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RESEARCH ARTICLE

ULTRASOUND ELASTOGRAPHY EVALUATION OF BREAST MASSES WITH FNAC AND/OR HISTOPATHOLOGICAL CORRELATION

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ABSTRACT

Background & Objectives: Ultrasound elastography is a non-invasive method for determining tissue mechanical properties. The aims of were to study:

1. The sensitivity and specificity of ultrasound elastography in the detection and characterization of various breast masses.
2. The role of ultrasound elastography in differentiating benign and malignant breast masses with FNAC and /or histopathology correlation.
3. Determine an optimal cut-off value for the traced area ratio by receiver operating characteristic (ROC) analysis for differential diagnosis in future applications.

Methods: It is a Hospital based prospective study carried on Philips iU22 ultrasound machine with high frequency probe, colour Doppler, and sono-elastography for 2.0 years on 116 cases. Patients presenting with small palpable breast lesions and those incidentally detected lesions on mammography were included in the study. Patients not willing for Ultrasonography & FNAC or Histopathology were excluded from the study.

Results: Among the benign nodules the common lesions were fibroadenoma 22 (19%) cases. Among the malignant lesions, the most common lesion was ductal carcinoma (invasive) 34 (29.3%). The mean elasticity score for benign lesions was 1.90 and 4.21 for malignant lesions. A sensitivity of 83.9% and a specificity of 91.7% was obtained for elasticity score with a cut-off point of 3. A sensitivity of 91.1% and a specificity of 88.3% was obtained for strain ratio with a cutoff point of 2.94.

Interpretation & Conclusions: The present study shows elasticity score (qualitative) and strain ratio (quantitative) methods in ultrasound elastography are good for the diagnosis of benign and malignant breast lesions with high sensitivity as well as high accuracy rate.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. Currently, palpation, mammography, and ultrasonography (USG) are the common diagnostic tests performed to detect breast cancer. (Saarenmaa *et al.*, 2001) Clinical palpation is the easiest examination method and has some value for early detection of breast tumors. However, clinical palpation is not very accurate because of its poor sensitivity and limited accuracy. For patients with dense breast tissue, even experienced clinicians cannot detect breast tumors in nearly 50% of the patients. (Breast imaging reporting and data system (BI-RADS)) Mammography can detect early breast cancer by revealing indirect signs, such as sand like calcifications. In addition, some researchers reported that there are some limitations to mammography when trying to detect lobular cancer, intraductal cancer without characteristic micro calcifications, multifocal cancer, local invasive cancer, and recurrent cancer after hormone replacement therapy. (Breast imaging reporting and data system (BI-RADS)) Compared to the aforementioned methods, USG is much more suitable as a screening examination because it is simple, non invasive and provides real-time dynamic imaging. Although USG is much more sensitive for detection of tumors compared to other methods, the specificity is poor, as most solid tumours are benign. To obtain acceptable specificity, various characteristics of the tumors must be evaluated according to the Breast Imaging Reporting and Data System (BIRADS) criteria defined by the American College of Radiology (ACR). (Breast imaging reporting and data system (BI-RADS)) Unfortunately, even according to these criteria, some tumors still cannot be differentiated. (Athanasiou *et al.*, 2010) This leads to increase in number of breast lesions biopsies. (Chiou *et al.*, 2006) Ultrasound elastography is a non-invasive method for

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determining tissue mechanical properties. This examination can yield tissue elasticity information that cannot be acquired via routine imaging modalities, which are mainly used for detecting tumors occurring in the breast, prostate, and vessel walls as well as in damaged tissue caused by high-intensity focused ultrasound. This technique combines ultrasound technology with the basic physical principles of elastography. (Krouskop *et al*., 1987) It is based on the premise that there are substantial differences in the mechanical properties of tissues that can be detected by applying an external mechanical force. (Krouskop *et al*., 1987) Ultrasound elastography compensates for the deficiencies of conventional USG. Compared to conventional USG, ultrasound elastography can clearly identify and locate breast tumors in the E-mode (Elasticity mode). In this study, compared the value of real-time ultrasound elastography for differentiating malignant and benign breast tumors to that of conventional USG to investigate whether it can improve the diagnosis, and determined an optimal cut-off value for the traced area ratio by receiver operating characteristic (ROC) analysis for differential diagnosis in future applications.

MATERIALS AND METHODS

The study was carried out in Dept. of Radiodiagnosis, in a Tertiary care centre for a duration of 2.0 years. It was a hospital based prospective study done on 116 patients after obtaining an informed consent.

