Original Research Article

Role of Mammography and Ultrasound in Non- palpable lesions of the Breast presenting with Mastalgia and Nipple Discharge

Ritu Ojha[1],Adity Prakash[2],Ashish Verma[3],Pramod Kumar Singh[4*],Ram C Shukla[5],Seema Khanna[6]

[1]Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[2]Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[3]Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[4]Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[5]Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[6]Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Received: 19-06-2021 / Revised: 21-07-2021 / Accepted: 11-08-2021

Abstract

Objectives: This article aims to assess the diagnostic value of mammography and ultrasound in mastalgia and nipple discharge without any palpable breast mass.**Materials and Methods:** In this retrospective cross-sectional study, 250 ultrasound-guided biopsies performed for various breast lesions were reviewed and 50 women were included in the study. Mammography and ultrasound features of these lesions were analyzed as per ACR BI-RADS lexicon 5th edition by two radiologists. The lesions were classified as benign or malignant based on histopathology. **Results:** Out of the 50 cases, 5 [10%] were found to be malignant, and 45 [90%] were found benign. Of these 22 [44%] had mastalgia, 12 [24%] had nipple discharge, and 11 [22%] had both mastalgia and nipple discharge. Malignant lesions more frequently showed segmental distribution of calcifications [3/5, 60%; p= 0.039], increased distance of the lesion from the nipple [mean= 3.7 +/- 2.1; p=0.004], irregular shape [3/5, 60%; p= 0.02], microcalcifications [2/5, 40%, p= 0.028] as compared to benign lesions. The sensitivity and specificity of mammography were 60%, and 68% respectively, and of ultrasound were 100% and 35.6%, respectively. **Conclusion:** Mammography and ultrasound assessment are reliable in characterizing malignancy in non-palpable breast lesions, with ultrasound being more sensitive and mammography being more specific.

Keywords: mammography, ultrasound, non- palpable, mastalgia, nipple discharge

Introduction

Mastalgia occurs in 70-80% of women during their lifetime and amounts to 45-70% of breast-related complaints in primary care settings[1-4]. Among patients with focal breast pain and no clinically palpable lump, a benign etiology is always the cause of pain [5]. Nipple discharge accounts for 4.8- 7.4% of daily outpatient visits [6] and the incidence of breast cancer has been reported to be 2.8- 21.3% in patients with nipple discharge [7-11]. Often, mastalgia and nipple discharge are not associated with a palpable mass on clinical examination. However, imaging may pick up clinically non-palpable lesions in such cases. In a study including 225 women with non-palpable breast lesions who underwent biopsy, a 27% rate of malignancy was found [12]. The role of imaging in non-palpable lesions of the breast with mastalgia and nipple discharge is a rapidly evolving field in a bid to early diagnosis of breast carcinoma. Mammography and ultrasound are invaluable in the evaluation of clinically non- palpable breast lesions. Often such lesions present with complaints of mastalgia and nipple discharge [13]. Although studies have been done to evaluate the role of mammography or ultrasound in mastalgia and nipple discharge, most of these studies have not stated whether a palpable lesion was associated with these symptoms. This is important as the presence of a palpable lesion significantly affects the diagnostic utility of mammography as well as ultrasound. Gulay et al. found that the incidence of breast cancer in cases with spontaneous nipple discharge with a palpable lesion was 61.5% compared to 6.1% in cases with nipple discharge without a palpable lesion [14]. Moreover, studies employing multi-modality imaging techniques and comparing their performances in non-palpable lesions are limited. This study was carried out to evaluate the role of mammography and ultra sonography with guided biopsy to elucidate their role in diagnosis of patients presenting with mastalgia or nipple discharge without breast lump.

**Correspondence*
Dr. Pramod Kumar Singh
Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India
E-mail: pksimsbhu@gmail.com

Materials and Methods

Patient selection [Figure 1]**:**After approval by the ethical committee of the Institute, patients who underwent ultrasound-guided biopsies Between November 2019 to February 2020, [n=250] were reviewed for their clinical details. All those who had a palpable mass on clinical examination were excluded[n=176].Of the remaining 74

cases, 50 cases had complaints of mastalgia or nipple discharge or both and were included in the study. The mammography and ultrasound data of these patients were evaluated. All 50 patients had their ultrasound data collected on the same day of the ultrasound-guided biopsy. 30/50 patients had previous mammography reports, all of which were done within three months of the date of ultrasound-guided biopsy.

