The role of US elastography in the evaluation of benign and malignant breast lesions in relation to histopathological examination

Poster No.: C-1802
Congress: ECR 2013
Type: Scientific Exhibit
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Keywords: Diverticula, Chronic obstructive airways disease, Arteriovenous malformations, Diagnostic procedure, Biopsy, Angioplasty, MR, Ultrasound, Elastography, Musculoskeletal bone, Interventional vascular, Breast
DOI: 10.1594/ecr2013/C-1802

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Purpose

Breast carcinomas are usually harder in consistency compared to benign lesion. However, palpation is limited to superficial lesions. B Mode ultrasound can distinguish benign from malignant breast lesions based on the appearance of the lesion, i.e.: margin, shape, echogenicity and shadowing (1). Compressibility has also been used to assess a lesion. However, this may be subjective and operator-dependent (2).

Elastography is a non-invasive medical imaging technique that can differentiate tumours based on their stiffness. Malignant lesions tend to be many times stiffer than normal tissue (3). Elastography has been available since the 1990s however has only been approved for clinical use and research only in 2006 by the US Food and Drug Administration (FDA). The elastography imaging demonstrate variable degrees of tissue stiffness which are displayed as gray scale or colour map. Elastography imaging has been reported to be highly specific for distinguishing benign from malignant breast lesions. It also has the potential to greatly reduce the number of breast biopsies performed (4). The previously developed ultrasound elastography software offers the ability to differentiate between malignant and benign breast tissue by the strain images produced. These obtained data, however, was qualitative and not quantitative (5, 6). There are limited studies using quantitative measurements. Garra et al utilized the quantitative measurements by comparing the value of stiffness within the target lesion with the fatty tissue in the breast and this is known as strain ratio (7). The discrepancies between the size of breast lesions on B-mode and strain images of elastogram is known as the lesion size comparison technique or width ratio (7). Malignant lesions tend to be larger on strain images than on corresponding B-mode images, thought to be secondary to the surrounding desmoplastic reaction that accompanies most malignant lesions (2, 6).

The purpose of this study was to evaluate the diagnostic value of ultrasound strain elastography in differentiating between benign and malignant breast lesions in comparison to conventional B mode ultrasound.
Methods and Materials

Patient

This prospective clinical study was conducted at the Biomedical Imaging Department of University Malaya Medical Centre. Approval from the institutional review board of Ethics Committee was obtained and all patients provided informed consent. Conventional B-mode ultrasound and strain elastography was performed on 169 consecutive women who were scheduled for percutaneous ultrasound-guided core biopsy, excision surgery or fine-needle aspiration in the imaging department. The final histopathology was based on the surgical specimen when available.

Ultrasound

The evaluation of the sonographically visible breast lesions were performed using Philips iU22 ultrasound system (Philips Healthcare Bothell, Washington, USA). B-mode ultrasound and elastography were carried out using the equipped high-definition linear L12-7 MHz probe and small part advanced breast tissue specific imaging (TSI) preset for elastography. Each breast lesion was evaluated with conventional B-mode US alone, as well as with a combination of B-mode and elastography independently by two dedicated breast radiologists. Assessment of the B-mode US findings was done according to the Classification of ACR BI-RADS US lexicon. Elastography assessment of a breast lesion was based on strain pattern, width ratio and strain ratio (fig 1-5). The gray scale elastogram strain pattern was assessed according to the following five categories: homogeneously black, homogenously white, gray, mixed, and bull's-eye sign or elastographic posterior enhancement (Fig 1-). Darker or black strain was considered to be hard or stiff relative to the normal breast tissue and the brighter or white strain was considered to be softer tissue ( fig 6-8).

Statistical Analysis

The data was analyzed using Microsoft Excel (Redmond, WA) spreadsheets and computerized statistic software Statistical Package for Social Sciences (SPSS) version 17.0. Receiver Operating Characteristic curve (ROC) was constructed for B Mode ultrasound, elastography, and combination of both methods. The sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) were also calculated for the three imaging techniques B Mode ultrasound, elastography, and combination of both methods.
Fig. 1: B-mode Ultrasound (left) and corresponding elastography image (right) for five-strain pattern. Top row: (left to right) i) Homogenously black ii) Homogenously white iii) Grey iv) Bottom row: (left to right) Mixed v) Bull's-eye or Elastographic posterior enhancement.

