International Journal of Advances in Medicine
Kand HS et al. Int J Adv Med. 2022 Jun;9(6):729-736
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20221360

Original Research Article

Evaluation and correlation of clinicopathological and radiological findings of axillary node positivity in clinically node negative carcinoma breast

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Received: 30 March 2022
Revised: 28 April 2022
Accepted: 11 May 2022

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ABSTRACT

Background: In 2015, there will be an estimated 155,000 new cases of breast cancer and about 76,000 women in India are expected to die of the disease. By the time a breast lump becomes palpable for clinical detection, it is usually advanced. We conducted a study to compare the status of axillary lymph node between the radiological and histopathological finding with the clinically negative lymph mode in carcinoma breast in order to limit the axillary lymph node dissection.
Methods: This prospective study 50 female patients of carcinoma breast freshly detected and those with non-palpable axillary lymph admitted in S.C.B M.C.H, Cuttack, were included in the study.
Results: The mean age of the patients was 51.26 years with standard deviation of 12.26 years with a range of 20 to 80 years. All 50 cases included in the study was done mammography of both breast and among them BIRADS IV 18 cases, BIRADS V 19 cases, BIRADS VI 5 cases and 08 cases were benign. 44 (88%) patients had Karnofsky performance score of 90-100 and 6 (12%) patients had score of 80-90. None (0.00%) of the patients had <80 performance score. Out of the 50 cases enrolled in the study, 04 were underwent wide local excision, 09 were breast conservation surgery and 37 were modified radical mastectomy along with axillary clearance.
Conclusions: Higher sensitivity due to axillary ultrasound helps to reduce surgery time as patients with positive axillary lymph nodes directly get an Axillary Lymph Node Dissection (ALND) without preceding Sentinel lymph node biopsy (SLNB).

Keywords: Breast cancer, Axillary lymph node, Mammography, Computed tomography

INTRODUCTION

Breast cancer over the centuries has remained a dogma to the patient and an enigma to the oncologists. Since the Halstedian days of disfiguring extirpative surgery till the modern day approach of conservative surgery, management of breast cancer has seen many changes. Epithelial malignancy of the breast is the most common cause cancer in women accounting for about one-third of all cancer in women. Breast cancer develops by malignant proliferation of epithelial cells lining the ducts or lobule of the breast.

Breast cancer is the most common cancer diagnosed in the United States, after skin cancer. It is the second leading cause of cancer deaths in women today, after lung cancer. According to the American Cancer Society, more than 230,000 women will be diagnosed with breast cancer annually in the United States, and more than 39,000 will die from the disease.[1]

The incidence of occurrence of breast cancer in women depends on multiple risks, several factors which have been studied in great detail. This may include family history, genetic preponderance, the duration of estrogenic insult to the body (early menarche, late menopause and nulliparity etc), and many other factors that have not yet been identified. Early child bearing and breast feeding reduces the chances of malignancy. Early first child birth reduces the risk; late 1st child birth after 35 years of age increases the risk. It is more common in obese individuals.

Risk is 3-5 times more common if 1st degree relative is having breast cancer. Risk is more if 1st degree relative is younger or premenopausal or having bilateral breast cancers. A benign breast disease with atypia, hyperplasia and epitheliosis has got higher risk in a patient with family history. It is more common in individuals who are on hormone replacement therapy for more than 5 years.

Hormone receptors expressed i.e ER, PR and HER2/neu, urokinase plasminogen activator, and plasminogen activator inhibitor 1 are important prognostic factors.[2-5] The tumors expressing ER and PR strongly are related to low grade nuclei and positive expression of HER-2/ neu are related to the high grade nuclei.[6,7]

Mutation of tumor suppressor genes BRCA1/BRCA2 is thought to be involved with high risk of breast cancer. BRCA1 mutation is having more risk (35-45%) than BRCA2 mutation. It is located in long arm chromosome 17, whereas BRCA2 is located in long arm of chromosome 13. BRCA1 more commonly shows ER negative status, high grade, aneuploid with raised S fraction than BRCA2 which shows ER positive status.

