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Will Sonoelastography be the Virtual Biopsy of Future: A Study on Efficacy of Sonoelastography in Differentiation of Breast Lesions

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Abstract: ***Breast carcinoma is most common cancer worldwide. Awareness and precise diagnosis of breast lesions is of utmost significance. A novel modality that is subject of active research for clinical application is sonoelastography along with triple assessment. Tumors are usually stiffer and the relative stiffness can be mapped on elastography due to different tissue contrast. This property can help us in obtaining biopsy samples from suspicious target tissue and arriving at precise diagnosis thus making elastography the virtual biopsy of future. Out of 70 cases 50 were benign and 30 malignant on histopathology and there existed statistical significance between the elastography score and histopathology with 66.7% of cases being benign on histopathology with elastography score of 1-3 and 40% of cases being malignant on histopathology with elastography score of 4 to 5. After B-mode sonography analysis, the evaluation with the 5-point scoring method by sonoelastography might be a complementary method that increases specificity to differentiate between benign and malignant solid breast masses.***

Keywords: Ultrasonography, Sonoelastography, B- mode sonography, Breast lesions, Breast Imaging Reporting and Data System

1. Introduction

Once upon a time, breast cancer could only be diagnosed when a tumor was big enough to see or feel. Now it can be recognized and cured far earlier, often beyond any symptoms appear. Since 1950s, advances in mammography and ultrasonography are credited for raising the five year survival rate for localized breast cancer from 80% to 98%. Sonoelastography is one such tool that helps in differentiating benign from malignant lesions. Vital tissues have important property known as elasticity. Elasticity is defined as the lengthening change due to tension caused by a certain load on a tissue.[1,2]By physical examination elasticity can be measured but it is subjective method. For small or deep seated lesions examination by palpation may not be useful, in such cases elastography helps in evaluation. It is a non- invasive modality that can help in reducing the number of percutaneous or surgical biopsies.[4-9]It is new emerging modality that helps in imaging stiffness of breast lesion in relation to the background adipose and fibroglandular tissues. On palpation malignant lesions tend to be hard to feel, while benign lesions are typically firm to soft.[10]On compression softer tissues deform to a greater degree and therefore show higher strain compared to background tissue. Conversely, hard tissues tend to deform less and show a lower degree of starin.[4,7] The reason behind such discrepancy is that malignant tissues have wide desmoplastic reactions therefore are harder than the benign tissues and less elastic on elastography.[1-3] The elastogram can be used to predict the likelihood of malignancy, based on the measured hardness of the target lesions in the breast.[4,6,9]

In this study, we used B-mode sonography followed by sonoelastography for evaluation of solid breast lesions and the effect of this method on differentiating benign and malignant lesions by elasticity property scores.

2. Materials and Methods

A) Patient Selection

A feasibility study was conducted as part of a prospective study at JSS Hospital & Medical College. Informed consent was obtained from all patients. Seventy patients (age 15-89) with breast lesions, in whom FNAC or core needle biopsy or surgery was applied, were evaluated during one year. The lesions were evaluated by B-mode sonography and sonoelastography. Prior to biopsy or surgical intervention, all evaluations were done. Lesions were scored from 1 to 5 by sonoelastography(Table 1). The findings were compared with histopathology results.

Table 1: Sonoelastographic scores for breast lumps

Score	Sonoelastographic view
1	Three color layering (blue green red)
2	Diffuse elastic (near complete green except some blue dots)
3	Mostly elastic (mixture of green and blue but mostly green)
4	Mostly non elastic (mixture of green and blue but mostly blue)
5	Firm (near complete blue)

B) Mode sonography and sonoelastography

All evaluations were done by ultrasound – Phillips iU22 with Linear probe- L 12-5 and elastography probe – X 6-1 that enables sonoelastographic assessment .Simultaneous B-mode sonography and sonoelastography of the lesions were done by same radiologist, who is experienced in breast imaging. Static and motion images of all cases were recorded to the hard disk of the ultrasonography device.

Through B-mode ultrasonography, transverse and longitudinal plane views were obtained. Lesion size, shape, number, site, quadrant, margin, orientation, border, echogenicity, posterior acoustic shadowing, vascularity, lymph node status and calcification properties were evaluated by B-mode sonography. The B-mode sonography images were classified according to American College of Radiology's Breast Imaging Reporting and Data System-BIRADS.[11] According to this classification, cases in which

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no lesions were found were categorized as class 1.Category 2 lesions were accepted as benign; category 3 lesions probably benign; category 4 lesions low suspicion for malignancy and category 5 lesions highly suspicious for malignancy.

