Original Research Article

Evaluation of non-palpable axillary lymph nodes metastasis with ultrasonography guided fine needle aspiration cytology in carcinoma breast and comparing with histopathological report

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ABSTRACT

Background: Breast malignancies are the second most common cause of cancer related mortality among women. As the size of the primary breast cancer increases, some cancer cells are shed into cellular spaces and transported via the lymphatic network of the breast to the regional lymph nodes, especially the axillary lymph nodes. Objective of the study is to evaluate the diagnostic accuracy of axillary ultrasound (US) guided fine-needle-aspiration cytology (FNAC) in patients with breast carcinoma, in comparison with the final histological examination (sentinel node biopsy and/or axillary dissection).

Methods: This prospective study will be conducted on 40 consecutive patients with biopsy proven breast cancer with clinically negative axilla, who had attending the OPD or IPD in our department of surgery, SGRD hospital Amritsar. All of these patients are planned to undergo surgery (breast conservation or modified radical mastectomy with axillary clearance).

Results: Patients detected with LN metastasis on FNAC can directly undergo axillary dissection without the need of any other diagnostic technique like SLNB in non-palpable axillary lymph nodes.

Conclusions: Thus, we can conclude that ultrasonography (USG) guided FNAC due to its moderate sensitivity, high specificity and PPV in relation to histopathological examination (HPE) is a good diagnostic technique for diagnosing patients with axillary lymph node metastasis in case of clinically non palpable axillary lymph nodes in carcinoma breast patients.

Keywords: Ultrasound guided FNAC, HPE, Axillary clearance

INTRODUCTION

The Smith surgical Papyrus (3000-2500 B.C.) is the earliest known document to refer to breast cancer. The cancer was in a man, but the description encompassed most of the common clinical features. In reference to this cancer, the author concluded, "There is no treatment."[1]

Breast cancer is the most commonly occurring cancer in women and the second most common cancer overall.[2]

Breast cancer causes 5,19,000 deaths in a year worldwide, about 9,00,000 women are diagnosed each year. Incidence of breast cancer is 0.26/1,00,000 in males and 20.01/1,00,000 in females. While mortality associated with breast cancer is 1.20/1,00,000 in males and 4.32/1,00,000 in females. Mortality rates from breast cancer increased during past 60 years in every country.[3]

Breast cancer burden has well-defined variations by geography, regional lifestyle, and racial or ethnic background.[4] In general, both breast cancer incidence and

mortality are relatively lower among female populations of Asia and Africa, relatively underdeveloped nations, and nations that have not adopted the westernized reproductive habits like late marriage and eventually late first full-term pregnancy, lack of breast feeding and dietary patterns. In contrast, European and North American women and women from heavily industrialized or westernized countries have a substantially higher breast cancer burden. These international patterns are mirrored in breast cancer incidence and mortality rates observed for racially, ethnically, and culturally diverse population of the United States.[5]

The status of axillary lymph node metastasis, in addition to being the most important prognostic factor in this group of patients, has a critical place in the management of this disease. For many years, axillary lymph node dissection (ALND) was the choice of method for axillary nodal evaluation which reliably staged and effectively treated metastatic lymph node involvement. However, for those cases that had no nodal involvement ALND gave no advantage and sometimes was associated with significant complications such as lymphedema, wound infections, stiffness, shoulder weakness, pain and numbness of the affected arm. Afterwards, the concept of sentinel lymph node biopsy (SLNB) was developed.[6]

This method has been shown to be a valuable tool in determining whether the cancer has spread from its original site and for axillary staging. It has proven to be an effective alternative to ALND. Those patients whose SLNB is disease free require no further treatment and are spared from unnecessary axillary surgery. Despite its wide acceptance for practice, SLNB has some drawbacks; it is a slow and meticulous process for surgeons in the operating room, requires the administration of radioisotopes to patients, and needs multiple microscopic sections for final histological examination. Also, SLNB is not available in all centres and is not cost effective.

An ultrasound examination is recommended by previous studies to detect suspicious involved axillary lymph nodes. High resolution ultrasound, which establishes structural features of lymph nodes and structural changes suggesting malignant involvement, is being increasingly accepted as an appropriate non-invasive method. In addition to imaging, FNAC is a minimally invasive intervention that establishes the cytological features of image-suspicious lymph nodes.[7]

Normal lymph node

A normal lymph node has a thin cortex and a relatively large fatty hilum. Blood flow usually passes through a single artery and drains into a single vein, with both vessels being located in the fatty hilum, much as in a small kidney.[10-11] This normal blood flow is observed as bidirectional flow in the hilum. Microscopy demonstrates a vascular network within the lymph node cortex, but this network is not usually observed in a normal lymph node

at color doppler US.[10] The size of the lymph node is not an indicator of benignity or malignancy, since normal lymph nodes larger than 5 cm can be present in the axilla and lymph nodes as small as 5 mm can contain metastases.

