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Research article

Diagnostic accuracy of shear wave elastography – Virtual touch™ imaging quantification in the evaluation of breast masses: Impact on ultrasonography's specificity and its ultimate clinical benefit

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ABSTRACT

Objectives: To evaluate the diagnostic performance and the clinical benefit of Shear-Wave Elastography - Virtual Touch™ Imaging Quantification (SWE-VTIQ) as a complement to ultrasonography (US).

Methods: From October 2016 through Jun 2017, B-mode US and SWE-VTIQ were prospectively performed in 396 breast masses in 357 women who consented to undergo this study. Quantitative elastography values were recorded: V_{max} (maximum elasticity), V_{mean} (median elasticity), $V_{ratio(max)}$ (ratio of V_{max} and surrounding parenchyma) and $V_{ratio(mean)}$ (ratio of V_{mean} and surrounding parenchyma). The histopathology of the lesions was considered the reference standard for benign or malignant definition. The performance of the four elastographic parameters was evaluated trough sensitivity, specificity and AUC. The parameter with the best performance was tested in six different diagnostic approaches defined based on clinical practice.

Results: Of the 396 masses, 122 (30.8%) were benign and 274 (69.2%) were malignant. All SWE parameters were significantly higher in malignant masses (all $p < 0.01$). V_{max} and $V_{ratio(max)}$ performed significantly better then $V_{ratio(mean)}$ ($p = 0.01$ and $p = 0.03$, respectively). SWE-VTIQ improved US specificity in all diagnostic approaches, except when applied to BI-RADS 3 lesions. SWE-VTIQ reduced the false positive rate in 25% if applied only to BI-RADS 4A masses, maintaining a high sensitivity (98.9%, 95% confidence interval 97.1–100%) and a negative predictive value of 95.5%. When applied to BI-RADS 4A and 4B masses, SWE-VTIQ reduced the false positive rate in 54.4%. However, 13 malignant cases would be missed in this approach (4.7% of all malignant cases).

Conclusions: SWE-VTIQ increases US specificity when applied to BI-RADS 4 A lesions, significantly reducing unnecessary interventions and preserving the diagnosis of malignant lesions. When applied also to BI-RADS® 4B lesions, SWE-VTIQ increases the number of false negative cases, which should be evaluated with caution.

1. Introduction

Breast ultrasonography (US) is primarily used to evaluate abnormalities detected by physical exam or by mammography, but it also has the potential of detecting early breast cancer not seen on mammography, particularly in women at high risk for breast cancer or with mammographically dense breast tissue [1–6]. Breast US has the advantages of being widely available, do not requiring radiation or contrast, being well tolerated by patients, and of having a sensitivity greater than 90% [5–7]. Nonetheless, it has a moderate specificity (31%–67.8%) [6,8] and literature shows that US increases the number of biopsies and the recall rates [9]. After a negative mammography, a median of 56 biopsies per 1000 women are performed because of suspected lesions in US (range 27–107) [9]. Therefore, cost-effective, practical and reproducible methods capable of reducing the false-positive rate of US are urgently needed.

Elastography is a relatively new technique that can provide additional information concerning the tissue stiffness, and improve US performance [10–12]. There are two types of elastography: strain elastography (SE) and shear wave elastography (SWE). The first one requires multiple freehand compressions to produce a stiffness map [10,12,13]. In SWE, an initial ultrasound pulse is applied to the tissue to

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induce mechanical vibrations and create shear waves. The velocities of the waves are directly correlated to the lesion stiffness. SWE is more reproducible and less operator-dependent than SE [10].

There are currently three technical modalities of SWE: 1-dimensional transient elastography; point shear wave elastography; and 2-dimensional shear wave elastography. This last modality has five different presentations: Virtual Touch™ Imaging Quantification/Acoustic radiation force impulse (VTIQ) by Siemens, Shear Wave™Elastography by SuperSonic Imagine (SSI), Shear Wave Elastography by Philips, Acoustic Structure Quantification™(ASQ) by Toshiba, and 2D-SWE by GE Healthcare) [14,15]. In the VTIQ 2-dimensional shear wave elastography presentation, tracking vectors can be used to detect the velocity in multiple regions of interest (ROI), displayed as a shear wave speed.

Several studies have already been published in the literature, utilizing different technologies, demonstrating that SWE helps in the characterization of breast benign and malignant masses [12,16–23]. Three recent meta-analysis demonstrated values of sensitivity and specificity, respectively, of 0.85-0.89 and 0.82-0.93 for the VTIQ elastography and of 0.88-0.91 and 0.86-0.91 for the SSI technology [12,23,24]. However, the studies published so far show substantial heterogeneity among themselves due to various factors, including the design of the study, population analyzed and rate of symptomatic lesions [24,25]. Furthermore, there is no consensus regarding the best SWE parameter to be utilized and the best cutoff value to differentiate benign and malignant lesions. Therefore, although there is evidence that SWE increases the specificity of US, it is not yet known what the real clinical benefit of elastography is (when to use it) and there still no standardization of its use.

In face of the lack of sound information concerning the ultimate value of adding SWE-VTIQ in clinical practice, we decided to evaluate the diagnostic performance and the clinical benefit of Shear-Wave Elastography - Virtual Touch™ Imaging Quantification (SWE-VTIQ) as a complement to the Breast Imaging-Reporting and Data System (BI-RADS) classification. To our knowledge, our study is the first attempt to establish a clinical roadmap for the use of SWE-VTIQ.

2. Materials and methods

2.1. Patients

From June 2016 to August 2017, 357 women with 396 breast masses categorized into BI-RADS category 3 to 5 were prospectively enrolled in this study. Patients underwent breast US at our breast imaging section for different medical reasons, *e.g.*, sonographic follow-up of breast masses previously coded as BI-RADS-US category 3, assessment of palpable masses, sonographic screening in high-risk patients and sonographic evaluation of masses categorized as BI-RADS-mammography 0. The institutional review board approved this study. Informed consent was obtained from each woman (Protocol 1714081). Standards for the reporting of diagnostic accuracy studies (STARD) criteria were applied.

All patients underwent B-mode ultrasonography and SWE-VTIQ. All BI-RADS categories were assessed with B-mode morphological variables alone. Core needle biopsy guided by US was performed in all BI-RADS 4 or 5 masses. Core needle biopsy was performed under US guidance, using a semiautomatic gun system with a 14-gauge needle. All biopsies were performed with the patient in a supine or supine-oblique position. At least three core samples were obtained.

BI-RADS 3 masses were only included in this study if at least two years of stability (ranked as benign) or a core biopsy had been performed.

2.2. Conventional ultrasonography

An Acuson S2000 Ultrasound System (Siemens®, Munich, Germany) was the diagnostic equipment used. Standard B-mode US and SWE-VTIQ were performed using a 9-MHz linear transducer. Investigators with at least one-year of experience with breast US performed the exams. A senior radiologist with more than 15 years of experience in breast imaging and with 3-year experience in elastography supervised all exams.