Inclusion Criteria—

A. Patients presenting to the department of radiodiagnosis with all palpable breast lumps confirmed by USG.
B. Patients with incidentally detected lesions on imaging modalities like mammography.

Exclusion Criteria—

A. Patients who have already being diagnosed.
B. Patients not willing for Ultrasonography and FNAC or Histopathology.

Machine- Philips iU22 ultrasound machine having capability of high frequency small part probe, colour Doppler, and sonoelastography was used during the study.

In this prospective study, consecutive patients presenting with palpable breast lesions were assessed with conventional B-mode USG. Those confirmed to have a breast lesion were then assessed with SonoElastography after informed consent was obtained. The patients were examined in the supine position with the arm placed behind the head. The USG probe, lubricated with gel, was placed on the breast and a radial, ductal exploration was made as follows: the transducer was placed perpendicularly to the skin and radially on the breast, with one end overlapping on the areola and the other end directed toward the periphery. The orientation of the transducer was such that the nipple appeared at the left-hand side of the image. The transducer was then rotated around the areola. When a duct was identified, the rotation of the transducer was halted and it was moved back and forth laterally for thorough evaluation of the duct and its branches and the lobules. The transducer was then rotated again until the next ducto-lobular complex was found. This procedure was repeated until all the ductal structures were evaluated. A second rotating sweep was performed over the upper outer peripheral part of each breast. The B-mode USG image was displayed alongside the elastography strain image to ensure that the assessment was made in the area of interest. Included in the area of interest the lesion and also the subcutaneous layers and the pectoralis muscle, without the costal cartilages.
Conventional ultrasound images and real-time elastographic data sets were obtained using a 12-MHz linear transducer (Philips iU22). The sonoelastographic function of the Philips software is based on tissue compression during thoracic respiratory excursions. In order to obtain appropriate images, the transducer has to be applied with only the light pressure necessary to maintain contact with the skin. The results are displayed as colour-coded images, with blue representing hard tissue and red to green representing soft tissue on a continuous scale. The strain ratio describes the fat to lesion ratio, indicating the stiffness of a lesion. It is obtained by setting a oval Region of Interest (ROI) to cover the normal breast fatty tissue and a second ROI to cover the lesion. Fine needle aspiration cytology (FNAC) or excision biopsy is used for histopathological analysis of the malignant lesions. The benign lesions were diagnosed by a combination of FNAC or excision biopsy and follow-up for 6 months.

RESULTS

This study comprises of 116 patients with breast lesions confirmed on USG. The average age of the women was 41.9 years with minimum age 20 & maximum age 68 years. There were 56 (48.30%) malignant and 60 (51.70%) benign lesions most of the benign lesions observed between 20 to 50 years, while most of the malignant lesions observed between 30 to 60 years. Among the benign nodules the common lesions were fibroadenoma 22 (19%) cases, others were benign cystic lesion 15 (12.9%) cases and fibrocystic disease 21 (18.1%) cases. Among the malignant lesions, the most common lesion was ductal carcinoma (invasive) 34 (29.3%). Ductal carcinoma in situ was diagnosed in 18 (15.5%) cases and lobular carcinoma (invasive) in 2 (1.7%) cases. Infiltrating ductal carcinoma was diagnosed in 2 (1.7%) cases. (Table I). The elasticity scoring was done using the Tsukuba scoring system. Fibroadenomas appeared either softer than or had the same elasticity as adjacent glandular tissue (Fig. 1). Breast cysts had an elasticity score of 1 with a characteristic three-layered appearance: blue-green-red (BGR), blue being the superficial colour and red the deep one, even in large dimension lesions (Fig. 2). Breast carcinomas appeared larger on the elastography image because of better visualization of the surrounding desmoplastic reaction. The mean elasticity score for benign lesions was 1.90. Breast carcinomas showed an average elasticity score of 4.21(Table II). After FNAC and excision biopsy, seven lesions (11.6%) with elasticity score 3, three lesions (5.0%) with elasticity score 4 (Figure 3), and two lesions (3.3%) with elasticity score 5 were found to be benign; also, two lesions (3.5%) with elasticity score 1 and seven lesions (12.5%) with elasticity score 3 turned out to be malignant lesions (Table II). The maximum frequency (N=27) was seen with elasticity score 1 & 5 both. Minimum frequency (N=14) is seen with elasticity score 3 (Figure 4). The average SR for benign lesions was 2.20, which was significantly lower than that for malignant lesions (average SR: 5.80). To calculate the sensitivity and specificity of ultrasound elastography, lesions with elasticity scores 1-3 were classified as benign, while those with scores of 4 or 5 were classified as malignant.

