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Research Article

A PILOT STUDY FOR EVALUATION OF ROLE OF B-MODE ULTRASOUND AND STRAIN ELASTOGRAPHY IN DIFFERENTIATING BENIGN AND MALIGNANT BREAST MASSES

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ABSTRACT

Background: Early detection of malignant lesions is critical key stone for the successful management of breast cancer. Conventional B-mode ultrasound although could not replace the histopathology which is still gold standard, plays an important role in the diagnostic pathways by using the Breast Imaging Reporting and Data System (BIRADS) lexicon (standardized by American College of Radiology [ACR]). Although characterization of solid breast masses by sonography has improved greatly since the early 1990s, specificity remains low and a large number of biopsies result in benign diagnosis. Strain elastography and strain ratio (SR) are recent techniques which may help in increasing the specificity of ultrasound.

Methods: The present study was a pilot study aimed to establish a correlation between B-mode ultrasound and strain elastography in differentiating benign and malignant breast masses and to compare the results of B- mode ultrasound and Strain Elastography with fine-needle aspiration cytology/ biopsy findings. It was a prospective study conducted in the Department of Radio-diagnosis of Rajindra Hospital, Patiala. A total of 40 patients who presented with the complaint of palpable breast lump were evaluated with B-Mode Ultrasonography (USG) and Strain elastography (using elastography score [ES] and SR).

Results: The study group (40 patients with breast lumps) comprised 38 (95%) female patients and 2 (5%) male patients. Among the group 29 were benign and 11 were malignant. Fibroadenoma followed by fibrocystic disease was the most common benign pathologies and invasive ductal carcinoma followed by Ductal Carcinoma *in situ* was the most common malignant pathologies. Sensitivity, specificity, and diagnostic accuracy of B-Mode USG in diagnosing palpable breast lump are 72.7%, 86.2%, and 82.5%, respectively, while that of strain elastography in diagnosing palpable breast lump are 81.8%, 93.10%, and 90.0%, respectively. Using strain ratio (SR) only the sensitivity, specificity, and diagnostic accuracy was found to be 93.1%, 100%, and 95% better than B-Mode USG and shear elastography alone separately and combined. The mean SR for a benign mass is 2.00±0.97 and for a malignant mass is 5.40±1.55.

Conclusion: Ultrasound elastography (using ES) has a higher sensitivity, specificity and diagnostic accuracy in differentiating benign and malignant breast masses then B mode USG (using BIRADS). Using SR alone has shown better sensitivity, specificity, and diagnostic accuracy but its standalone or in combination diagnostic application has to be followed up with further studies.

Keywords: Breast lump, Elastography, Strain ratio, Breast imaging reporting and data system.

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INTRODUCTION

Palpable breast mass is one of the common complaints of all ages particularly during the reproductive age. Palpable breast masses are usually benign however efficient evaluation along with prompt diagnosis is necessary to rule out malignancy [1]. Breast cancer is the most common type of cancer among women worldwide, affecting 2.1 million women each year. It is the leading cause of cancer related deaths among females today with around 15% of cancer related deaths among women. In India also breast cancer is the most common cancer among women accounting for 14% of all cancers. According to GLOBACAN 2020; 178 361 new cases of breast cancer were registered and 90,408 deaths were registered due to breast cancer [2].

Benign breast masses include cysts, fibroadenoma, fibro adenosis, fibro-adenomatous hyperplasia, intra-ductal papilloma, inflammation, lipomas, and benign phyllodes tumor [3].

Malignant breast masses include invasive ductal carcinoma (IDC), ductal carcinoma *in situ* (DCIS), intra-ductal papillary carcinoma, and mucinous carcinoma.

Several studies have described the sonographic characteristics commonly seen in benign lesions of the breast [4,5].

- Smooth and well circumscribed
- Thin echogenic capsule
- Hyperechoic, isoechoic, or mildly hypoechoic
- Ellipsoid shape, with the transverse diameter more than anteroposterior diameter
- Three or fewer gentle lobulations
- Absence of any malignant findings.

Malignant lesions are usually hypoechoic lesions with ill-defined borders. Typically, a malignant lesion presents as a hypoechoic lesion, which is "taller than broader" and has spiculated margins, posterior acoustic shadowing and microcalcifications [4]. Color Doppler has not proven to be very efficacious in improving the specificity of ultrasonography (USG); however, in certain situations it may help to resolve the issue, particularly when there is significant vascularity present within highly cellular types of malignancies [6].

The downside of USG is an increased false positive rate and lower positive predictive value (PPV). To obtain an acceptable specificity various eight characteristics of the lesion must be evaluated according to the breast imaging reporting and data system (BIRADS) criteria defined by American College of Radiology (ACR). However, BIRADS criteria generate significant number of false positive results [7].

Ultrasound elastography aims to overcome the limitations of ultrasound and to obtain an accurate characterization of breast lesions. It depicts the stiffness of tissues [8]. Elastography techniques are of two types; first is dynamic elastography which included shear wave and acoustic radiation force pulse while the second is static elastography which includes strain elastography [8].

Strain elastography allows evaluation of the elasticity score (ES) as a qualitative parameter of stiffness and the strain ratio (SR) as a semi-quantitative method for numerically evaluating how many times stiffer a target mass is compared to the subcutaneous fat [9].

The elastography score (ES) will be interpreted according to the 5-point TSUKUBA Scoring method proposed by Itoh *et al*. in 2006 [8].

A score of 1–3 indicates toward a probably benign mass while a score of 4 and 5 should raise a suspicious of malignancy. This system is said to have a sensitivity of 87%, specificity of 90%, and diagnostic accuracy of 88%.

SR is defined as the fat to mass SR and will be automatically calculated by the embedded software program in the ultrasound unit. The higher the strain-ratio the higher the likelihood of malignancy.

SR = Mean strain of fat area/mean strain in lesion of interest [10].

Although characterization of solid breast masses by sonography has improved greatly since the early 1990s, specificity remains low and a large number of biopsies (>50%) result in benign diagnosis. Strain elastography is a recent technique which may help in increasing the specificity of ultrasound and hence reducing the biopsy load. The study aimed at assessing the diagnostic role of strain elastography and its parameters.

Aims and Objectives

The objectives are as follows:

1. Assess the diagnostic role of strain elastography and SR
2. Compare the results of B-mode ultrasound and strain elastography with fine-needle aspiration cytology (FNAC)/biopsy findings.

METHODS

This prospective observational analytic pilot study was carried out in the Department of Radio-Diagnosis, Rajindra Hospital, Patiala. The study included 40 consenting patients of 18 years and above among the ones presenting with breast lump in the outpatient department or admitted in the wards in Rajindra Hospital, Patiala, who were referred to the Department of Radiodiagnosis for investigation and were after enrollment were latter followed up to histopathology of the lump. The patients who are below 18 years, already diagnosed and treated for breast lump, or had physiological or post-traumatic or post-infective breast swelling and who did not give consent were excluded from the study.