All lesions were classified according to the BI-RADS US fifth edition recommendations into categories: BI-RADS US 3 (probably benign); BI-RADS US 4 A (low suspicion for malignancy); BI-RADS US 4B (moderate suspicion for malignancy); BI-RADS US 4C (high suspicion for malignancy); and BI-RADS US 5 (highly suspicion for malignancy) [26]. Current and previous mammography and ultrasound exams were available to the evaluators during the examination. The final BI-RADS category was given by the senior radiologist.

Table 1
Main clinical and sonographic features of the patients and their breast lesions.

Characteristics	Benign (%) (n = 122)	Malignant (%) (n = 274)	*p*
Age (years)	45.03 (15-90)	58.33 (28-92)	< **0.01**
Family history of BC			
Yes	17 (13.9)	45 (16.4)	0.58
No	99 (81.2)	221 (80.7)	
Unknown	6 (4.9)	8 (2.9)	
Personal history of BC			
Yes	14 (11.5)	21 (7.7)	0.19
No	102 (83.6)	245 (89.4)	
Unknown	6 (4.9)	8 (2.9)	
Main Indication for US			
Symptomatic	36 (29.5)	93 (33.9)	< **0.01**
Follow-up	23 (18.9)	1 (0.4)	
High risk for BC	9 (7.4)	4 (1.5)	
MMG BIRADS 0	12 (9.8)	20 (7.3)	
Suspected mass	42 (34.4)	156 (56.9)	
Lesion diameter (mm, SD)	21.44	23.05	0.32
Shape			
Oval/round	59 (48.4)	24 (8.8)	< **0.01**
Macrolobulated	10 (8.2)	8 (2.9)	
Irregular	53 (43.4)	242 (88.3)	
Margins			
Circunscribed	68 (55.7)	19 (6.9)	< **0.01**
Microlobulated	25 (20.6)	55 (20.1)	
Indistinct	17 (13.9)	90 (32.9)	
Angular	2 (1.6)	22 (8.0)	
Spiculated	10 (8.2)	88 (32.1)	
Echo pattern			
Hypoechoic	82 (67.2)	202 (73.7)	0.14
Mixed echoic	18 (14.8)	20 (7.3)	
Heterogeneous	21 (17.2)	50 (18.3)	
Isoechoic	1 (0.8)	2 (0.7)	
Orientation			
Parallel	94 (77.1)	96 (35.0)	< **0.01**
Not parallel	28 (22.9)	178 (65.0)	
Vascularity			
Present	87 (71.3)	256 (93.4)	< **0.01**
Absent	35 (28.7)	18 (6.6)	
BI-RADS			
3	43 (35.3)	1 (0.4)	
4 A	26 (21.3)	10 (3.6)	
4B	28 (22.9)	58 (21.2)	
4C	17 (13.9)	117 (42.7)	
5	8 (6.6)	88 (32.1)	
SWE parameters			
V_{max} (m/s)	4.65 (±2.33)	8.28 (±2.75)	< **0.01**
V_{mean} (m/s)	3.19 (±1.31)	5.24 (±2.06)	< **0.01**
$V_{ratio(max)}$	2.44 (±2.09)	5.48 (±2.16)	< **0.01**
$V_{ratio(mean)}$	0.95 (±0.93)	2.43 (±1.92)	< **0.01**

Abbreviations: BC, breast cancer; US, ultrasound; MMG, mammography; SWE, shear-wave elastography; m/s, meters per second.

2.3. Elastography

SWE-VTIQ was performed in sequence to B-mode US. The angle of

Table 2
Performance comparison of SWE parameters at optimal cutoff points for the diagnosis of malignant tumors in women breast lesions detected using ultrasonography.

SWE Parameter	Diagnostic performance					*p* values for pairwise AUC comparison			
	Cutoff	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV	AUC	Vmax	Vmean	Vratio(max)
Vmax	6.49	81.3 (74.8-88.3)	79.8 (74.8-84.8)	90.2	65.1	0.838	–		
Vmean	4.14	75.0 (67.3-82.8)	81.7 (76.6-86.7)	90.1	59.4	0.820	0.52	–	
Vratio(max)	2.94	85.8 (79.4-92.2)	73.0 (67.7-78.4)	88.1	68.8	0.828	0.78	0.64	–
Vratio(mean)	1.59	69.4 (61.1-77.8)	77.6 (71.9-83.2)	87.6	52.6	0.773	**0.01**	0.14	**0.03**

Abbreviations: SWEshear-wave elastography; PPVpositive predictive value; NPVnegative predictive value; AUCarea under the ROC curve.