Table I: Histopathological diagnosis of lesions (N=116)

Histopathology	Frequency (N)	Percentage (%)
Benign cystic lesion.	15	12.9
Ductal ca.(invasive)	34	29.3
Fibroademona	22	19
Fibroadenoma (calcified)	1	0.9
Fibrocystic disease	21	18.1
In situ ductal carcinima	18	15.5
Infected benign cystic lesion	1	0.9
Infiltrating ductal ca.	2	1.7
Lobular ca.(invasive)	2	1.7
Total	116	100

Table II: The elasticity score for benign and malignant lesions (N=116)

Type		Elasticity score					Total
		1	2	3	4	5	
Benign	N	25	23	7	3	2	60
	%	41.7%	38.3%	11.7%	5.0%	3.3%	100.0%
Malignant	N	2	0	7	22	25	56
	%	3.6%	0.0%	12.5%	39.3%	44.6%	100.0%
Total	N	27	23	14	25	27	116
	%	23.3%	19.8%	12.1%	21.6%	23.3%	100.0%

N-frequency

Table III: Area under the curve (elasticity score)

Test Result Variable(s):Elasticity score				
			Asymptotic 95% Confidence Interval	
Area	Std. Error	Asymptotic Sig.p	Lower Bound	Upper Bound
0.924	0.028	0.0001	0.869	0.979

Table IV: Coordinates of the curve (elasticity score)

Test Result Variable(s): Elasticity score		
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
0	1	1
1.5	0.964	0.583
2.5	0.964	0.2
3.5	0.839	0.083
4.5	0.446	0.033
6	0	0

TABLE V: Area under the curve (strain ratio)

Test Result Variable(s):Strain ratio				
			Asymptotic 95% Confidence Interval	
Area	Std. Error	p-value	Lower Bound	Upper Bound
0.969	0.013	0.0001	0.943	0.995

Table VI: Coordinates of the curve (strain ratio)

Test Result Variable(s):Strain ratio		
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
0.05	1	1
1.08	1	0.983
1.94	1	0.517
2.03	1	0.483
2.85	0.946	0.133
2.91	0.911	0.133
2.94	0.911	0.117
2.96	0.911	0.1
2.98	0.893	0.1
2.99	0.875	0.1
3	0.875	0.083
4.44	0.821	0.083
5.06	0.821	0.067
5.94	0.589	0
6.04	0.554	0
6.91	0.107	0
7.03	0.089	0
7.65	0.018	0
8.85	0	0

Table VII: Descriptive statistics

	Mean	Std. Deviation	N
Strain ratio	3.94	2.215	116
Elasticity score	3.02	1.515	116

N-frequency

Table VIII: Correlations analysis

		Strain ratio	Elasticity score
Strain ratio	Pearson Correlation	1	.936**
	Sig. (2-tailed)		0
	N	116	116
Elasticity score	Pearson Correlation	.936**	1
	Sig. (2-tailed)	0	
	N	116	116