Sample size was calculated using formula $(Z_{1-\alpha/2}^{2}\,p\,(1-p))/d^2$ where $Z_{1-\alpha/2}$ is Standard normal variate 1.96, d is absolute error which is taken 10% in this study and p is expected proportion in population which in this study is expected population getting histopathology out of population who have lump in breast which was taken as 10% based on previous records who fulfill the inclusion criteria. The calculated sample size was 35 and keeping 10% as expected loss during study and follow-up the sample size was rounded up to 40 patients.

Instrumentation, Patient Positioning, and Breast Survey Techniques

B-Mode ultrasound and Strain Elastography were performed using PHILIPS EPIQ5 S.NO. U5318C0517 machine using high frequency L12-5 transducer. Each lesion was assessed with the BIRADS).

Sonographic parameters including size, shape, margin, orientation, posterior acoustic features, calcifications, axillary lymphadenopathy, and internal vascularity. The BIRADS categories were assigned according to the BIRADS US lexicon, 5th edition, by the ACR in 2013.

BIRADS staging	Interpretation
BIRADS 1	Normal
BIRADS 2	Definitely benign
BIRADS 3	Probably benign
BIRADS 4	Probably malignant
BIRADS 5	Definitely malignant
BIRADS 6	Known malignancy

BIRADS: Breast Imaging Reporting and Data System

Doppler characteristics such as absence of flow, distribution, and pattern of vessels in the mass lesion were also noted. The location of the lesion was labeled according to o'clock position and distance from the nipple. The anterior, posterior, and lateral dimensions were recorded for the reference of AP/L ratio.

Then using the same probe, strain elastography was performed while keeping the probe perpendicular to the skin during compression. The region of interest (ROI) was set for elastography acquisition; superior margin includes subcutaneous fat; inferior margin include pectoral muscle; and lateral margin should have 10 mm distance from the lesion. The target lesion was compressed vertically by applying light pressure. High levels of pressure were avoided because in such cases the association between pressure and strain is no longer proportional and false results may be found.

The ES and SR were measured on coupled B-Mode and Elastography images. Inside the field of view box, we positioned the first ROI in the lateral subcutaneous fat tissue at the same depth as the target lesion and with the second ROI we outlined the entire lesion.

The ES was interpreted according to the 5-point TSUKUBA Scoring method proposed by Itoh *et al*. in 2006 [8] [Figure 1].

TSUKUBA scoring system [8]

Score 1 – even strain for entire hypo-echoic lesion (i.e. the entire lesion is evenly shaded in blue).

Score 2 – strain in most of the hypo-echoic lesion (i.e. the hypo-echoic lesion has the mosaic pattern of blue and green).

Score 3 – strain at the periphery of the hypo-echoic lesion (i.e. peripheral part is blue and the central part is red)

Score 4 – no strain in the entire hypo-echoic lesion (i.e. the entire lesion is red but the surrounding area is not included).

Score 5 – no strain in the entire hypo-echoic lesion or in the surrounding area (i.e. both the entire lesion and its surrounding area are red).

A ES of 1 to 3 indicates toward a probably Benign mass while a score of 4 and 5 should raise a suspicious of malignancy.

Data collection and analysis

Data collection and analysis was done using Microsoft Excel, Epi info version 7.2.4.0 (CDC Atlanta) and Medcalc Statistical Software version [12]. Most of the values are described in percentages and means, while other analytic tests included Shapiro–Wilk Test (For normality of data, Chi-square test, Fisher's Exact, Mann–Whitney test, ROC analysis, and Kendell Rank correlation coefficient test. Diagnostic utility parameters such as sensitivity, specificity, Youden index (50% benchmark for diagnostic utility), PPV, negative predictive value (NPV), and Kappa were also calculated.

RESULTS

The final pathological diagnosis showed the benign masses to be 72.5 % (29 cases) and malignant breast lumps to be 37.5% (11 patients) of

Table 1: Distribution of study population according to the age

(a) Mean

Age	Obs	Mean	Std Dev	Min	25%	Median	75%	Max	Mode	p-value
Study population	40	37.28	13.21	20	28	32	49.5	70	30	
Benign	29	31.83	8.98	20	27	30	32	63	30	<0.001*
Malignant	11	51.64	11.91	33	38	52	60	70	60	

*Mann–Whitney test for two independent samples (z=4.128)

(b) Age groups

Age groups	Benign*	Malignant*	Total	Test	p-value
15–30 years	13 (100%, 44.83%)	0	13	Fischer exact	0.0002
30–45 years	13 (81.25%, 44.83%)	3 (18.75%, 27.27%)	16		
45–60 years	2 (25%, 6.9%)	6 (75%, 54.55%)	8		
60–75 years	1 (33.33%, 3.45%)	2 (66.67%, 18,18%)	3		
Total	29	11	40		

*In () the first % is of respective age group while second % is of respective pathology category

Table 2: Frequency of distribution of breast lump according to the histopathological diagnosis

Histopathology	Frequency	Percent	Exact 95% LCL	Exact 95% UCL
Benign	29	72.50	56.11	85.40
Fibroadenoma	17	42.50	27.04	59.11
Fibroadenoma with atypia	1	2.50	0.06	13.16
Fibrocystic disease	2	5.00	0.61	16.92
Intraductal Papilloma	1	2.50	0.06	13.16
Ductal Ectasias	3	7.50	1.57	20.39
Lipoma	1	2.50	0.06	13.16
Nodular gynecomastia	1	2.50	0.06	13.16
Phyllodes	1	2.50	0.06	13.16
Idiopathic Granulomatous mastitis	1	2.50	0.06	13.16
Sclerosing adenitis	1	2.50	0.06	13.16
Malignant	11	27.50	14.60	43.89
IDC	6	15.00	5.71	29.84
Ductal carcinoma *in situ*	2	5.00	0.61	16.92
Medullary carcinoma	2	5.00	0.61	16.92
Malignant lymph node	1	2.50	0.06	13.16
Total	40	100.00		

IDC: Invasive ductal carcinoma

the study population. The mean age of the cases was 37.28 years with a standard deviation of 13.21. The malignant masses were present significantly higher in older age groups than the benign as shown in Table 1a and b.

Histopathology of lump masses

The histopathological report (Table 2) showed that fibroadenoma followed by fibrocystic disease was the most common benign pathology and IDC followed by ductal carcinoma *in situ* was the most common malignant pathology in patients presenting with palpable breast lumps.

BIRADS Ultrasound and other descriptors

Antiparallel placement (taller than wider), Spiculation-micro lobulation, Posterior acoustic shadow, presence of microcalcifications, internal vascularity, and axillary lymphadenopathy are the characteristics which were significantly higher present in malignant than benign masses. No significant difference was found in hypoechoic dominance in the two groups (Table 3a).