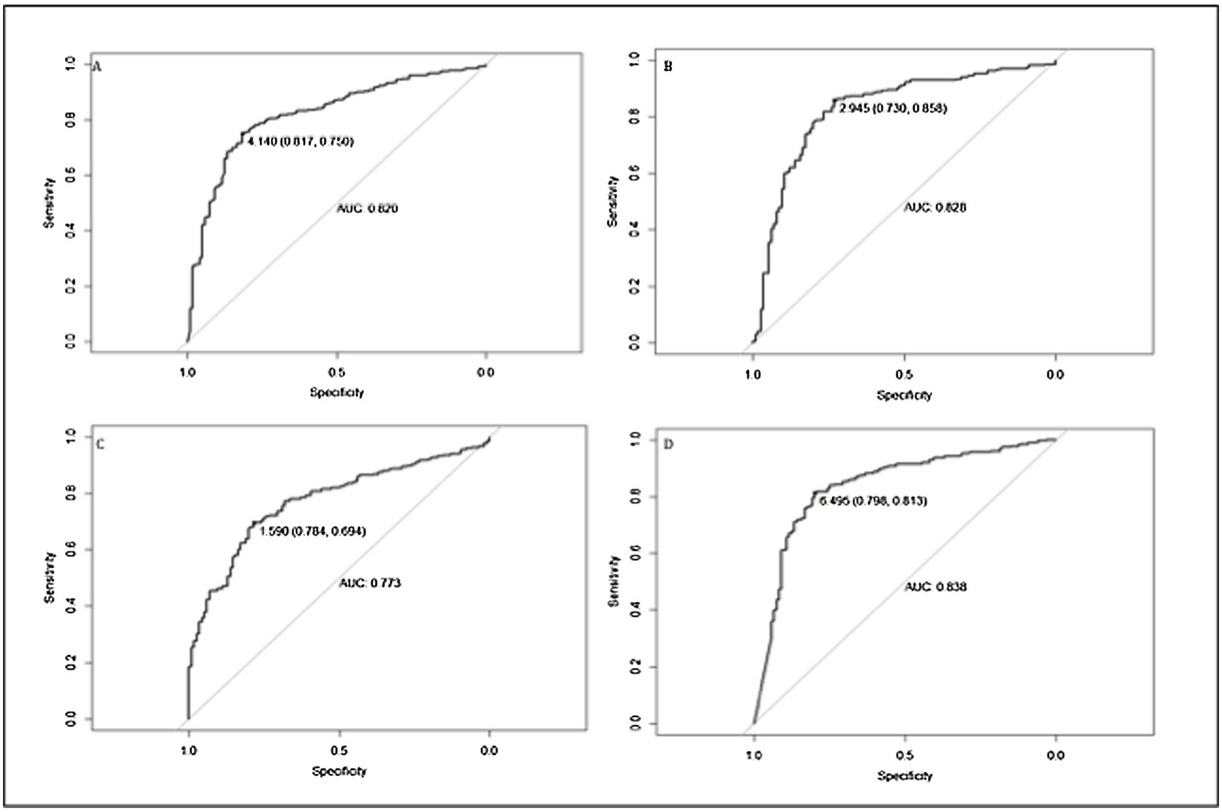

Fig. 1. Receiver operating characteristic curves of SWE_VTIQ parameters: A, V_{max}; B, V_{mean}; C, $V_{ratio(max)}$; D, $V_{ratio(mean)}$.

the probe was kept perpendicular to the skin, applying minimal pressure on the breast. The SWE velocity map was obtained, displaying SWE velocity distribution in 2D-colour images. Red, green and blue indicated hard, intermediate and soft elasticity, respectively. The SWE velocity map was adjusted from 0.5 (blue) to 10.0 cm/s (red). Quantitative SWE values were obtained from the static velocity map with Virtual Touch Quantification (VTQ) by placing a 2-mm square ROI on three different locations: on the breast parenchyma adjacent to the mass (surrounding parenchyma), on the mass area with the highest SW velocity (maximum elasticity (V_{max})) and on the mass area representative of the median SW velocity (median elasticity (V_{mean})) The ratio between V_{max} and surrounding parenchyma ($V_{ratio(max)}$) and between V_{mean} and surrounding parenchyma ($V_{ratio(mean)}$) were calculed later in the database.

2.4. Statistical analysis

Statistical analysis was performed using R: a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). The quantitative data were expressed in the form of mean ± standard deviation. Differences in quantitative data between the malignant and benign groups were compared with independent *t*-tests. The optimal cutoff values for SWE-VTIQ parameters (V_{max}, V_{mean}, $V_{ratio(max)}$ and $V_{ratio(mean)}$) were calculated using receiver operator characteristic (ROC) curves. The best cut-off value was determined when the maximal sum of sensitivity and specificity was achieved. In order to improve SWE-VTIQ specificity, a cutoff point was established for each BI-RADS category. Sensibility, specificity and the area under the ROC curve (AUC) were used to assess diagnostic performance of BI-RADS categories and of each parameter of SWE-VTIQ. We next performed a pairwise comparison of the AUCs for each scenario using 500 permutations. The best SWE-VTIQ parameter was chosen considering the best diagnostic performance. After this, the parameter chosen was applied in different diagnostic approaches to determine the ultimate clinical benefit of elastography.

3. Results

3.1. Clinical, US and pathologic findings

Of the 396 masses, 122 (30.8%) were benign and 274 (69.2%) were malignant. Benign lesions included 33 fibroadenomas (27.1%), 9 papillomas (7.4%), 22 usual and atypical hyperplasia (18%), 10 fibrosis (8.2%), 3 pseudoangiomatous stromal hyperplasia (2.5%), 3 steatonecrosis (2.5%), 2 Phyllodes tumors (1.6%), 2 adenomas (1.6%), one

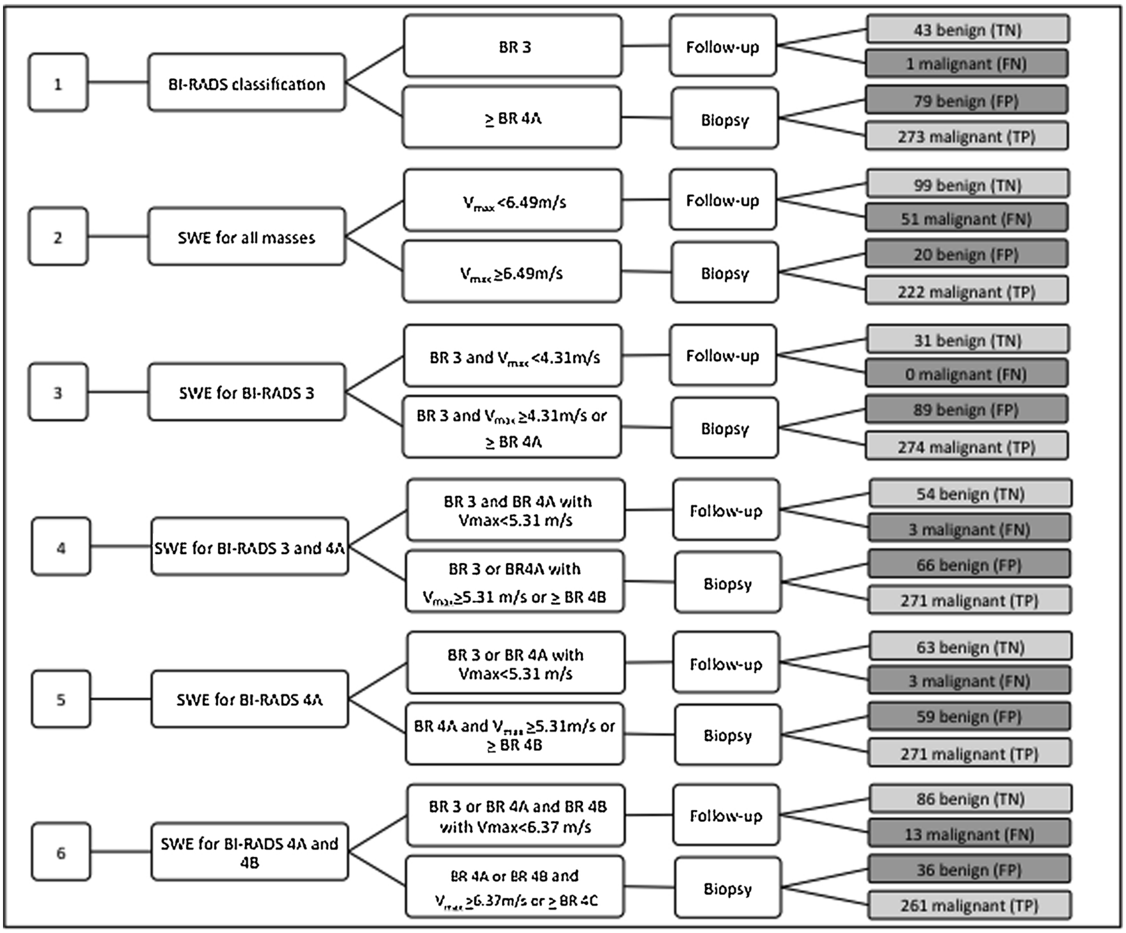

Fig. 2. Simulation of six diagnostic approaches and their results.
Notes: BR, BI-RADS; TN, true negative; FN, false negative; FP, false positive; TP, true positive; SWE, shear-wave elastography; V_{max}, maximum elasticity of SWE; m/s, meters per second.

