

Elastography as a Method for the Detection of Breast Cancer

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Abstract

Breast cancer is a disease characterized by the increase and lack of control in the growth of mammary epithelial cells. In recent years, research has been carried out on new technologies with the aim of being more precise and less radical in the methods used for the diagnosis of breast cancer, where a new use of ultrasound based on the properties of elastic tissues emerged, a technology that uses the name of elastography, which greatly improves the accuracy of diagnosis, the development and application of elastography in the breast, it has made it possible to characterize the elasticity of lesions detected by B-mode (fundamentally nodules) and in certain cases to raise or lower the degree of suspicion of lesions initially assessed by B-mode and color doppler, for breast cancer, has been shown that elastic ultrasound provides information on prognosis and response to neo adjuvant therapy, considering that cancer breast is a heterogeneous disease. Prognostic factors are represented by histological type, tumor size, histological grade, axillary lymph node metastasis and lymphatic vascular invasion, considering the above, when using this technique for early diagnosis, assess prognosis and grade of malignancy of the patients, thus achieving timely treatment which will allow a decrease in the morbidity and mortality of these patients.

Key words: Elastography; Breast cancer detection; Breast cancer; Mammary epithelial cells

Introduction

Breast cancer is a disease characterized by an increase and lack of control in the growth of mammary epithelial cells, it represents one of the main causes of death in women, many of these cancers are discovered by tumors found incidentally by the patient or on routine physical examination and in more advanced cases with manifestations such as fixation of the mass to the chest wall or overlying skin, satellite nodules or skin ulcers, skin edema caused by intrusion of cutaneous lymphatics (skin of orange), the usually exaggerated skin marks, the fixed or hard axillary lymph nodes indicate the spread of the tumor and the presence of inflammation of the superior or subclavian lymph nodes, associated with risk factors such as age, gynecological, family history, diet, radiotherapy and genetic changes associated with the appearance of breast cancer, according to statistics it is established that one every ten women will develop breast cancer at some point in her life, however, with the current increase in the use of mammography and ultrasound, it has allowed an increase in breast cancer diagnoses in less serious stages [1].

In recent years, research has been carried out on new technologies with the aim of being more precise and less radical in the methods used for the diagnosis of breast cancer, where a new use of ultrasound based on the properties of elastic tissues emerged. A technology that uses the name of elastography, which greatly improves the accuracy of diagnosis, first described in 1987 by Krouskop, based on the theory that soft tissues in the

presence of malignancy present alterations and morphological changes leading to a deformation process.

The development and application of elastography in the breast has made it possible to characterize the elasticity of lesions detected by B-mode (fundamentally nodules) and in certain cases raise or lower the degree of suspicion of lesions initially assessed by B-mode and color doppler [2].

This method has proven to be useful by adding information on the structure of the breast cancer property to morphological data provided by grayscale ultrasound, it is a method used to evaluate the level of hardness or elasticity of a section of an organ or nodule, through the tension and compressibility produced by the ultrasound waves in the body's tissues in real time.

Elastography features of breast nodules provide additional tools for morphologic features, which can improve diagnostic specificity and efficiency. The greatest utility of elastography has been shown in lesions classified as Bi-Rads 3 (possibly benign lesions), elastography is also more useful in circumscribed cancers and are categorized as possibly benign B-mode lesions. These localized cancers can be identified as suspicious by 2D-SWE, thus subsequently recommending a biopsy, considering the breast to be suspicious. These lesions found by this technique are classified using a scale, the most used elasticity scale is the UENO, which defines a score or score between 1 and 5, which has greater elasticity when there is no elasticity. Lesions with a score between 1 and 3 are considered benign, if the score is 4 or 5, it is considered malignant [3].

There are two main types of elastography, quantitative (shear-wave) and qualitative (strain). Quantitative elastography sends micropulses to measure tissue displacement independent of applied acoustic pressure with minimal energy levels for different tissues. So, it creates an organization chart of displacement relative to adjacent structures. Qualitative techniques indicate the existence of hardness in the area of interest. These qualitative parameters focus on showing relative hardness between different areas, that is, they separate the hard from the soft tissues and can distinguish the presence of a lump. The information obtained is presented by means of contrast images on a scale of colors that indicate hardness and softness. This diagnostic alternative is 100% effective when there is no cancer, which avoids unnecessary biopsies and it is 92% effective when the cells are malignant. In the latter three, a biopsy is recommended [4].