In this study, the descriptors antiparallel placement, spiculations, microcalcifications, and Posterior acoustic shadow have shown more than 95% specificity, more than 80% PPV and fall in Rule in category which means that if present than it is a malignant lesion, while hypoechoic dominance has a high sensitivity, high NPV and falls in rule out category which means that if not present than it rules out malignancy. But as spiculations, microcalcifications, posterior acoustic shadow, and hypoechoic dominance have a Youden index less than 50%; hence, the parameter does not meet empirical benchmarks for being used for diagnostic purposes. Internal vascularity and axillary lymphadenopathy have near 90% NPV and a good PPV may strongly indicate toward malignancy [Table 3b].

Diagnostic cutoff values and diagnostic utility parameters of procedures

The cutoff values and diagnostic utility parameters of BIRADS, strain elastography, and SR were calculated for the study [Tables 4(a-c) and 5], [Figure 2].

In our study, the cutoff values (maximum Sensitivity +Specificity) are BIRADS III, ES of 3 and SR of 3. These cutoffs are similar to the cutoff values in the standards literature and scoring system for BIRADS and strain elastography.

In the study, the diagnostic utility indicators are summarized in Table 6 show that the indicators of strain elastography are better than that of BIRADS, while those of SR are better than BIRADS and strain elastography.

Correlation of conventional ultrasound, strain elastography, and SR with histopathology

- Conventional ultrasound (BIRADS) and Histopathology: With the cutoff value of BIRADS III, out of 29 benign lesions 25 were diagnosed as benign while four lesions showed BIRADS IV or more. While eight masses with BIRADS IV and V were diagnosed, as malignant out of 11

Table 3a: Frequency of ultrasound and other descriptors in benign and malignant groups

Ultrasound and other descriptors	Benign				Malignant				p-value
	No.	Percent	Exact 95% LCL	Exact 95% UCL	No.	Percent	Exact 95% LCL	Exact 95% UCL	
Antiparallel placement	0	0.00	0.00	0.00	6	54.55	23.38	83.25	<0.0001
Spiculations	1	3.45	0.09	17.76	5	45.45	16.75	76.62	<0.0001
Microcalcifications	0	0.00	0.00	0.00	4	36.36	10.93	69.21	<0.001
Hypoechoic dominance	21	72.41	52.76	87.27	10	90.91	58.72	99.77	0.211
Posterior acoustic shadow	0	0.00	0.00	0.00	4	36.36	10.93	69.21	<0.001
Internal vascularity	5	17.24	5.85	35.77	8	72.73	39.03	93.98	<0.001
Axillary lymphadenopathy	3	10.34	2.19	27.35	8	72.73	39.03	93.98	<0.0001

Table 3b: Diagnostic utility parameters of ultrasound and other descriptors

Ultrasound and other descriptors	Sensitivity %	Specificity %	Youden index %	"Rule in"	"Rule out"	PPV %	Negative predictive value %	Accuracy %
Antiparallel placement	54.55	100.00	54.55	True	False	100.00	85.29	87.50
Spiculations	45.45	96.55	42.01	True	False	83.33	82.35	82.50
Microcalcifications	36.36	100.00	36.36	True	False	100.00	80.56	82.50
Hypoechoic dominance	90.91	27.59	18.50	False	True	32.26	88.89	45.00
Posterior acoustic shadow	36.36	100.00	36.36	True	False	100.00	80.56	82.50
Internal vascularity	72.73	82.76	55.49	False	False	61.54	88.89	80.00
Axillary lymphadenopathy	72.73	89.66	62.38	False	False	72.73	89.66	85.00

PPV: Positive predictive value

proven malignant cases. Three malignant cases had been categorized as probably benign with ≤BIRADS III. This was statistically significant (Fisher exact, p<0001)

- Correlation of Elastography using ES and Histopathology: 27 of the 29 benign masses had an ES 3 or less which was the cutoff. Two cases with ES 4 were found out to be benign. On the other hand, two with a score of 3 were malignant besides other 9 who had a score of 4 (5 masses) and 5 (4masses). This was statistically significant (Fisher exact, p<0001)
- Correlation of SR and Histopathology: The mean SR of the study population and histopathology groups of benign and malignant is shown in Table 7 [Figure 3].

From Table 4c, the cutoff value of SR is 3. Hence, at this level, 27 of the 29 diagnosed benign cases had value less than or equal to 3 while two of them had SR >3. All the diagnosed malignant cases had an SR value>3. This was statistically significant (Fisher exact, p<0.001).

- Correlation of conventional ultrasound (BIRADS) and elastography using ES: Out of the 29 benign cases 25 had both BIRADS III or less and ES of 3 or less. While among the 4 benign cases who had BIRADS more than 3, two cases had an ES <3. On the other had among the histopathologically diagnosed malignant lesions, seven both had >BIRADS III and ES >3; two cases with ≤BIRADS III had an ES>3, one case had >BIRAD III but ES<3; and one case had both BIRADS III and ES 3. Both the finding in benign and malignant groups were statistically significant (Kendell's rank correlation test; p<0.001)
- Correlation of conventional ultrasound (BIRADS) and SR: 25 cases of benign pathology had both ≤BIRAD III and SR≤3, 2 cases had > BIRAD III but SR≤3 and remaining 2 cases had both >BIRAD III and SR>3. In the malignant group, all cases had an SR>3 but 3 cases had BIRAD III. (Statistically significant for benign, Fisher exact, p<0.05)
- Correlation of elastography using ES and SR: 27 cases of benign pathology had both ES≤3 and SR≤3, and 2 cases had both ES>3 and SR>3. In the malignant group all cases had an SR>3 but 2 cases had ES≤3. (Statistically significant for benign, Fisher exact, p<0.05).

Discordant cases from correlation observation

The cases who had discordant values than for benign and malignant diagnostic modalities are summarized in Table 8a and b.

From Table 8a, if ES or SR was combined with BIRADS, 2 of the benign lesions would have been labeled as benign before histopathology. This in practical terms means a reduction of 25% in BIRADS IV (total eight patients) FNAC/Biopsies in this study presuming that all BIRAD Cases above BIRAD III are subjected to FNAC/Biopsy.

