows the percentage of patients as clinically nonpalpation or palpation in relation to size of the mass. The chance of palpation is about 50 percent when the tumor size is between 0.51-1.0 cm or T1b staging. When tumor size is more than 2 cm the chance of palpation is more than 90 percent or T2 staging. Table 5 shows a variety of laboratory and pathologic parameter for invasive breast cancer 203 patients, stratifying them by palpibility of 39 nonpalpable lesions versus 164 palpable lesions. Nonpalpable lesions are more favorable. They were

Table 1 T category predicts nodal positivity.

T category	Node positive/patients (no.)	p
Tis	0/1 (0%)	0.773
T1a	1/13 (7.7%)	0.593
T1b	3/22 (13.6%)	0.363
T1c	8/34 (23.5%)	0.015
T2	46/97 (47.4%)	0.025
T3	20/28 (71.4%)	0.038
T4	8/9 (88.9%)	
Total	**86/204 (42.2%)**	

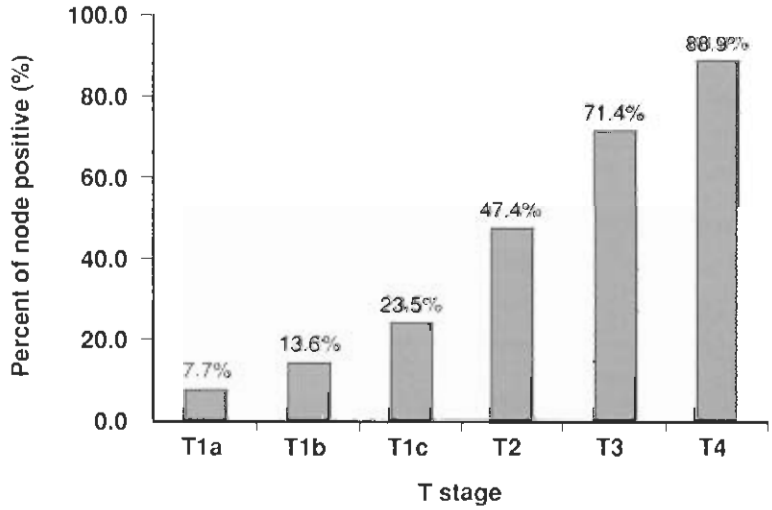

Fig. 1 Axillary node positivity by T category , the subgroup of patient shows statistically significant increased nodal positivity as the T category increased in T1c, T2 and T3 subgroups or tumor size 2 cm and above.

Table 2 Nodal positivity by T category : nonpalpable versus palpable lesions.

T category	Nonpalpable (no. node positive/patients)	Palpable (no. node positive/patients)	p
Tis	0/1 (0%)	-	-
T1a	0/7 (0%)	1/6 (16.7%)	0.261
T1b	1/12 (8.3%)	2/10 (20.0%)	0.427
T1c	1/9 (11.1%)	7/25 (28.0%)	0.306
T2	2/9 (22.2%)	44/88 (50.0%)	0.112
T3	1/2 (50.0%)	19/26 (73.1%)	0.486
T4	None	8/9 (88.9%)	-
Total	**5/40 (12.5%)**	**81/164 (49.4%)**	**0.000**

Table 3 Average tumor size of T1a-T2 tumors.

T category	Size (cm)			p
	Total patients	Nonpalpable	Palpable	
T1a	13	0.41	0.46	0.155
T1b	22	0.72	0.97	0.000
T1c	34	1.27	1.92	0.000
T2	97	2.47	3.18	0.000

Table 4 Association between tumor size and incidence of palpability : 203 patients with invasive breast cancer.

Tumor size (cm)	Nonpalpable	Palpable	Total
0.1 - 0.5	7 (53.8%)	6 (46.2%)	13 (100%)
0.51 - 1.0	12 (54.5%)	10 (45.5%)	22 (100%)
1.01 - 2.0	9 (26.5%)	25 (73.5%)	34 (100%)
2.01 - 5.0	9 (9.3%)	88 (90.7%)	97 (100%)
> 5.0	2 (5.4%)	35 (94.6%)	37 (100%)
Total	**39 (19.2%)**	**164 (80.8%)**	**203 (100%)**

Table 5 Laboratory and pathologic findings 203 patients (invasive cancers only).