fibromatosis (0.8%), one adenosis (0.8%), one granulomatous mastitis (0.8%). The remaining 36 benign lesions were BI-RADS 3 masses with more than two years of follow-up and did not have pathology analysis. The majority of malignant lesions were invasive ductal carcinomas (n = 229 – 83.6%). Other malignant results were: 12 invasive lobular carcinomas (4.4%), 11 mucinous carcinomas (4.0%), 13 ductal carcinomas *in situ* (DCIS, 4.7%), 3 papillary carcinomas (1.1%) and 6 other special subtypes (2.2%).

Table 1 shows the clinical and US features of the study cohort. Patients diagnosed with benign masses were younger (45.03 years (range 15–90 years)) than their malignant counterpart 58.33 (range 28–92 years) ($p < 0.01$). There was no statistical difference in the mass mean diameter ($p = 0.32$), in patient's personal history of cancer ($p = 0.19$) or in family history of cancer ($p = 0.58$) for patients with benign or malignant masses. Irregular shape, non-circumscribed margins, a non-parallel orientation to the skin and presence of vascularity were all significantly associated with malignant lesions (all $p < 0.01$).

As expected, there was an upward trend of the percentage of malignancy from women with BI-RADS 3 lesions to those with BI-RADS 5: 2.3% for BI-RADS 3, 27.8% for BI-RADS 4 A, 67.4% for BI-RADS 4B, 87.3% for BI-RADS 4C and 91.7% for BI-RADS 5.

The V_{max}, V_{mean}, $V_{ratio(max)}$ and $V_{ratio(mean)}$ mean (± SD) values were 4.65 m/s (±2.33), 3.19 m/s (±1.31), 2.44 (±2.09) and 0.95 (±0.93), respectively, for benign masses, and 8.28 m/s (±2.75), 5.24 m/s (±2.06), 5.48 (±1.26), 2.43 (±1.92), respectively, for malignant lesions. All SWE parameters were significantly higher in malignant lesions (all $p < 0.01$).

3.2. Elastography performance

Table 2 shows the performance comparison for SWE-VTIQ parameters. At the ROC-derived optimal cutoff threshold points, the $V_{ratio(max)}$ yielded the best sensitivity among all parameters (85.8%, 95%Confidence Interval (CI) = 79.4–92.2%). On the other hand, the V_{mean} provided the best specificity (81.7%; 95%CI = 76.6–86.7%). The AUC values were 0.838 for V_{max}, 0.820 for V_{mean}, 0.828 for $V_{ratio(max)}$ and 0.773 for $V_{ratio(mean)}$ (Fig. 1). When we compared the AUC's, V_{max} and $V_{ratio(max)}$ were both significantly better then $V_{ratio(mean)}$ ($p = 0.01$ and $p = 0.03$, respectively). V_{max} was chosen to be tested in different diagnostic approaches as it is easiest to use when compare to $V_{ratio(max)}$. The optimal cutoff value of V_{max} for each BI-RADS category was calculated.

3.3. SWE-VTIQ application in different diagnostic approaches

Fig. 2 shows a simulation of six diagnostic approaches and their results considering the gold standard: the histopathology of the lesion or a follow up of two years for BI-RADS 3 masses. Diagnostic approach "1" corresponds to what is used nowadays: US BI-RADS classification to define the biopsy indication. In this scenario, 79 unnecessary biopsies were performed (22.4% of all biopsies), but only one case of cancer classified as BI-RADS 3 would be missed (0.4% of all malignancies). This false negative case was related to a patient whom has had a breast cancer diagnosed in the contralateral breast and a new mass was identified on the first mammogram after the end of the treatment. Thus, although the mass had probably benign characteristics, the biopsy was

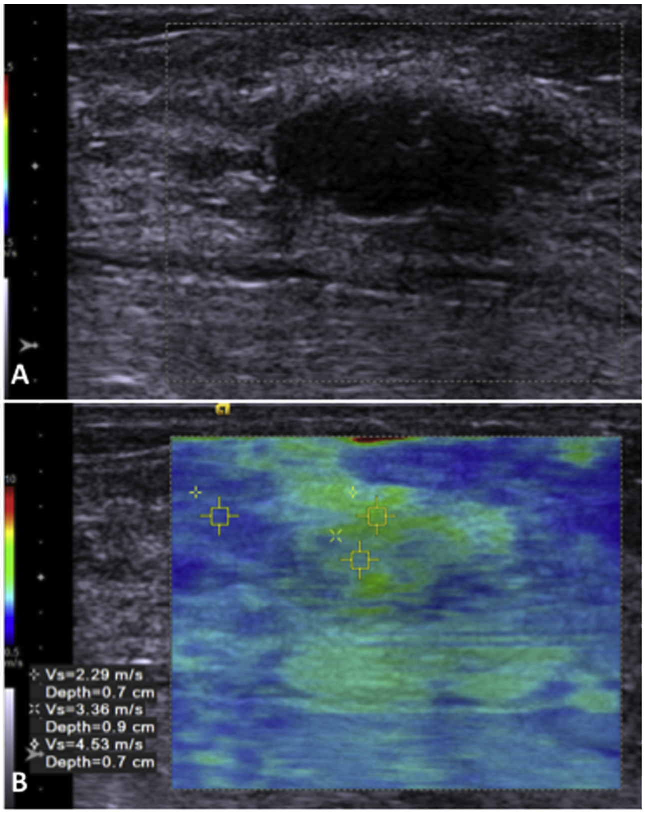

Fig. 3. (A) B mode image of oval, not circumscribed, parallel mass classified as BI-RADS 4 A. (B) SWE shows that the mass has homogenous blue/green color and low elasticity values (maximum velocity, 4.53 m/s; mean velocity 3.36 m/s). Pathologic diagnosis on core biopsy was fibroadenoma. The lesion would be correctly downgraded to BI-RADS 3 with SWE-VTIQ.