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Fig. 2: Strain ratio is a relative strain of two regions of interest with larger value of strain ratio suggest a malignant lesion and smaller value suggest the lesion is more likely to be benign. (HPE: fibroadenoma)
Fig. 3: Strain ratio is a relative strain of two regions of interest with larger value of strain ratio suggest a malignant lesion and smaller value suggest the lesion is more likely to be benign. (HPE: Infiltrating ductal carcinoma)

Fig. 4: Width ratio is a lesion comparison technique which measures discrepancy between the size of breast lesion on B mode ultrasound and elastogram. The width ratio is
obtained when the maximum horizontal distance of the lesion measured on elastography is divided by the maximum horizontal distance measured in the B-mode image. Larger value of width is more likely for the lesion to be malignant and smaller value for benign lesion. (HPE: fibroadenoma)

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**Fig. 5:** Width ratio is a lesion comparison technique which measures discrepancy between the size of breast lesion on B mode ultrasound and elastogram. The width ratio is obtained when the maximum horizontal distance of the lesion measured on elastography is divided by the maximum horizontal distance measured in the B-mode image. Larger value of width is more likely for the lesion to be malignant and smaller value for benign lesion. (HPE: Infiltrating ductal carcinoma)

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**Fig. 6:** B-mode US showed a well defined hypo echoic lesion with posterior enhancement (left) with corresponding elastography image right) of predominantly white strain pattern. Strain ratio is 4.3 and width ratio is < 1. Histopathology confirmed fibroadenoma.

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**Fig. 7:** Infiltrating ductal carcinoma. B-mode US showing a hypoechoic lesion with posterior acoustic shadow with corresponding elastography image of predominantly black strain pattern. The strain ratio was 7.8 and the width ratio was 1.5.

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**Fig. 8:** B-mode US of a simple cyst showing a well defined anechoic lesion with posterior enhancement (left) with corresponding elastography image of Bull's eye sign. Strain ratio was 1.2 and width ratio was 0.9.

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Results

The study samples included 169 breast lesions from 158 women and one man from three main ethnic groups in Malaysia. The racial distributions were Malay 44.4%, Chinese 39.1%, Indian 14.8%, and other races 1.7%. The patients’ age ranged from 18 to 84 years with mean age of 49.5 years. The most common age-range in the study samples was 50-59 age groups. The studied breast lesions comprised of 92 benign and 77 malignant lesions. The mean transverse and AP diameter diameter for benign lesions were 1.6 and 1.0 cm respectively. For malignant lesions, the mean for transverse diameter and AP diameter were 1.9 and 1.4 cm respectively.

The malignant lesions comprised of 62 infiltrating ductal carcinoma (80.5%), 8 ductal carcinoma in situ (DCIS) (10.4%), 2 mucinous carcinoma (2.6%) and the rest of histology malignant result with 1 lesion each was infiltrating lobular carcinoma, medullary carcinoma, metaplastic carcinoma, residual carcinoma and pleomorphic sarcoma. The benign lesions were fibroadenoma (n=47) and fibrocystic disease (n=16) and others (n=29).

Based on the B-mode imaging characteristics, the number of lesions assigned to the BI-RADS scores was: 64 BI-RADS 3 (38%); 105 BI-RADS 4 and 5 (62%). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), for B-Mode ultrasound in predicting malignancy were 98.6%, 67.7%, 71.4% and 98.4% respectively (Fig. 9).