Parameter	Nonpalpable	Palpable	p
No. of patients	39	164	-
Positive axillary nodes	5 (12.8%)	81 (49.4%)	0.000
ER - positive	30/39 (76.9%)	105/164 (64.0%)	0.125
Lymphatic / vascular invasion	3/39 (7.7%)	35/164 (21.3%)	0.05
High histologic grade (Poorly differentiated)	19/39 (48.7%)	81/164 (49.4%)	0.940

ER : estrogen receptor

Table 6 Five - year breast cancer specific survival node negative versus node positive lesions.

Category	Node negative (n = 117)	Node positive (n = 86)	p
Nonpalpable	32/34 (94.1%)	3/5 (60.0%)	0.0166
Palpable	71/83 (85.5%)	63/81 (77.7%)	0.1108
All patients	103/117 (88.0%)	66/86 (76.7%)	0.0135

Table 7 Five-year breast cancer-specific survival nonpalpable versus palpable lesions : 203 patients with invasive breast cancer.

Category	Nonpalpable (%) (n = 39)	Palpable (%) (n = 164)	p
Node - negative	32/34 (94.1%)	71/83 (85.5%)	0.2328
Node - positive	4/5 (80.0%)	61/81 (75.3%)	0.4686
All patients	36/39 (92.3%)	132/164 (80.4%)	0.0217

statistically more likely to be node-negative and less likely to have lymphatic or vascular invasion of tumor but there were no difference in the estrogen receptor and histologic grade based on palpibility. The 5-year breast cancer - specific survival for node negative versus node positive and nonpalpable versus palpable invasive lesions without regard to T category is shown in Table 6 and Table 7. For node negative and nonpalpable patients had a higher survival rate than patients with node positive and palpable lesions. Figure 2 shows the survival curve of node negative versus node positive breast cancer patients after surgery.

Table 8 analyzes clinicopathologic factors variables among the 203 patients with invasive breast cancer by

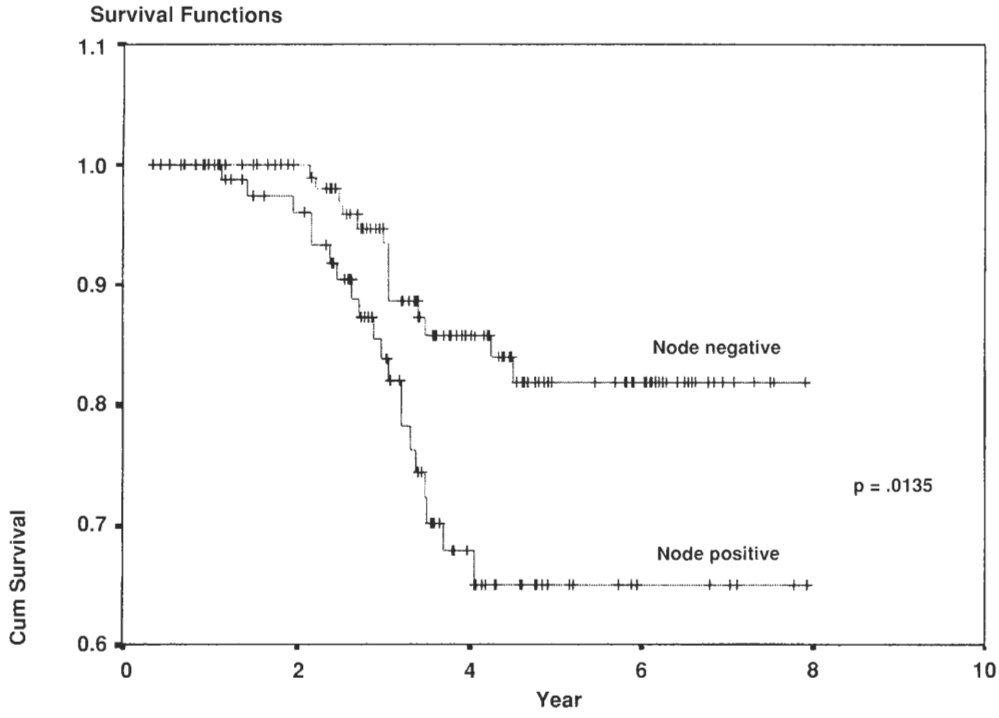

Fig. 2 Survival curve of node negative versus node positive breast cancer patients after surgery, node negative patient had a higher survival rate than node positive patients.

