



ACCURACY OF AXILLARY ULTRASOUND IN THE DETECTION OF LYMPH NODAL METASTASIS IN BREAST CANCER

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INTRODUCTION

Malignant breast neoplasia is the main cause of deaths caused by cancer in women worldwide. The introduction of screening has allowed the diagnosis of early-stage lesions and more conservative treatments. Currently, the histopathological diagnosis of axillary lymph node metastasis is carried out by means of minimally invasive methods, whenever possible by means of imaging-guided percutaneous biopsy.^[1]

The metastasis to axillary lymph node constitutes one of the most relevant prognostic indicators for outcome of breast cancer treatment,^[2-8] as the axilla is the receives approximately 95% of the breast lymphatic drainage.^[9,10]

Number of metastatic nodes on axillary lymph node dissection (ALND) to assess metastasis to lymph nodes is an established and reliable prognostic factor for overall outcome as well as subsequent distant metastasis in cases of carcinoma breast. Axillary lymph node dissection has high morbidity rates; hence current standard in early breast cancer for assessment of metastasis is Sentinel Lymph Node Biopsy. Morbidity rates are considerably lower with sentinel node biopsy compared to axillary lymph node dissection.^[11]

However, doing SLNB is time consuming, needs technical expertization and also requires a team of nuclear medicine specialist, frozen section machine, Surgeon and pathologist. More over SLNB is not available at many of the centers and is also not cost effective. Axillary ultrasound (AUS) is a emerging technique for preoperative assessment of axillary node status and is a cost effective and non-invasive method.^[12-18]

Elastography, Contrast enhanced ultrasonography, USG guided FNAC/FNAB are used methods to improve sensitivity and specificity for detecting axillary lymph node metastasis.^[19,20]

It can detect alterations in the size, shape, contours of lymph nodes, as well as detecting changes in the morphology and texture of the nodal cortex. Depending on specific morphological features, it can thereby identify the presence of the underlying metastasis.^[21]

Therefore if the node-positive patients can be identified pre-operatively by non-invasive or minimally invasive method, they can proceed directly to single stage breast and axillary surgery without SLNB.^[22]

As there are no guidelines or consensus about the use of USG at present, we aimed to assess accuracy of preoperative axillary ultrasound in the Detection of Lymph Nodal Metastasis in Breast Cancer at our center.

MATERIALS AND METHODS

Study Design: It is a hospital based prospective study of newly diagnosed carcinoma breast patients admitted in the Department of Surgery, Acharya Vinoba Bhave Rural Hospital, Wardha. We included the patients who had operable breast carcinoma i.e. Any T with N0 or N1 axillary Lymph Node status on clinical examination, who have not received any modalities of treatment prior to admission and are newly diagnosed cases.

Patients who have received neoadjuvant chemotherapy, radiotherapy, or primary endocrine therapy and patients with previous axillary surgery were excluded from the study group.

Patients were thoroughly assessed for clinical T staging and size of the tumour. Primary tumours were assessed by USG. Axilla was assessed clinically for present of lymph nodes. Patients with positive N1 and clinically N0 axilla were evaluated by high frequency probe ultrasonography only for categorization in to non-metastatic or suspicious of metastasis depending on its morphological features.

Lymph nodes were classified as benign if the cortex was even and measured <3 mm, indeterminate if the cortex was even but measured > 3 mm or measured <3 mm but was focally thickened, and suspicious if the cortex was

focally thickened and measured > 3 mm or the fatty hilum was absent.^[23]

After fitness for operative intervention all patients underwent mastectomy and axillary lymph node dissection and histopathological confirmation of metastasis to lymph node and were compared with ultrasound categorization of lymph nodes.

All the suspicious and indeterminate lymph node category was considered to be positive and patients with non-suspicious were categorized as benign.

Statistical analysis was done by using descriptive and inferential statistics using chi-square test, multiple regression analysis and predictive values and software used in the analysis were SPSS 22.0 version and Graph Pad Prism 6.0 version and $p < 0.05$ is considered as level of significance.

