



US Elastography – Chapter 1

Principles and Applications in Breast Imaging

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Summary

Ultrasound (US) elastography is one of the most recent and interesting radiological methods for non-invasive evaluation of breast masses. The specified technique significantly improves the characterization of breast masses by helping to accurately "downgrade" and "upgrade" BI-RADS B3 and B4A lesions. International practice guidelines point out the importance of a comprehensive theoretical and practical training in the application of elastosonography with high accuracy and repeatability, and in minimizing intra and inter-operator variability. In this context, users should be thoroughly familiar with technical

steps and adjustments, maneuvers and limitations before starting US elastography on actual patients. The elastography technique is highly subjective and requires a long learning curve. Therefore, the users' guidance, which includes one-to-one training and monitoring of the technique and its application by a very experienced user, is vital. The aim of this article is to convey the necessary knowledge and experience about the use of US elastography in the diagnosis of breast masses to future users in a well-structured and targeted manner.

Introduction

Breast cancer is the most common cancer in women of all races^[1]. To give an example, in the United States of America (USA), roughly 1/8 of women will develop an invasive breast cancer during her life^[2]. However, the mortality of breast cancer has decreased rapidly after 1989, for a total decline of 39% through 2015^[2]. This decline is primarily attributed to improvements in early diagnosis and treatment^[3].

Today, almost 90% of breast masses can be detected clinically or radiologically. However, more than 80% of surgically removed masses are eventually proved to be benign^[4]. Therefore, the American College of Surgeons (ACS) and the American Society of Breast Surgery (ASBS) recommend pre-surgical biopsy in all clinical/radiological masses.

Comprehensive scientific studies on conventional B-mode ultrasonography (US) for the diagnosis of breast cancer dates back to 1995. At that year, Stavros et al^[5], defined B-mode criteria for breast cancer. The diagnostic accuracy levels of those criteria have been the subject of many studies in the following years, and although they showed high sensitivity (98.4%) for breast cancer, it has been concluded that they were low in terms of specificity (67.8%)^[6]. The B-mode criteria, which were included in the BI-RADS classification in 2003 due to their high sensitivity levels, continue to cause many false positive results, despite the technological developments and scientific knowledge since then^[7]. Therefore, more than 1.6 million breast biopsies are continued to be performed annually in the USA^[8]. More than 75% of these biopsies are reported as benign in pathological examination.

The information presented above on the prevalence of breast masses and the efficiency of conventional imaging methods in the differential diagnosis clearly reveal the need for preoperative discrimination of benign and malignant masses with non-invasive, reliable and cost-effective methods. In this context, the main developments in US method in recent years are elasticity studies. Qualitative elasticity assessments were included in BI-RADS in 2015 as an "associated finding". However, the technique was mentioned not as an endorsement but as an acknowledgment in that classification system. This is because the technique and its results still require standardization, evidence and validation^[9].

US Elastography Technique

Elastography was first used as a US technique in 1998 by Krouskop et al.^[10]. Elasticity is the tendency of the tissue to resist deformation caused by an applied force. Elastography, as its name suggests, measures the elasticity of the tissue. The area of interest (ROI) selected for measurement is subjected to a compression force (stress) and the degree of distortion (strain) resulting from this force is assessed. During the application of force, stiff tissues are less deformed, that is they exhibit

less strain. Cancer tissue is harder than normal tissue and therefore has a lower strain value. It is believed that the stiffening process begins in the early stage of cancer^[11].

Measurements in US elastography are performed in special imaging modes that can detect tissue stiffness against the applied compression force. Several elastography techniques using different compression methods have been developed to date. Although these methods share the common name (i.e., elastography), they differ significantly in terms of theory, development and accuracy. Therefore, applications and terms for the use of techniques in diagnostic evaluation are also quite different from each other. These differences are detailed below.

Strain elastography (SE) technique

Internal or external vibration sources are used in strain imaging, which is the most basic technique. In the external method, the user applies manual pressure on the tissue with the US probe (Figure 1). This method is suitable for superficial organs (e.g., breast). In the internal method, the US probe is kept fixed and tissue displacement is created by internal (i.e., cardiovascular and respiratory) physiological movements. This method is suitable for deeply located organs (e.g., liver and sometimes breast). In both methods, the relative differences in tissue motion, that is the tissue displacement that develops in parallel with the applied stress, are calculated to estimate tissue deformation. Since the magnitude of the applied stress can be very difficult to control due to the variability inherent in manual compression and physiological movements, it is completely operator dependent and the results are not parametric, that is not quantifiable.