Table 4a: Diagnostic cutoff values and diagnostic utility parameters of BIRADS

BIRADS category→	BIRADS II	BIRADS III	BIRADS IV	BIRADS V
Sensitivity	65.5%	86.2%	100.0%	100.0%
Specificity	90.9%	72.7%	36.4%	0.0%
PPV	95.0%	89.3%	80.6%	72.5%
Negative predictive value	50.0%	66.7%	100.0%	
Sensitivity + Specificity	156.4%	158.9%	136.4%	100.0%
Accuracy	72.5%	82.5%	82.5%	72.5%
Youden index	56.4%	58.9%	36.4%	0.0%
Kappa	45.0%	57.3%	45.3%	0.0%

BIRADS: Breast imaging reporting and data system, PPV: Positive predictive value

Table 4b: Diagnostic cutoff values and diagnostic utility parameters of strain elastography using ES

ES→	ES 2	ES 3	ES 4	ES 5
Sensitivity	72.4%	93.1%	100.0%	100.0%
Specificity	100.0%	81.8%	36.4%	0.0%
PPV	100.0%	93.1%	80.6%	72.5%
Negative predictive value	57.9%	81.8%	100.0%	
Sensitivity +Specificity	172.4%	174.9%	136.4%	100.0%
Accuracy	80.0%	90.0%	82.5%	72.5%
Youden Index	72.4%	74.9%	36.4%	0.0%
Kappa	59.1%	74.9%	45.3%	0.0%

ES: Elastography score, PPV: Positive predictive value

Table 4c: Diagnostic cutoff values and diagnostic utility parameters of SR

Strain Ratio→	SR 1	SR 2	SR 3	SR 4	SR 5	SR 6
Sensitivity	17.2%	55.2%	93.1%	96.6%	96.6%	100.0%
Specificity	100.0%	100.0%	100.0%	72.7%	63.6%	27.3%
PPV	100.0%	100.0%	100.0%	90.3%	87.5%	78.4%
Negative predictive value	31.4%	45.8%	84.6%	88.9%	87.5%	100.0%
Sensitivity +Specificity	117.2%	155.2%	193.1%	169.3%	160.2%	127.3%
Accuracy	40.0%	67.5%	95.0%	90.0%	87.5%	80.0%
Youden index	17.2%	55.2%	93.1%	69.3%	60.2%	27.3%
Kappa	10.3%	40.4%	88.1%	73.4%	65.8%	35.2%

SR: Strain ratio, PPV: Positive predictive value

Similarly in Table 8b, three malignant lesions would have been missed if BIRAD III were not subjected to biopsy it means that approx. 27% of would have been missed. But if combined with ES two cases of three would have been biopsied resulting <10% of cases would remain undiagnosed; but with SR all three cases would have been biopsied in this study.

One malignant case had ES≤3 with BIRADS IV; this was again clarified with SR and the patient lump would have been biopsied.

From Table 9, its evident that using BIRADS or ES in combination with SR is better than that of BIRADS and ES combined. And using SR in BIRADS or ES where SR and BIRADS/ES are in discordant in labeling benign/malignant lesion is better than combining the two.

Taking the above discordant cases as in Table 8a using SR, 2 of the BIRADS labeled malignant would have been labeled as benign before histopathology. While in Table 8b, all the discordant cases whether with BIRADS or ES would have been labeled malignant.

DISCUSSION

Breast cancer has a high mortality rate due to the higher stages of malignancy at the time of diagnosis. Hence, more accurate modalities for better diagnosis are required to be used in the primary stages. In the present study, we used SE additionally to conventional B-mode ultrasound imaging. Two different features of SE were included in our results ES and SR.

Table 5: ROC analysis of BIRADS, strain elastography using ES and SR

Feature	BIRADS	Strain elastography using ES	Strain ratio
Area under the ROC curve (AUC)	0.870	0.953	0.980
Standard error	0.0660	0.0277	0.0198
95% confidence interval	0.726–0.955	0.835–0.995	0.876–1.000
Z statistic	5.605	16.348	24.256
Significance level P (Area=0.5)	<0.0001	<0.0001	<0.0001

SR: Strain ratio, BIRADS: Breast imaging reporting and data system

Table 6: Summary of diagnostic utility indicators

Diagnostic Utility Indicators	BIRADS	Strain elastography using ES	SR
Sensitivity	86.2%	93.1%	93.1%
Specificity	72.7%	81.8%	100.0%
PPV	89.3%	93.1%	100.0%
Negative predictive value	66.7%	81.8%	84.6%
Sensitivity + Specificity	158.9%	174.9%	193.1%
Accuracy	82.5%	90.0%	95.0%
Youden index	58.9%	74.9%	93.1%
Kappa	57.3%	74.9%	88.1%
AUC	0.870	0.953	0.980

SR: Strain ratio, BIRADS: Breast imaging reporting and data system, PPV: Positive predictive value

Lesions graded as BIRADS 3 are probably benign and short term follow-up is recommended. Nevertheless, malignancy is eventually diagnosed in about 3% of these lesions resulting in delayed diagnosis of cancer in a considerable number of patients [13].

In our study, the malignant masses were present in older age groups and with higher mean age than the benign. This age statistics is comparable with the present trend in the incidence of breast cancer among Indian women which is in increasing numbers of female from 25 to 40 years of age as stated by Sandhu *et al*. [14] and Somdatta *et al*. [15]

The present study revealed that the benign masses (72.5%) are more frequent than malignant ones (27.5%). Our study (Table 2) correlates with studies of Nigam *et al*. [16] and Phurailatpam et al. [17] which also show fibroadenoma followed by fibrocystic disease as the most common benign pathology and IDC followed by DCIS as the most common malignant pathology in patients presenting with palpable breast lumps.

The ultrasound descriptors in study, antiparallel placement, Spiculation-microlobulation, Posterior acoustic shadow, presence of microcalcifications, internal vascularity, and axillary lymphadenopathy are that the characteristics were found significantly in the malignant breast masses but due to low Youden index spiculations, microcalcifications and posterior acoustic shadow cannot be used for diagnostic purposes. Stavros *et al*.,[4] Constatini *et al*., [18] and Hong *et al*. [19] documented the characterization of solid breast masses and found these present in the malignant breast masses with high PPV.

We found that using BIRADS (with a sensitivity of 86.2% and specificity of 72.7%) out of 40 cases, 33 (82.5%) cases were diagnosed correctly as per histopathological grouping (benign and malignant) which increased to 36 (90%) cases using ES in strain elastography (with a sensitivity of 93.1% and specificity of 81.8%) and further to 38 (95%) cases using SR in strain elastography (with a sensitivity of 93.1% and specificity of 100%).

The diagnostic accuracy and AUC increased from 82.5%, 0.870 with BIRADS to 90%, 0.953 with ES and 95%, 0.980 with SR respectively. SR has also been found better than ES and Conventional by Parajuly *et al*. and Thomas *et al*. Parajuly *et al*. reported a higher AUC with SR (0.96) than ES (0.90) and conventional ultrasound (0.88) while Thomas *et al*. had documented a sensitivity and specificity of 96% and 56% for B-mode scanning, 81% and 89% for elastography, and 90% and 89% for SR.

We found that combined use of B-mode USG with ES score or SR is more effective in differentiating malignant and benign lesions than sonography alone. Different combinations were tried using BIRADS, strain elastography using ES and SR (Table 9). The AUC increased from 0.870 using BIRADS alone to 0.886 while using BIRADS and ES combined and to 0.920 if ES was used in discordant cases only. On the other hand, AUC increased from 0.870 using BIRADS alone to 0.931 while using BIRADS and SR combined and to 0.961 if SR was used in discordant cases only. SR has shown better parameters than ES in this study.

Similar increase in AUC from BIRADS to combining it with ES was seen by Hao *et al*. [20] (0.73–0.87) and Yeo *et al*. (0.65–0.86) [21].