**. Correlation is significant at the 0.01 level (2-tailed).

N-frequency

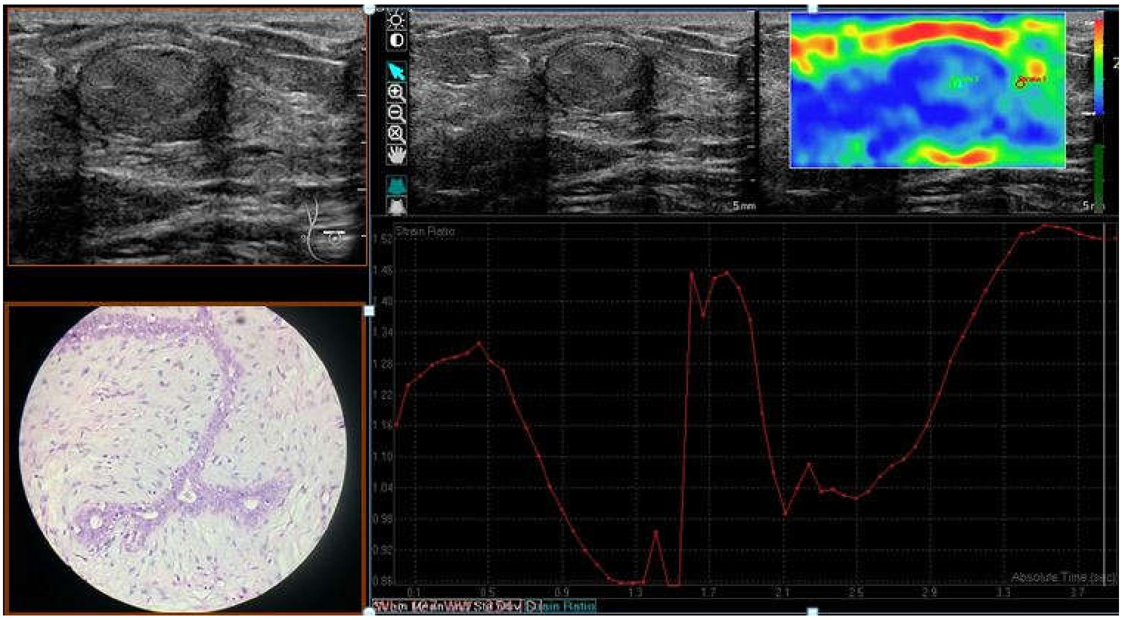
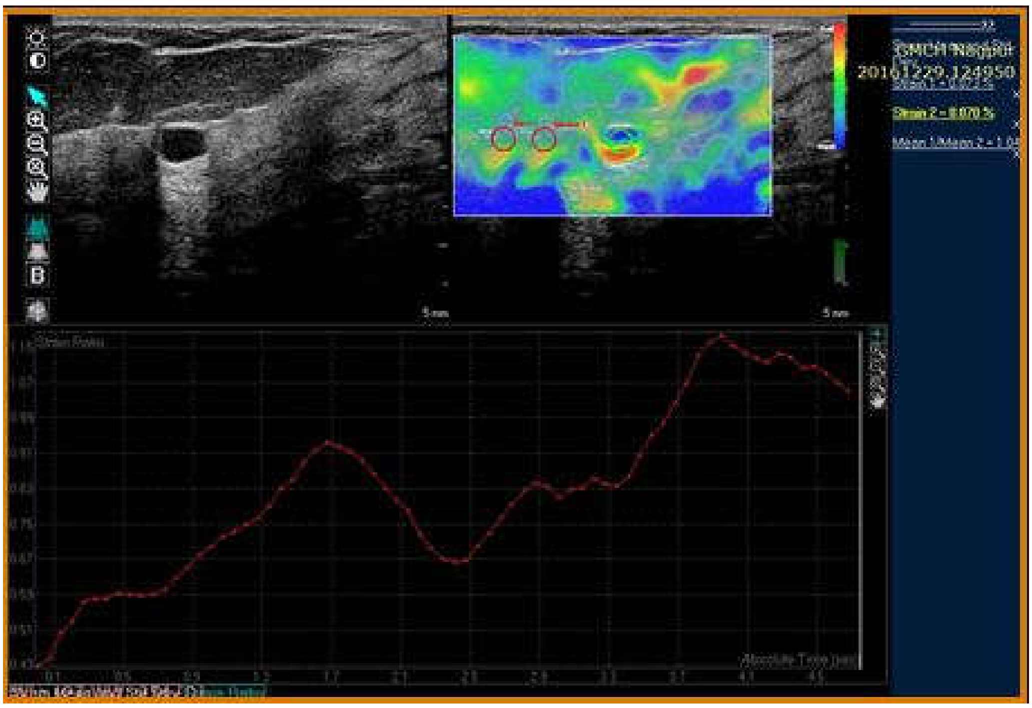


Figure 1. On elastography the strain elastography score was 2 and strain ratio was 1.5 s/o benign lesion. FNAC was suggestive of fibroadenoma