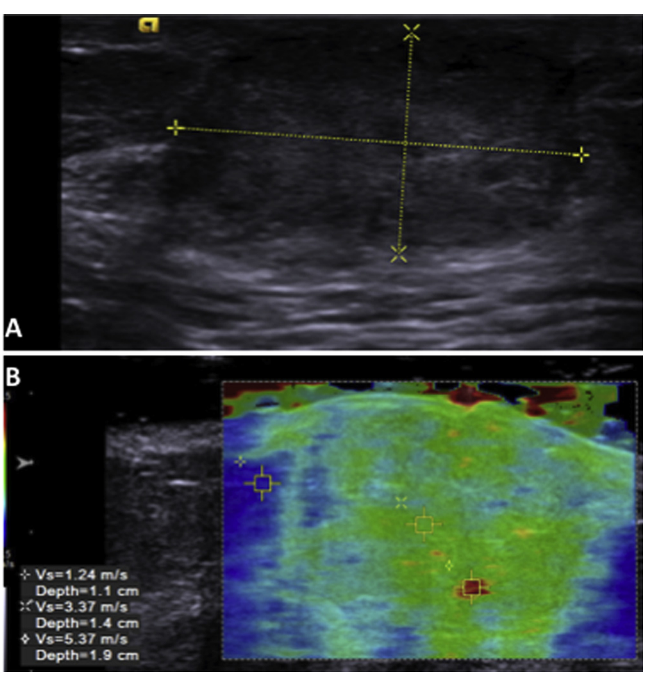

Fig. 4. (A) B mode image of oval, not circumscribed, parallel to the skin mass classified as BI-RADS 4 A. (B) SWE shows that mass has homogenous green color, but with a stiff peripheral region (maximum velocity, 5.37 m/s; mean velocity 3.37 m/s). Pathologic diagnosis on core biopsy was mucinous carcinoma. The lesion would be incorrectly downgraded to BI-RADS 3 in diagnostic approach number 6.

performed due to clinical reasons and a mucinous carcinoma was diagnosed.

In diagnostic approach “2”, SWE-VTIQ was the only criteria for biopsy indication. In this approach, 59 pathologic benign masses would be spared from a biopsy (reduction of 75% in false positive rate). However, 51 malignant cases would not have been identified (false negative of 18.6%).

In the diagnostic approaches “3” to “6”, we combined BI-RADS classification with SWE-VTIQ results. When SWE-VTIQ was used for BI-RADS 3 masses (diagnostic approach “3”), the only BI-RADS 3 malignant mass would be correctly identified. However, a biopsy would be indicated for 10 other benign masses. In diagnostic approach “4” (SWE-VTIQ for BI-RADS 3 or 4 A lesions), 13 patients would be spared from a biopsy (reduction of 16.5% in false positive rate). Only three malignant cases would be erroneously classified as benign (1.1% of all malignant cases): the previously described mucinous carcinoma classified as BI-RADS 3; one case of DCIS inside a fibroadenoma; and one breast cancer recurrence. When SWE-VTIQ was applied only for BI-RADS 4 A masses (diagnostic approach “5”), the same three malignant cases would be missed, whereas 20 biopsies would be spared: a 25% reduction in false positive rate (Fig. 3). In diagnostic approach “6” (SWE-VTIQ for BI-RADS 4 A and 4B), 43 patients would be spared from a biopsy (54.4% reduction in false positive rate), while 13 malignant cases would be missed (4.7% of all malignant cases) (Fig. 4). Of these 13 cases, seven were infiltrating ductal carcinomas (53.8%), two DCIS (one inside a fibroadenoma) (15.4%), two were mucinous carcinomas (15.4%), and two special subtypes (15.4%): one sarcoma and one case of lymphoma.

Table 3 shows the performance contribution of SWE in different diagnostic approaches. BI-RADS classification alone presented a sensitivity of 99.6% (95%CI = 98.5–100%), 35.2% of specificity (95%CI = 30.2–40.2%), 77.5% of positive predictive value (PPV), 97.7% of negative predictive value (NPV) and 79.8% of accuracy. SWE-VTIQ improved BI-RADS specificity in all diagnostic approaches, except for number 3. Diagnostic approaches 5 and 6 showed the best accuracy (87.6% and 84.3%, respectively). However, diagnostic approach 6 had a worsen NPV (86.9% compared to 95.5%), as 13 of 274 malignant cases would not be correctly identified in this approach.

4. Discussion

In this study, we have shown that all SWE-VTIQ parameters (V_{max}, V_{mean}, $V_{ratio(max)}$ and $V_{ratio(mean)}$) perform well in differentiating malignant from benign breast masses. Furthermore, our data shows that the diagnostic benefit is optimal in women with BIRADS 4 A lesions. For this specific subgroup, the use of SWE-VTIQ allowed a 25% reduction in false positive rate, without compromising the diagnosis of breast cancer.

The majority of studies utilizing VTIQ technology, published so far, have measured only the maximum SWE velocity of the masses [22,27–34]. We decided to analyze three other parameters in order to choose the one with the best performance and clinical application. In our practice with SWE-VTIQ, we noticed that many masses are heterogeneous and have only a small “red” portion (stiff portion). Because of that, there was a possibility that V_{mean} would perform better than V_{max}. In addition, it is known that the pressure applied to the tissue when performing US may change its elastic properties, overestimating the SWE velocity of the mass. $V_{ratio(max)}$ and $V_{ratio(mean)}$ would be expected to reduce the compression effect, since the same pressure is applied to the mass and to the adjacent tissue. To our knowledge, this was the first study to analyze these four SWE-VTIQ parameters separately, in search for a best stand-alone parameter that could yield the best diagnostic accuracy.

All four SWE-VTIQ parameters were significantly higher in malignant masses. The optimal cutoff point for each of the parameters was: 6.49 m/s for V_{max}, 4.14 m/s for V_{mean}, 2.94 for $V_{ratio(max)}$ and 1.59 for $V_{ratio(mean)}$. Our V_{max} cutoff is higher when comparing to some studies

Table 3
Performance contribution of SWE in different diagnostic approaches*.

Diagnostic approach[a]	Description	Performance					
		Cutoff for Emax	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV	Accuracy
1	BI-RADS classification		99.6 (98.5-100)	35.2 (30.2-40.2)	77.5	97.7	79.8
2	SWE for all masses	6.49	81.3 (74.8-88.3)	83.2 (78.5-87.9)	91.7	66.0	81.9
3	SWE for BR3	4.31	100	25.8 (21.3-30.3)	75.5	100	77.4
4	SWE for BR3 and 4 A	5.31	98.9 (97.0-100)	45.0 (39.7-50.3)	80.4	94.7	82.5
5	SWE for BR4 A	5.31	98.9 (97.1-100)	51.6 (46.2-57.0)	82.1	95.5	84.3
6	SWE for BR4 A and 4B	6.37	95.2 (91.5-99.0)	70.5 (65.3-75.7)	87.9	86.9	87.6

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; SWE, shear-wave elastography; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the ROC curve; NC = non-calculable.
[a] Please refer to Fig. 2 for a detailed description of each diagnostic approach.