Table 7: Descriptive statistics of SR of study population and histopathology groups

Parameter Assessed	Obs	Total	Mean	Var	Std Dev	Min	25%	Median	75%	Max	Mode
Study population	40	117.34	2.93	3.67	1.91	0.56	1.78	2.21	3.85	8.1	2.2
Benign*	29	57.9	2.00	0.94	0.97	0.56	1.3	2	2.24	5.4	2.2
Malignant*	11	59.44	5.40	2.41	1.55	3.5	3.9	5.2	6.7	8.1	3.5

*****Significant difference, Mann–Whitney Test for Two Independent Samples (z=4.6208; p<0.0001). SR: Strain ratio

The cutoff values of the three diagnostic utilities in our study were BIRAD III for conventional ultrasound, ES of 3 for strain elastography and SR 3 for SR in strain elastography. The cutoff of BIRADS and ES was documented to be similar to that of BIRADS guidelines and scoring system, respectively [8].

SR cutoff was documented 1.90 by Ranjkesh *et al*., [22] 2.54 by Thomas *et al*., [9] 3.1 by Ozel *et al*., [23] 3.5 by Bojanic *et al*., [24] 3.54 by Parajuly *et al*., [25] 3.65 by Gheonea *et al*., [26] 4.15 by Li *et al*., [27] 4.8 by Barr *et al*., [28] and 5.6 by Alhabshi *et al*. [29]

The variation in the cutoff values among these studies 1.90–5.6 can be a result of pre-compression, especially by a radiologist with inadequate clinical experience [24,30]. Pre-compression increases the stiffness of all tissues hence changing the strain value of fat. This stiffness variation in fat tissue is more prominent than those in normal breast tissue and masses; thus, with pre-compression, the SR will decrease [24]. The other reason that could explain the SR results obtained in our and other studies is ROI inconsistency [24] and movement of patient [9] during procedure besides this variation in SR can be attributed to the different equipment used [22].

Another aspect of the study was the type of lesions that were discordant on different diagnostic utilities.

In our study, the benign lesion which was diagnosed as malignant, that is, false-positive lesions is IGM, Sclerosing adenitis, a fibroadenoma and phyllodes. IGM and fibroadenoma appeared soft on Elastography both with ES and SR. Sclerosing adenitis and phyllodes were false positive in all diagnostic utilities used.

Table 8a: Different diagnostic values of discordant benign cases

Cases	Histopathology	BIRADS	ES	SR	Antiparallel placement
1	Phyllodes	IV	4	5.34	No
2	Sclerosing adenitis	IV	4	3.5	No
3	Fibroadenoma	IV	3	2	No
4	Idiopathic Granulomatous mastitis	IV	3	2.65	No

BIRADS: Breast imaging reporting and data system

Table 8b: Different diagnostic values of discordant malignant cases

Cases	Histopathology	BIRADS	ES	SR	Antiparallel placement
1	Medullary Carcinoma	III	4	4.3	No
2	Medullary Carcinoma	III	3	3.5	Yes
3	Malignant Lymph Node	III	4	3.8	No
4	IDC	IV	3	3.69	No

BIRADS: Breast imaging reporting and data system, IDC: Invasive ductal carcinoma

Arslan *et al*. [31] reported that IGM was categorized BIRADS III on B-Mode USG based on its characteristics of irregular heterogeneously hypoechoic mass with tubular extensions. However, IGM appeared soft on SE with elasticity score of 2 and lower SR.

Chen *et al*. [32] reported that sclerosing adenitis is a benign proliferative disease which exhibits USG characteristics of malignancy such as calcifications, indistinct margins, PAS, and hypervascularity which contributed to the overestimation of this lesion on USG. Moukhtar et al. [3] reported that B-Mode USG revealed BIRADS score IV and Elasticity score 3 for Sclerosing adenitis.

Li *et al*. [33] reported approximately 25% of phyllodes masses reporting an ES score more than 3. Similar false-positive results with phyllodes were reported by Khanduri *et al*. [34]

Li *et al*. [33] has documented 5% of fibroadenoma to have an ES more than 3 as compared to 5.8% reported in our study.

In our study, one case of Infiltrating ductal carcinoma – Adenoid cystic type (IDC-ACT) which was reported as BIRADS IV on B-Mode USG, displayed ES 3 and higher SR of 3.9.

Huang *et al*.,[35] Ichikawa *et al*., [36] and Tang *et al*. [37] stated that adenoid cystic carcinoma is a rare breast tumor which can mimic benign lesion on ultrasound. Elastography may be helpful in differentiating between malignancy and benignity.

In our study, we reported one case of adenoid cystic tumor which showed well defined margins with minimal internal vascularity, no calcification or no PAS and was reported as BIRADS III on B-Mode USG. On elastography it displayed ES 3 and higher SR of 3.9.

In our study, two cases of medullary carcinoma were discordant among diagnostic utilities. Jin *et al*. [38] stated that 60% of medullary carcinoma mimicked a benign appearance on B-mode USG and exhibited high stiffness on Strain elastography. Meyer *et al*. [39] stated that medullary carcinoma of breast appears as well defined, non-calcified mass with no PAS on B-mode ultrasound and mimics as benign mass.

One malignant lymph node was present among discordant masses (Table 8b). Choi *et al*. [40] reported that metastatic lymphadenopathy can be misdiagnosed as reactive adenitis on B-Mode USG. Strain elastography combined with B-mode USG increased the sensitivity of axillary lymph node metastasis

Table 9: Comparison of various diagnostic utility indicators using individual and combined parameters

Diagnostic utility indicators	Combined BIRADS and SR*	Combined BIRADS and ES*	Combined ES and SR*	Combined E BIRADS and SR**	Combined E BIRADS and ES**	Combined E ES and SR**
Sensitivity	86.21%	86.21%	93.10%	93.10%	93.10%	93.10%
Specificity	100.00%	90.91%	100.00%	100.00%	90.91%	100.00%
PPV	100.00%	96.15%	100.00%	100.00%	96.43%	100.00%
Negative predictive value	73.33%	71.43%	84.62%	84.62%	83.33%	84.62%
Sensitivity +Specificity	1.862	1.771	1.931	1.931	1.840	1.931
Accuracy	0.900	0.875	0.950	0.950	0.925	0.950
Youden index	0.862	0.771	0.931	0.931	0.840	0.931
Kappa	0.775	0.711	0.881	0.881	0.817	0.881
AUC	0.931	0.886	0.966	0.966	0.920	0.966

*Combination made by combining the common and either diagnosed histopathological groups by individual modalities. **Combination made by combining common + ones with difference the superior finding prevailing, that is, SR prevails over ES and BIRADS while ES prevails over BIRADS, SR: Strain ratio, BIRADS: Breast imaging reporting and data system, PPV: Positive predictive value