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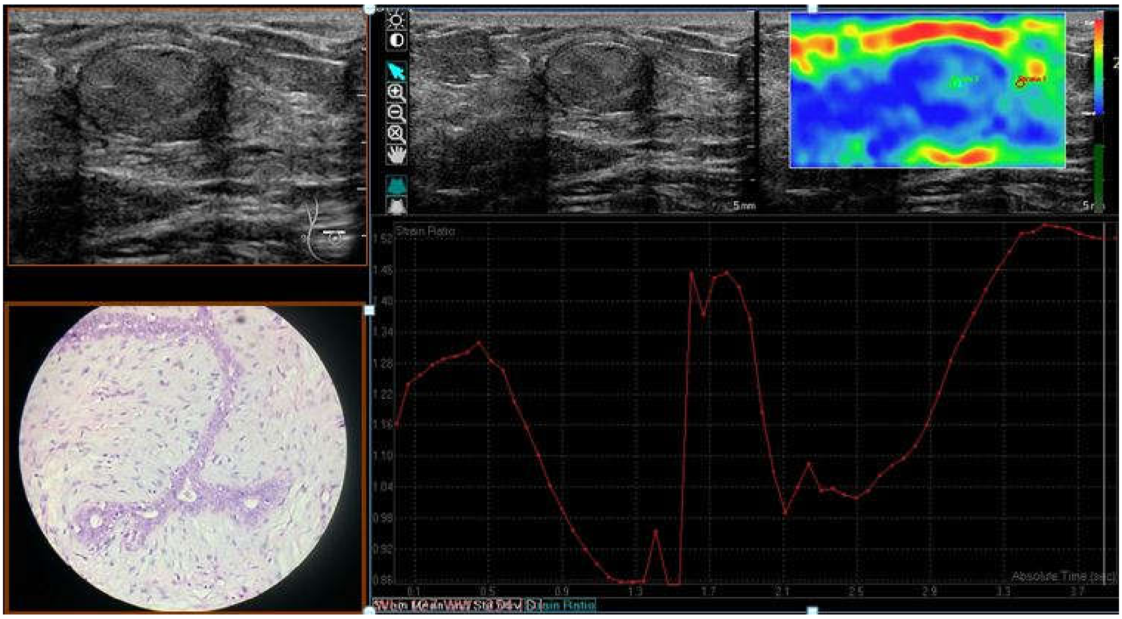

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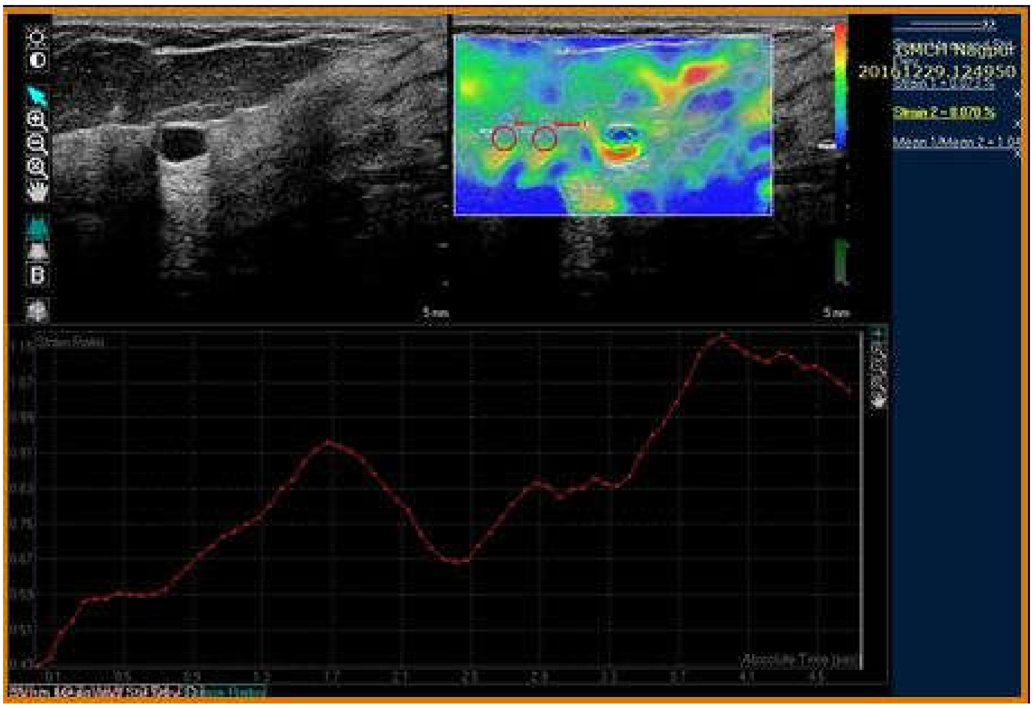

