Screening of Breast Lesions: a comparative study between mammography, ultrasound b-mode, ultrasound elastography and histological measurements.

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Authors: R. C. Pardal\textsuperscript{1}, A. F. Abrantes\textsuperscript{2}, T. L. Figueiredo\textsuperscript{3}, L. P. V. Ribeiro\textsuperscript{2}, S. Rodrigues\textsuperscript{2}, R. P. P. Almeida\textsuperscript{2}, K. B. Azevedo\textsuperscript{4}, \textsuperscript{1}Castro Verde/PT, \textsuperscript{2}Faro/PT, \textsuperscript{3}Faro, Al/PT, \textsuperscript{4}Faro, EU/PT
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Purpose

The Breast Cancer designates the most common neoplasm in the female world, comprising about 16% of all tumors of women. Its incidence is variable throughout the world, having been calculated in North America as 99.4 per 100,000. In regions such as Eastern Europe, South America, South Africa and Western Asia the incidence presented is moderate and are nevertheless increasing [1]. Regarding the Portuguese reality, the incidence recorded is about 4000 new cases/ year [2].

In the diagnosis of breast lesions, the B-mode Ultrasound (U.S.) appears to be quite important as a supplement to other diagnostic modalities. The echographic study should, wherever possible, be preceded by a complete Mammographic study [3]. With the advancement in medical technology, it is possible to use the U.S. Elastography technique in routine diagnostics. It shows up now as a promising technique in evolutionary control of suspicious breast lesions at older ages and intervals of mammographic control, thus guiding the diagnosis and prognosis. At young ages, this technique enables increased information for diagnosing solid lesions, allowing avoid unnecessary biopsy. It shows a complementary technique in the diagnosis of breast pathology, being associated with B-mode U.S. Its main advantages is that it's free of ionizing radiation, providing more specific information on the possible lesion and not imply a significant increase of time to study in suspicious lesions. It's a method to quantify the degree of elasticity of tissues by conducting pressure on them [5]. The lesions are quantified according to a color scale. It's used a transducer, which superimposes the color information in images of B-mode ultrasound [6]. The color scale ranges between red and blue. This presents strongly related to the degree of benign/malignancy, and that the absence of deformation, characterized by a blue color, is associated with malignancy grade [7]. The patient's follow-up is decided after the Breast Biopsy, which depends on the histologic findings [8].

The realization of this research is of great importance in that U.S. Elastography is a relatively new technique, whose diagnostic accuracy is rarely described in the literature. If it's recognized the reliability of the technique to screen benign vs. malignant, it will be possible to reduce the amount of breast biopsies done today, which although suspicious, are proven benign.

Thus, the present study has as main objective to determine the capacity for differentiation of benign vs. malignant breast lesions by the Mammography, B-mode U.S. and U.S. Elastography using as Gold Standard technique the histological lesions results, and to compare the U.S. Elastography results with the others imagiologic techniques.
Methods and Materials

The target population for this study focused on a group of female users who owned unilateral or bilateral breast pathology and have performed imaging studies in Imaging Services of the Faro’s Hospital and Faro’s Santa Maria Hospital. The sample corresponded to 12 breast lesions, which were documented through pictures Mammography, B-mode U.S. and U.S. Elastography (figure 1). The resulting Histologic Results of biopsies of the lesions studied worked as Gold Standard technique, in order to expand the specificity of the results. The exclusion criteria for the study was defined by the absence of any diagnostic imaging techniques.

Fig. 1: Patient with 50 years old and a history of breast pathology who went under surgery. The patient realize a Mammography composed by a CC (a) and OML (b) incidences, which revealed some surgical clips and a discrete area of densification by convergent fibrotic images, classified with BI-RADS 4a. In the ecographic study (c) is shown a hypoechoic area with poorly defined border lines, classified with BI-RADS 4b. The U.S. Elastographic study (d) identified a lesion essentially elastic with some areas of no elasticity, classified with Level 2 of Ueno Scale. The histopathologic result revealed some fibrotic tissue fragments (benign).