Growth factor receptors play an essential role in initiating both proliferative and cell survival pathways in breast as well as other epithelia. In breast cancer biology, the EGFRs and insulin-like growth factor receptors have been studied most extensively. These receptors have an extracellular ligand-binding region, a transmembrane region, and a cytoplasmic tyrosine kinase containing domain that can activate downstream signalling cascades. Growth factor receptors can be constitutively activated by excessive ligand levels, activating mutations, or gene amplification/over expression that ultimately leads to inappropriate kinase activity and growth promoting second messenger activation

By the time a breast lump becomes palpable for clinical detection, it is usually advanced. The newer methods of early detection include breast radiographic imaging which aids in detecting small, non-palpable breast abnormalities, to evaluate clinical findings and to guide diagnostic procedures.

Mammography is the most sensitive and specific imaging test currently available, though 10% to 15% of clinically evident breast cancers may be missed out on mammography due to adjacent fibrodense tissue obscuring the tumour, absence of calcification, small size, a diffuse infiltrative pattern with little or no desmoplastic reaction or a location close to chest wall or in periphery of the breast. The effective diagnosis and management of breast lesions involves multidisciplinary approach to their assessment.

Patients presented with symptom of suspected breast cancer underwent detail history, clinical examination, Fine needle aspiration cytological examination, mammography, ultrasonography of breast and axilla both side, true cut biopsy and CECT of chest and abdomen for confirmation of diagnosis and stage the disease to plan the management.

With the above background we conducted a study to compare the status of axillary lymph node between the radiological and histopathological finding with the clinically negative lymph mode in carcinoma breast in order to limit the axillary lymph node dissection.

METHODS

This prospective study 50 female patients of carcinoma breast freshly detected and those with non-palpable axillary lymph admitted in S.C.B M.C.H, Cuttack, were included in the study.

Study period

The study was conducted from July 2017 to July 2019.

Inclusion criteria

Patients aged between 20 to 80 years. Only female patients. All patients with breast lumps and FNAC positive reports. Patients who belong to node negative disease status.

Exclusion criteria

Patients with proven benign breast diseases. Clinically positive axillary lymph node. All metastatic advanced breast malignancies. Patients with inflammatory breast carcinomas. Recurrent breast lump in a previously operated case of carcinoma breast.

Study design

Fifty female patients of Carcinoma breast freshly detected and those attending the Malignant Disease Treatment

Centre of a tertiary care hospital were included in the study, after obtaining their informed written consent.

Demographic profile of patient's such as name, age, sex etc was recorded. Under structured pro forma as attached in appendix-A, in depth history of the patients was taken to note the indication for which patient was being evaluated for Carcinoma Breast and the duration of illness with clinically node negative Carcinoma Breast. Any past or concomitant co morbidity was noted. Detailed clinical examination including vital parameters recording was done. The functional status of patient was noted in the form of Karnofsky performance scale.[22] Breast was examined thoroughly to look for any abnormality like swelling, lump, and nipple areola complex bilaterally.

Examination of axilla was done bilaterally to look for any lymphadenopathy or not. Systemic examination viz neurological, cardiovascular, respiratory, gastrointestinal was done thoroughly to look for any abnormality. All patients fulfilling the inclusion criteria were subjected to have presented with breast lump with FNAC positive carcinoma breast those are clinically axillary node negative. Imaging of the breast in the form of mammography and Ultrasonographic study of the breast and axilla was done in all cases. CECT was done as and when indicated.

Staging ultrasonography of the axilla should include careful evaluation of levels I and II as well as the axillary tail of the breast. For examination, the patient is placed supine, with the proximal arm positioned upward adjacent to her head and the distal arm either above her head or on her forehead. Evaluation should be performed with a high frequency linear transducer in the range of 12 MHz to 17 MHz. Rarely, a 9-MHz probe may be necessary for deeper penetration in larger patients. The medial aspect of the axilla extending into the upper outer quadrant, or axillary tail of the breast, should be carefully examined. The pectoralis major and minor are easily visible on ultrasonography (Figure 2). Level I nodes and intramammary nodes in the axillary tail are easily evaluated. Normal level II nodes, which lie beneath the pectoralis minor, are usually not seen, but abnormally enlarged level II nodes can be readily identified. Our institutional protocol also calls for evaluation of the first and second intercostal spaces, where metastatic internal mammary nodes most commonly occur. The determination of abnormal lymph nodes is based on several well-established morphologic characteristics rather than the absolute nodal size. Suspicious morphologic characteristics include cortical thickening with concomitant narrowing of the hilum, focal eccentric cortical thickening (bulge in cortical contour), and absence of a central fatty hilum.[20,21] The nodal contour is also important in differentiating malignant from benign nodes. This distinction is evaluated by determining the ratio of the long-to short axis. Malignant nodes tend to be more round, possessing a long-to-short axis ratio of less than 2. Nodes with spiculated margins suggest extranodal tumor extension. Nodal color-flow Doppler characteristics may also enhance the diagnostic sensitivity of ultrasonography. This pattern is characterized by hypervascularity and visualization of multiple feeding vessels for single lymph node.[22] Lymph nodes with one or more of these characteristics are more likely to be malignant.