Elastography should not be used to avoid biopsy of nodules classified as BI-RADS 4B or C or BI-RADS 5 (highly indicative of malignancy), nor should it be recommended for nodules classified as BI-RADS 2 (usually benign). For breast cancer, elastic ultrasound has been shown to provide information on prognosis and response to neoadjuvant therapy, considering that breast cancer is a heterogeneous disease. Prognostic factors are represented by histological type, tumor size, histological grade, axillary lymph node metastasis and lymphatic vascular invasion, considering the above, when using this technique for early diagnosis, assess prognosis and grade of malignancy of the

patients, thus achieving timely treatment which will allow a decrease in the morbidity and mortality of these patients [5].

Materials and Methods

To carry out this article, a bibliographic search was carried out in various databases such as Elsevier, Scielo, Medline, PubMed, ScienceDirect and Ovid, thus selecting original articles, case reports and bibliographic reviews from 2008 to 2021, but more extensive bibliographies were used. Old 2000-2007 due to its weight and information necessary to carry out this work, in Spanish and English using MeSH terms: Elastography, breast cancer detection, breast cancer. Thus including all the documents that will deal with elastography as a method for the detection of breast cancer and information related to it, the data found were between 15-40 records, thus using 30 articles for the preparation of this document [6].

Results

Santos Aragon, et al., have compared the use of conventional ultrasound versus elastography in the mammary gland with respect to a benign solid nodule and a malignant nodule. Where it was observed that, in a benign nodule, such as fibroadenoma, with elastography, it is observed as an area of greater rigidity typically smaller than the limits of the lesion. In elastography it is visualized with a bull's-eye appearance, bright posterior enhancement or with an aliasing effect. In addition, a complicated cyst can be differentiated from a solid mass, the propagation of shear waves does not occur in cysts, in which it provides values of zero (Figure 1) [7].

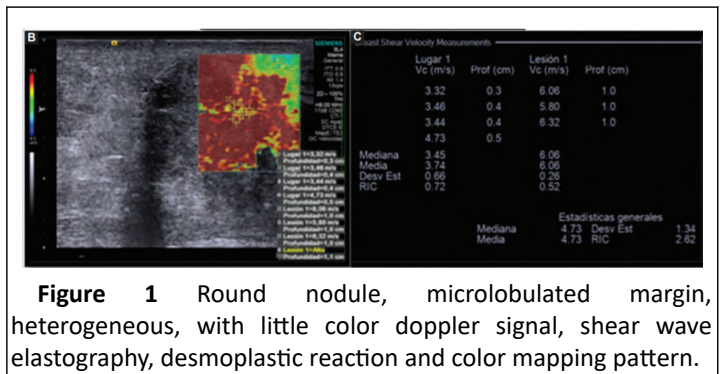


Figure 1 Round nodule, microlobulated margin, heterogeneous, with little color doppler signal, shear wave elastography, desmoplastic reaction and color mapping pattern.

In a study of 101 confirmed invasive breast cancers, Evans, et al. They showed that high mean stiffness on shear wave elastography was significantly correlated with high histologic grade, large invasive size, nodal involvement and vascular invasion (Figure 2).



Figure 2 Ultrasound with elastography showing an index of 17 of the studied nodes, suggestive of axillary involvement. B-mode image showing a rounded node with thickening of its cortex and loss of its central hilum, findings suggestive of axillary involvement, which was later shown to have tumor involvement.

In a study carried out in 2013 with 24 women, it was found that the frequency of axillary metastatic disease was 50%, finding 17 patients with positive elastography and 12 with confirmed histopathological involvement. The sensitivity of elastography in this study was 100% with a specificity of 58% and the combined use of elastography and ultrasound demonstrated a sensitivity and specificity of 100% [8].