(range 2.03–4.5) [28,30–32,34]. Nevertheless, two other authors found values similar to ours: 6.37 and 7.13 [22,27]. The use of different limits for SWE-VTIQ velocity could be an explanation of why our cutoff for V_{max} is higher than that reported by others: in some studies, the measurement was limited to 8.4 m/s due to the software version, whereas our equipment allowed velocities of up to 10 m/s [20,21,35]. Another explanation for this higher value of V_{max} could be a higher pressure applied by the operator. However, our fat velocity values (2.21 m/s or 14.6 kPa for benign lesions and 2.78 m/s or 20 kPa for malignant lesions) were similar to those found in two other studies (13.8 kPa and 14 kPa for benign; 18.8 kPa and 18.2 kPa for malignant) [17,36].

The pairwise comparison of the four SWE-VTIQ parameters showed that V_{max}, V_{mean} and $V_{ratio(max)}$ were statistically equivalent. Only V_{max} and $V_{ratio(max)}$ were statistically superior to $V_{ratio(mean)}$. We choose V_{max} over $V_{ratio(max)}$ because it is easier to use, since it does not need to be calculated. We established different cutoff points of V_{max} for each BI-RADS category in order to improve SWE specificity.

To our knowledge, this is the first study to test SWE-VTIQ in different scenarios with the aim to establish which niche of patients would have a real clinical benefit with this technology. Therefore, we evaluated the performance of US (trough BI-RADS category) alone, SWE-VTIQ alone and the combination of methods in different diagnostic approaches. In line with the literature, ultrasound showed excellent sensitivity (99.6%) and a fair specificity (35.3%) [8,35]. As expected, SWE improved BI-RADS specificity in all diagnostic approaches, except for number 3 (SWE applied to BI-RADS 3 lesions increased in 10 cases the number of unnecessary biopsies, in order to diagnose one cancer). The diagnostic approaches with the best accuracies were numbers 5 and 6: SWE applied to BI-RADS 4 A lesions (84.3%) and SWE applied to BI-RADS 4 A and 4B lesions (87.6%), respectively.

When SWE was applied to BI-RADS 4 A lesions, three malignant lesions would be erroneously considered benign: one case of ductal carcinoma *in situ* inside a fibroadenoma, and two cases of breast cancer recurrence (one in the ipsilateral breast and the other in the contralateral breast). In these two cases, the biopsy would have been indicated due to the clinical suspicion. The only study that investigated the applicability of SWE-VTIQ as a complementary method for the evaluation of suspected local breast recurrence showed that, although the technique demonstrate reasonable sensitivity and specificity (87% and 77.8%, respectively), the use of this method to determine biopsy may lead to poorer outcomes [37]. Therefore, considering the clinical practice, in which the two recurrences would have been biopsied by clinical suspicion, only one case of a DCIS inside a fibroadenoma would not have been identified (0.4% of all malignancies). Breast cancer arising within a fibroadenoma is a rare condition (0.002% to 0.125% in fibroadenoma specimens) and its clinical relevance has not yet been well established [38]. Therefore, this case may be considered an incidental finding.

When BI-RADS 4B lesions were included in the evaluation (approach 6), we found the second-best specificity rate (70.5%) and maintained a high sensitivity (95.2%). In this approach, there would be a 54.4% reduction in the number of false positives. However, besides the three malignant cases mentioned above, another 10 cases of cancer would not have been diagnosed (4% of the total cancers, considering that the two suspected recurrences would be biopsied by clinical indication). These 13 false negative cases had a higher proportion of DCIS (15.4% vs 4.7%), mucinous carcinoma (15.4% vs 4.0%) and other special subtypes (15.4% vs 3.3%) when compared to all malignant cases. Studies have shown that both DCIS and mucinous carcinoma have lower stiffness values and present higher false negative rates [16,20,39,40]. In addition, tumors smaller than 1 cm, young age, low histological grade and dense breasts are associated with cases of false negative in the elastography evaluation [40,41]. One possibility to reduce this false negative rate would be to decrease the cutoff value of V_{max}, at the expense of decreasing elastography's specificity. On the other hand, we still do not know if a 4% false negative rate that in its large proportion includes cases of CDIS, mucinous carcinoma, low grade lesions has a real impact on patients' treatment and prognosis.

Our study is flawed in that it was entirely conducted in a specialized breast cancer center, leading to an unrealistic high proportion of BIRADS 4 or 5 masses. In addition, our positive rate in masses classified as BIRADS 4 A and 4B was higher than expected, suggesting that we work with a high-risk population or that our criteria for diagnoses are excessively rigorous. However, we understand that a high percentage of malignancy in BIRADS 4 A and 4B may offset any potential diagnostic benefit brought about by the use of SWE. In fact, considering this unexpectedly high proportion of malignant lesions in women with B4 A, SWE contributed with more diagnoses, which makes us confident that our results and interpretations are valid. Finally, we did not assess interobserver variability, as one senior operator supervised all exams.

5. Conclusions

In essence, our study shows how a relatively simple, inexpensive addition to standard US examination of breast lesions can significantly improve US specificity, reducing unnecessary interventions and preserving the diagnosis of clinically significant masses. Furthermore, this study demonstrates that the ultimate clinical benefit of SWE-VTIQ is when it is applied to BI-RADS 4 A lesions. In this situation, SWE allows a 25% reduction in false positive rate, without compromising the diagnosis of malignancies. SWE may also be applied to BI-RADS 4B lesions, but attention must be given to an increase in false negative rate. Until we have larger and prospective studies to answer if this increase in false negative rate has a real impact in breast cancer treatment and prognosis, we do not recommend the routine use of elastography for BI-RADS 4B lesions.

Declaration of interests

None.

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References

[1] W.A. Berg, J.D. Blume, J.B. Cormack, E.B. Mendelson, D. Lehrer, M. Böhm-Vélez, E.D. Pisano, R.A. Jong, W.P. Evans, M.J. Morton, M.C. Mahoney, L.H. Larsen, R.G. Barr, D.M. Farria, H.S. Marques, K. Boparai, ACRIN 6666 Investigators, combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer, JAMA 299 (2008) 2151–2163, https://doi.org/10.1001/jama.299.18.2151.

[2] W.A. Berg, A.I. Bandos, E.B. Mendelson, D. Lehrer, R.A. Jong, E.D. Pisano, Ultrasound as the primary screening test for breast cancer: analysis from ACRIN 6666, J. Natl. Cancer Inst. 108 (2016) djv367, , https://doi.org/10.1093/jnci/djv367.

[3] P. Crystal, S.D. Strano, S. Shcharynski, M.J. Koretz, Using sonography to screen women with mammographically dense breasts, Am. J. Roentgenol. 181 (2003) 177–182, https://doi.org/10.2214/ajr.181.1.1810177.

[4] E.Y. Chae, H.H. Kim, J.H. Cha, H.J. Shin, H. Kim, Evaluation of screening whole-breast sonography as a supplemental tool in conjunction with mammography in women with dense breasts, J. Ultrasound Med. 32 (2013) 1573–1578, https://doi.org/10.7863/ultra.32.9.1573.