The process begins with conventional gray- scale ultrasound imaging of the traget lesion. During the procedure, the vertical amplitude of the transducer was 1-2 mm perpendicular to the skin and the mean velocity of transducer movement was one or two per second. Differences in the echo reflection from selected lesion tissue and background tissue during compressed and non-compressed intervals are quantified and then used to produce elastogram. Current image processing allows for the production of a color elastogram that can be used to further categorize the stiffness of the target tissue.[7] Areas with easily compressible tissues such as adipose tissue suggested high strain area, generated a red pixel on ultrasound-viewing screen. Areas that tend to compress to the same degree as fibroglandular or benign tissue, generated green pixel. Areas of lower strain, indicating hard or malignant tissue, generated blue pixel. A color map is then generated and superimposed over the gray-scale ultrasound images.
Itoh et al proposed a grading scale to categorize lesions based on the color signature generated by evaluation of target lesions. Lesions were classified according to sonoelastographyby 5 score method.[12]Cystic lesions were accepted as category 1, demonstrated a uniform pattern of high strain marked by an evenly distributed green color throughout the lesion. Diffuse elastic lesions were classified as score 2, mostly green signature indicating predominantly high strain pattern of the lesion. Predominantly elastic lesions as score 3 that showed high peripheral strain with low central strain producing a small central blue area that is surrounded by a green peripheral color.Predominantly firm lesions as score 4 which produce a low strain pattern and a uniformly blue color signature confined to the visible margin of the lesion, while score 5 lesions lack significant elasticity show a similar blue signature that extends beyond the lesion into the adjacent tissues (Table 1, Figure 1-4).

The scoring of sonoelastographic views were done by independent reviewer, blinded to the histopathology results, after evaluation of all images separately and subsequent to reaching an agreement. Histopathologic evaluation following excision of the lesion was accepted as standard reference. Elasticity scores were compared with histopathology.

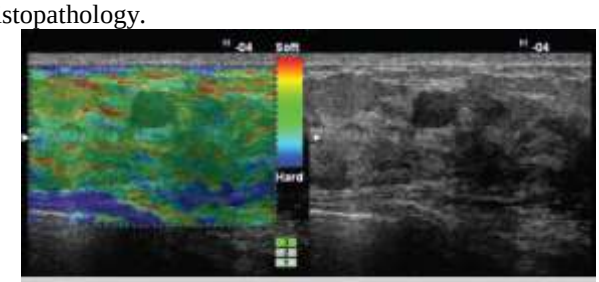


Figure 1. Fifty years-old female with a breast lesion (pathologic diagnosis: Fibroadenoma). Sonoelastograhic score was accepted as 2 due to diffuse elasticity (homogenous diffuse green) (Left side). BIRADS score with B-mode ultrasonography was accepted as category 3 (probably benign) due to hypoechoic lesion with regular borders (right side)

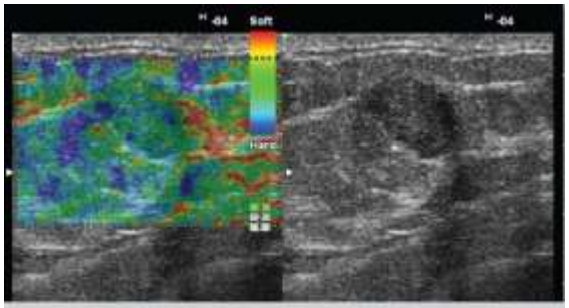


Figure 2. Fourty-six years-old female with a breast lesion (pathologic diagnosis: Fibroadenoma). Sonoelastograhic score was accepted as 3 due to mosaic appearance with abundant elasticity (mostly green) (Left side). BIRADS score with B-mode ultrasonography was accepted as category 4 (low suspicious for malignancy) due to hypoechoic lesion with lobulated borders (right side)