Table 8 Association between incidence of axillary lymph node metastases and clinicopathologic factors by univariate and multivarite analysis.

Variable	No.	% Node positive	Univariate p	Multivariate p
Palpable				
Yes	164	49.8	0.000	0.018
No	39	12.8		
Histologic grade				
Nonpoorly diff	103	33	0.006	0.087
Poorly diff	100	52		
LVI				
Present	38	81.6	0.000	0.000
Absent	165	33.3		
Size				
Tumor $<$ 1.5 cm	69	17.4	0.000	0.001
Tumor $\geq$ 1.5 cm	134	55.2		
ER				
Positive	135	40.7	0.509	
Negative	68	45.6		
Age (years)				
$<$ 50	81	43.2	0.843	
$\geq$ 50	122	41.8		
Histology				
Ductal	197	42.6	0.650	
Lobular	6	33.3		

LVI : lymphaticvascular invasion

univariate and multivariate analysis. On univariate analysis the palpability, histologic grade (nonpoorly differentiated versus poorly differentiated), lymphovascular invasion, and size (as a tumor size less than 1.5 cm versus tumor size more than 1.5 cm) were significant predictors of lymph node positivity. A multivariate analysis yielded three variables predictors of lymph node involvement : palpibility, lymphovascular invasion, and size.

In our study of 204 patients there were 27 patients in whom three factors were favorable. In these 27 patients, there is only 1 patient had lymph node metastases or 3.7% of patients. If any two of these factors were favorable, the positivity of lymph node metastasis was 12.7% or less.

Discussion

Koscielny and associates[6] demonstrated that metastases are positively correlated with tumor size, this correlation does not occur in one-half of the cases until the primary tumor attains a size of 3.6 cm in diameter. Nemoto and colleagues[1] and Fisher and colleagues[3] have shown a distinct relationship between the increase in tumor size, the probability of axillary nodal metastasis, and disease-free survival. In our study shows the statistically significant relationship between tumor size and axillary nodal metastasis in the subgroup of T1c, T2 and T3 patients or the tumor size 2.0 cm and above (Table 1). When the tumor size is smaller than 2.0 cm in diameter the relationship between tumor size and nodal metastasis may occur in some patient but the incidence is not significant, until the tumor size is 2.0 cm and larger than 2.0 cm up to 5.0 cm the incidence of nodal metastases is progressively increased.