Equivalence between the BIRADS classification and the UENO classification has been established in different studies, considering the cut-off point between benign/malignant lesions between elastographic scores 3 and 4. The results of the mean scores of benign and malignant lesions in the different published series are similar (they range between 4.2 and 3.9 for malignant cases, between 2.1 and 1.8 for benign cases and between 3.7 and 3.3 for ductal carcinoma *in situ*) and in all cases it is stated that these differences in elasticity between benign and malignant lesions are significant. Equivalence with the BI-RADS classification is made considering that BI-RADS 2 lesions correspond to elastography scores 1 and 2 and the rest of the lesions correspond unequivocally to elastography scores (Figure 3).

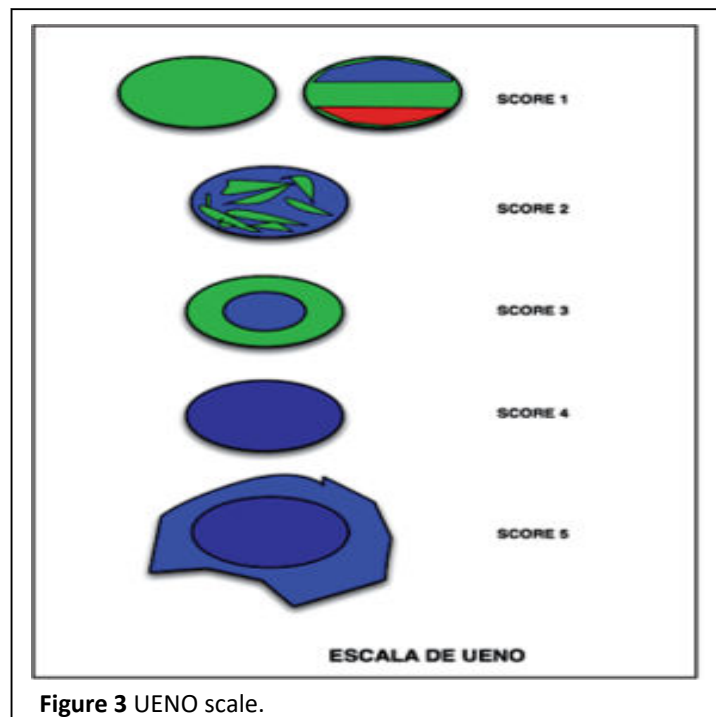


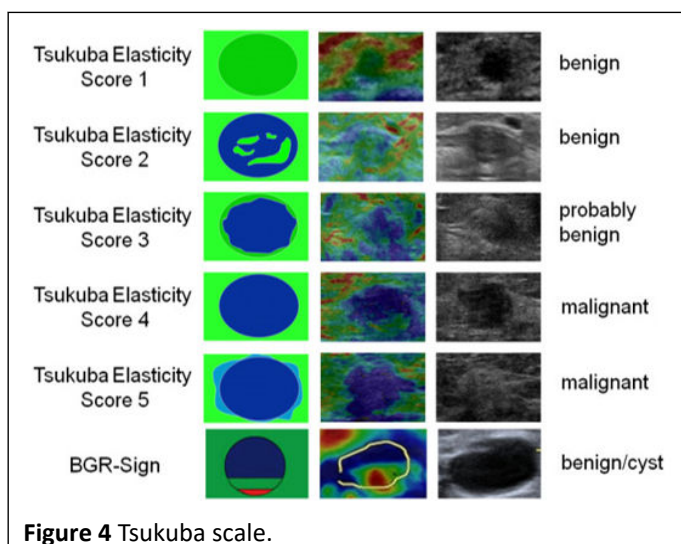
Figure 3 UENO scale.

Diagnostic validity analyzes of elastosonography compared to ultrasound indicate that the technique shows equal or better results than B-mode ultrasound. The specificity values of elastography are usually better than those of B-mode ultrasound, which is why many authors propose that elastography improves the rates of false positive results of B-mode ultrasound. The comparison of the diagnostic performance of both techniques is limited by the fact that the elastographic image is always superimposed on the B-mode image, introducing an interpretation bias [9].