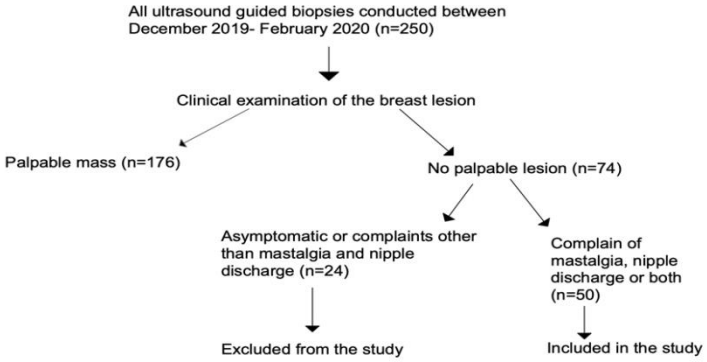

Fig 1: Flowchart showing selection of patients for the study

Imaging evaluation and biopsy: Ultrasound was done for all 50 patients on the same day of biopsy using Philips IU22 machine by Philips Medical System California, USA. 5-12 MHz linear array probe was used for scanning. B- mode scanning was done in both radial and anti- radial directions. Doppler was used whenever needed. Breast ultrasound was performed by one radiologist with two years of experience in breast imaging under the supervision of another radiologist with ten years of experience in breast imaging. The lesions were classified as per ACR- BIRADS lexicon 5th edition [23]. Mammography films were available for 30/50 patients. All mammograms were done using Xtromam 2000-HF digital mammography machine. Both cranio- caudal view and medio- lateral oblique views and any additional views were analyzed as per ACR-BIRADS lexicon 5th edition [23]. U.S.- guided percutaneous biopsy was performed on all the 50 lesions using 14- gauge automated core needle [Stericut® with coaxial; TSK Laboratory, Tochigi, Japan]. Biopsy report was accessed later, so the radiologists were blinded for the pathological outcome at the time of interpreting the ultrasound and mammography. Based on histopathology, lesions were classified as either benign or malignant.

Image analysis: On mammography, the composition of breasts was classified as A= entirely fatty, B= scattered fibroglandular tissue, C= heterogeneously dense and D= extremely dense. The presence or absence of any mass lesion, architectural distortion was recorded. Morphology [typically benign or suspicious] and distribution [diffuse, regional, grouped, linear or segmental] of calcifications, if any, were evaluated as per the BI-RADS lexicon. Amorphous, coarse heterogeneous, fine pleomorphic, fine linear, and fine linear branching calcifications were considered suspicious. Rest all other morphologies of calcification were considered as typically benign. The final mammographic BI-RADS assessment category of all 30 lesions was assigned.

On ultrasound, size of the lesion, the distance of the mass from nipple, background echotexture[Homogeneous- fat, homogeneous-fibroglandular or heterogeneous], the shape of lesion [round,oval or irregular],margins[circumscribed,indistinct,angulated,microlobulated or spiculated], orientation [parallel or not- parallel], echogenicity [hypoechoic,isoechoic,solid-cystic,anechoic/heterogeneous],posterior features [none,accentuation or shadowing], presence of calcifications [micro or macro] and association of the lesion with dilated ducts [Not associated with dilated ducts or dilated ducts outside lesion, an intra-ductal lesion within a solitary dilated duct, intra- ductal lesion with multiple dilated ducts]. The final ultrasound BI-RADS assessment category for all 50 lesions was assigned.

Statistical analysis: For statistical analysis, Fisher exact tests were done to compare categorical variables like mammography and ultrasound features. Mann- Whitney U-tests were performed for numerical variables, such as age, size of the lesion, and distance of lesion from nipple.

Sensitivity and specificity were calculated for mammography and ultrasound. For calculation of above, lesions with BIRADS category 4A and above were considered test positive, and all lesions with BIRADS 3 and below were considered test negative. The maximum likelihood of carcinoma as per BIRADS category [BIRADS 1= 0%, BIRADS 2= 0%, BIRADS 3 = 2%, BIRADS 4A= 10%, BIRADS 4B= 50%, BIRADS 4C= 94%, BIRADS 5= 100%] were recorded separately for mammography and ultrasound. Receiver operator characteristics [ROC] curve for mammography and ultrasound were plotted using these likelihood data and area under the curves calculated [Figure 2]. All statistical analysis was performed using SPSS version 16.0 software [IBM Corporation, Chicago II, United States]. P values <0.05 were considered statistically significant. Sensitivity and specificity of each imaging modality was calculated.