This was followed by breast conservative surgery or modified radical mastectomy was done and whole specimen was sending for histopathological examination. The histopathological reports of tumor grade, lymph node positivity, margin of involvement, pathological staging and hormonal receptors (ER, PR, and Her2Neu) study was done.

The results were compared with the inferences drawn from ultrasonography of axilla and histopathological examination of the dissected axillary lymph node.

Data analysis

The findings were analysed in terms of sensitivity, specificity, positive predictive value and negative predictive value of clinical stage, finding of ultrasonography of axilla, mammographic finding in carcinoma breast with no axillary node with respect to grade keeping histopathology as the gold standard. The results were collected, evaluated, calculated, tabulated and statistically analysed using a Chi-square test. P value less than 0.05 was considered significant.

All fifty (50) patients included in the study underwent imaging of the axillary region in the form of Ultrasonographic study. Few patients also underwent CECT chest as per the indications. Among the study group of patient 37 patients were underwent modified radical mastectomy, 09 patients were underwent breast conservation surgery and axillary lymph node dissection and 04 patient were underwent wide local excision and axillary lymph node dissection. Whole specimen was examined histologically. The lymph node was positive in 15 cases and negative in 35 cases. The sensitivity of the imaging (ultrasonography of axilla) were 65.21%, specificity were 85.18%, positive predictive value of the study is 78.94% and negative predictive value the study was 74.19%.

Type of study

Two years' prospective analysis of cases.

Ethical approval

The study was approved by the Institutional Ethics Committee.

Sensitivity of imaging

$$= true\ positive \div true\ positive + false\ negative$$
$$= 15 \div 15 + 08 = 15 \div 23 = 6.21\%$$

Specificity of imaging

$$= true\ negative \div true\ negative + false\ positive$$
$$= 23 \div 23 + 07 = 23 \div 27$$
$$= 85.18\%$$

Positive predictive value

$$= true\ postitive \div true\ positve + false\ positive$$
$$= 15 \div 15 + 05 = 15 \div 19$$
$$= 78.94\%$$

Negative predictive value

$$= true\ negative \div true\ negative + false\ negative$$
$$= 23 \div 23 + 08 = 23 \div 31$$
$$= 74.19\%$$

Positive likelihood ratio

$$sensitivity \div (1 - specificity)$$
$$= 0.652 \div (1 - 0.852) = 4.405$$

Negative likelihood ratio

$$= (1 - sensitivity) \div specificity$$
$$= (1 - 0.62) \div 0.852 = 0.408$$

Table 1: Distribution of patients according to BMI.

Body mass index	Frequency	Percent (%)
<18.5	2	4.0
18.5-19.99	15	30.0
20-21.99	16	32.0
22-24.99	12	24.0
>25.0	5	10.0
Total	50	100.0

RESULTS

The mean age of the patients was 51.26 years with standard deviation of 12.26 years with a range of 20 to 80 years.

Presenting site of tumour

Out of 50 patients participating in study, 27 (54%) were right sided and 23 (46%) were left sided.

Mammography

All 50 cases included in the study was done mammography of both breast and among them BIRADS IV 18 cases, BIRADS V 19 cases, BIRADS VI 5 cases and 08 cases were benign.