In a meta-analysis carried out in 2018, it was found that the main use of introducing elastography in clinical practice could be to reduce the number of unnecessary biopsies. These pose a problem for the patient, even from an emotional point of view, in addition to an economic cost for health systems. Other indications for elastography in breast cancer described in the literature could be the evaluation of the intraductal component of the cancer because it does not present as a mass, the evaluation of the response to neoadjuvant chemotherapy and the study of axillary lymphadenopathies for which elastography in real time it seems more sensitive than palpation and ultrasound. In this meta-analysis, 8 meta-analyses published between 2011 and 2017 were included. They have studied different forms of elastography, from compression elastography and real-time elastography to various quantitative modalities. The number of patients included in the studies ranged between 1,245 and 5,397 and the number of breast lesions between 1,408 and 5,838. In all of them, the presence of great heterogeneity between studies was detected. The diagnostic parameters were calculated for the different qualitative and quantitative techniques and depending on the way of interpreting the test (color pattern, SR, length ratio) and have ranged from 0.83 to 0.94 for the added sensitivity, for the aggregate specificity between 0.81 and 0.93 and the area under the SROC curve between 0.84 and 0.96. In general, no significant

differences were found between the diagnostic capacity of the different elastographic techniques [10].

Elastography can be seen as a method used to make diagnoses, based on ultrasound, it allows evaluating the elasticity or rigidity of a fragment of an organ or nodule that is subjected to study, focusing on the tension and compressibility produced by pressure with the transducer and changes of the ultrasonic waves of the tissues of the evaluated organ. This technique can be considered as innovative in ultrasonography, it allows studying the hardening of a tumor, using quantitative values expressed in numerical units called kilopascal (kPa). Establishing an estimate of stiffness in the examined nodule, depending on the number of kPa, which increases the specificity; elastography can be applied to any type of body structure that can be compressed, five degrees of elasticity are estimated on the tsukuba scale, qualitative elastography of mammary masses (Figure 4).



Elastography has higher specificity but lower sensitivity than B-mode images when evaluated separately. A meta-analysis of the Tsukuba score of 29 studies using a cutoff between three and four in 5,511 breast tumors found a mean sensitivity and specificity of 79% and 88%, respectively. In another meta-analysis of nine SR studies in 2087 tumors, the mean sensitivity and specificity were 88% and 83%, respectively. SWE and pSWE have shown good sensitivity and specificity in differentiating benign from malignant breast lesions in a recent meta-analysis [11].

Several studies have reported the diagnostic benefits of combining B-mode imaging with SE or SWE, but the combinations have not been performed consistently. Therefore, a recommendation or guideline on how to combine elastography and BI-RADS scores is not yet available. By combining elastographic evaluations with B-mode BI-RADS scoring, either sensitivity or specificity can be improved compared to B-mode imaging alone, depending on the method of combining the two diagnostic tests. When elastographic evaluations are used to alter the initial BI-RADS classifications,

primarily class 3 and class 4 are considered for re-evaluation, as these are the BI-RADS classes with the highest number of false negatives and false positives, respectively. Combining B-mode imaging with elastography can improve the specificity of breast tumor evaluation, which is low on the BI-RADS score, without significantly lowering sensitivity (Figure 5).

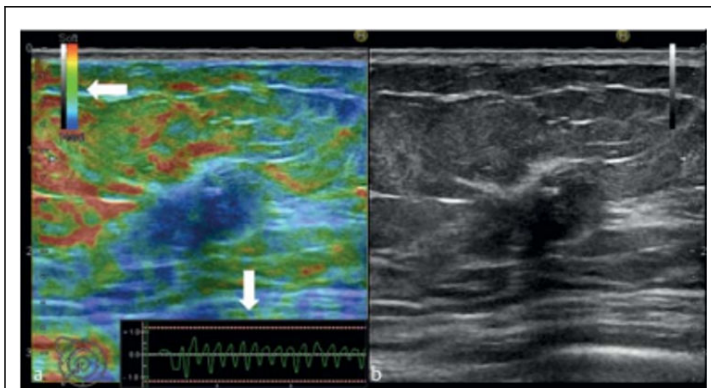


Figure 5 SE image of a malignant breast tumor. The strain image is displayed as an overlay on the B-mode image and the B-mode image is displayed alongside the elastogram. The color bar shows the qualitative color scale, from red to yellow and green to blue. The quality indicator shows the manual applied relative to the displacement of the transducer.