OBSERVATIONS AND RESULTS

Out of 104 patients in our study group, 4 patients were in

the age group of <30 years, while 17 patients were in the age group of 31-40 years. Maximum number of patients was in the age group of 41-50 years i.e. 43(41.35%).

Twenty-three patients were in the age group of 51-60 years and rest 17 patients were in the age group of >60 years.

In our study population of 104 patients, 61 patients were in the premenopausal state and 43 were postmenopausal.

Patients were classified in three categories depending on the tumour size by means of clinical examination, USG and Histopathological assessment. These 3 categories were <2cm, >2cm to <5cm and >5cm group.

According to clinical size of the tumour, 2 patients were in the group of <2cm, 57 patients were in the group of >2cm to <5cm and 45 patients in the group of >5cm. There was statistical significant difference in the clinical size compared to US and histopathology size.

Table 1: Showing descriptive statistics for size of tumour.

	N	Minimum	Maximum	Mean	Std. Deviation
Pathological tumour size	104	1.50	12.00	4.71	2.22
USG size of Tumour	104	2.00	12.00	4.82	2.16
Clinical Size of Tumour	104	2.00	12.00	5.62	1.99

One way ANOVA					
Source of variation	Sum of Squares	df	Mean Square	F	p-value
Between Groups	52.27	2	26.13	5.75	0.004,S
Within Groups	1402.92	309	4.54		
Total	1455.19	311			

Multiple Comparisons: Tukey Test

		Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Pathological	USG	0.11	0.29	0.926,NS	0.58	0.80
	Clinical	0.91	0.29	0.006,S	0.22	1.61
USG	Clinical	0.80*	0.29	0.018,S	0.11	1.50

However, according to the clinical T staging of the tumour 1 patient was in T1 stage, 49 patients were in T2 stage, 31 patients were in the T3 stage and 23 patients were in the T4 stage of the tumour. Maximum positive axillary lymph node was present in the T4 stage of tumour i.e. 82.61% and p-value was significant i.e.0.002.

USG size and Histopathological size of the tumour were also similarly categorized with maximum number of patients in the group of >2cm to <5cm which were 64 and 63 respectively.

Table 2: Showing clinical T staging of tumour and distribution of lymph node categorization of enrolled Subjects.

Clinical T staging	% in study population	Lymph Node Categorization			% of +ve LN	x2-value
		Benign (n=29)	Intermediate (n=28)	Suspicious (n=47)		
T1	1(0.96%)	0(0%)	1(100%)	0(0%)	0(0%)	17.60 p=0.002,S
T2	49(47.12%)	19(38.78%)	14(28.57%)	16(32.65%)	25(51.02%)	
T3	31(29.81%)	9(29.03%)	9(29.03%)	13(41.94%)	16(51.61%)	
T4	23(22.12%)	1(4.35%)	4(17.39%)	18(78.26%)	19(82.61%)	

In our study population of 104 patients, 77 patients (74.04%) were having Lymphovascular invasion on histopathology, while rest 27 patients (25.96%) were without Lymphovascular invasion.

Of the 104 enrolled patients, 36 patients were with grade-I tumour, 48 patients were with grade- II, and patients having grade III tumour were 20.

Table 3: Showing clinical nodal stage and distribution of lymph node categorization of enrolled subjects.

Clinical nodal stage	% in study population	Lym	ph Node Categorization		% of +ve LN	x2-value
		Benign (n=29)	Intermediate (n=28)	Suspicious (n=47)		
No	45(43.27%)	22(48.89%)	13(28.89%)	10(22.22%)	15(33.33%)	21.95
N1	59(56.73%)	7(11.86%)	15(25.42%)	37(62.71%)	45(76.27%)	P=0.0001,S

Out of 104 patients in our study group, 45 patients were having non-palpable lymph nodes (N0) on clinical examination and 59 were having clinically palpable nodes (N1).

In the N1 group, out of 59 patients, 45 patients were having positive lymph node on histopathology and only 15 patients out of 45 patients were positive for axillary lymph nodes metastasis in the N0 group with significant p-value of 0.0001.