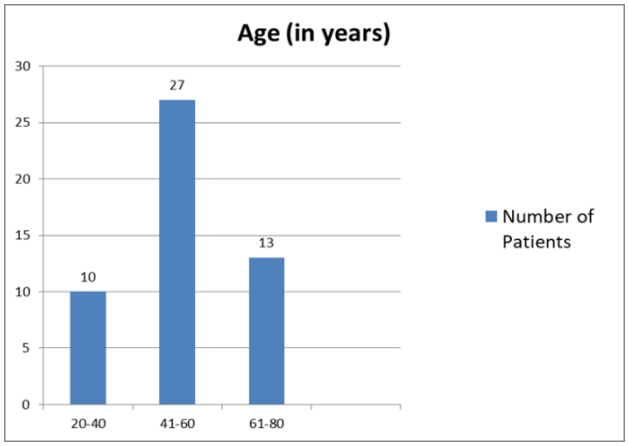

Figure 1: Distribution of patients according to age.

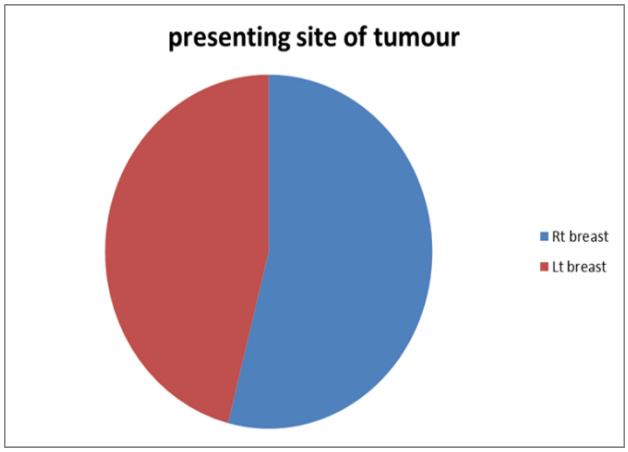

Figure 2: Distribution of patients according to site of tumour.

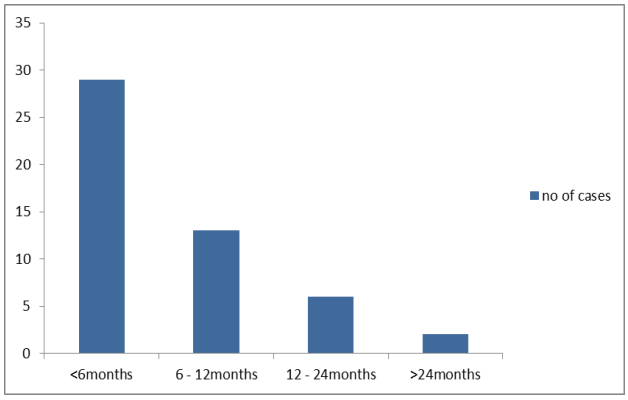

Figure 3: Distribution of patients according to duration of illness.

Duration of illness

The duration of breast lump in 50 cases was diagnosed as carcinoma breast in between 1 week to 2 years and the mean duration of illness was 5.7 months.

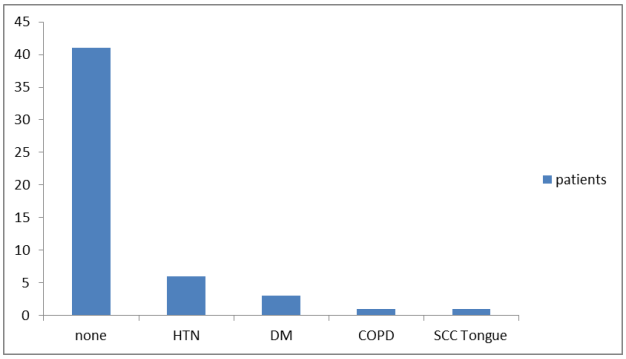

Figure 4: Comorbidities.

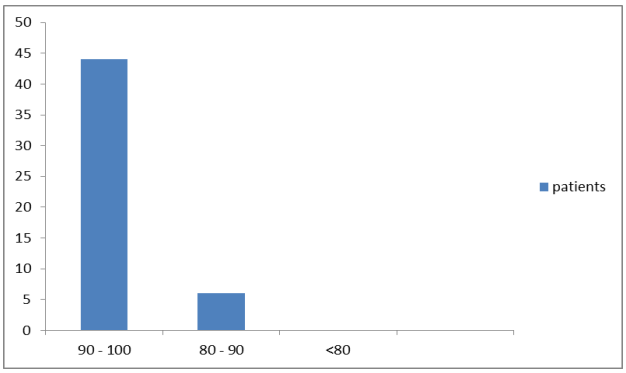

Figure 5: Functional Status of patients.