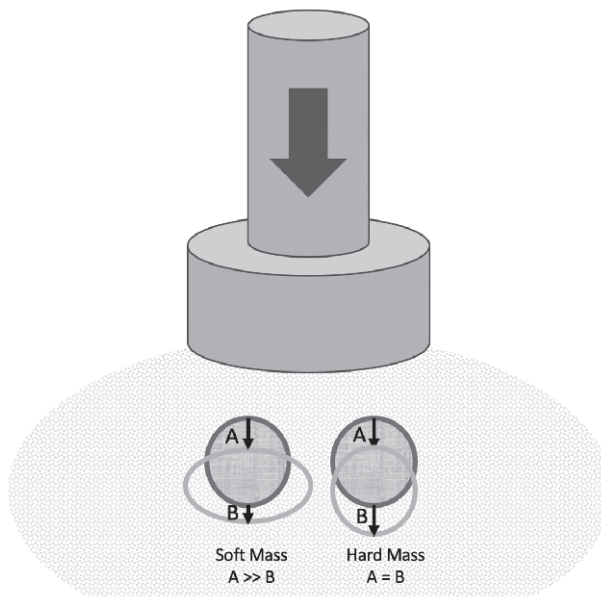


Figure 1. Deformations in soft and stiff masses during the application of external force on the skin with the probe in strain elastography

In SE, the calculations give a qualitative estimate of Young's coefficient (E) and thus tissue elasticity (stiffness). Strain measurements (deformation measurements) are displayed as a semitransparent colored map called an "elastogram" overlaid on the conventional B-mode image. In these maps, low strain (hard texture) is shown in colors close to red, while high strain (soft tissue) is represented by colors close to blue (Figure 2 A and B). However, there is no consensus on the shape of the colored scale. The specified scale varies from manufacturer to manufacturer and can be changed by users on some devices.

As mentioned above, quantitative evaluation is not possible in SE technique. In qualitative evaluation, the two most important criteria are size and stiffness. Size refers to largest diameter in B-mode and the elastogram. Tissues that are less compressible than surrounding tissues appear much larger in elastograms than they actually are. This situation leads to a mismatch in terms of tumor's size between B-mode and elastogram images. This discordance can be expressed as the ratio of lesion size in elastography to B-mode size (EI / B-mode ratio). The EI / B-mode ratio greater than 1 is suggestive of malignancy and, possibly, of desmoplastic reaction^[12] (Figure 2 C and D). The sensitivity of this criterion in distinguishing between benign and malignant breast masses is 98% and its specificity is 72%. In this context, the SE technique has equal sensitivity and slightly higher specificity than the B-mode technique. However, it should be kept in mind that this evaluation method gives false positive results in dense breasts. Since the EI / B mode ratio is an indirect indicator of tissue stiffness, it is significantly affected by the grade of the malignancy. Accordingly, the higher the grade of the tumor, the higher the EI / B-mode ratio^[13] (Figure

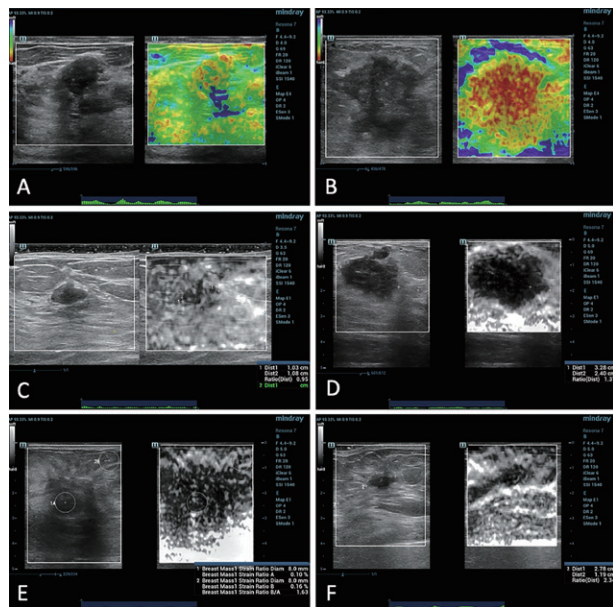


Figure 2 (A-F). Strain elastographic studies. In color images, soft tissues such as fibroadenoma are represented in blue (A), and hard tissues are represented nearly red (B). However, gray scale maps should be preferred, especially in evaluating the size mismatch. In these maps, the dimensions of benign tissues such as fibroadenomas are the same or smaller (C) than those in B-mode images, and the size of malignant masses is larger (D-F). The discordance in diameter is proportional to the degree of malignancy of the mass. The higher the grade, the greater the EI / B mode ratio. The EI / B mode ratio was calculated as 1.37 (D) for IDC grade II, 1.62 (E) for IDC grade III and 2.34 (F) for invasive lobular carcinoma in these examples.

2 D and F). This ratio is less than 1.5 for mucinous carcinoma, in situ ductal carcinoma (DCIS) and invasive ductal carcinoma (IDC) grade I; about 1.5 for IDC grade II; and is greater than 1.5 for IDC grade III and invasive lobular carcinoma^[13] (Figure 3).