Table 4: Multiple Regression analysis of status of lymph node on USG.

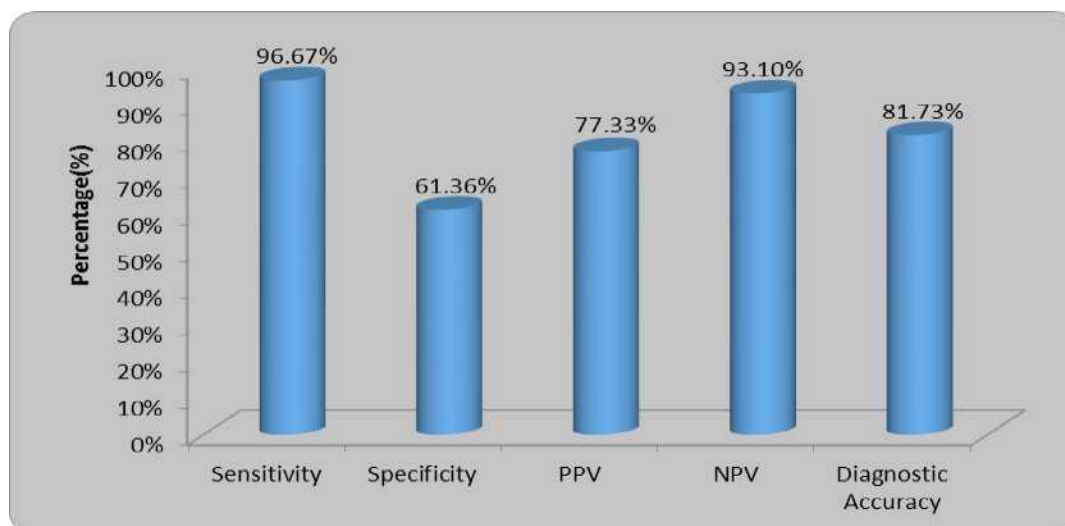
Parameters	Unstandardized Coefficients		Standardized Coefficients	t	p-value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Status of lymph node	0.624	0.704					
Age in yrs	-0.005	0.006	-0.059	0.761	0.448,NS	-0.017	0.008
T Staging	0.188	0.114	0.182	1.647	0.103,NS	-0.039	0.415
N Staging	0.176	0.166	0.111	1.062	0.291,NS	-0.153	0.505
Tumor size on HP	0.149	0.207	0.395	0.720	0.474,NS	-0.263	0.561
Tumor size on USG	-0.192	0.213	-0.493	0.901	0.370,NS	-0.616	0.232
Grade of Tumor	0.015	0.095	0.013	0.154	0.878,NS	-0.173	0.202
Lymphovascular Invasion	0.063	0.158	0.033	0.400	0.690,NS	-0.250	0.376
No of positive lymph node on HP	0.944	0.149	0.557	6.340	0.0001,S	0.649	1.240

On multiple regression analysis only number of Lymph node positive on histopathology was only having the significance of p-value <0.0001.

Table 4: Correlation between sonographic lymph node category and positive lymph node on histopathology.

USG	No of lymph node on HPE		x2-value
	Positive	Negative	
Positive	58 TP(True positive)	17 (False Positive)	42.51 p=0.0001,S
Negative	2 (False Negative)	27 (True Negative)	
Total	60	44	

	Percentage(95% CI)
X2-value	42.51
p-value	0.0001, Significant
Sensitivity	96.67% (88.47-99.59%)
Specificity	61.36% (45.50-75.64%)
Positive Predictive Value	77.33% (66.21-86.21%)
Negative Predictive Value	93.10% (77.23-99.15%)
Likelihood Ratio	2.50
Diagnostic Accuracy	81.73%
False Positive Rate(c/c+d)	6.89%
False Negative Rate(b/a+b)	22.66%



In our study the overall sensitivity of US to detect suspicious lymph node for metastasis is 96.67%, specificity is 61.36%, positive predictive value is 77.33%, negative predictive value is 93.10%, likelihood ratio is 2.50 and diagnostic accuracy is 81.73%.