It should ideally be between the two red dots. The rate of compressions can be seen on the x-axis, where the distance between the two white markers is one second. The tumor is blue on the elastogram, while the surrounding tissue is red, yellow and green (mild and intermediate stiffness). On B-mode image, a 17 mm, nearly oval, hypoechoic tumor with irregular borders, calcifications, mild shadowing and invasion of surrounding adipose tissue and Cooper's ligament is seen. The tumor was classified as BI-RADS 5. Histopathology showed invasive ductal carcinoma.

In a 2019 study where a total of 373 were included, 196 had benign lesions and 177 had malignant lesions based on pathology results. Detailed demographic and pathologic types of lesions. When the TS and SR values of malignant and benign breast lesions were analyzed, we found that malignant lesions usually had higher TS ($p < 0.001$) and RS ($p < 0.001$) than benign lesions. SR demonstrated significantly better performance than TS in distinguishing malignant from benign lesions. The AUCs for TS and SR were 0.902 and 0.995, respectively. Strain elastography achieved a sensitivity of 96.0%, a specificity of 98.5%, a positive predictive value of 98.3% and a negative predictive value of 96.5% in differentiation. Meanwhile, with the best cutoff value at 2.5, the TS yielded a sensitivity of 93.8%, a specificity of 80.6%, a positive predictive value of 81.4% and a negative predictive value of 93.5% in the differentiation between benign and malignant tumors (Table 1).

Table 1. Patient demographics, histopathologic diagnosis and imaging biomarkers for patients with benign breast and malignant lesions (n=373).

Characteristics	Benign (n=196)	Malignant (n=177)	P value
Age (years)	49.9 ± 11.5	50.6 ± 10.9	0.54
Final diagnosis; n (%)			
Fibrocystic changes	9 (4.6)	-	-
Plasma cell mastitis	39 (19.9)	-	-
Introductal papilloma	23 (11.7)	-	
Fibroadenoma	57 (33.3)	-	
Mastopathy	48 (25.1)	-	
Sclerosing mastopathy	20 (10.0)	-	
Infiltrating ductal carcinoma	-	76 (42.9)	
Malignant phyllodes tumor	-	20 (11.3)	
Mucinous carcinoma	-	16 (9.0)	
Invasive lobular carcinoma	-	65 (36.7)	
TS	1.86 ± 0.98	3.63 ± 0.77	<0.001**
SR	1.67 ± 0.51	4.8 ± 2.55	<0.001**

Discussion

Technological advances have been developed in the three methods mentioned, which has allowed an improvement in the detection, characterization, management of injuries and follow-up of patients. Breast ultrasound is widely used as a diagnostic tool to characterize nodules detected on mammography, evaluation of palpable areas, suspicious discharge through the nipple and guidance for invasive procedures. At the same time, we can observe that, in addition to ultrasound, the development and application of elastography in the breast has made it possible to characterize the elasticity of the lesions detected by means of B mode, where we mainly look for nodules and in certain cases, raise or lower the degree of suspicion of lesions initially. Assessed by B-mode and color doppler.

Physical examination of the breast by palpation can guide towards benign and malignant pathology, since breast cancer is harder and more fixed than the adjacent normal breast parenchyma, unlike benign lesions that are soft and mobile. Although breast palpation can guide, it is sometimes difficult to reproduce and its main limitation is based on its low sensitivity and diagnostic accuracy.

Elastography is a useful, fast and non-invasive method in the diagnosis of breast lesions. The primary use of elastography in the breast is as an adjunct to conventional ultrasound to improve differentiation between benign and malignant lesions and several studies attest to the value of EUS in refining breast imaging reporting data system scoring. US breast to avoid

unnecessary biopsies. The technique is easy to learn, reproducibility is better than with B-mode ultrasound and fits well into standard examination protocol. It is also useful to confirm that a lesion is a cyst when the content is echogenic. We proposed a practical examination protocol for strain elastography and ARFI to avoid sonographer dependency, while providing images, which are useful in differentiating benign from malignant breast lesions [12].