Abnormal lymph node

An abnormal lymph node has a thickened or eccentrically bulging cortex and a diminished or absent hilum.[12] The thickened cortex should be the target at biopsy. Metastases embed sub-cortically in the end vasculature. Color doppler US shows hyperemic blood flow in the hilum and central cortex or abnormal (non-hilar cortical) blood flow.[4,5] However, this abnormal blood flow is not pathognomonic for a metastatic lymph node; it can also be observed in other pathologic conditions such as reactive lymph nodes with inflammation. Maximizing the sampling of the cortex and specifically targeting the peripheral cortex are recommended for biopsy. Biopsy is recommended usually when thickened cortex or non-hilar cortical blood flow is seen.

In this respect, ultrasound-guided fine needle aspiration (USG-FNAC) is a suggested technique for axillary lymph node staging. However, USG-FNAC is not as sensitive as SLNB and its false-negative rate is high to entirely replace SLNB. Additionally, FNAC is more operator dependent compared with other methods such as the core-needle biopsy (CNB). The reported rate of insufficient cytological material following USG-FNAC is 0%-54%. Until now, the findings of ALND or its alternative method, SLNB, have been used as the gold standard for axillary staging in breast cancer cases that have clinically negative axilla. However, if nodal positivity can be proven pre-operatively, it helps diagnosing one-stage axillary clearance and SLNB can be avoided. In addition, it may also have an impact on the decisions to offer neo-adjuvant therapy and breast reconstruction.[1]

Therefore, it is helpful for both the patient and surgeon to establish a simple pre-operative method in patients with metastatic lymph nodes who could directly undergo an axillary dissection and eliminate the need to search for the sentinel lymph node. The aim of this study is to evaluate the clinical usefulness of axillary ultra-sonogram and USG guided FNAC in diagnosing axillary nodal metastasis in cases with breast cancer.

METHODS

Study design

The study design was prospective, interventional and observational type of study.

Source of data

This study was conducted at Sri Guru Ram Das institute of medical sciences and research, Vallah, Sri Amritsar

with a sample size of 50 patients after attaining approval from hospital ethics committee and taking informed written consent from the patients. Study was conducted from September 2018 to September 2020. Sample size was calculated using G-power software at 95% confidence interval with precision of 3.3% (prevalence 5%). Cases were selected on the basis of inclusion and exclusion criteria.

Inclusion criteria

Its assumptions were- precision=5.00 %, prevalence=3.30%, population size=infinite and 95% confidence interval specified limits (0%-8.3%) (these limits equal prevalence plus or minus precision).

Estimated sample size: n=50. 95% binomial exact confidence interval with n=50 and n*prevalence=2 observed events: (0.488143%-13.7138%).

Warning: #succ or (sample size- #succ) <5, you may try different combinations of #obs and #succ and assess binomial exact confidence intervals.

Informed consent included all diagnosed cases of carcinoma breast, female patients, clinically lymph node negative cases and any age group,

Exclusion criteria

It excluded the patients unwilling to participate, clinically palpable lymph node, previously operated or treated patients, patients who have received neo-adjuvant chemotherapy and radiotherapy and those with negative nodes but having evidence of systemic metastasis

Method of collection of data

Patients diagnosed with carcinoma breast were evaluated clinically for axillary LN metastasis and 50 patients with clinically non palpable axillary LNs were selected for the study.

A radiologist performed the axillary USG examinations and USG guided FNACs.

The histopathology report of the subsequent surgical staging of the axilla were correlated with the FNAC data.

The data fields recorded for the axillary specimen included, the number of LN dissected as part of an axillary clearance, the total number of LNs resected and the number of positive LN in each of these categories.

During the US examination, the axillae were carefully scanned, with particular attention to the lower axilla, which is a common location for sentinel node.[8] The axillary nodes were assessed for the morphologic characteristics of the cortex and the presence or absence of the fatty hilum.

The nodes were considered as abnormal if the cortex is eccentrically or concentrically thickened to greater than 2 mm and was instantly sampled by US-guided FNAC. When 2 or more abnormal nodes are identified in the axilla, the node that looked the most suspicious was aspirated. During the US guided FNAC, a 21-or 23-gauge needle was attached to a 10-mL syringe that was inserted into the thickest portion of the cortex and moved back and forth within the targeted node.