DISCUSSION

Physical examination alone is very unreliable in assessing axillary lymph node status because metastatic lymph nodes cannot always be distinguished from normal or reactive ones. Specifically, the overall false-negative rate of physical examination alone has been reported to be as high as 50-60%.^[24]

US examination can improve the sensitivity of clinical examination in assessing axillary lymph node staging process. There are several sonographic features that are used to categorize a lymph node as benign, indeterminate or suspicious for metastatic. Some of the sonographic features that favour a benign lymph node include a predominantly hyperechoic lymph node due to fat at hilum, presence of a thin homogeneous symmetrical cortical rim around the hyperechoic hilar fat, and symmetric cortical lobulations similar to contralateral axillary lymph nodes.^[25]

When there is thickening or eccentric lobulation of the hypoechoic cortical rim, compression or displacement of the fatty hyperechoic hilum, or complete replacement of the hilar fat by hypoechoic tissue, the lymph node is categorized sonographically as suspicious or metastatic appearing.^[26]

Suspicious ultrasound finding for axillary metastasis included:

The overall sensitivity and specificity of US alone in detecting axillary lymph node metastasis range from 42% to 56% and from 70% to 90%, respectively.^[15]

It is generally well recognized that the rate of detection of suspicious lymph nodes increases significantly as the

number of lymph nodes visualized on US examination of the axilla increases. Some authors have described specific sonographic features to be particularly helpful. Bonnema et al.^[28] used the echogenic pattern at the centre of lymph nodes, thereby classifying lymph nodes having a hyperechoic centre as benign and those having a hypoechoic centre or in homogeneous architecture as malignant; they found a sensitivity of 36% and a specificity of 95%. Kanter et al.^[29] also found this criterion to be helpful in detecting malignancy.

Feu et al.^[30] studied 158 excised axillary lymph nodes in 40 patients surgically treated for breast carcinoma in vitro using a 7.5-MHz US probe. They found that the absence of hilum to be the most specific sonographic feature for the diagnosis of metastasis. A Moore et al (2008)^[31] reported overall sensitivity and specificity for sonography alone were 81% and 69% respectively in 112 patients. Martha B M et al. (2010)^[32] found that the sonographic feature most predictive of a positive USG Guided FNA result was the absence of a fatty hilum. Bedi et al. (2008)^[33] suggested that hypoechoic cortex with focal cortical thickening is most predictive of malignancy.

Sensitivity and specificity of SLNB were 92% and 87.5%, in comparison to ALND, the accuracy of SLNB was 90.9% and false negative rate of this method was also 8%.^[34]

Results showed that the pooled sensitivity, specificity and DOR (Diagnostic Odds Ratio) of CEUS in diagnosing SLN metastasis were 80%, 94% and 49.10%, respectively.^[35]

Various studies conducted by various authors reported the sensitivity ranging from 55.6% to 79.1% and specificity in the range of 77.7% to 91.3%, PPV ranging from 82.6% to 90% and NPV ranging from 69% to 78.7%.^[23-26]

US has been proved to have a higher sensitivity (45-84%) and specificity (72-97%) for the detection of metastatic axillary lymph nodes in breast cancer than a clinical examination or the other imaging techniques in various

studies.^[34]

Our study had false positive rate of 6.89% which emphasize that it does not lead to over diagnosis of axillary lymph node metastasis and helpful in avoiding the ALND and related morbidity.

SUMMARY AND CONCLUSION

Thus, it was concluded from our study that the high sensitivity and specificity and relatively low false negative rate of US of axillary lymph nodes indicate that it is a useful procedure in the initial staging of breast carcinoma and can be immensely valuable in planning the appropriate management plan for axillary nodes.

US is the preferred method for evaluation, because of its low cost, wide accessibility and good reproducibility.

US should be included in preoperative staging of all invasive breast cancer patients who are candidates to SLNB, regardless the tumour size and clinical evaluation of the axilla. Thus, it is possible to optimize the detection of axillary lymph nodes involvement.

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