Table 2: Comparison of imaging (ultrasound of axilla) with final HPE.

N = 50	Final HPE (Positive)	Final HPE (Negative)	Total
Imaging Positive	15	04	19
Imaging Negative	23	08	31
Total	38	12	50

Out of 50 cases included in the study, 41 (82.0%) cases did not have any other illness at the time of study. 6 (12%) cases were hypertensive, 3(6%) cases were diabetics and 1 (2%) patients had COPD.

1 (2%) patient was a known case of squamous cell carcinoma tongue (OPTD). Two patients had more than one comorbidities.

As shown in Figure 5, 44 (88%) patients had Karnofsky performance score of 90-100 and 6 (12%) patients had score of 80-90. None (0.00%) of the patients had <80 performance score.

Body mass index

The mean body mass index of the patients was 19.77 kg/m^2 with standard deviation of 2.39 kg/m^2 with a range of 18.22 to 25.46 kg/m^2.

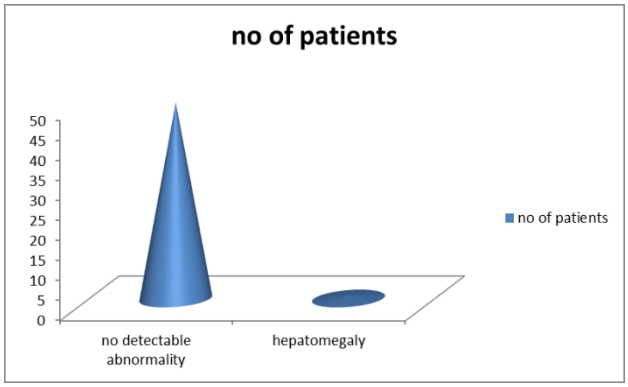

Figure 6: Abdominal examination.

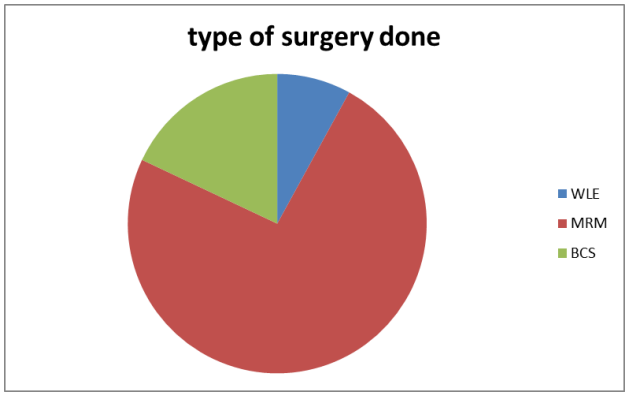

Figure 7: Type surgery done.

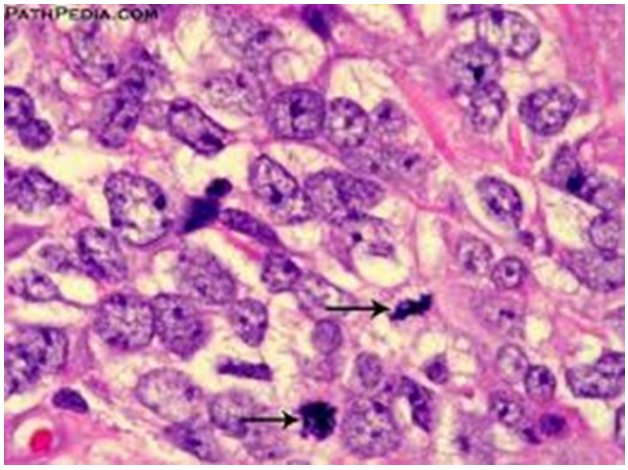

Figure 8: Invasive ductal carcinoma.

Abdominal examination all 50 patients was done, among them 49 patients have within normal limit and one have hepatomegaly. There was no free fluid in any patient.

Out of the 50 cases enrolled in the study, 04 (four) were underwent wide local excision, 09 (nine) were Breast Conservation Surgery and 37 (thirty seven) were modified radical mastectomy along with axillary clearance. All these specimen were send for histopathological and immunohistochemistry examination.