The obtained sample material was placed on glass slides and sent to a cytology laboratory, where smears were prepared, fixed in alcohol, and then stained with hematoxylin-eosin. All smears were evaluated by experienced cytopathologists. If the cytopathologists found that the cytologic samples of the lymph node was insufficient for diagnosis, another USG-guided FNAC was performed. Therefore, in our study, cytologic results were reported as negative or positive for malignancy.[9]

Similarly, after axillary dissection, LNs were examined and were embedded, stained with HPE and examined. Sensitivity, specificity, PPV and NPV were calculated using Fischer's exact test. The level of statistical significance was defined as $p < 0.05$.

RESULTS

In this study 50 patients of carcinoma breast with non-palpable axillary lymph nodes have been included. USG guided FNAC was done pre-operatively from axillary lymph nodes in all the 50 patients. Breast surgery either MRM/BCS was done in all the patients along with axillary LN dissection and postoperatively histopathological examination of lymph nodes was done. Study was done in the department of surgery of Sri Guru Ram Das institute of medical sciences and research, Vallah, Sri Amritsar.

Then we compared the results of FNAC with final histopathological report of lymph nodes. Various parameters like tumor size, grade, LVI, type of carcinoma etc. and their association with axillary lymph node metastasis was also studied in the present study.

As in Table 1 maximum no. of patients in our study maximum patients 17 (34%) were from age group of 51-60 years. and minimum no. of patients 5 (10%) were from 30-40 years with mean age of 53.26±9.20 years.

Table 1: Age distribution of carcinoma breast.

Age group (years)	No. of cases	Percentage (%)
30-40	5	10
41-50	16	32
51-60	17	34
61-70	12	24
Total	50	100
Mean age		53.26±9.20

In the Table 2, 35 (70%) patients had mean no. of lymph nodes dissected were 13.11±1.40 and 17.07±1.35 mean lymph nodes in 15 patients. It shows more no. of patients (35) had lymph nodes from 10-15 range. The data is statistically significant as p<0.05.

Table 2: Mean number of lymph nodes dissected in axillary dissection.

Total no. of lymph nodes	No. of cases	Percentage (%)	Mean±SD
10-15	35	70	13.11±1.40
15-20	15	30	17.07±1.35
Total	50	100	14.30±2.27

P:0.001

Table 3 shows out of 50 patients, 27 patients have right sided breast carcinoma and 23 patients have left sided breast carcinoma.

Table 3: Side distribution in patients of carcinoma breast.

Side of breast	No. of cases	Percentage (%)
Right side	27	54.00
Left side	23	46.00
Total	50	100.00

As depicted in Table 4, maximum number of patients i.e., 26 (52%) have tumor in the upper outer quadrant of breast and the minimum no. of patients 2 (4%) have tumor in lower inner quadrant of the breast. Also, lymph node metastasis is also maximum in patients 13 (26%) having tumor in UOQ of breast.

Table 4: Distribution of ln metastasis with involvement of quadrant.

Quadrant involved	LN status on HPE (%)		Total
	Positive	**Negative**	
LIQ	2 (4)	2 (4)	4
LOQ	4 (8)	3 (6)	7
UIQ	4 (8)	9 (18)	13
UOQ	13 (26)	13 (26)	26
Total	23 (46)	27 (54)	50

X^2: 1.757; df:3; p=0.624

As depicted by the Table 5, 16 (32%) patients had LN metastasis and 34 (68%) patients were free from LN metastasis on USG guided FNAC of non-palpable axillary lymph node.

Table 5: Distribution of cases according to FNAC results.

USG guided FNAC	No. of cases	Percentage (%)
Negative	34	68.0
Positive	16	32.0
Total	50	100.0

Table 6 shows out of 50 cases 23 cases (46%) were found to have lymph node metastasis and 27 patients (54%) were free from metastasis on final HPE.

Table 6: Distribution of cases according to final HPE of lymph node.

HPE of lymph node	No. of cases	Percentage (%)
Malignant	23	46
Benign	27	54
Total	50	100

This Table 7 shows that the present study was done in 50 patients of carcinoma breast. USG guided FNAC was done from axilla in which 16 (32%) patients out of 50 came positive for lymph node metastasis. After axillary dissection HPE was done of all the 50 patients in which 23 (46%) patients out of 50 had positive axillary lymph nodes. Out of 23 (46%) patients of axillary LN metastasis, 16 (32%) came positive on FNAC and 7 patients which were positive on HPE came negative on FNAC.