References: Department of Radiology, Health School - University of Algarve

Tables have been prepared in order to simplify the data collection. These included the essential features that allowed classifying the lesions as to its benignity/malignancy in four strands of diagnostic. Through the observation and analysis of the images of the three imaging techniques, as well as the proper completion of the tables mentioned above, it was concluded that the lesions studied were benign or malignant.
All images in study were evaluated by an experient Radiology Doctor. The data collected were used exclusively in this work, being safeguarded the identity of the patients that are part of the sample, ensuring their anonymity and confidentiality.

**A) Mammography**

All patients had mammograms. There were realized basic Cranio-Caudal (CC) and the Mid-Lateral Oblique (OML) projections, which allow the demonstration of external and internal quadrants, upper and lower quadrants and infra-mammary angle, respectively. Other supplementary views were made when there was a suspected lesion.

Mammography Images are analyzed according to the Breast Imaging Reporting and Classification Data System (BI-RADS) of the American College of Radiology (ACR). Through this it's possible to standardize any mammographic terminology used in the report, making it clear, concise and easily understandable [9].

**B) U.S. B-mode and Elastossonografía**

The images of B-mode U.S. and U.S. Elastography were obtained using echographs with a high frequency linear transducer. Frequencies ranged between 7.5 MHz and 14 MHz depending on the depth of the lesion and the thickness of the breast. The acquisition technique varies between patients, the lesion location, indications and type of the lesion. The sonographic findings were documented in two orthogonal planes (longitudinal and transverse), in order to check all its features [4].

Selected the U.S. Elastography mode, the color gamut is superimposed on the B-mode image [6]. Both images are shown simultaneously on the screen in real time echograph, and the B-mode image is represented at the left and the elastogram is shown on the right.

Regarding U.S. Elastography, measurements were made before and after uniform compression of tissues, to assess the multidirectional deformation of suspect breast tissue.

The evaluation of the images of B-mode U.S, like the mammogram is performed according to the Classification of ACR BI-RADS. Already the images obtained by U.S. Elastography, namely the elastic properties of tissues are analyzed qualitatively by the UENO Elasticity Scale, which is composed of five levels (figure 2) [10]:

- Level 1 - lesion uniformly elastic, shaded green. One example of a variance is the diagnostic image of a cyst (1*) in which are shown three layers (blue, green and red);
• Level 2 - essentially elastic lesion with some areas of no elasticity, characterizing by a mosaic pattern of blue and green;

• Level 3 - elasticity on the periphery of the lesion and absence of it in the central region, verifying a shaded green in the periphery and blue within the lesion;

• Level 4 - lack of elasticity in the entire lesion, being viewed with a blue fill;

• Level 5 - lack of elasticity not only throughout the lesion but also in the surrounding tissues, visualizing a blue region more extensive than the injury itself.

**Fig. 2:** Ueno Scale, where are represented, schematically, the elasticity levels
Levels assigned by U.S. Elastography can be compared to the BI-RADS classification. Levels 1 and 2 of the Ueno Scale correspond to category 2 of the BI-RADS classification. The remaining levels of the Ueno Scale have a one-to-one correspondence with the BI-RADS classification [6]. Thus, level 1 of U.S. Elastography represents negative findings for malignancy, level 2 displays benign findings and level 3 shows probably benign findings. Level 4 shows findings suspicious of malignancy and level 5 represents findings highly suspicious for malignancy [11]. It could be said, therefore, that the level of elasticity of a lesion is closely correlated to the category of BI-RADS, in that low levels of elasticity correspond to higher categories of the referred classification. The opposite is also true [12].

C) Histology

The histopathological results were available for all users. The biopsies were Ecoguide and performed by Percutaneous Fine Needle Aspiration (FNA) on 9 users (75%) and by Percutaneous Thick Needle Biopsy Stereotaxic with Automatic Booster - Core Biopsy on 3 users (75%). Samples were taken and analyzed histopathologically in laboratory.

D) Statistical Analysis

The results were analyzed using the software Microsoft® Excel 2010 and Statistical Package for Social Sciences (SPSS) 20.0 V®.

With the software Microsoft Excel 2010® were calculated Sensitivities, Specificities, Positive Predictive Values (PPV) and Negative Predictive Values (NPV) for the three imaging techniques.