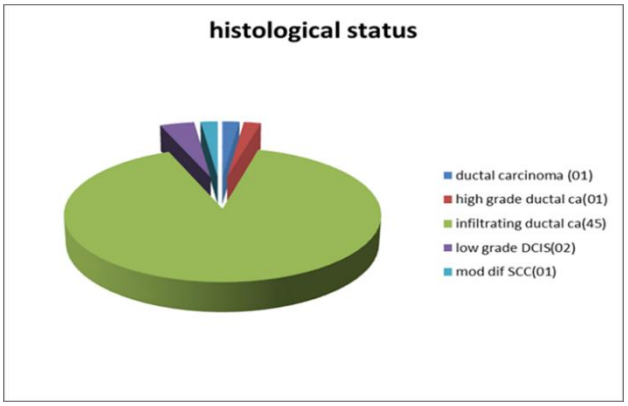

Figure 9: Histological status.

Table 2: Comparison of imaging (ultrasound of axilla) with final HPE.

N=50	Final HPE (positive)	Final HPE (negative)	Total
Imaging positive	15	04	19
Imaging negative	23	08	31
Total	38	12	50

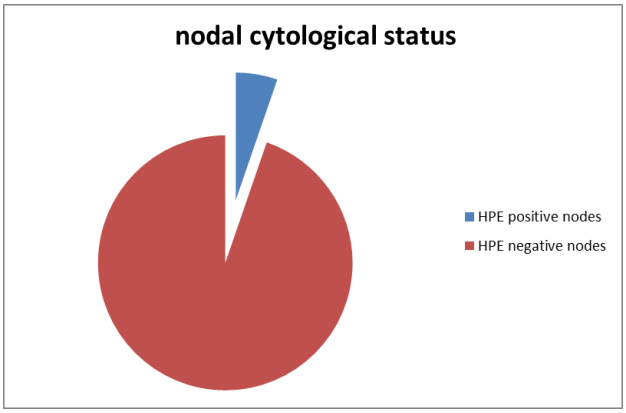

Figure 10: Nodal cytological status.

The results were analysed for node negative breast cancer and sensitivity, specificity, positive predictive value and negative predictive value of ultrasonography of axilla and resected axillary lymph node positivity was compared with relation to final histopathology as a gold standard.

Out of the 50 cases enrolled in the study, histopathological reports of specimen of all 50 cases are, 01 cases had ductal carcinoma, 01 had high grade ductal carcinoma, 45 cases had infiltrating ductal carcinoma, 02 cases had low grade DCIS and 01 cases had moderately differentiated squamous cell carcinoma.

Total 870 axillary lymph node were send for histopathological examination and 46 (5.3%) lymph nodes are found positive for carcinoma and 824 (94.7%) lymph nodes were negative.

All 50 patients included in the study underwent imaging of the axillary region in the form of ultrasonographic study. Few patients also underwent CECT chest as per the indications. It was positive in 15 cases and negative in 35 cases.

Sensitivity of imaging

$$= true\ positive \div true\ positive + false\ negative$$
$$= 15 \div 15 + 08 = 15 \div 23$$
$$= 65.21\%$$

Specificity of imaging

$$= true\ negative \div true\ negative + false\ psotive$$
$$= 23 \div 23 + 04 = 23 \div 27$$
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Positive predictive value

$$= true\ positive \div true\ positive + false\ positive$$
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$$= 78.94\%$$

Negative predictive value

$$= true\ negative \div true\ negative + false\ negative$$
$$= 23 \div 23 + 08 = 23 \div 31$$
$$= 74.19\%$$

Positive likelihood ratio

$$= sensitivity \div (1 - specificity)$$
$$= 0.652 \div (1 - 0.852) = 4.405$$

Negative likelihood ratio

$$(1 - sensitivity) \div specificity$$
$$= (1 - 0.652) \div 0.852 = 0.408$$

Nodal cytology

Dissected nodal cytology was done in all 50 cases. Total 870 lymph nodes were examined histologically. Among these 46 nodes (5.38%) were microscopically positive for malignant cells and 824 nodes (94.7%) were free from malignant invasion.