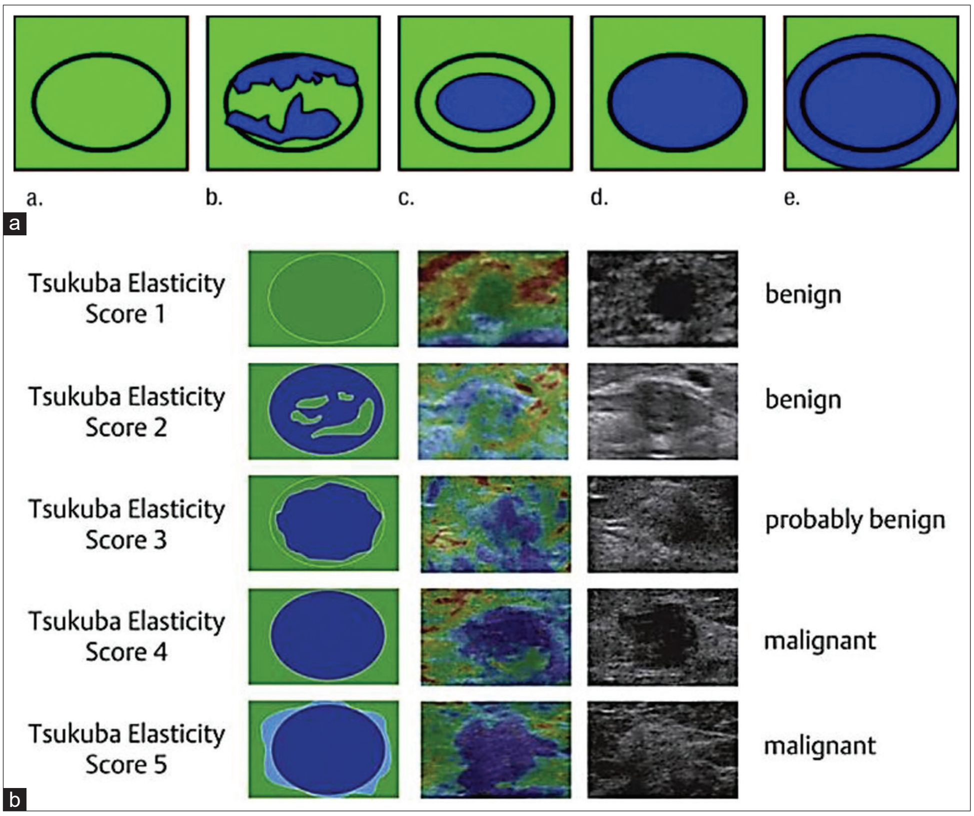

Figure 1: (a-b): 5-point TSUKUBA Scoring method*. *Images present general appearance of lesions for elasticity scores of (a) 1, (b) 2, (c) 3, (d) 4, and (e) 5. Black circle indicates outline of hypoechoic lesion (i.e., border between lesion and surrounding breast tissue) on B-mode images [8]. **Breast elastography images are classified in five categories (Tsukuba elasticity scores 1–5) based on strain image patterns superimposed on B-mode images. Lesions scored 1 or 2 are considered benign, lesions scored 3 are considered to be probably benign and lesions scored 4 or 5 are considered malignant [11]

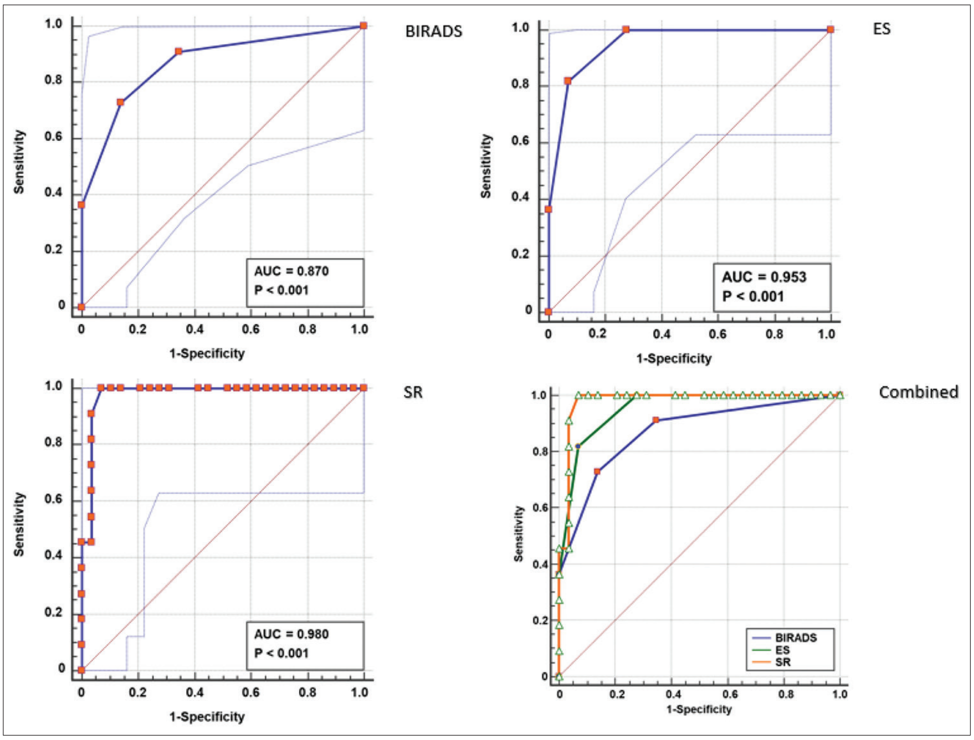

Figure 2: ROC of breast imaging reporting and data system, strain elastography using ES and strain ratio

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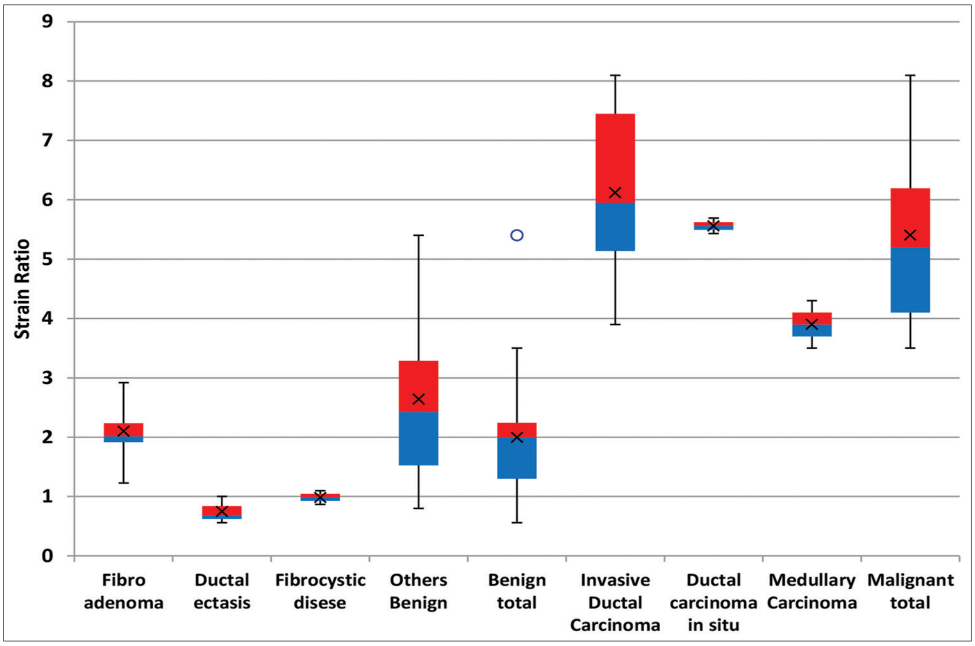