The sensitivities, specificities, positive and negative predictive values (PPV and NPV) for strain ratio and width ratio were analysed for variable cut off points. In the assessment of strain ratio, we tested the cut off point of 3 different values which were at 4.5, 5.0 and 5.5. Strain ratio of 5.0 were chosen based on the receiver operating characteristic curves (ROC) which showed a balanced result of sensitivity and specificity. The sensitivity, specificity, positive predictive value and negative predictive value for cut off points of strain ratio 4.5, 5.0 and 5.5 were 100%, 71.7%, 74.8 and 100%, 97.4%, 82.6%, 82.4% and 97.4%, 92.2%, 89.1%, 87.7% and 93.2% respectively (Figs 10 & 12). From the ROC curve, width ratio that provides the highest sensitivity (of 100%) lies between 1.05 & 0.95, with varying specificities. We tested 3 different cut off points (1.0, 1.1 & 1.2), and found that to attain a 100% sensitivity without compromising the specificity, a cut off ratio of 1.1 was selected. The sensitivity, specificity, positive predictive value and negative predictive value for width ratio 0.9, 1.0, 1.1 and 1.2 are 100%, 22.8%, 52.0% and 100%, 100%, 41.3%, 58.8%, and 100%, 96.1%, 71.7%, 74.0% and 95.7% and 85.7%, 79.3%, 77.6% and 86.9% respectively (Fig 11 & 12).

For combination of B-mode ultrasound and elastography, we also tested three different combinations. Cut off point for malignancy for strain ratio, width ratio and B mode ultrasound were 5.0, 1.1 and BI-RADS 3 respectively. Combination of at least one
positive result yield 100% sensitivity however the specificity is very low which is 47.8%. Combination of all positive result showed sensitivity, specificity, positive predictive value and negative predictive value were 92.2%, 92.4%, 91.0%, and 93.4% respectively and combination of at least two positive results showed 100% sensitivity without compromising specificity with 80.4% (Fig 13 & 14).

The predominantly black strain pattern was observed in 87 lesions, which consisted of 55 malignant and 32 benign lesions. A predominantly white pattern was seen in 7 lesions which were all confirmed to be benign. Gray strain patterns were seen in 7 lesions, which consisted of 6 benign and 1 malignant lesions. Mixed strain pattern was observed in 68 lesions, which consisted of 47 benign and 21 malignant lesions. Only 1 lesion demonstrate a bull's-eye pattern or "elastographic posterior enhancement" and histology proven as fibrocystic disease (Fig 15).

The kappa value with respect to the inter-observer agreement of the radiologists' readings using the parameters of the B-mode and combined imaging technique imaging was good, (kappa value 0.87, p< 0.001, 95% CI (confidence interval) 0.69-1.0).
Fig. 9: sensitivity, specificity, positive predictive value and negative predictive value of B Mode ultrasound

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<table>
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<tr>
<th>Strain Ratio</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
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<tr>
<td>4.5</td>
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<td>5.0</td>
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<td>92.2</td>
<td>89.1</td>
<td>87.7</td>
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Fig. 10: Sensitivity, specificity, positive and negative predictive value of strain ratio

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<table>
<thead>
<tr>
<th>Width Ratio</th>
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<th>Negative Predictive Value (%)</th>
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<tr>
<td>0.9</td>
<td>100</td>
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<td>1.0</td>
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<td>41.3</td>
<td>58.8</td>
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<tr>
<td>1.1</td>
<td>96.1</td>
<td>71.7</td>
<td>74.0</td>
<td>95.7</td>
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<tr>
<td>1.2</td>
<td>85.7</td>
<td>79.3</td>
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<td>86.9</td>
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Fig. 11: Sensitivity, specificity, positive and negative predictive value of width ratio.

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Fig. 12: Box plot for width and strain ratio

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<table>
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<tr>
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<th>At least 1 Positive (%)</th>
<th>At least 2 positive (%)</th>
<th>All 3 Positive (%)</th>
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<tr>
<td>Sensitivity</td>
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<td>100</td>
<td>92.2</td>
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<td>Specificity</td>
<td>47.8</td>
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<td>Positive predictive value</td>
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<tr>
<td>Negative predictive value</td>
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<td>93.4</td>
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*Strain ratio cut off point 5.0, *Width ratio cut off point 1.1, *BI-RADS cut off point 3

**Fig. 13:** Summary of the combined B mode and elastography findings

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**Fig. 14:** Receiver Operating Curve (ROC) for width ratio, strain ratio, B Mode US and combination elastography and B Mode US