With the SPSS® 20.0 V, were calculated central tendency measures (mean) and dispersion measures (standard deviation). It was also constructed a Receiver Operating Characteristic curve (ROC) for all diagnostic methods in which are represented the values of sensitivity in the ordinate axis and on the abscissa the values of 1-specificity for all cutoffs set. The knowledge of the area under the curve allows to quantify the accuracy of diagnostic tests. It was also calculated the T-Test for the equality of means, considering an alpha of 0.05.
Results

The study sample is constituted by 12 female patients, who had a mean age of 54.8 ± 10.4, ranged between 43 and 73 years. The breast lesions were evaluated through Mammography, the B-mode U.S. and U.S. Elastography. The Histology Results of the lesions was obtained in all users and there was identified 6 benign and 6 malignant. These showed a mean size of 15.1 mm ± 10.6 mm and 13.8 mm ± 3.8 mm, respectively.

In order to quantify the lesions detected by diagnostic techniques in the study, frequencies were calculated according to the scores. Mammography identified 3 lesions classified as BI-RADS 3, 5 lesions with BI-RADS 4b and 4 lesions with BI-RADS 4c. B-mode U.S. detected 4 lesions classified as BI-RADS 3, 1 lesion with BI-RADS 4a, 2 lesions with BI-RADS 4b and 5 lesions with BI-RADS 4c. U.S. Elastography identified 7 lesions quantified with Level 2, a lesion with level 3 and 4 lesions with level 4.

Aiming to identify the number of benign and malignant lesions correctly diagnosed by imaging techniques, based on the Histology Results, there were calculated frequencies. Mammography correctly identified 9 of the 12 lesions in the study (3 lesions with BI-RADS 3, 3 lesions with BI-RADS 4b and 3 lesions classified as BI-RADS 4c). B-mode U.S. correctly identified 7 of the 12 lesions studied (4 lesions with BI-RADS 3, 1 lesion with BI-RADS 4a, 1 lesion with BI-RADS 4b and 1 lesion with BI-RADS 4c). Finally, U.S. Elastography correctly identified 10 of the 12 study lesions (5 lesions with level 2, 1 lesion with level 3 and 4 lesions with level 4).

Thus, to better understand the diagnostic accuracy of the techniques in the study, we calculated the respective sensitivities, specificities, PPV and NPV for Mammography, Ultrasound B-mode and U.S. Elastography (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>100%</td>
<td>50%</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>B-mode U.S.</td>
<td>100%</td>
<td>71%</td>
<td>71%</td>
<td>100%</td>
</tr>
<tr>
<td>U.S. Elastography</td>
<td>67%</td>
<td>83%</td>
<td>80%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Table 1: Sensitivity, Specificity, PPV and NPV of imaging techniques in the study.
To quantify the performance of imaging techniques in study, the ROC curve was constructed, representing the values of the sensitivity in the Y axis and 1-specificity values in the X axis (Figure 3).

According to Figure 3, the area under the ROC curve calculated in Mammography was 0.792, B-mode U.S. showed a value below the ROC curve of 0.847. Finally, U.S. Elastography showed an area under the ROC curve of 0.806.

Fig. 3: ROC curve of the imagiologic techniques.

Regarding to U.S. Elastography were also calculated the means and respective standard deviations of UENO classification for benign and malignant lesions. There was a mean of 2.17 ± 0.408 for benign lesions and a mean of 3.33 ± 1.033 for malignant lesions. In order to test whether the mean UENO classification for malignant lesions is significantly
higher than the mean UENO classification for benign lesions was applied T-Test for the equality of means, obtaining a value p <0.05, reaching a higher mean value with statistical significance in UENO classification for malignant lesions.
Conclusion

Knowing that the incorrect diagnosis of breast pathologies is often directly related to the errors at the level of perception of lesions by the examiner, it is crucial to verify the diagnostic ability of the methods under study in detection of true positives (sensitivity) and true negative (specificity).

Previous studies demonstrate a low sensitivity and a high specificity of U.S. Elastography in respect to B-mode U.S. [6, 7, 14]. Regarding to Mammography, there is still little information respecting to the calculation of sensitivity and specificity in comparison with other imaging techniques.