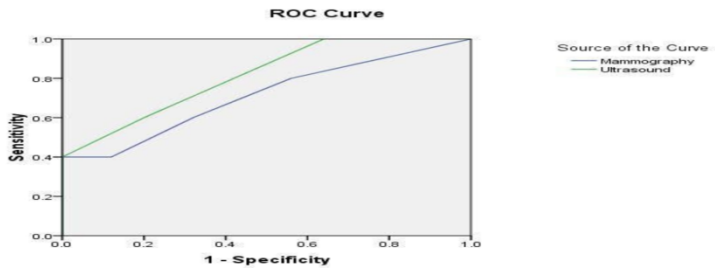

Fig 2:ROC curves for mammography and ultrasound

Results

For all the 50 biopsies done, the pathological outcome showed 5 malignant lesions [3 invasive ductal carcinoma and 2 ductal carcinoma in situ] and 45 benign lesions [14 fibrocystic disease, 10 papilloma, 7 ductal ectasia, 6 fibroadenomas, 4 mastitis, 2 benign lymph nodes, 1 apocrine metaplasia and 1 stromal fibrosis. Thus, the rate of malignancy in non-palpable lesions was 10% [5/50].

The demographic and clinical complaints of benign and malignant lesions are shown in Table 1. The mean age for benign lesions was 40.8 +/- 9.4 years, and for malignant lesions was 50.4 +/- 11.0 years. Mastalgia was the most common clinical complaint overall and was present in 68% [34/50] patients. Only mastalgia was seen in 44% [22/50], only nipple discharge in 32% [16/50], and both mastalgia and nipple discharge in 24% [12/50]. All cases with only mastalgia had a benign outcome. No malignancy was found in any of the patients who had only mastalgia. Malignancy was found in 25% [4/16] of cases with nipple discharge only and 8.3% [1/12] of cases with both mastalgia and nipple discharge. The differences between benign and malignant lesions were statistically significant [p= 0.022].

Table 1: Demographic and clinical data of benign and malignant non-palpable lesions of the breast

	Benign [n=45]	Malignant [n=5]	p value
Age^{+}	40.8 +/- 9.4	50.4 +/- 11.0	0.06
Clinical complains			
Mastalgia only	22 [100]	0 [0]	**0.022**
Nipple discharge only	12 [75]	4 [25%]	
Both mastalgia and nipple discharge	11 [91.7]	1 [8.3%]	

[Numbers indicate frequency, value in parenthesis indicates percentage. +Mean +/- S.D.]

The mammographic features of benign and malignant lesions are shown in Table 2[Figure 3].Malignant lesions more frequently showed segmental distribution of calcifications [25%, 2/8] as compared to benign lesions[0%,p=0.039].The rest of the mammographic features such as breast composition, presence of mass, architectural distortion, and morphology of calcifications were not statistically different between benign and malignant lesions [Figure 3]. The final mammographic BI-RADS category showed malignancy rates of 25% [1/4] in BIRADS 1, 0% [0/8] in BIRADS 2, 14.3% [1/7] in BIRADS 3, 16.7% [1/6] in BIRADS 4B, 0% [0/3] in BIRADS 4C and 100% [2/2] in BIRADS 5 lesions. Malignant lesions more frequently corresponded to higher [BIRADS 4A or above] BIRADS category [60%, 3/5] as opposed to benign lesions [32%, 8/25].

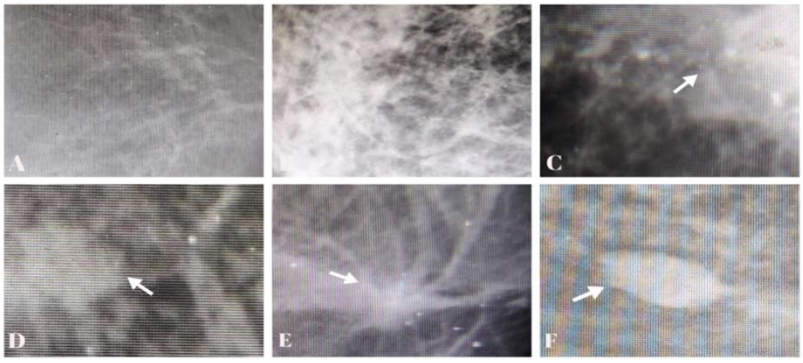

Fig 3: Mammographic findings in various lesions. A. Type A breast. B. Type D breast.C. fine linear macrocalcifications in segmental distribution. Histopathology showed ductal carcinoma in situ. D. grouped popcorn calcifications. Histopathology showed fibroadenoma. E. Irregular spiculated mass. Histopathology showed invasive ductal carcinoma F. Oval circumscribed mass. Histopathology showed papilloma.