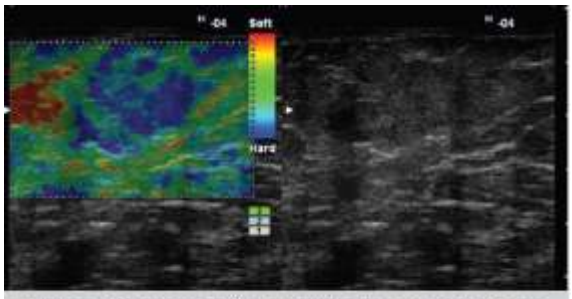


Figure 3. Sixty years-old female with a breast lesion (pathologic diagnosis: invasive ductal carcinoma). Sonoelastograhic score was accepted as 4 due to mosaic appearance with abundant firmness (mostly blue) (Left side). BIRADS score with B-mode ultrasonography was accepted as category 4 (low suspicious for malignancy) due to isoechoic lesion with lobulated borders (right side)

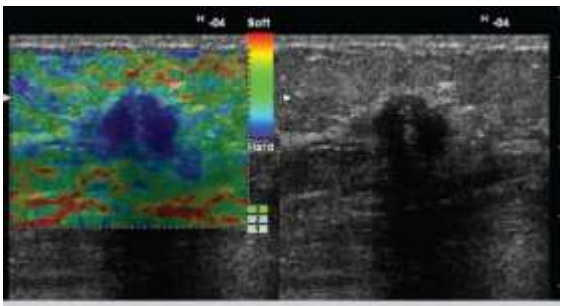


Figure 4. Fifty-five years-old female with a breast lesion (pathologic diagnosis: invasive ductal carcinoma). Sonoelastograhic score was accepted as 5 due to diffuse firmness(almost completely blue) (Left side). BIRADS score with B-mode ultrasonography was accepted as category 5 (highly suspicious for malignancy) due to ill-defined hypoechoic lesion with microcalcifications (right side)

Statistical Analysis

The differences between scores were evaluated by Student's t test. $P<0.05$ was accepted as statistically significant. Accuracy, sensitivity, specificity, positive and negative predictive values were calculated for B-mode US sonography and sonoelastographic scoring. The cut-off value was accepted as score 3 and score 4 in assessing performance of B-mode sonography and as 4b and 4c for sonoelastography methods. Statistical Packages for the Social Sciences (SPSS 22) program was used for statistical analysis.

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3. Results

Age

In our study, the mean age of presentation for benign and malignant lesions was 48.96+/- 12.99 and 51.37+/- 10.25 respectively. P value was 0.389 which was statistically insignificant, which might be due to low sample size. Study done by Jennifer L Gnerlich et al., showed that there was increased risk of harmone negative and aggressive histologic pattern of breast cancer in age group less than 40 years (13).But there is increasing trend of carcinoma breast as age progress, with benign lesions being more common among younger age group.

Lesions

Descritpive characteristics of breast lesions are depicted in table 2. Out of 70 lesions histopathologic evaluation revealed 30 benign pathologies (42.9%), and 40 malignant pathologies (57.1%). Benign lesion group included 8fibroadenoma, 1 intraductal papilloma, 5 benign proliferative breast disease, 7 benign epithelial lesions, 3phyllodes tumor. Malignant lesion group included 26 invasive ductal carcinoma, 3 lobular invasive carcinoma, 3 colloid (mucinous) carcinoma, 4 medullary carcinoma, 11 non- specified carcinoma breast.

B-mode sonography&sonoelastography findings

Table 2 depicts the mean scores obtained by sonoelastography according to five score method and the mean scores obtained by B-mode sonography according to BI-RADS method. In both methods, calculated mean scores were higher for malignant lesions than benign lesions (Table 2, $p<0.05$). Table 3 depicts histopathologic results and malignancy rates on B- mode sonography and sonoelastography for each score level. A score of 4 was found to be more common in benign lesions in B- mode sonography and score of 2 in sonoelastography method. When a cut-off value of 3 to 4 was used with B-mode scoring method, 13 false positive and 3 false negative results were detected. When scores 1-4b were accepted as benign and scores of 4c-5 as malignant, sonoelastographic scoring method revealed 3 false positive and 15 false-negative results. Table 4depicts,comparision of B-mode sonography and sonoelastography methods compared in terms of diagnostic performance.