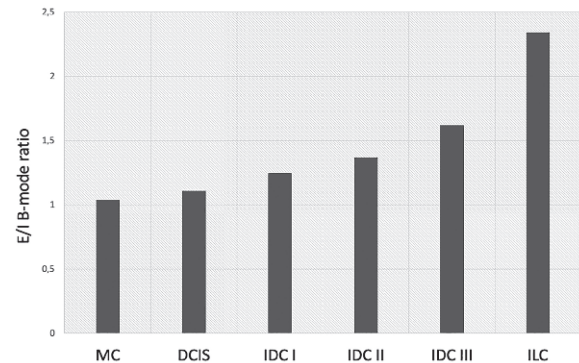


Figure 3. Representative EI / B mode ratios for various tumor types and grades. MC: Mucinous carcinoma, DCIS: Ductal carcinoma in-situ; IDC: Invasive ductal carcinoma (Karakas HM and Yildirim G, unpublished study).

The size and stiffness assessments mentioned above were standardized and categorized with a scale called Tsukuba (elasticity) score. This 5-point color scale is based on the assessment of lesion stiffness relative to the background tissue stiffness [14]. The scale is as described above: (1) Less than or equal stiffness to the surrounding tissue, (2) Mixed areas of stiffness compared to the surrounding tissues, (3) Stiffer than the surrounding tissue and is a smaller size on the elastogram, (4) Stiffer than the surrounding tissue and is the same size on the elastogram, (5) Stiffer than the surrounding tissue and is larger in size on the elastogram. The scale can be simply expressed as follows: (1) Soft, (2) Mixed, (3) Stiff-Small, (4) Stiff-Equal, (5) Stiff-Large. High scores on the Tsukuba scale indicate a high probability for malignancy. If the score is between 1 and 3, the lesion is likely benign. If the score is between 4-5, a biopsy should be performed for tissue diagnosis (Table 1). The sensitivity, specificity and accuracy values of the Tsukuba score were reported as 86.5%, 89.9%, and 88.3%, respectively^[14]. However, the evaluation is completely subjective, as stated in the section on the technique of SE. The scoring cannot be used in tumors large enough to fill the imaging window and in deeply located lesions, due to the lack of normal tissue for comparison within the window.

Table 1. Tsukuba (elasticity) score

Score	Stiffness relative to surrounding tissues	Size relative to B-mode	Elastographic description	Assessment	Need for biopsy
1	Less/Equal	N/A	Soft	Benign	No
2	Mixed	N/A	Mixed	Benign	No
3	High	Small	Stiff-Small	Probably benign	No
4	High	Equal	Stiff-Equal	Malignant	Yes
5	High	Large	Stiff-Large	Malignant	Yes

In SE, the limitations of the Tsukaba scoring system are attempted to be overcome by semi-quantitative evaluations. Strain ratio (fat to lesion ratio / FLR) is used in this evaluation. FLR is the ratio of strain in subcutaneous fat to strain in the mass [15]. The elastic coefficient of adipose tissue is constant at different compression degrees. Thus, the FLR provides a semi-quantitative measure showing the relative stiffness of the lesion [16]. The cut-off value reported in the literature for the differentiation of benign and malignant FLR varies between 2.9 and 5.6 [11]. Values that are above this value indicate malignant lesions. The diagnostic sensitivity of FLR in breast cancer was found to be 88% and its specificity as 83% [17]. Therefore, when semi-quantitative evaluation is used together with qualitative evaluations, it leads to a very significant increase in the accuracy of the US examination. Another advantage of FLR is that it can be used in very big masses and non-mass abnormalities.

Practical applications of strain elastography

As summarized in the previous section, SE provides the user with an overall estimation about of the nature of breast masses. The main criteria used for this purpose are elastographic size and stiffness. However, there are some specific signs and findings that are significant in the differential diagnosis of masses in SE. The main ones are:

A. White shadowing: This sign is caused by the inability to make strain measurements of the areas behind (and sometimes within) very stiff lesions. These areas that cannot be measured are coded in white in gray scale SE elastograms and indicate the malignant character of the mass that causes such shadowing (Figure 4).

B. Breast conserving surgery (BCS): BCS is the mainstay of modern cancer surgery. For this procedure assessment of the extent of the resection is important. Evaluation of extension can be possible by demonstrating the presence of intraductal components and their radial propagation. SE can reveal the presence of these components with high sensitivity [11] (Figure 5 A and B).

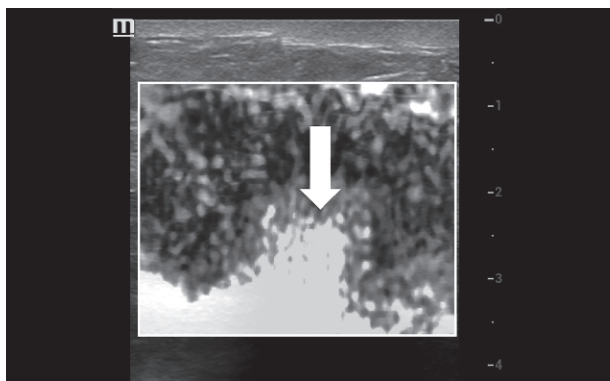


Figure 4. White shadowing (arrow) indicating malignancy in the posterior of a large breast mass.