DISCUSSION

The present study was a prospective study to evaluate the efficacy of preoperative axillary ultrasonography for clinical staging of the disease and planning of the management of carcinoma breast compared to post operative histopathology axillary node as a gold standard with reference to its grade. All patients fulfilling the

inclusion criteria were subjected to do ultrasonography of axilla and breast both sides who have no palpable axillary lymph node and FNAC positive report. Imaging of the breast and axilla in the form of mammographic study and true cut biopsy was done all cases prior to surgery. The diagnosis, determined from the clinical examination, FNAC, ultrasonography, mammography findings and biopsy findings of the suspicious lesion, was accepted as the reference standard.

In this study, 50 cases were included. Mean age of patients was 51 years, commensurate with it being common in middle aged and elderly people. Except for 12% of patients, who had Karnofsky performance score of 80, others were in fair general condition with Karnofsky performance score being either 90 or 100.

The sensitivity of axillary ultrasonography of our study is 65.21%, a statistically significant (p, 0.001), specificity 85.18%, positive predictive value 78.94% and negative predictive value 74%. In comparison, our sensitivity was in the range of data reported by Jung et al (sensitivity of 54%), Ertan et al (58%), Garcia-Ortega et al (63%) and Mills et al (59%) but somewhat lower than findings reported by other groups.[8-11] In particular, Vaidya et al reported (82%), Das et al (79%), Kebudi et al (79.1%), Strauss et al 90%, Yang et al 841% and Bonnema et al 87%.[12-17] However, specificity, PPV and NPV were almost in the same range.[4,5,12-15] Since our study population is very typical for patients with first diagnosis of breast cancer, the differences might be explained by the fact that axillary ultrasound examinations were done by a team of trained radiologists during their residency and not by one highly specialized individual in a retrospective study setting. In general, higher sensitivity due to axillary ultrasound helps to reduce surgery time as patients with positive axillary lymph nodes directly get an ALND, without preceding SLNB. Higher specificity might help patients with negative lymph nodes, as an ALND can be avoided if a negative nodal

We could show that clinical/pathological parameters like age at diagnosis, BMI, tumor localization, multi-centricity, carcinoma type, grading, hormone receptor status, HER2/neu status, had no impact on sensitivity and specificity of palpation plus axillary ultrasound. This result is in line with the findings of Bedrosian et al, who conducted a very similar study on 208 patients 18. In contrast to Bedrosian et al, we could provide evidence for four factors increasing either sensitivity (number of affected lymph nodes), specificity (tumor size), or both (axillary palpation, distant metastases). It appears quite conclusive that sensitivity increases parallel to the number of affected lymph nodes. Unfortunately, we were not able to demonstrate a clear-cut relationship between tumor size and sensitivity.

The findings of Aitken et al provide strong evidence that tumor size.[19] 5 cm is one of the strongest predictors of lymph node metastases.[18] Susini et al found tumor localization in the outer quadrants to be a significant independent predictor of axillary lymph node metastases.[20] The factors affecting the sensitivity of axillary ultrasonography include obesity, size and number of the tumor invasion nodes, presence of vascularity, and radiologist's expertise. Patients with locally advanced carcinoma were excluded from the study.

Axillary ultrasonography is a valuable tool that accurately predicted malignant axillary disease in 78.94% of patients with clinically node-negative breast cancer. Elaboration of standard criteria for nodal evaluation will improve usefulness of this imaging modality in preoperative staging of the axilla In our study histopathology has been referred as a gold standard, further advancements in primary ultrasonography of axilla should be considered and incorporated in practice for initial evaluation of clinical staging of early breast cancer, especially in India. Patients suffering from breast carcinoma by FNAC positive cytology and by imaging should be scheduled directly and promptly for true cut biopsy for hormonal receptor study.

CONCLUSION

This study was to evaluate the diagnostic value of axillary ultrasonography for detection of non-palpable axillary lymph node metastases in breast cancer patients. Fifty patients included in the study underwent axillary ultrasonography and colour Doppler preoperatively. A total of 870 nodes were surgically removed from 50 patients; 46 were metastatic lymph nodes. Sensitivity and specificity in this preliminary study was 65.20% and 85.18%, respectively. . In general, higher sensitivity due to axillary ultrasound helps to reduce surgery time as patients with positive axillary lymph nodes directly get an ALND, without preceding SLNB.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kand HS, Mohapatra M, Panda S, Sarangi AK, Babu KK, Sarangi A. Evaluation and correlation of clinicopathological and radiological findings of axillary node positivity in clinically node negative carcinoma breast. Int J Adv Med 2022;9:729-36.