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<table>
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<tr>
<th>Strain Pattern</th>
<th>Benign n (%)</th>
<th>Malignant n (%)</th>
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<tbody>
<tr>
<td>Homogenously black</td>
<td>32 (35)</td>
<td>55 (71.4)</td>
</tr>
<tr>
<td>Homogenously white</td>
<td>6 (6.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grey</td>
<td>6 (6.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Mixed</td>
<td>47 (51)</td>
<td>21 (27.4)</td>
</tr>
<tr>
<td>Bulls’ eye pattern</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
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**Fig. 15:** Distribution of strain pattern with histopathology

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Conclusion

Our current study has shown that the combined B-mode US and strain elastography significantly increases the sensitivity, specificity, positive predictive value and negative predictive value in differentiating between malignant and benign breast lesions in comparison with B Mode ultrasound alone. Our results were comparable with that of (8), in which the combination of B-mode US and elastography improved the diagnostic performance of radiologists in distinguishing benign from malignant masses compared with B-mode US alone.

The parameters of strain ratio and width ratio were useful in differentiating between benign and malignant breast lesions. Previous studies adopted the qualitative strain assessment system by Itoh et al. which depended on five elastography colour patterns (5). Only few studies have assessed both the qualitative strain pattern and semi-quantitative strain ratio with width ratio measurements, which were undertaken in this study. To the authors' knowledge, this study is also one of the few breast elastography studies performed to evaluate the specificity and sensitivity of combining elastography with conventional breast ultrasound.

We found strain ratio of 5.0 and more to be highly suggestive of malignancy with 96.2% sensitivity and 82% specificity. Yerli et al. showed that the strain ratio and elasticity scoring methods have the same diagnostic value of differentiating between benign and malignant breast lesions (9). However, evaluation of the lesions with visual five elasticity scoring by Yerli et al showed that additional strain index did not significantly contribute to the differentiation between benign and malignant lesions. Athanasiou et al. used quantitative sonoelastography with supersonic shear wave imaging to assess lesion stiffness (measured in kilopascals) and were able to differentiate between benign and malignant breast lesions (10).

A multicenter study of 578 patients using 1.0 as the cut off point for width ratio in classifying breast lesions resulted in high sensitivity (98.6%), moderate specificity (87.4%), and a high negative predictive value (99.2%). In our study, cut off point of 1.1 provided a better balance with sensitivity of 94.7% and specificity 66.7%. We also found that to attain 100% sensitivity (at cut off point 1.0), the specificity would be compromised (40.9%). Leong et al had chosen an optimal cut off values of 1.1 for both width and area ratios based on the ROC curves (sensitivity 92.3% and specificity 69.1%) (3). Another study by Hall et al. recommended a width ratio cut-off of 1.2 to differentiate between malignant and benign lesions (11). We found that width ratio at 1.2 yield higher specificity 74.2%, however the sensitivity has drop to 85.5%.

In comparing the sensitivity and specificity between strain ratio and width ratio, this study showed that the width ratio was more sensitive than strain. However the strain ratio was found to be more specific . The additional use of the semi-quantitative elastography value of strain ratio and width ratio in this study to evaluate breast lesions was more objective
compared to the single visual qualitative strain pattern scoring by Itoh et al.(5). We also found very good inter-observer agreement in the B-mode and elastography assessment readings between the radiologists (kappa value of 0.87, p< 0.001).

This study showed that a combination technique of B-mode ultrasound and elastography can significantly improve the specificity and PPV in the differentiation of malignant and benign breast lesions, thus potentially reducing the necessity of biopsy for indeterminate or questionable breast lesions.

Acknowledgement:

Preliminary work from this study has been accepted and will be published in the Ultrasound in Medicine in Biology (USMB) with the article title 'Semi-quantitative and qualitative assessment of breast ultrasound elastography in differentiating between malignant and benign lesions'.

This study obtaine financial support from the University Malaya Research Grant (UMRG) RG 327/11 from the University of Malaya, Malaysia.
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