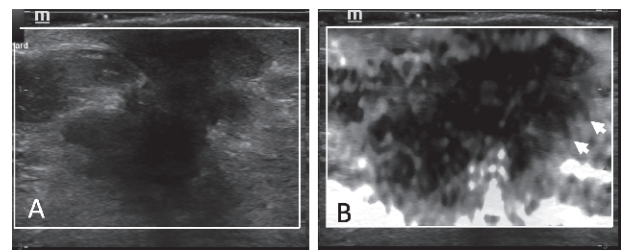


Figure 5 A and B. Elastographic examination reveals spiculated extensions to neighboring tissues (arrows).

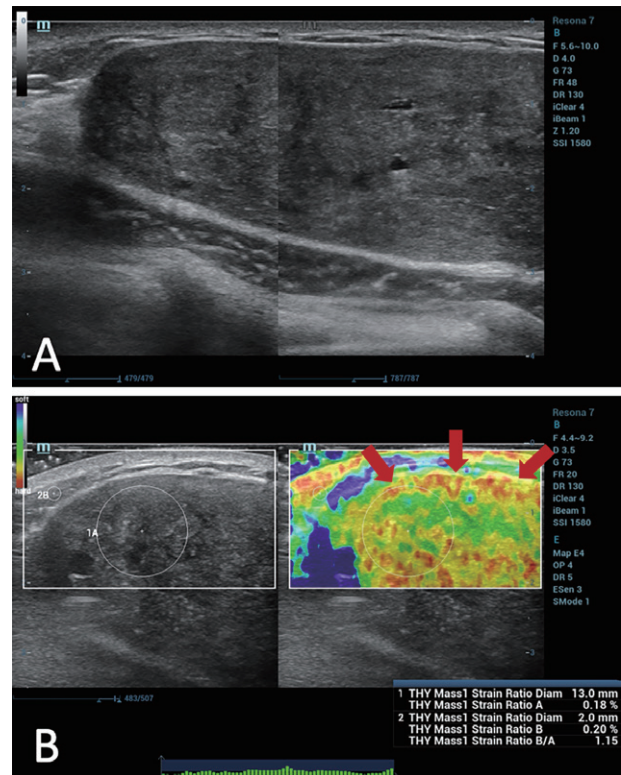


Figure 6 A and B. A giant phyllodes tumor that fills almost the entire breast. This lesion, which is impossible to distinguish from fibroadenomas in B-Mode US (A), can be recognized by the ring sign (red arrows), which is caused by the inelastic tissue surrounding it

C. Diagnosing phyllodes tumor: All phyllodes tumors has a similar elastic pattern with an elastic center and inelastic outer limits, referred to as the "ring sign". This sign is found in only 5% of all fibroadenomas [18]. It differentiates them from fast-growing phyllodes tumors that are likely to recur (Figure 6 A and B).

D. Diagnosing cysts: B-mode US examination may not clearly differentiate simple cysts from complex cysts with malignant potential. However, the bull's eye sign and BGR (blue-green-red) artifact detected for the cyst in the SE method may indicate the benign nature of the cyst. Bull's-eye artifact is described as a centrally located white signal within a black outer circle and a bright spot posterior to the lesion [19] (Figure 7 A and B). The artefact is probably caused by fluid motion, which causes the decoration between images. Bull's-eye artifact has a high predictive value that the lesion is a benign

cyst. Any solid component (e.g., papilloma) in the cyst is displayed as a black area. BGR sign is the name given to the red layer seen in the deep parts of the lesion that is almost completely anechoic in some US systems. The red (R) layer is accompanied by the blue (B) layer in the superficial section and the green (G) layer in the middle section (Figure 6D). This unique pattern is due to the presence of low strain in the deep parts of the anechoic mass, indicating that the mass content is liquid. If there is a BGR sign, the other sign (i.e., bull's eye) is absent (Figure 7 C). Likewise, if there is bull's eye sign, the other sign (BGR) cannot be observed.

E. Diagnosing non-mass abnormalities: SE depicts not only stiff regions (with little strain) but also minimally stiff regions (moderate strain) and soft regions (with considerable strain), greatly increasing the diagnostic range of US by detecting subtle anomalies (Figure 8). With this capability, it significantly enhances the diagnostic capability of US by revealing ambiguous abnormalities.