Breast elastography is a modality that helps in the diagnosis after the identification of changes in the mammography, it is also used as mammographic screening in symptomatic patients under 40 years of age and also as a complementary method to mammography, especially in young patients or with dense breasts. This breast study has the advantages of being a widely available method that does not require radiation or contrast and is well tolerated by patients. A meta-analysis carried out by Xue et al., showed high sensitivity and specificity values for this type of evaluation, 85% and 89%, respectively. Despite this, there is great heterogeneity regarding the ideal cutting bridges to differentiate between benign and malignant breast masses. In addition, breast cancer is a heterogeneous disease, with several differences depending on the histological type found. These findings demonstrate the need to investigate the effectiveness of elastography in patients with breast nodules. Taking this into account, the objective of the present study is to evaluate the effectiveness of elastography to differentiate the histological types of nodules and to compare its effectiveness with the BI-RADS classification.

In a study Letman, et al., they evaluated 82,980 routine mammograms and compared category 3 cases that progressed to malignancy with those that were truly benign after 3 years of radiological follow-up. Of the 1,711 cases classified as BIRADS 3, 2.1% of the total and the 82,898 routine mammograms, 150 were malignant, with a predictive value of malignancy (PPV) of 8.8%. However, after careful review of the 150 cases that were initially classified as B3 and progressed to malignancy, only 20% of the lesions actually met the clearly defined morphologic criteria for this category. Graf, et al., in a study with 450 solid nodules and morphological characteristics of category 3, observed a PPV of only 0.2%. Early diagnosis of breast cancer has been shown to reduce the risk of death by providing a better chance of identifying a treatment. In general, palpation, ultrasound and mammograms are the most common forms of diagnosis.

However, ultrasound elastography currently plays a vital role in the process of diagnosing breast cancer. Computer-aided diagnosis using a combination of ultrasound (B-mode) and elastography images show a marked superiority over other digital imaging techniques due to their accurate classification of lesions. Machine learning makes use of mathematical and statistical methods and thus establishes models to learn from the data. This method finds an important role in biomedical applications in which the precision of these algorithms help in the early diagnosis and measurement of pre-malignant lesions and in making an early approach [13].

Conclusion

Physical examination of the breast by palpation can guide towards benign and malignant pathology, since breast cancer is harder and more fixed than the adjacent normal breast parenchyma, unlike benign lesions that are soft and mobile. Although breast palpation can guide, it is sometimes difficult to reproduce and its main limitation is based on its low sensitivity and diagnostic accuracy. Elastography is a useful, fast and non-invasive method in the diagnosis of breast lesions. The primary use of elastography in the breast is as an adjunct to conventional ultrasound to improve differentiation between benign and malignant lesions and several studies attest to the value of EUS in refining breast imaging reporting data system scoring. US breast to avoid unnecessary biopsies. The technique is easy to learn, reproducibility is better than with B-mode ultrasound and fits well into standard examination protocol. It is also useful to confirm that a lesion is a cyst when the content is echogenic.

There are two main types of elastography, quantitative (shear-wave) and qualitative (strain). Quantitative elastography sends micro pulses to measure tissue displacement independent of applied acoustic pressure with minimal energy levels for different tissues. So, it creates an organization chart of displacement relative to adjacent structures. Qualitative techniques indicate the existence or absence of hardness in the area of interest. These qualitative parameters focus on showing relative hardness between different areas, that is, they separate the hard tissues from the soft ones and can distinguish the presence of a lump. The information obtained is presented by means of contrast images on a scale of colors that indicate

hardness and softness. This diagnostic alternative is 100% effective when there is no cancer, which manages to avoid unnecessary biopsies and it is 92% effective when the cells are malignant. In the latter three, a biopsy is recommended. In addition, the elastography in breast cancer described in the literature could be the assessment of the intraductal component of the cancer because it does not present as a mass, the assessment of the response to neoadjuvant chemotherapy and the study of axillary lymphadenopathies for which elastography in time real seems more sensitive than palpation and ultrasound.

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