The 27 patients (54%) which came negative on the HPE were also negative on FNAC. The data is compared and the observation is statistically significant as p value of <0.05.

Table 7: Comparison between the USG guided FNAC and HPE for detecting axillary lymph nodes metastasis.

USG guided FNAC	Lymph node status on HPE (%)				Total no. of patients	
	Positive		**Negative**			
	No.	**%**	**No.**	**%**	**No.**	**%**
Positive	16	32	0	0	16	32
Negative	7	14	27	54	34	68
Total	23	86	27	54	50	100

X^2: 30.237; df:1; p=0.001,

Sensitivity:69.56, specificity:100, positive predictive value: 100, negative predictive value: 79.41.

This Table 8 shows that out of 23 patients of axillary lymph node metastasis detected on HPE, 2 patients are of T1 stage, 15 patients were of T2 stage and 6 are of T3 stage. USG guided FNAC detected 1 out of 2 patients of T1 stage, 10 out of 15 patients of T2 stage and 5 out of 6 patients of T3 stage for LN metastasis. As the size of tumor increasing sensitivity of FNAC to detect metastasis also increased. The data is statistically significant as p<0.05.

T1: Sensitivity: 50%, specificity: 100%, NPV: 92.86%, PPV: 100%, T2: Sensitivity: 66.67%, specificity: 100%, NPV: 70.59%, PPV: 100% and T3: Sensitivity: 83.33%, specificity: 100%, NPV: 100.00%, PPV: 66.67%, in the below table.

Table 8: Correlation between tumor size and USG guided FNAC from axilla.

USG	HPE				Total		P value
	Present, (n=23)		Absent, (n=27)				
	No.	%	No.	%	No.	%	
T1							
Present	1	6.67	0	0	1	2	
Absent	1	6.67	13	86.67	14	28	0.008
Total	2	13.33	13	86.67	15	30	
T2							
Present	10	37.04	0	0	10	20	
Absent	5	18.52	12	44.44	17	34	0.003
Total	15	55.56	12	44.44	27	54	
T3							
Present	5	62.50	0	0	5	10	
Absent	1	12.50	2	25	3	6	0.035
Total	6	75	2	25	8	16	

Table 9 shows 16 patients out of 50 were positive for lymph nodes on FNAC and 23 out of 50 patients were positive on final HPE.16 patients had <3 positive LN and 7 patients had >3 positive LN on HPE. 11 (68.75%) out of 16 patients having positive LN <3 and 5 (71.42%) out of 7 having positive LN >3 came positive on USG guided FNAC. FNAC result was better in patients with >3 positive LN. Data is statistically insignificant as p value of >0.05.

Table 9: Correlation of USG guided FNAC with no. of positive lymph nodes on HPE.

No. of positive nodes on HPE	USG guided FNAC				Total patients with LN metastasis on HPE	
	Positive		Negative			
	No.	%	No.	%	No.	%
<3 LN	11	68.75	5	31.25	16	69.57
>3 LN	5	71.42	02	28.57	7	30.43
Total	16	32.00	7	14.00	23	100.00

X^2:0.017; df:1; p=0.896

Table 10 shows out of 23 patients of lymph node metastasis, 10(43.47%) patients have lymphovascular invasion and 13 (56.52%) patients are free from lymphovascular invasion.

Table 10: Correlation of lymphovascular invasion with axillary lymph node metastasis.

Lymphovascular invasion	Patients with positive LN on HPE, (n=23)	Percentage (%)
Present	10	43.47
Absent	13	56.52
Total	23	100

DISCUSSION

The present study was undertaken to evaluate the non-palpable lymph nodes with the help of USG guided FNAC in diagnosed cases of carcinoma breast and then to compare with final histopathological report of lymph nodes. Study was done in the department of surgery of Sri Guru Ram Das institute of medical sciences and research, Vallah, Sri Amritsar.

A total of 50 patients of carcinoma breast with non-palpable axilla were studied. Pre operatively USG guided FNAC from axillary lymph nodes was done in all patients. After doing axillary dissection of every patient histopathological examination of lymph nodes was done.

The following observations were made from the above study.

In our present study the most common age group involved with carcinoma breast was 51-60 years. Ramesh et al did a study in clinically node negative carcinoma breast patients in which the most common age group involved was 30-40 years.[13] Similarly median age was 47 years in a study done by Sandoughdaran et al.[14] This difference in age distribution may be due to geographical variation.