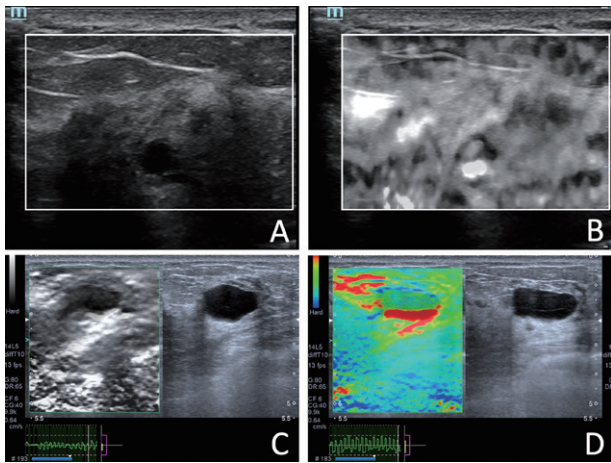


Figure 7 A-D. SE in diagnosing simple cyst. The anechoic structure observed in B-mode U (A) elastographically consists of a hyperechogenic area in the center of a black ring and a bright spot posteriorly (B). In another case that was examined using a different system bull's eye artifact cannot be seen (C). However, BGR artifact is detected in this device (D).

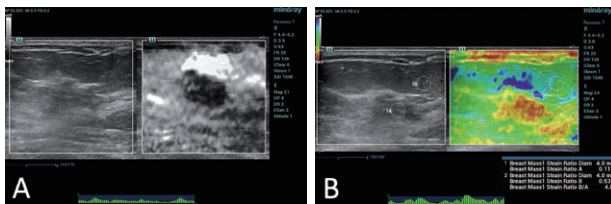


Figure 8 A and B. Suspected hypoechoic irregularity in the deep plane of the breast. The grey scale strain elastogram shows a distinct hypoechoic appearance, indicating the presence of a high very stiff mass in this area (A). The FLR of the lesion was found to be 4.0, indicating very high-grade malignancy.

Shear wave elastography (SWE) technique

SWE employs dynamic stress to generate shear waves in paral-

lel or perpendicular dimensions through the use of an external vibration source. The vibration source in clinical applications is the ultrasound probe. There are two different techniques in routine radiological applications. In the first of these, the point shear wave elastography (pSWE, STQ), horizontal shear waves are created perpendicular to the direction of the propagation of the ultrasound waves by applying a single acoustic pulse to a single measurement area. In a newer two-dimensional shear wave elastography (2D-SWE, STE), multiple focal zones are interrogated a near cylindrical shear wave cone (Figure 9). Measurement of the shear wave speed results in qualitative and quantitative estimates of tissue elasticity. Unlike SE, tissue displacement is not measured in SWE. Instead, the speed of the shear waves perpendicular to the plane of excitation are measured.

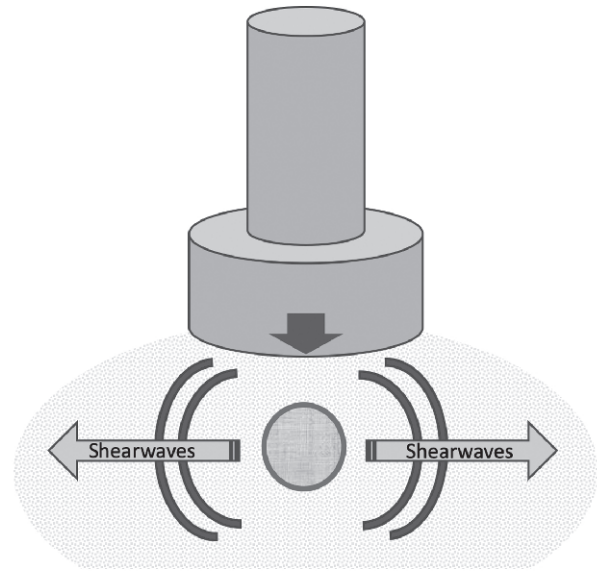


Figure 9. Shear waves propagating perpendicular to the force applied with an external ultrasonic vibration source on the skin in shear wave elastography

In SWE, the technique is not user dependent, unlike the SE detailed in the previous section, since the compressive waves are not created manually by the user but automatically by the US probe. However, some degree of variability may occur if too much pressure is applied on the probe causing an artificial increase in measured values. Tissue elasticity is presented in the pSWE as a single numerical value representing the mean elasticity of the region of interest (ROI) (Figure 10 A and C). In 2D-SWE, on the other hand, it is presented as color quantitative elastogram which is overlaid on the B-mode image (Figure 10 B and D). The appearance on these maps resembles to SE maps and low strain (stiff tissue) is displayed in red whereas high strain (soft tissue) is displayed in blue. Elastometric measurement is given either for a small ROI or for each pixel in the FOV. There are three different quantitative measurements that are linked and derived from each other in SWE. These are shear wave velocity C_s (m/sec), shear modulus G (kPa) and Young's modulus E (kPa).