Table 2:Mammographic findings of benign and malignant non-palpable lesions of the breast [Numbers indicate frequency, value in parenthesis indicates percentage]

Mammographic findings	Benign [n=25]	Malignant [n=5]	p value
Breast composition			0.611
Type A	6 [100.0]	0 [0]	
Type B	7 [87.5]	1 [12.5]	
Type C	10 [76.9]	3 [23.1]	
Type D	2 [66.7]	1 [33.3]	
Mass			0.245
Present	17 [89.5]	2 [10.5]	
Absent	8 [72.7]	3 [27.3]	
Architectural distortion			0.405
Present	6 [75.0]	2 [25.0]	
Absent	19 [86.4]	3 [13.6]	
Calcification morphology			0.159
No calcification	18 [90.0]	2 [10.0]	
Typically benign	5 [83.3]	1 [16.7]	
Suspicious	2 [50.0]	2 [50.0]	

Calcification distribution			**0.039**
No calcifications	18 [90.0]	2 [10.0]	
Grouped	4 [100.0]	0 [0]	
Linear	3 [75.0]	1 [25.0]	
Segmental	0 [0]	2 [100.0]	
BIRADS category			**0.044**
BIRADS 1	3 [75.0]	1 [25.0]	
BIRADS 2	8 [100.0]	0 [0]	
BIRADS 3	6 [85.7]	1 [14.3]	
BIRADS 4B	5 [83.3]	1 [16.7]	
BIRADS 4C	3 [100.0]	0 [0]	
BIRADS 5	0 [0]	2 [100.0]	

The ultrasound features of benign and malignant lesions are shown in Table 3 [Figure 4]. Malignant lesions more frequently showed increased distance from the nipple [mean 3.7 +/- 2.14 cm] as compared to benign lesions [1.39 +/-1.11 cm], irregular shape [60%,3/5] as compared to benign lesions [11.1%, 5/45, p= 0.02], presence of microcalcifications [40%, 2/5] as compared to benign lesions [2.2%,1/45,p=0.028]. Other ultrasound features such as lesion size, background echotexture, orientation,margins, echogenicity, posterior features, and association with dilated ducts of the lesions were not statistically significant [Figure 4]. The final ultrasound BI-RADS assessment category showed malignancy rate of 0% [0/16] in BIRADS 3, 7.4% [2/27] in BIRADS 4A, 20% [1/5] in BIRADS 4B, 100% [1/1] in BIRADS 4C, and 100% [1/1] in BIRADS 5 lesions. Malignant lesions more frequently demonstrated BIRADS 4A or higher category [100%, 5/5] as opposed to benign lesions [64.4%, 29/45].

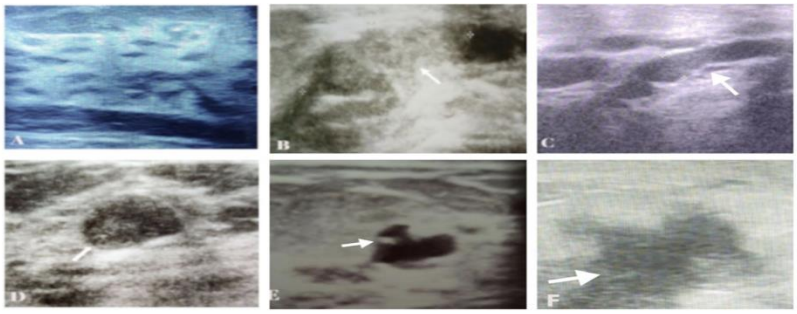

Fig 4: Ultrasound findings in various cases. A. Homogeneous- fibroglandular background echotexture. B. Oval circumscribed intra-ductal lesion. Histopathology showed papilloma.. C. Multiple dilated ducts. Histopathology showed duct ectasia. D. Circumscribed, parallel hypoechoic lesion. Histopathology showed fibroadenoma. E. Irregular angulated hypoechoic lesion with posterior acoustic accentuation. Histopathology showed fibrocystic disease. F. Irregular microlobulated lesion. Histopathology showed invasive ductal carcinoma.