In this study, Mammography had a sensitivity of 100%, a specificity of 50%, a PPV of 67% and a NPV of 100%; B-mode U.S. demonstrated a sensitivity of 100%, a specificity of 71%, a PPV of 71% and a NPV of 100%; the U.S. Elastography showed a sensitivity of 67%, a specificity of 83%, a PPV of 80% and NPV of 71%. This is in agreement with previous studies, concerning to the low sensitivity and high specificity of U.S. Elastography in relation to B-mode U.S. In the study by Thomas et al. 2006, Mammography had a sensitivity of 87%, a specificity of 85%, a PPV of 89% and an NPV of 83%; B-mode U.S. achieved a sensitivity of 94%, a specificity of 84%, a PPV of 81% and NPV of 95%; U.S. Elastography showed a sensitivity of 82%, a specificity of 87%, a PPV of 83% and NPV of 86% [6]. It is concluded from this study that U.S. B-mode showed greater sensitivity, U.S. Elastography showed a greater specificity, Mammography showed an increased PPV while B-mode U.S. showed a higher NPV. Again, the sensitivities and specificities of B-mode U.S. and U.S. Elastography are consistent with earlier studies. The study by Lee et al. (2011) obtained in B-mode U.S. a sensitivity of 95.8%, a specificity of 23.7%, a PPV of 19.2% and an NPV of 97.3%; U.S. Elastography already obtained a sensitivity of 93.8%, a specificity of 45.7%, a PPV of 23.7% and an NPV of 97.6% [14]. Again the results coincided with earlier studies, although the U.S. Elastography had a similar sensitivity of US B-mode. Also in the study by Mansour & Omar (2012), there was obtained the values of sensitivity, specificity, PPV and NPV for B-mode U.S., which accounted for 89.7%, 86.2%, 81.4% and 92.6% respectively; U.S. Elastography obtained a sensitivity of 92.3%, a specificity of 74.1%, a PPV of 70.6% and a NPV of 93.4% [15]. Contrary to previous studies, there was verified the presence of a higher sensitivity and a lower specificity relatively to B-mode U.S.

In this study there was calculated the mean of UENO classification of U.S. Elastography for benign and malignant lesions, had been obtained a mean of 2.17 ± 0.408 for benign lesions and a mean of 3.33 ± 1.033 for malignant lesions. Then was made the T-Test for the equality of means. It was obtained a p value <0.05, statistically confirming the significant difference of the mean values of the lesions studied. In the study by Lee et
al. (2011), malignant lesions were studied with a mean classification of 3.02 ± 1.33 and benign lesions a mean classification of 1.72 ± 0.78. The p-value (<0.001) was less than the alpha, there is also a significant difference between the mean values of malignant and benign lesions [14]. Thus, these results are consistent with those obtained in the present study.

The ROC curve is shown as a powerful tool for quantifying the performance of imaging techniques. The areas under the ROC curve of the Mammography, B-mode U.S. and U.S. Elastography were 0.792, 0.847 and 0.806, respectively. According to the classifications given to areas of the ROC curves, the Mammography showed a reasonable performance, whereas the performance of the B-mode U.S. and U.S. Elastography was rated as good. It can be seen that the values obtained by B-mode U.S. and the U.S. Elastography are very similar and can assert themselves through this analysis that both have a similar diagnostic performance. Thus, this result doesn't meet some previous studies, in which U.S. Elastography showed an area under the ROC curve greater than the area under the ROC curve of B-mode U.S. Lee et al. (2011) obtained an area under the ROC curve of U.S. B-mode (0.616) lower than the U.S. Elastography (0.784), showing these a poor and reasonable performance, respectively [14]. The study by Schaefer et al. (2009) showed areas under the curves of B-mode U.S. and U.S. Elastography of 0.820 and 0.884, respectively [13]. Again the area of U.S. Elastography was superior compared to the remaining technique in the study. In this study, both diagnostic techniques showed good performance.

With this study it can be concluded that although the U.S. Elastography presents a good diagnostic sensitivity and high specificity in differentiating benign and malignant lesions, isn't yet possible to reduce the number of breast biopsies performed today. This statement is due to the fact that it was obtained several false negatives and false positives. Although the methods under study don't have equal sensitivities and specificities for the same lesions, their combination can clearly improve the diagnostic accuracy of breast lesions. As the main limitation of this study, it can be enumerated the reduce sample conditioned by the poor number of breast biopsies performed during the period of data collection. As future recommendations, the authors suggest that prospective studies are elaborated with larger samples and in different hospitals.
References