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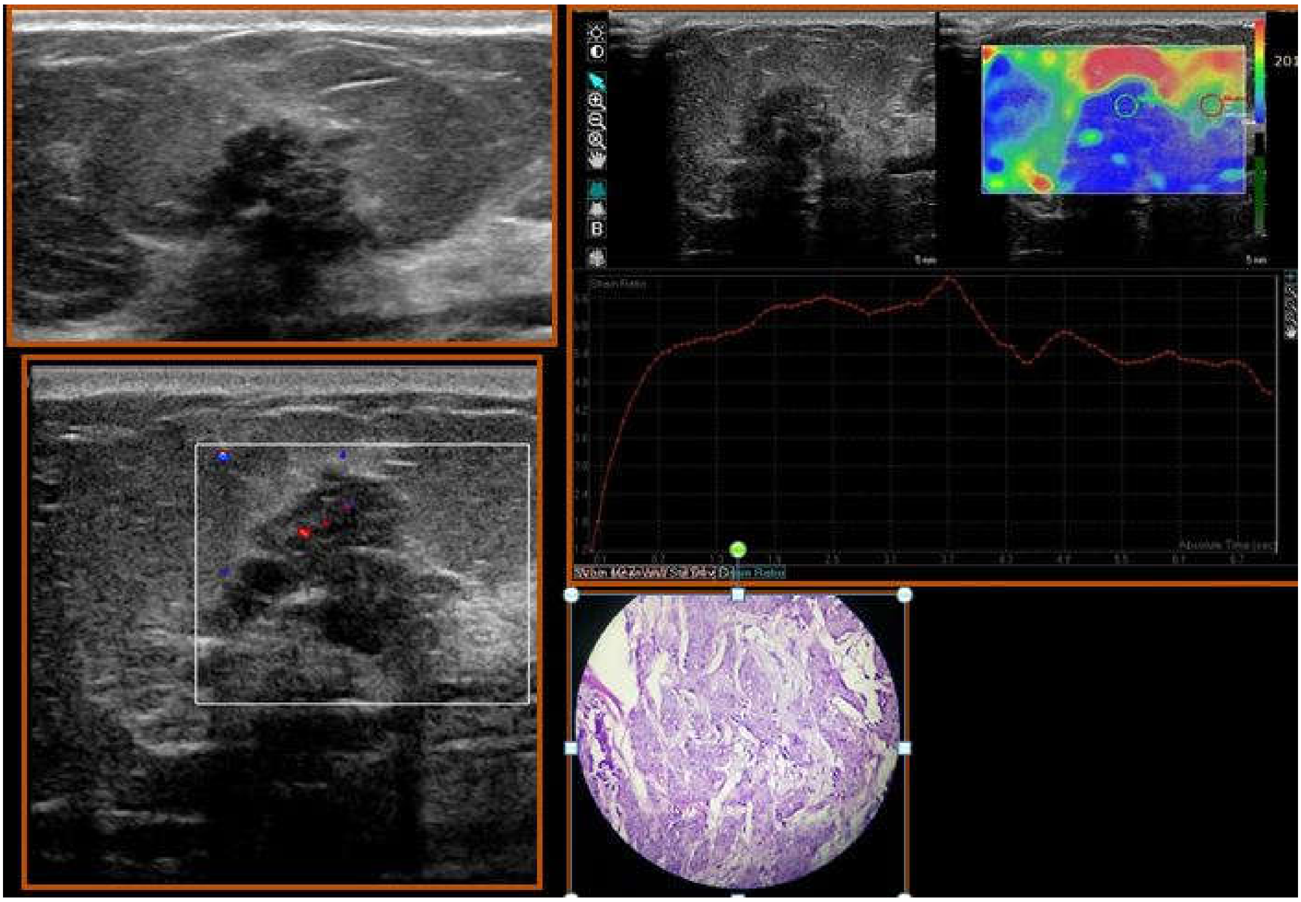


Figure 3. On Strain elastography score was 4 and strain ratio was 4.4 s/o malignant lesion. FNAC confirmed to be invasive ductal carcinoma