Table 3: **Ultrasound findings in benign and malignant non-palpable lesions of the breast [Numbers indicate frequency, value in parenthesis indicates percentage. +Mean +/- S.D.]**

Ultrasound findings	Benign [n=45]	Malignant [n=5]	p value
Size of lesion [cm]$^{+}$	1.80 +/- 1.45	1.28 +/- 0.66	0.64
Distance of lesion from nipple [cm]$^{+}$	1.39 +/- 1.11	3.70 +/- 2.14	**0.004**
Background echotexture			1.0
Homogeneous- fat	6 [85.7]	1 [14.3]	
Homogeneous- fibroglandular	12 [92.3]	1 [7.7]	
Heterogeneous	27 [90.0]	3 [10.0]	
Shape of lesion			**0.02**
Oval	30 [96.8]	1 [3.2]	
Round	10 [90.9]	1 [9.1]	
Irregular	5 [62.5]	3 [37.5]	
Margins of lesion			0.06
Circumscribed	26 [96.3]	1 [3.7]	
Indistinct	2 [66.7]	1 [33.3]	
Angular	1 [100]	0 [0]	
Microlobulated	16 [88.9]	2 [11.1]	
Spiculated	0 [0]	1 [100.0]	
Orientation of lesion			0.06
Parallel	37 [94.9]	2 [5.1]	
Non- parallel	8 [72.7]	3 [27.3]	
Echogenicity of lesion			0.552
Hypoechoic	16 [84.2]	3 [15.8]	
Isoechoic	26 [92.9]	2 [7.1]	

Mixed solid- cystic	1 [100.0]	0 [0]	
Heterogeneous	2 [100.0]	0 [0]	
Posterior features			0.269
None	31 [88.6]	4 [11.4]	
Accentuation	11 [100]	0 [0]	
Shadowing	3 [75.0]	1 [25.0]	
Calcifications			**0.028**
No calcification	36 [92.3]	3 [7.7]	
Microcalcifications	1 [33.3]	2 [66.7]	
Macrocalcifications	8 [100.0]	0 [0]	
Association with dilated ducts			0.09
Not associated with dilated ducts or dilated ducts outside lesion	25 [86.2]	4 [13.8]	
Intra- ductal lesion within a solitary dilated duct	2 [66.7]	1 [33.3]	
Intra- ductal lesion with multiple dilated ducts	18 [100.0]	0 [0]	
BIRADS category			**0.004**
BIRADS 3	16 [100.0]	0 [0]	
BIRADS 4A	25 [92.6]	2 [7.4]	
BIRADS 4B	4 [80.0]	1[20.0]	
BIRADS 4C	0 [0]	1 [100.0]	
BIRADS 5	0 [0]	1 [100.0]	

The comparison of diagnostic value of mammography and ultrasound is shown in Table 4.

The sensitivity and specificity, of mammography were 60% and 68% respectively, whereas ultrasound were 100% and 35.6% respectively. The AUC of mammography was 0.71, whereas that of ultrasound was 0.81 [Figure 2]

Table 4:Comparison of diagnostic value of mammography and ultrasound in non-palpable lesions of the breast

	Sensitivity [%]	Specificity [%]	AUC
Mammography	60	68	0.71
Ultrasound	100	35.6	0.81