In present study out of 50 patients of carcinoma breast 27 patients had right side breast carcinoma and 23 patients had left side breast carcinoma, that is right breast is involved more commonly then left. Kocic et al conducted a similar study in which left breast was more commonly involved than right side.[39] Results are not similar with our study which may be due to geographical variation or due to variation in sample size.

In our study the most common site of primary tumor was upper outer quadrant (UOQ). 26(52%) out of 50 patients

had tumor in upper outer quadrant. Our results are in concordance with the study done by Kocic et al in which also the most common site of primary tumor was upper outer quadrant.[15]

Ramesh et al also concluded in his study that upper outer quadrant is the most common quadrant involved in carcinoma breast patients.[14] Results are similar to our study.

In current study 16 patients (32%) revealed metastatic deposits out of 50 patients on USG guided FNAC. These 16 patients were 69.56% of all patients (n=23) with proven histological involvement. In 27 patients both USG guided FNAC and histopathology were negative. Similarly, Schiettecatte et al conducted a study in which US-guided FNAC of the axilla revealed metastasis in 34 (23.0%) of the 148 patients. These 34 patients were 53.1% of all patients (n=64) with proven axillary lymph node involvement. In 66 patients (44.6%), both ultrasound and histopathology were negative.[16]

In current study on USG guided FNAC there is high sensitivity of 73.91%, specificity of 100%, PPV of 100% and NPV of 81.82% in relation to HPE with p=0.005 which is highly significant. Similarly, Baruah et al did a study and concluded that AUS-FNAC had a sensitivity of 28.5% (39 of 137 patients), a specificity of 100 per cent (365 of 365 patients) a positive predictive value of 100 percent (39 of 39 patients) and negative predictive value of 78.8 per cent (365 of 463 patients). They concluded that Preoperative AUS-FNAC avoided unnecessary SNB in 28.5 per cent of node-positive patients.[17] Sensitivity was comparatively higher in our study which may be due to different technique of doing FNAC's. Therefore, high sensitivity in our study indicates that we may directly go for axillary dissection in patients with positive USG guided FNAC results without doing SLNB.

A rising success rate of US-FNAC in detecting nodal metastases is observed in patients with larger tumors. In our study sensitivity of FNAC increased from T1 stage (50% sensitivity) to T3 stage (83.33% sensitivity) and NPV was highest in T1 (92.86%) and was lowest in T3 (66.67%) tumors which was statistically significant (p<0.05). This is in agreement with the study conducted by Hayes et al in which the axillary FNAC reports were correlated with sentinel node biopsy and axillary clearance reports, and sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated. The NPV was highest in pT1 (86.7%) and the PPV was 100% in stage pT2 and pT3 tumours.[18]

Similarly in a study published by Kramer et al to select early breast cancer patients with three or more tumour-positive axillary lymph nodes demonstrated sensitivity to detect three or more positive nodes was 44.8%, specificity 95.7%, PPV 58.1% and NPV 92.9%.[19] The results of this study are almost in concordance with our present study indicating that FNAC positivity rate

increases as the number of positive LN increases on HPE. Low sensitivity in this study can also again maybe due to variations in the technique of FNAC.

In our present study 23 out of 50 patients had lymph node metastasis, out of which only 10 patients (43.47%) had lymphovascular invasion and was absent in 13 patients. Thus, in our study LVI has not emerged as a predictor of ALNM. A study by Sandoughdaran et al, LVI (lymphovascular invasion) emerged as the most powerful independent predictor of ALNM; in the risk for axillary nodal involvement was 3.5-fold greater in the presence of LVI.[20] The results of this study do not match with our present study which may be due to sample size variations between the studies.

On the other hand, there were some limitations to our study which need possible further developmental directions. FNAC via ultrasound is operator-dependent to such an extent that sampling may vary. A unified protocol should be established. In addition, the enrolled number of patients was relatively small, leading to difficulty in evaluating the atypia group. To combine other diagnostic tools with the design criteria may interfere with sensitivity. In addition, cost data should be collected to evaluate cost-effectiveness. Furthermore, comparative studies and meta-analyses may be required to identify adequate sensitivity, accuracy in order to make the tool worthwhile.

CONCLUSION

Thus, we can conclude that USG guided FNAC has moderate sensitivity, high specificity and PPV in relation to HPE and therefore is a good diagnostic technique for diagnosing patients with axillary lymph node metastasis in case of clinically non palpable axillary lymph nodes in carcinoma breast patients and can be used in place of SLNB. USG guided FNAC can be used to prevent unnecessary axillary dissection in patients having no axillary metastasis.

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