Figure 3: Boxplot graphs demonstrating a difference in elastography strain ratio for different breast lesions. Whiskers and lines delineate 95% confidence intervals

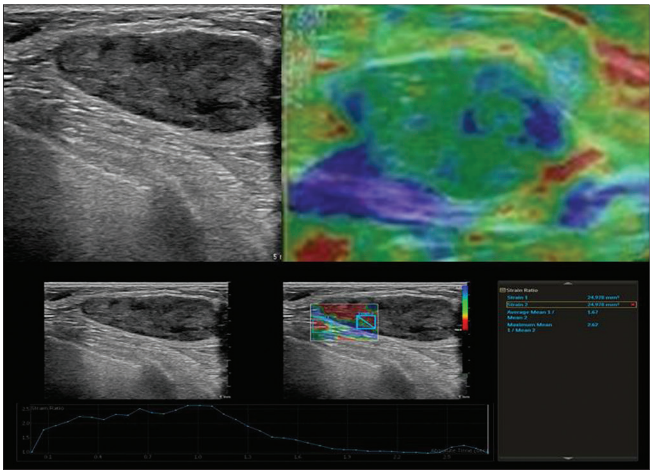

Figure 4: Case 1: Fibroadenoma

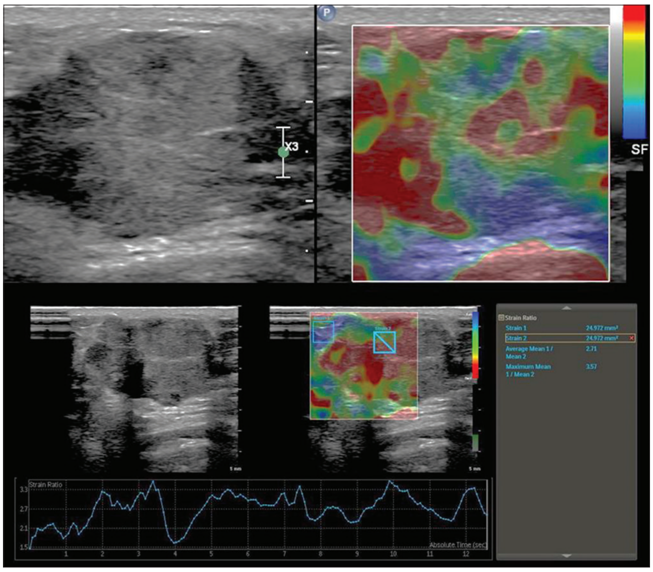

Figure 5: Case 2: Medullary carcinoma

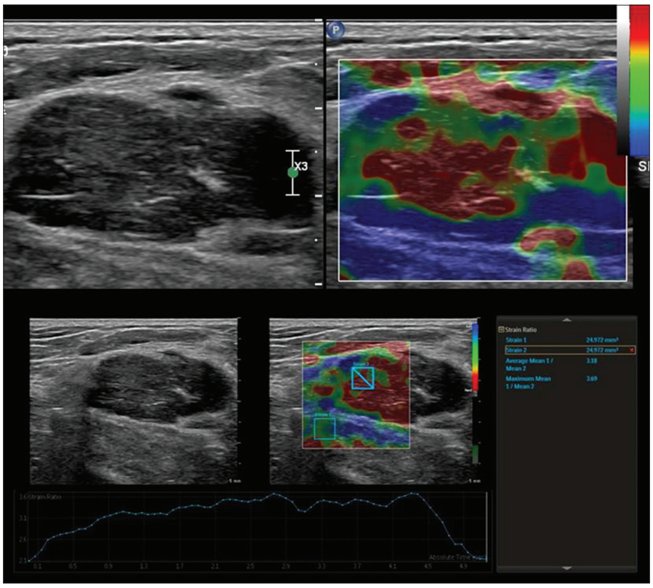

Figure 6: Case 3: Adenoid cystic carcinoma

Table 10: Disagreement Pattern and proposed diagnostic utility addition

BIRADS	Discordant masses	ES	SR
II	No disagreement		
III	Yes	Add	Add
IV	Yes	Add	Add
V	No disagreement		

SR; Strain ratio, BIRADS: Breast imaging reporting and data system, ES: Elastography score

detection. Sonographic elastography is helpful in differentiating reactive and metastatic axillary lymph nodes.

Ozel *et al*. [23] calculated the mean SR for benign lesions was as 2.1±1.6 (mean±standard deviation) and malignant lesions was 4.6±2.6 while Bojanic *et al*. [24] documented that mean SR for the benign lesions was 2.3 (1.5-3.1) and for malignant lesions was 4.9 (3.8-6.1). Other studies