[5] T.M. Kolb, J. Lichy, J.H. Newhouse, Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations, Radiology 225 (2002) 165–175, https://doi.org/10.1148/radiol.2251011667.

[6] W. Buchberger, A. Niehoff, P. Obrist, P. DeKoekkoek-Doll, M. Dünser, Clinically and mammographically occult breast lesions: detection and classification with high-resolution sonography, Semin. Ultrasound CT MR 21 (2000) 325–336 (Accessed June 26, 2017), http://www.ncbi.nlm.nih.gov/pubmed/11014255.

[7] W. Berg, Z. Zhang, D. Lehrer, R. Jong, E. Pisano, R. Barr, M. Böhm-Vélez, M. Mahoney, W. Evans, L. Larsen, M. Morton, E. Mendelson, D. Farria, J. Cormack, H. Marques, A. Adams, N. Yeh, G. Gabrielli, A. 6666 Investigators., detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk, JAMA 307 (2012) 1394–1404, https://doi.org/10.1001/jama.2012.388.

[8] A.T. Stavros, D. Thickman, C.L. Rapp, M.A. Dennis, S.H. Parker, G.A. Sisney, Solid breast nodules: use of sonography to distinguish between benign and malignant lesions, Radiology 196 (1995) 123–134, https://doi.org/10.1148/radiology.196.1.7784555.

[9] J.R. Scheel, J.M. Lee, B.L. Sprague, C.I. Lee, C.D. Lehman, Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts, Am. J. Obstet. Gynecol. 212 (2015) 9–17, https://doi.org/10.1016/j.ajog.2014.06.048.

[10] R.G. Barr, K. Nakashima, D. Amy, D. Cosgrove, A. Farrokh, F. Schafer, J.C. Bamber, L. Castera, B.I. Choi, Y.-H. Chou, C.F. Dietrich, H. Ding, G. Ferraioli, C. Filice, M. Friedrich-Rust, T.J. Hall, K.R. Nightingale, M.L. Palmeri, T. Shiina, S. Suzuki, I. Sporea, S. Wilson, M. Kudo, WFUMB guidelines and recommendations for clinical use of ultrasound elastography: part 2: breast, Ultrasound Med. Biol. 41 (2015) 1148–1160, https://doi.org/10.1016/j.ultrasmedbio.2015.03.008.

[11] T. Faruk, M.K. Islam, S. Arefin, M.Z. Haq, The journey of elastography: background, current status, and future possibilities in breast cancer diagnosis, Clin. Breast Cancer 15 (2015) 313–324, https://doi.org/10.1016/j.clbc.2015.01.002.

[12] B. Liu, Y. Zheng, G. Huang, M. Lin, Q. Shan, Y. Lu, W. Tian, X. Xie, Breast lesions: quantitative diagnosis using ultrasound shear wave Elastography-a systematic review and meta-analysis, Ultrasound Med. Biol. 42 (2016) 835–847, https://doi.org/10.1016/j.ultrasmedbio.2015.10.024.

[13] C. Balleyguier, L. Ciolovan, S. Ammari, S. Canale, S. Sethom, R. Al Rouhbane, P. Vielh, C. Dromain, Breast elastography: the technical process and its applications, Diagn. Interv. Imaging 94 (2013) 503–513, https://doi.org/10.1016/j.diii.2013.02.006.

[14] R.M.S. Sigrist, J. Liau, A. El Kaffas, M.C. Chammas, J.K. Willmann, Ultrasound elastography: review of techniques and clinical applications, Theranostics 7 (2017) 1303–1329, https://doi.org/10.7150/thno.18650.

[15] J. Bamber, D. Cosgrove, C. Dietrich, J. Fromageau, J. Bojunga, F. Calliada, V. Cantisani, J.-M. Correas, M. D'Onofrio, E. Drakonaki, M. Fink, M. Friedrich-Rust, O. Gilja, R. Havre, C. Jenssen, A. Klauser, R. Ohlinger, A. Saftoiu, F. Schaefer, I. Sporea, F. Piscaglia, EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology, Ultraschall Der Medizin - Eur. J. Ultrasound. 34 (2013) 169–184, https://doi.org/10.1055/s-0033-1335205.

[16] F.W.-F. Au, S. Ghai, H. Moshonov, H. Kahn, C. Brennan, H. Dua, P. Crystal, Diagnostic performance of quantitative shear wave elastography in the evaluation of solid breast masses: determination of the most discriminatory parameter, AJR Am. J. Roentgenol. 203 (2014) W328–36, https://doi.org/10.2214/AJR.13.11693.

[17] T. Klotz, V. Boussion, F. Kwiatkowski, V. Dieu-de Fraissinette, A. Bailly-Glatre, S. Lemery, L. Boyer, Shear wave elastography contribution in ultrasound diagnosis management of breast lesions, Diagn. Interv. Imaging 95 (2014) 813–824, https://doi.org/10.1016/j.diii.2014.04.015.

[18] W.L. Ng, K. Rahmat, F. Fadzli, F.I. Rozalli, M.N. Mohd-Shah, P.A. Chandran, C.J. Westerhout, A. Vijayananthan, Y.F. Abdul Aziz, shearwave elastography increases diagnostic accuracy in characterization of breast lesions, Medicine (Baltimore) 95 (2016) e3146, , https://doi.org/10.1097/MD.0000000000003146.

[19] S. Xian-Quan, L.I. Jun-Lai, L.I. Qiu-Yang, H. Yan, W. Wen-Bo, T. Jie, Performance of ultrasonic shear wave elastography in assessing benign and malignant breast lesions, Zhongguo Yi Xue Ke Xue Yuan Xue Bao 37 (2015) 294–299, https://doi.org/10.3881/j.issn.1000-503X.2015.03.009.

[20] W.A. Berg, D.O. Cosgrove, C.J. Doré, F.K.W. Schäfer, W.E. Svensson, R.J. Hooley, R. Ohlinger, E.B. Mendelson, C. Balu-Maestro, M. Locatelli, C. Tourasse, B.C. Cavanaugh, V. Juhan, A.T. Stavros, A. Tardivon, J. Gay, J.-P. Henry, C. Cohen-Bacrie, BE1 Investigators, Shear-wave elastography improves the specificity of breast US: the BE1 multinational study of 939 masses, Radiology 262 (2012) 435–449, https://doi.org/10.1148/radiol.11110640.

[21] R.G. Barr, Z. Zhang, Shear-wave elastography of the breast: value of a quality measure and comparison with strain elastography, Radiology 275 (2015) 45–53, https://doi.org/10.1148/radiol.14132404.