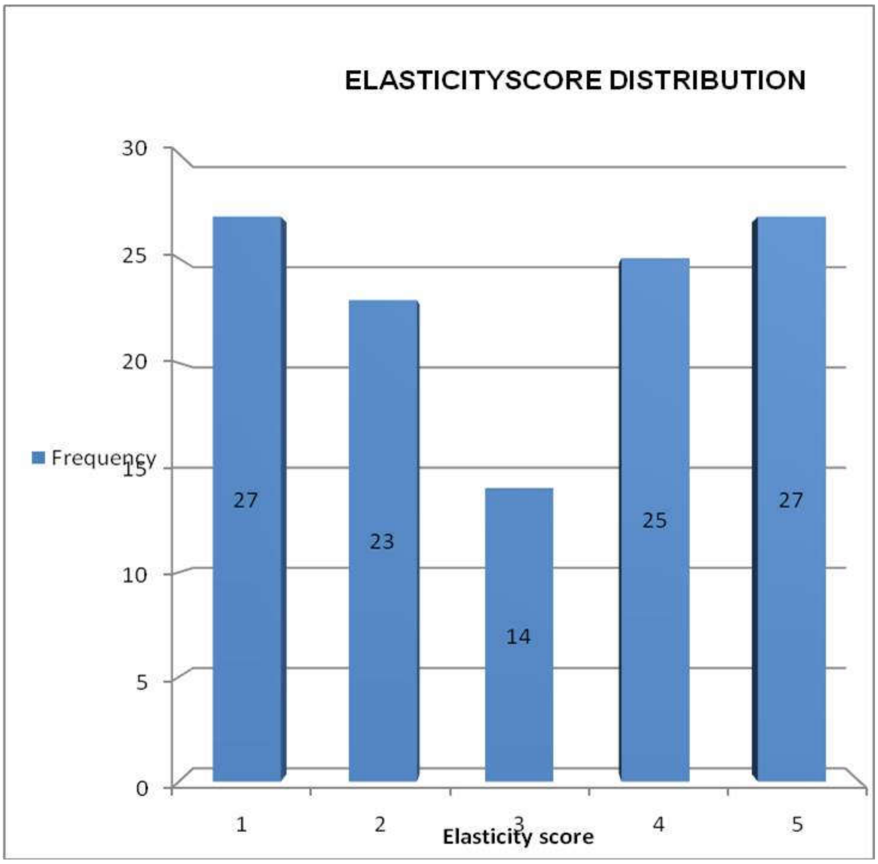
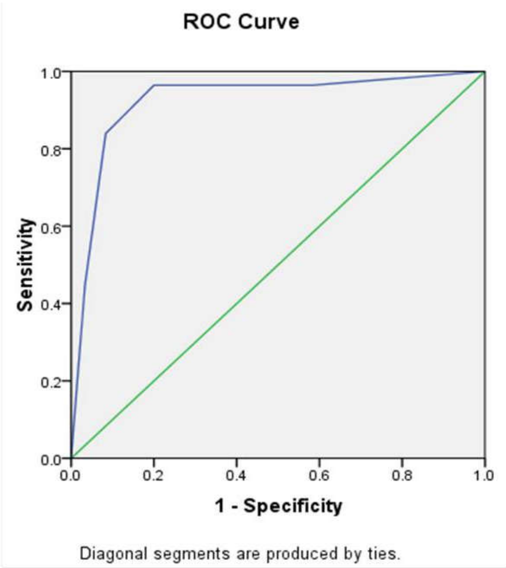
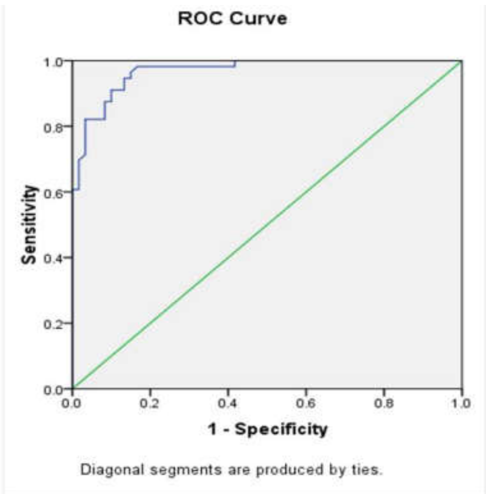


Figure 4. Chart with elasticity score distribution



Cut off point	3.5
Sensitivity	0.839
Specificity	0.917

Figure 5. Sensitivity and specificity values on ROC analysis for elasticity score



Cut off point	2.94
Sensitivity	0.911
Specificity	0.883

Figure 6. Sensitivity and specificity values on ROC analysis for strain ratio

For assessment of the role of SE in the differential diagnosis of breast lesions, a receiver operator characteristic (ROC) analysis was performed. (Figure 5) A sensitivity of 83.9% and a specificity of 91.7% obtained (Figure 8) for elasticity score when cut-off value of 3.5 is used (area under the ROC curve=0.924; 95% CI=0.869 to 0.979; *P*=0.0001) (TABLE III, IV). A sensitivity of 91.1% and a specificity of 88.3% for SR obtained, when a cutoff point of 2.94 was used (area under the ROC curve=0.969, 95% CI=0.943 to 0.995; P=0.0001) (Figure 6, TABLE V, VI). The Pearson coefficient of correlation for SR values and elasticity score was 0.936 (TABLE VII & VIII), showing that there was very good agreement (correlation) between the two methods.