Most breast carcinomas presented as palpable, visibly obvious masses. With the development and utilization of high quality mammography and ultrasonography approximately 30% to 50% of all newly diagnosed breast carcinoma cases from centers utilizing these techniques are nonpalpable at diagnosis. Patients who undergo routine screening mammography are more likely to have their tumors diagnosed as nonpalpable lesions.[2,7,8,16] These nonpalpable tumors are more likely to be smaller and their nodal positivity lower. Despite the 3-to 4-year lead-time bias introduced by mammographic screening, these favorable prognostic features should translate into a superior long - term survival advantage for patients with nonpalpable lesions. Long-term studies of breast cancers detected by mammography reveal that these cancers are different from palpable breast lesions. Nonpalpable cancers have a low overall nodal positivity rate of approximately 12% to 15% and far superior survivals when compared with patients who present with palpable breast cancer.[10,11,16] In our study patients with nonpalpable breast cancer had a 12.5% chance of nodal positivity compared with a 49.4% chance of nodal positivity for patients with palpable breast cancer ($p = 0.000$). The average tumor size of nonpalpable lesions are smaller than palpable lesions in all subgroups and statistically significant in subgroups of T1b, T1c and T2 (Table 3). In our series we found that the chance of clinically palpable is about 50% when the tumor size is 0.51 - 1.0 cm or T1b lesion and the chance of palpibility is more than 80% when the tumor is larger than 2.0 cm (Table 4). The single most significant predictive factor of 10 and 20 year survival is the absolute number of lymph nodes involved with metastatic neoplasm. Physical examination is notoriously inaccurate in determining the presence of lymphatic involvement and may have false - positive rates and false - negative rates for detection of axillary metastases that range from 25 to 31 per cent and from 27 to 33 per cent, respectively.[3] Henderson and Canellos[2] report that patients with negative axillary lymphatics have 5 - year and 10 - year survival rates of 78 and 65 per cent, respectively ; for patients with four or more positive lymphatics, survival rates are 32 and 13 per cent, respectively. Fisher and associates[3] observed that the number of positive nodes is correlated with the percentage of 5 - year and 10 - year treatment failures. The absence of positive nodes was associated with a 20 per cent failure rate at 10 years ; the presence of more than four positive nodes was associated with a 71 per cent treatment failure rate ; the presence of more than 10 positive nodes increased the failure rate to 87 percent. Patients with occult micrometastases in lymph nodes initially reported as histologically negative may have survival rates that are not significantly different from those of patients with negative nodes.[1,10,12] Rosen and associates[9] described a large group of patients followed a median of 18 to 20 years. They showed that tumor size, the number of axillary lymph node metastases, lymphatic tumor emboli, tumor histology

and differentiation, blood vessel invasion, and lymphophasmocytic reaction around the primary tumor were important predictors of survival. They also showed that as tumors increased in size the probablity of nodal positivity increased. In our study, the patients with nonpalpable lesions had a number of prognostic factors in their favor (Table 5). They were less likely to be positived axillary node ($p = 0.000$). Nonpalpable tumors were less likely to demonstrate lymphatic tumor emboli or vascular invasion ($p = 0.05$) and nonpalpable tumor had a higher survival rate than patients with palpable tumor. Althrough the surgical approach to the breast in patients with breast carcinoma has become less aggressive over recent years, routine axillary lymph node dissection continues to be performed for most patients either conservative breast surgery or standard modified radical mastectomy[13,17] because lymph node status is inaccurated by physical examination alone[3] and continues to be the single most important prognostic factor in breast cancer patients. Furthermore, axillary dissection lowers the risk of axillary recurrence and oncologist require axillary nodal status before determining the exact of the chemotherapy given. Clinical trials are investigating the issue of "sentinel node" biopsy as an alternative to formal axillary dissection for staging.[14,15] A radioisotope or a dye is injected into the region of the tumor, and radioactivity or presence of dye is assessed in the axilla. When a node is identified by this technique, it is removed for biopsy. If this so-called sentinel node shows no tumor, this is regarded as equivalent to a negative axilla.

There are subgroups of patients in whom the risk of axillary positivity is low, in patients with nonpalpable T1a, T1b lesions, or patients with three favorable factors in the multivariate analysis which has a predicted nodal positivity of 3.7% (Table 8). The relative low risk of axillary metastases in these patients must be weighed against the potential morbidity of the routine axillary dissection.[13] If it is assumed that the sentinel node biopsy has an accuracy of more than 90%,[14,15] a reasonable alteration may be the use of sentinel node biopsy in patients with low risks of axillary node metastases.

Conclusion

For the breast carcinomas patients, the axillary lymph nodes metastases are positively correlated with tumor size, as the tumor size is increased the incidence of nodal metastases is progressively increased. The axillary nodal status is the most significant predictive factor of survival. With the high quality mammography, some newly diagnosed breast carcinoma cases are nonpalpable. These nonpalpable tumors are more likely to be smaller and their nodal positivity lower. They were less likely to demonstrate lymphatic tumor emboli or vascular invasion, they had a higher survival rate than palpable tumors. The relative low risk of axillary metastases in these patients may be weighed against the potential morbidity of routine axillary dissection and the use of sentinel node biopsy may be considered in these patients.

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