Table 2

Age	Benign N=30	Malignant N=40
B-mode sono	1.6±0.56 Median=4	12.32±1.26
Elasto	2.43±0.67 Median=2	3.55±0.78 Median=4

Table 3: Elasticityscore * histopathology Crosstabulation

Sono level	Benign n=30	Malignant n=40	Malignant rate
2	1	1	0/10
3	10	0	0/10 (0)
4	19	37	37/56 (66)
5	0	2	2/2(100%)
6	0	1	1/1

Table 4: Elasticityscore * histopathology Crosstabulation

Diagnostic performance	B Mode	Sono
Accuracy (%)	77.14 (65.55-86.33)	74.29(62-83.99
Sensitivity (%)	92.5%(79.61-98.43)	62.5(48-77.27)
Specificity (%)	56.67(37.43-74.54)	90(73.41-97.89)
Positive predictive value (%)	74 (65.19-81.22)	89.29(73.5-96.16)
Negative predictive value(%)	85 (64.62-94.62)	64.29(54.25-73.21)

Table 5: Tsukuba classification

Score 1	Diffuse elastic lesions
Score 2	Mostly elastic lesions
Score 3	Peripherally elastic centrally firm lesions
Score 4	Mostly firm lesions
Score 5	Devoid of significant elasticity and firm even at the periphery of the lesion

4. Discussion

Worldwide breast cancer remains the most common malignancy in women.[14]B-mode sonography reflects intensity properties of the tissues examined as brightness on the screen by using acoustic energy interactions in the body.[15] In real time, the images are in the form of shades of gray. It is used to determine both location and the internal structures of breast lesions. B- modesonography can detect malignant masses with higher sensitivity. But, the major problem of this method is high rate of false positivity. To overcome this problem, research is being done with a new sonography method, sonoelastography.

Sonoelastography is a non- invasive technique that has shown potential for differentiating benign from malignant breast disease and could possibly reduce the overall number of breast biopsies. The firmness of tissues can be displayed with different color codes in real time by sonoelastography and this property can be qualitatively scored. In addition to this, elasticity maps can also be obtained which enables calculation of stretching of normal tissue and that of the lesion.[16,17]Itoh et al proposed " Tsukuba elasticity score" which is widely accepted in the sonoelastographic evaluation of breast lesions.[7]Tsukuba method classifies breast lesions as shown in table 5. The above mentioned scoring was modified by an Italian study group.[12]The modified score was more feasible in the practice of radiology as this scoring method is more compatible with the BIRADS. For these reasons, we have used the Italian group's scoring in the evaluation of breast lesions by sonoelastography. Low specificity values ranging from 21% to 56% was observed in the initial studies evaluating breast lesions by sonoelastography.[4,18,19]The drawback of these studies was that neither scoring methods nor quantitative evaluations were performed. Studies which use "autocorrelation method" for scoring methods in ultrasonography equipments showed specificity values of 70% to 99%, and sensitivity values of 35% to 97%. In our study, the sensitivity and specificity were found to be 62.5% and 90% respectively. The results of our study were consistent with most of the studies with scoring methods. Factor that alters sensitivity and specificity of a method is altering the cut- off value. When cut off value is taken on lower side there is increase in sensitivity and decrease in

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specificity. In our study, the sensitivity and specificity of B-mode sonography was found as 92.5 % and 56.67% respectively. The results of our study and most of the literature data, suggest that the sonoelastographic evaluation by 5 score method following B- mode sonography examination can be used as complimentary diagnostic method in order to increase specificity.

As a result, for breast lesions with category 4a on B-modesonography with elasticity score of 1 on sonoelastography with no other clinical risk factors can be followed up instead of biopsy. With this approach that will significantly reduce unnecessary biopies, there is a rare risk of overlooking some cancers. Sadighiet al[20] have a done a meta- analysis including 5,511 breast lesions and have discussed the issue. In their study, they recommended biopsy in low risk patient group with lesions on B- mode sonography and sonoelastography showing low- suspicious of malignancy. For patients in high- risk groups, they advocated that a biopsy should be performed if the mass is positive on B- mode sonography regardless of sonoelastographic findings.

The main limitation of our study was small sample size and lack of inter- observer compatibility. Another restriction is that sonoelastohgraphy evaluation couldnot be performed independently from B- modesonography evaluation. This is due to fact that, sonoelastography evaluation is performed by placing images on B- mode sonography views and using color- coded maps.

5. Conclusion

Sonoelastography scores in combination with B-mode sonography on quantitative analysis, of breast lesions might be a diagnostic tool that increases specificity. Therefore, with this method there are high chances of targetinglesions for biopsy which can reduce the error.Henceforth, unnecessary invasive procedures can be avoided along with financial and psychological burden on patient.

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