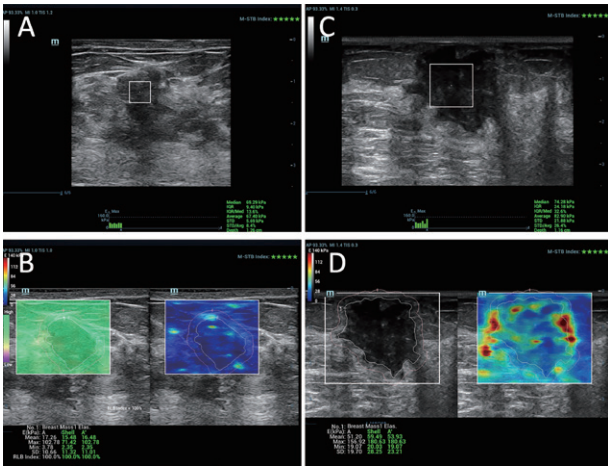


Figure 10 A-D. PSWE (A and C) and 2D-SWE (B and D) images of fibroadenoma (A and B) and invasive ductal carcinoma (C and D). pSWE takes a single median measurement from only a certain area of the tissue, and this value is 74 kPa for the IDC presented here. In 2D-SWE, the whole mass is evaluated separately with all its pixels including the peritumoral zone and it is determined that the mass has areas of very high stiffness (181 kPa).

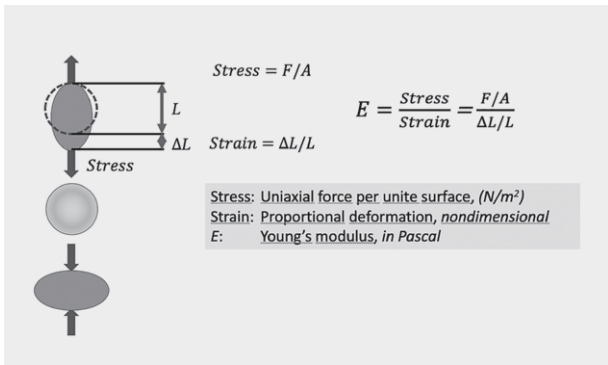


Figure 11. Calculation of Young's coefficient

The most common of these measurements is the Young's coefficient E, and this coefficient is defined as the ratio of stress to strain. When a rod is drawn, an elongation of L is produced, and thus L extends from its original length to L + ΔL. The ratio of this elongation (or shortening) to ΔL, the original length L, is called strain and is denoted by the ε (epsilon) sign. Young's coefficient is found by dividing the applied force (stress) per unit surface by the proportional strain (Figure 10). This formula also explains why applying excessive pressure to the patient with the probe will inadvertently cause an increase in quantitative measurements.

Practical applications of shear-wave elastography

In routine SWE applications, elasticity measurements can be made from a certain area (ROI) of the mass entering the field of view (FOV); from the entire mass (A), around mass' periphery

(shell); or from the entire mass including a certain thickness around it (A') (Figure 12). Although all three values (A, shell, A') are usually given in the radiological report, the measurement that is essential for diagnosis is generally the one obtained for A'. Distinguishing the mass lesion from surrounding tissues in elastograms presents difficulties in most cases. For this reason, the above-mentioned measurements are performed on the simultaneous B-mode images shown side by side with the elastogram (Figure 13).

In the above-detailed measurement technique, the cut-off value that will enable BI-RADS category 3 and BI-RADS category 4a lesions to be distinguished from each other with higher specificity is 80 kPa. However, there may be some differences due to the technology of each US system for this and other values stated below. For example, in the Resona 7 system of Mindray, the cut-off value was reported as 98.66 kPa in the measurements where a shell of 2 mm in thickness was included. The measurement of stiffness must be obtained from the area of highest stiffness (Emax) within the lesion and its surroundings shown on color elastograms (Figure 14 B). An alternative approach is to use the automatically produced summary table and taking Emax value for A' into consideration^[20] (Figure 10 D, 12). In a BI-RADS 3 mass lesion, if the A' value is measured as 160 kPa and above, the mass should be upgraded to BI-RADS 4a and tissue diagnosis should be obtained (Figure 14 A ve B). To downgrade, there are two different approaches. According to "aggressive" rule BI-RADS 4a masses with low stiffness (< 80 kPa) may be downgraded to follow-up. This will increase the specificity. According to "conservative" rule BI-RADS 4a masses with low stiffness (< 30 kPa) may be downgraded to follow-up (Figure 14 C and D). This will increase the sensitivity.