DISCUSSION

The interpretation of breast nodules detected on B-mode USG relies mainly on morphological criteria. To improve the accuracy of USG, additional techniques can be used, including Doppler and harmonic imaging. (Rizzatto, 2007; Itoh, 2007) Over the last decade, there has been increasing interest in imaging the elasticity of biological tissues to complement information from standard anatomical imaging. SE can differentiate between benign and malignant lesions on the basis of their firmness. The lesion's contours, dimensions, colour, SR, and appearance on elastography are some of the criteria used for differentiating benign from malignant lesions. The SR represents the relative compliance stiffness of lesions compared with surrounding tissues. Malignant lesions, which are very stiff, deform less and are displayed in blue on the elastography images, whereas benign lesions deform much more easily and are depicted in green colour. (Hong *et al*., 2005; Ueno *et al*., 2005) Results of the clinical use of SE were initially published in 1997-2001 (Amy, 2000), but it was only in 2003-2004 that USG equipment was developed that had incorporated software for real-time processing of elastography images and routine USG examinations. (Konofagou, 2004) For characterization of breast lesions, two elasticity scoring systems have been proposed: the Tsukuba score developed by Itoh *et al*. (2006) and another designed by the Italian Research Group after Rizzatto *et al*. (2006). In this study, when a cut-off point of 3 was used, a sensitivity of 83.9% and a specificity of 91.7% obtained for elasticity score, results that are consistent with other published data on the use of real-time USG elastography (Itoh *et al*., 2006). Some of the study results are compared in TABLE IX. A sensitivity of 81% and a specificity of 89% was reported by Thomas *et al*. (2010), in a study where 227 breast lesions were examined. As the SR ratio of >3 is generally considered suspicious for malignancy (Cho *et al*., 2010), there is ongoing research for establishing the correct values for better differentiation of benign and malignant lesions. In this study, the mean SR for benign lesions was 2.20 and for malignant lesions it was 5.80, with the cut-off point being 2.94, sensitivity of 91.1% and a specificity of 88.3% for SR obtained, results that are consistent with other published data. (Cho *et al*., 2010; Thomas *et al*., 2010; Todd *et al*., 2009; Kumm and Szabunio, 2010; Tan *et al*., 2008; Zhi *et al*., 2008) Some of the study results are compared in TABLE X. In comparison, the critical SR value for diagnosing breast cancer was 3.08 in a study by Zhi *et al*. (2008). Routine USG examination detects many nonpalpable lesions and it is not very specific for screening cases. (Stavros *et al*., 1995)

The advantages of ductal USG is that standardized anatomic examination of the breast is possible, with precise localization of lesions and the visualization of connections with epithelial/ parenchymal breast structures, generally in the area of specific ducto-lobular units described by histologists. Ductal USG is an anatomical method of breast investigation that allows the correct assessment of the internal structures of the breast. The recent introduction of SE, especially quantitative elastography with SR, has increased the specificity of USG and enabled early diagnoses of subcentimeter breast cancer and decreased the need for biopsies. (Thomas *et al*., 2006) In the clinical setting SE is useful for deciding whether to follow-up patients with imaging or to intervene. (Thomas *et al*., 2006) Sometimes it is difficult to differentiate between scores 2 and 3 on SE images, but it is very easy to diagnose a lesion as having score 1, because no blue area is observed. (Scaperrotta *et al*., 2008) This study showed that there was good correlation (Pearson coefficient=0.936) between qualitative and quantitative elastography methods (elasticity score and SR) and by performing both techniques a more confident diagnosis can be made. Some studies have also demonstrated the value of elastography in the benign-malignant differentiation of lymph nodes. (Lyshchik *et al*., 2007) The introduction and validation of the concept of full-breast USG have increased the sensitivity of SE. (Hong *et al*., 2005) Full-breast USG allows the systematic diagnosis of lesions using the ductal technique; it is not operator dependent, has high specificity, and allows the precise localization of lesions within the breast gland (galactophore ducts, lobules, and ducto-lobular terminal units). (Hong *et al*., 2005) Also the use of Doppler and elastography techniques permits evaluation of the risk of neoplastic transformation, with a specificity of over 90%. (Itoh *et al*., 2006; Amy, 2000)

Limitations

SE is less sensitive than standard USG when dealing with non focal anomalies and is not indicated for the evaluation of postoperative changes, diffuse lesions, or large ones that exceed the probe length or its field of view (FOV). (Giuseppetti *et al*., 2005) SE is also of limited usefulness in very dense fibrous parenchyma and in the case of hematomas or breast implants. (Amy, 2000)

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