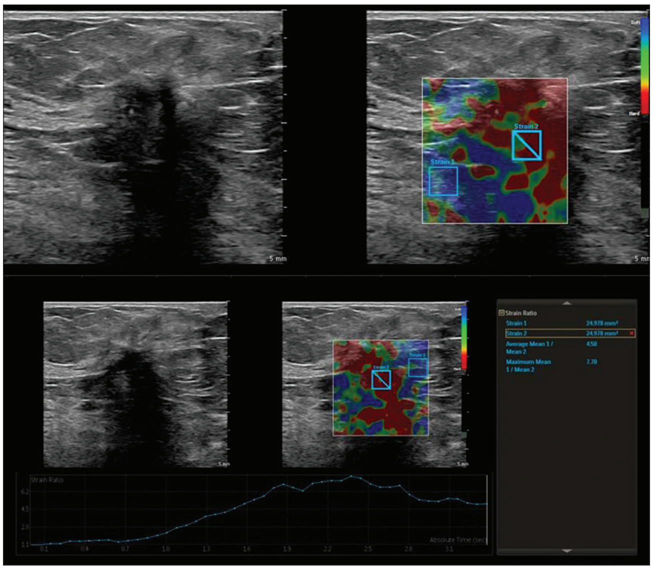

Figure 7: Case 4: Invasive ductal carcinoma

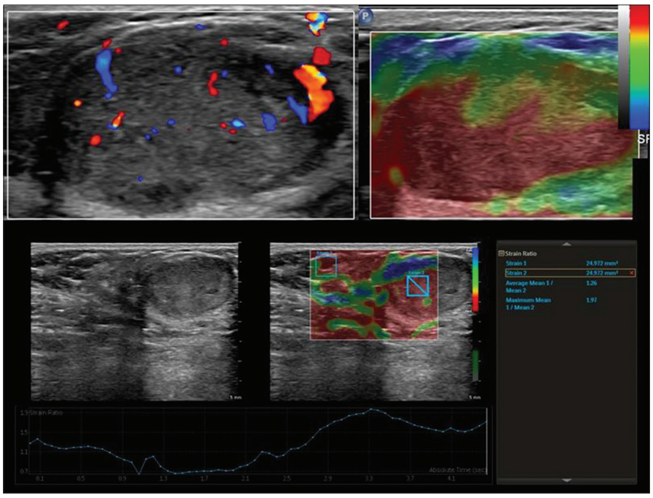

Figure 8: Case: 5: Fibroadenoma with atypia

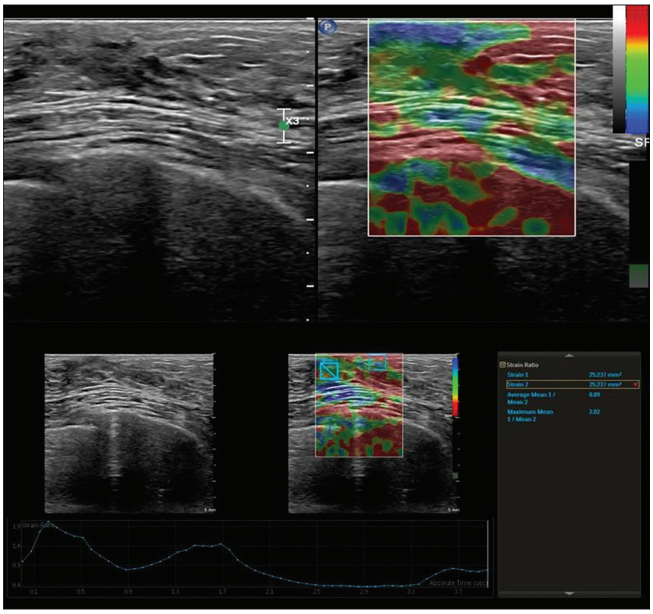

Figure 9: Case: 6: Nodular gynecomastia

had shown varied SR for malignant lesions as 3.02±1.3 in Lee *et al.* [6] and 7.9±5.8 Mu *et al.* [41]

Strain elastography as an imaging modality requires external compression, applied manually, hence is operator dependent, which influences its reproducibility. Yerli *et al.* [42] in a study concluded that after evaluation of lesions with the Tsukuba elasticity scoring system, additional evaluation of the SR increased calculation time and did not contribute significantly to the differentiation between benign and malignant lesions. Menezes *et al.* [30] assessed four elastography criteria (ES, SR, distance ratio, and area ratio) and reported that all four were able to differentiate benign and malignant lesions, but the ES was the most accurate. This is in agreement with our results that either ES or SR was able to differentiate benign and malignant lesions with statistical significance.

In our study, the disagreement/discordant masses fell in two categories of BIRADS, that is, BIRAD III and IV. If we add sonoelastography for these two categories the sensitivity and specificity show significant improvement; more if we use SR than ES [Table 10].

CONCLUSION

Ultrasound elastography was found to have high sensitivity, specificity, and diagnostic accuracy in differentiating benign and malignant breast masses than conventional B mode ultrasound. SR has shown potential to be used as a compliment to BIRADS better than ES. Using SR alone has shown better sensitivity, specificity, and diagnostic accuracy but its standalone or in combination diagnostic application has to be followed up with further studies.

Some case discussions of study

Case 1

24 years unmarried pre-menopausal female with painless lump left breast in the retro areolar region. Sonoelastography and B-mode US on split screen mode. B-mode USG revealed well defined smoothly marginated oval shaped hypodense lesion with no internal calcifications, no PAS, and no internal vascularity on color Doppler. No axillary lymphadenopathy was seen. BIRADS II. The strain elastography revealed the entire hypoechoic mass coded blue and green (Elasticity score 2 and SR of 2.6). This mass was considered as benign. Histopathological results proved a case of fibroadenoma [Figure 4].

Case 2

50 years married postmenopausal female presented with painless lump left breast in the Upper inner quadrant. Sonoelastography and B-mode US on split screen mode. B-Mode USG revealed a relatively well defined oval shaped hypodense mass in the upper inner quadrant with no internal calcifications or PAS. On CDFI internal vascularity is present. Axillary lymphadenopathy was seen. BIRADS III (probably benign). Elastography findings revealed mix pattern of blue green and red. The central part is harder than the periphery. The surrounding tissue displays blue color. Elasticity score 3 and SR- 3.5. This mass was considered as probably benign on B-Mode USG and equivocal on strain elastography. The histopathological results proved a case of Medullary Carcinoma [Figure 5].

Case 3

37 years old married premenopausal female with painless lump left breast in the retro areolar region. B-Mode USG revealed relatively well defined oval shaped hypodense mass in the retro areolar with no internal calcifications or PAS. On CDFI no internal vascularity is present. Axillary lymphadenopathy was seen. BIRADS III, that is, probably benign. Elastography revealed that the center of the mass is hard, that is, red in the center and soft at the periphery, that is, blue. Surrounding tissue also displays normal strain. Elasticity score 3 and SR- 3.69 Histopathology proved the mass was infiltrating ductal carcinoma – adenoid cystic type (IDC-ACT) [Figure 6].

Case 4

60 years married postmenopausal female presented with painless lump left breast in the retro areolar region. USG revealed Ill well defined hypodense, taller than wider mass with spiculated margins showing internal microcalcifications and PAS in the retro areolar region. On CDFI, internal vascularity was present. Axillary lymphadenopathy was seen. BIRADS V (definitely malignant). Elastography findings revealed the entire mass was hard, that is, the entire mass is red with infiltration of the surrounding tissue at places – Elasticity score 5 and SR- 7.7. Histopathology proved the mass as infiltrating ductal carcinoma (IDC) [Figure 7].

Case 5

63 years married postmenopausal female with painless lump right breast in the UOQ.USG revealed well defined, lobulated, oval shaped hypodense mass with lobulated margins showing no internal microcalcifications and PAS in the right upper outer quadrant. On CDFI, internal vascularity was present. Axillary lymphadenopathy was not seen. BIRADS IV, that is, probably malignant. Elastography revealed mixed strain of blue green and red. Elasticity score 3 and SR- 1.9. The mass was considered benign on elastography. Histopathology proved the mass as fibroadenoma with atypia [Figure 8].

Case 6

50 years male presented with lump in the retro areolar regions revealed Ill-defined hypoechoic mass with no internal calcifications or PAS in the left retro areolar region. On CDFI, internal vascularity was absent. Axillary lymphadenopathy was not seen. BIRADS III, that is, probably benign. Elastography revealed the entire lesion is soft and displays blue color – Elasticity score 2 and SR- 2.02. It was considered benign on elastography. Histopathology proved it to be Nodular gynecomastia [Figure 9].

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