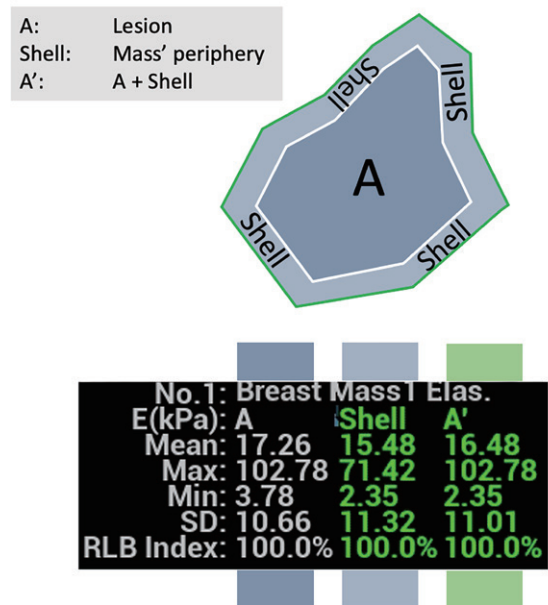


Figure 12. Marked areas and summary measures for the mass on SWE images

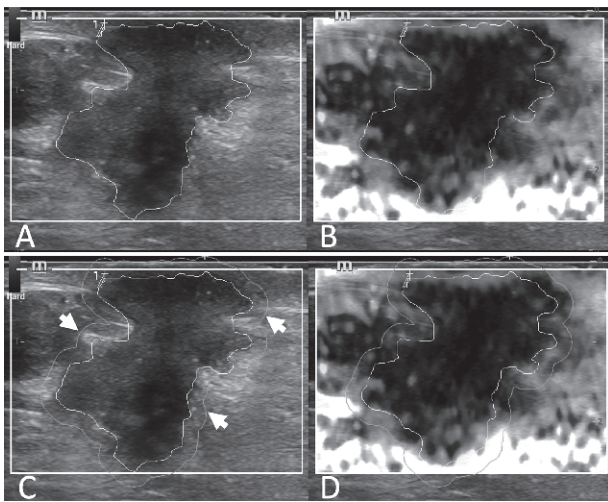


Figure 13. Malignant mass on SWE examination of the breast. Measurements can be made from the mass itself (B) or to include a certain thickness around it (D). In both cases, markings are performed on simultaneous B-mode images (A and C) where the mass is more clearly visible, rather than elastograms (B and D).

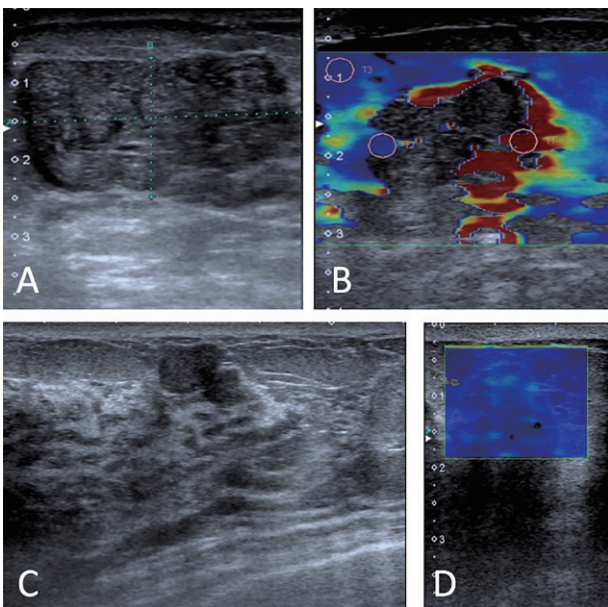


Figure 14 A-D. Two different cases of 36 years old. The mass evaluated as BI-RADS 3 in B-mode US (A) has been upgraded to BI-RADS 4a since the Emax value in SWE (B) was 143 kPa. The mass evaluated as BI-RADS 4 in B-mode US (C) was downgraded to BI-RADS 3 since the Emax value measured in SWE (D) was 15 kPa. In pathological examination, the first lesion was diagnosed as atypical papilloma, and the second as adenosis.

Clinical Studies on Elastography

Various studies have shown that the combined use of conventional and advanced US techniques including elastography increases specificity. According to the multinational study of Berg et al. [20], the combination of B-mode (BI-RADS) and SWE increases the specificity in diagnosis from 61% to 79%, and the

positive predictive value from 53% to 67%. In the single-center but homogenized study of Bicer et al. [21], the sensitivity of B-mode US in detecting malignancy was found to be 92%, and the specificity was found to be only 65%, and the stated values are in accordance with the studies conducted since the past [5]. According to Bicer et al. [21], the combined use of all US techniques (B-mode, SWE, CDUS) causes only a slight (95%) increase in sensitivity but a dramatic (99%) increase in specificity in the differential diagnosis of benign and malignant lesions.

One of the most interesting studies on SWE is a study conducted by Karakaş in 2018 to determine the extent to which the measurements obtained with the mentioned method are affected by the surrounding breast tissue in real cases. In this study, nine different mass lesions were initially evaluated by pSWE and 2D-SWE elastography methods (in-vivo) (Figure 15 B and C); they were removed with percutaneous lumpectomy on site [22] (Figure 15 A); and en-block specimens were immediately evaluated immediately again (ex-vivo) in identical conditions (Figure 15 D and E). In this study, there were significant and unpredictable differences between the elasticity values obtained with pSWE in-vivo and ex-vivo environment (Figure 15 B and D). The 2D-SWE method, on the other hand, produced similar results under in-vivo and ex-vivo conditions, favoring the reliability and use of this technique (Figure 15 C and E).