Discussion

The risk of malignancy in mastalgia as the sole presenting symptom has been estimated to be very low, no different from the risk in the general population as seen in present study [5]. Leung et al., conducted targeted ultrasound for focal breast pain and found no malignancies in any of these cases [15]. Joyce et al. studied 3331 cases with mastalgia as a sole complaint with no palpable findings and found 1.2% of these cases had cancer and all cancers were present in women aged above 35 years [16]The risk of malignancy in nipple discharge ranges from 5-23% [17]. Park et al. found that the rate of malignancy in mammographically occult and sonographically detectable lesions in nipple discharge was 15.1% [18]. Our study found a 25% rate of malignancy in cases of nipple discharge only and 8.3% in cases with both mastalgia and nipple discharge which was slightly higher than most of the previous studies. This could be because we selected patients with higher BIRADS category who were planned for a biopsy. This was a limitation of the design of our study. Mallik et al. studied 50 cases of non-palpable breast lesions, which were BIRADS 3 or more, and found 25% of them to be borderline and 16.6% to be malignant on histopathology [19]. Published reports show that 11-36% of breast biopsy specimens in non-palpable mammographically detected findings are positive for carcinoma, with the larger series having rates of 15-30% [20]. In our study, the overall rate of malignancy in such non-palpable lesions was 10%.On mammography, we found a significant difference in the distribution of calcifications, if any, between benign and malignant lesions.Malignant lesions more commonly had segmental distribution of calcifications than benign lesions in which grouped calcifications were most commonly seen. Melhado et al., in their study, found that microcalcifications were the most common mammographic finding in malignant non-palpable lesions [21]. Early cancers such as ductal carcinoma in situ usually present as fine linear branching microcalcifications in a segmental distribution and less often as a mass, asymmetry, or architectural distortion on mammography [22]. Mammographic BI-RADS assessment was reliably able to distinguish between benign and malignant lesions in our study. Melhado et al. also found higher rates of malignancy in higher BIRADS category in non-palpable lesions [21]. Multiple other studies have also established the efficacy of BIRADS in non-palpable lesions. On ultrasound, we found significant differences between the shape of the lesion and the morphology of calcifications, if any, between benign and malignant lesions. Malignant lesions more commonly had an irregular shape and higher frequency of associated microcalcifications. This is as per previous reports, which showed that an irregular lesion with microcalcifications is likely to be malignant in women with or without nipple discharge [23]. Ultrasound BIRADS assessment was reliably able to differentiate between benign and malignant lesions. Park et al. also found that a higher malignancy rate was associated with higher US BIRADS category in lesions with nipple discharge and occult on mammography[24].In our study, malignant lesions exhibited a greater distance from the nipple as compared to benign lesions. To our knowledge, no previous study has shown this finding. This could be because our study had 21/50 lesions that were intra- ductal on ultrasound, and 15/30 lesions who had mammography were found intra- ductal on ultrasound. Studies have shown a greater risk of malignancy in intra-ductal lesions more than 3 cm from the nipple [25]. Also, since our study included a significant proportion of intra-ductal lesions in combination with intra- parenchymal lesions, we infer that our findings apply to both the above type of lesions, thus increasing the strength of our study. We did not find significant differences in other mammographic and ultrasound findings between benign and malignant lesions. This could be due to our small sample size with a low count of malignant lesions.The reported sensitivity, specificity, positive and negative predictive values of mammography in pathologic nipple discharge are 10-26%, 94-95%, 18%, and 88% [26].The reported sensitivity, specificity, positive and negative predictive values of ultrasound for detecting malignancy in pathologic nipple discharge are 56-80%, 61-75%, 29-39%, and 90-91% [27]. The wide variability is because most of the studies did not specify whether a palpable lesion was associated with nipple discharge or not. In our study, we found the sensitivity of ultrasound

in non-palpable lesions to be 100%. This is due to the design of our study in which only lesions with BIRADS 3 or higher on ultrasound which required an ultrasound-guided biopsy, were included. Ashfaq et al. found the sensitivity of ultrasound to be 65-85% which was higher than that of 20-25% of mammography in cases of nipple discharge [28]. The specificity of mammography was higher than ultrasound [68% vs. 35.6%]. Bahl et al. also found the specificity of mammography was found to be higher [75%] as compared to ultrasound [56%] [29].

Nevertheless, our study is not free from limitations. Firstly, it is a retrospective study done at a single institute. The number of malignant cases in our study is low. We excluded all cases with BIRADS 1 and 2 on ultrasound. Thus, further evaluation of ultrasound for non-palpable BIRADS 1 and 2 lesions is needed. Another bias could have been due to the time of performance of ultrasound and mammography as all ultrasounds were done just before the biopsy, whereas mammography had been done months earlier to the biopsy. The oldest mammography was done three months earlier. It is possible that some findings could have changed within this interval. The interpretation of findings was done by consensus of the two radiologists and not independently.

Conclusion

Both mammography and ultrasound are reliable in differentiating benign and malignant non-palpable lesions of the breast with mastalgia and nipple discharge. This is true for both intra-parenchymal as well as intra- ductal lesions. Ultrasound has higher sensitivity, whereas mammography is more specific.

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Conflict of Interest: Nil

Source of support:Nil