[22] M. Golatta, M. Schweitzer-Martin, A. Harcos, S. Schott, C. Gomez, A. Stieber, G. Rauch, C. Domschke, J. Rom, F. Schütz, C. Sohn, J. Heil, Evaluation of virtual touch tissue imaging quantification, a new shear wave velocity imaging method, for breast lesion assessment by ultrasound, Biomed Res. Int. 2014 (2014) 960262, , https://doi.org/10.1155/2014/960262.

[23] Y. Xue, S. Yao, X. Li, H. Zhang, Benign and malignant breast lesions identification through the values derived from shear wave elastography: evidence for the meta-analysis, Oncotarget 8 (2017) 89173–89181, https://doi.org/10.18632/oncotarget.21124.

[24] G. Li, D.-W. Li, Y.-X. Fang, Y.-J. Song, Z.-J. Deng, J. Gao, Y. Xie, T.-S. Yin, L. Ying, K.-F. Tang, Performance of shear wave elastography for differentiation of benign and malignant solid breast masses, PLoS One 8 (2013) e76322, , https://doi.org/10.1371/journal.pone.0076322.

[25] L. Chen, J. He, G. Liu, K. Shao, M. Zhou, B. Li, X. Chen, Diagnostic performances of shear-wave elastography for identification of malignant breast lesions: a meta-analysis, J. Radiol. 32 (2014) 592–599, https://doi.org/10.1007/s11604-014-0349-2.

[26] E. Mendelson, M. Bohm-Vélez, W. Berg, E. Al, ACR-BIRADS® Ultrasound, 5th ed., American College of Radiology, Reston, 2013.

[27] W. Meng, G. Zhang, C. Wu, G. Wu, Y. Song, Z. Lu, Preliminary results of acoustic radiation force impulse (ARFI) ultrasound imaging of breast lesions, Ultrasound Med. Biol. 37 (2011) 1436–1443, https://doi.org/10.1016/j.ultrasmedbio.2011.05.022.

[28] M. Tozaki, M. Saito, J. Benson, L. Fan, S. Isobe, Shear wave velocity measurements for differential diagnosis of solid breast masses: a comparison between virtual touch quantification and virtual touch IQ, Ultrasound Med. Biol. 39 (2013) 2233–2245, https://doi.org/10.1016/j.ultrasmedbio.2013.07.012.

[29] S. Wojcinski, K. Brandhorst, G. Sadigh, P. Hillemanns, F. Degenhardt, Acoustic radiation force impulse imaging with Virtual Touch^{TM} tissue quantification: mean shear wave velocity of malignant and benign breast masses, Int. J. Womens Health 5 (2013) 619–627, https://doi.org/10.2147/IJWH.S50953.

[30] J. Zhou, W. Zhan, C. Chang, J. Zhang, Z. Yang, Y. Dong, C. Zhou, Y. Song, Role of acoustic shear wave velocity measurement in characterization of breast lesions, J. Ultrasound Med. 32 (2013) 285–294 (accessed January 14, 2018), http://www.ncbi.nlm.nih.gov/pubmed/23341385.

[31] K. Tamaki, N. Tamaki, Y. Kamada, K. Uehara, M. Miyashita, T. Ishida, H. Sasano, A non-invasive modality: the US virtual touch tissue quantification (VTTQ) for evaluation of breast cancer, Jpn. J. Clin. Oncol. 43 (2013) 889–895, https://doi.org/10.1093/jjco/hyt098.

[32] M. Yao, J. Wu, L. Zou, G. Xu, J. Xie, R. Wu, H. Xu, Diagnostic value of virtual touch tissue quantification for breast lesions with different size, Biomed Res. Int. 2014 (2014) 1–7, https://doi.org/10.1155/2014/142504.

[33] V. Ianculescu, L.M. Ciolovan, A. Dunant, P. Vielh, C. Mazouni, S. Delaloge, C. Dromain, A. Blidaru, C. Balleyguier, Added value of Virtual Touch IQ shear wave elastography in the ultrasound assessment of breast lesions, Eur. J. Radiol. 83 (2014) 773–777, https://doi.org/10.1016/j.ejrad.2014.01.021.

[34] R.G. Barr, Z. Zhang, Shear-wave elastography of the breast: value of a quality measure and comparison with strain elastography, Radiology 275 (2015) 45–53, https://doi.org/10.1148/radiol.14132404.

[35] M. Costantini, P. Belli, R. Lombardi, G. Franceschini, A. Mulè, L. Bonomo, Characterization of solid breast masses: use of the sonographic breast imaging reporting and data system lexicon, J. Ultrasound Med. 25 (2006) 649–659 quiz 661 http://www.ncbi.nlm.nih.gov/pubmed/16632790 (Accessed December 29, 2017)..

[36] A. Feldmann, C. Langlois, M. Dewailly, E.F. Martinez, L. Boulanger, O. Kerdraon, N. Faye, Shear wave elastography (SWE): an analysis of breast lesion characterization in 83 breast lesions, Ultrasound Med. Biol. 41 (2015) 2594–2604, https://doi.org/10.1016/j.ultrasmedbio.2015.05.019.

[37] R.M. Jales, M.T. Dória, K.P. Serra, M.M. Miranda, C.A. Menossi, K. Schumacher, L.O. Sarian, Power doppler ultrasonography and shear wave elastography as complementary imaging methods for suspected local breast cancer recurrence, J. Ultrasound Med. (2017), https://doi.org/10.1002/jum.14493.

[38] Y.-T. Wu, S.-T. Chen, C.-J. Chen, Y.-L. Kuo, L.-M. Tseng, D.-R. Chen, S.-J. Kuo, H.-W. Lai, Breast cancer arising within fibroadenoma: collective analysis of case reports in the literature and hints on treatment policy, World J. Surg. Oncol. 12 (2014) 335, https://doi.org/10.1186/1477-7819-12-335.

[39] J.M. Chang, W.K. Moon, N. Cho, A. Yi, H.R. Koo, W. Han, D.-Y. Noh, H.-G. Moon, S.J. Kim, Clinical application of shear wave elastography (SWE) in the diagnosis of benign and malignant breast diseases, Breast Cancer Res. Treat. 129 (2011) 89–97, https://doi.org/10.1007/s10549-011-1627-7.

[40] S.J. Vinnicombe, P. Whelehan, K. Thomson, D. McLean, C.A. Purdie, L.B. Jordan, S. Hubbard, A.J. Evans, What are the characteristics of breast cancers misclassified as benign by quantitative ultrasound shear wave elastography? Eur. Radiol. 24 (2014) 921–926, https://doi.org/10.1007/s00330-013-3079-4.

[41] M.Y. Kim, N. Choi, J.-H. Yang, Y.B. Yoo, K.S. Park, False positive or negative results of shear-wave elastography in differentiating benign from malignant breast masses: analysis of clinical and ultrasonographic characteristics, Acta Radiol. 56 (2015) 1155–1162, https://doi.org/10.1177/0284185114551400.