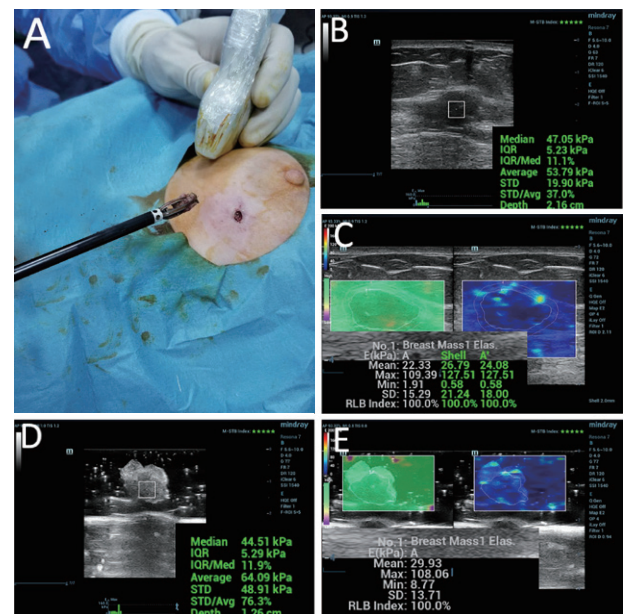


Figure 15 A-E. Evaluation of a breast mass by pSWE (B and D) and 2D-SWE (C and E) methods just before (B and C) and immediately after (D and E) its removal with percutaneous lumpectomy (A) method. The ex vivo Emax of the mass in this patient (108 kPa) was equal to the in vivo Emax value (109 kPa).

Conclusion

The combined use of conventional and advanced US methods (i.e., SWE & CDUS) in the assessment of breast masses to differentiate benign and malignant lesions can increase specificity to 99%. However, SWE and /or CDUS should only be performed and interpreted in conjunction with B-mode US for characterization of an abnormality identified on B-mode. As a general rule, if a BI-RADS 3 lesion has characteristics of malignancy on SWE + CDUS, it should be upgraded to a biopsy. If a BI-RADS 4 lesion has soft elasticity (maximum elasticity of ≤ 30 kPa on SWE) and mild vascularity (Adler's Grade 0/1) in CDUS, it should be downgraded warranting follow-up rather than biopsy. This approach is known as "conservative approach and it may substantially reduce the number of unnecessary biopsies without jeopardizing patients' life. The most important of guidelines and recommendations of World Federation of Ultrasound in Medicine and Biology (WFUMB) on the clinical use of SWE in imaging breast masses are summarized below (Table 2).

Table 2. WFUMB Guidelines and Recommendations for Clinical Use of Ultrasound Elastography in Breast ⁽¹¹⁾

<ul style="list-style-type: none"> Should elastography be performed/interpreted without B-mode? 	Elastography is a complimentary technique to B-mode imaging.
<ul style="list-style-type: none"> When should elastography be performed? 	Elastography should be used to characterize an abnormality identified on conventional B-mode imaging.
<ul style="list-style-type: none"> Should one perform SE or SWE imaging? 	There have been no comparative studies to suggest one technique is better than the other. Performing more than one technique on a patient may improve confidence in the findings.
<ul style="list-style-type: none"> Should a benign elastography downgrade a BI-RADS 4b, 4c, or 5 lesion to BI-RADS 2 or 3? 	Downgrading B3 or B4A is reasonable, but downgrading a B4b, B4c, or B5 is not recommended. If a B3 lesion has characteristics of a malignancy on SE or SWE, the lesion should be upgraded to a biopsy. If B-mode or another imaging technique is diagnostic of a BI-RADS 2 (e.g., fat necrosis), elastography should not be used to upgrade a lesion.
<ul style="list-style-type: none"> Should the Bull's Eye artifact be used to cancel breast biopsies? 	The Bull's Eye artifact (seen only with certain strain equipment) has been demonstrated to be highly specific for benign cystic lesions.
<ul style="list-style-type: none"> Are there situations when elastography should not be used? 	Elastography (SE or SWE) should not be used when a lesion is very superficial (3 mm) from the skin surface. SE should not be used if the lesion is larger than the FOV box.

Many studies have been conducted on the use of US elastography technique in breast imaging, especially in the last five years. On the other hand, more validity and reliability studies are needed for the physical principles of the technique and the methods for its application to be accepted definitively in the clinical context. These studies will be aimed at determining the appropriate cut-off values for SE and SWE in different US systems of the manufacturers, using more realistic viscoelastic models instead of pure elastic models that are the basis of the software we currently use, and using deep learning algorithms for multi-dimensional classification of lesions. At the end of all these studies, it will be possible to automatically detect the abnormal area and to indicate whether it is malignant or not.

Important notice: The equipment (Resona 7, Mindray) that was used within the framework of this paper was equipped with multi-frequency broadband linear transducers (L11-3U and L14-5WU). Resona 7 images and measurements were performed with these transducers.

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