Microstructural breast tissue characterization: A head-to-head comparison of Diffusion Weighted Imaging and Acoustic Radiation Force Impulse elastography with clinical implications

Panagiotis Kapetas, Paola Clauser, Ruxandra-Iulia Milos, Sara Vigano, Maria Bernathova, Thomas H. Helbich, Pascal A.T. Baltzer

Medical University of Vienna, Department of Biomedical Imaging and Image-guided Therapy, Waehringer Guertel 18-20, 1090 Vienna, Austria
Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Via della Commenda 10, 20122 Milan, Italy

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ABSTRACT

Purpose: Head-to-head comparison of Diffusion Weighted Imaging (DWI) and Acoustic Radiation Force Impulse (ARFI) elastography regarding the characterization of breast lesions in an assessment setting.

Method: Patients undergoing an ultrasound examination including ARFI and an MRI protocol including DWI for the characterization of a BI-RADS 3–5 breast lesion between 06/2013 and 10/2016 were eligible for inclusion in this retrospective, IRB-approved study. 60 patients (30–84 years, median 50) with a median lesion size of 16 mm (range 5–55 mm) were included. The maximum shear wave velocity (SWV<sub>max</sub>) and mean apparent diffusion coefficient (ADC<sub>mean</sub>) for each lesion were retrospectively evaluated by a radiologist experienced in the technique. Histology was the reference standard. Diagnostic performances of ARFI and DWI were assessed using ROC curve analysis. Spearman’s rank correlation coefficient and multivariate logistic regression were used to investigate the independence of both tests regarding their diagnostic information to distinguish benign from malignant lesions.

Results: Corresponding areas under the ROC curve for differentiation of benign (n = 16) and malignant (n = 49) lesions were 0.822 (ARFI) and 0.871 (DWI, p-value = 0.48). SWV<sub>max</sub> and ADC<sub>mean</sub> values showed a significant negative correlation (ρ = −0.501, p-value < 0.001). In multivariate analysis, combination of ARFI and DWI did not improve the results of each single modality, thus no significant independent diagnostic information was present.

Conclusion: Significant correlation between quantitative findings of ARFI and DWI in breast lesions exists. Thus, ARFI provides similar diagnostic information as a DWI-including protocol of an additional “problem-solving” MRI for the characterization of a sonographically evident breast lesion, improving the immediate patient management in the assessment setting.

1. Introduction

Breast cancer is the leading cause of cancer-related death among women worldwide [1]. For screening purposes, mammography is the first-line imaging modality with a proven efficacy in the reduction of breast cancer mortality [2]. However, in the assessment setting, there is usually the need for the characterization of a breast lesion identified either in screening (recall) or as a clinical abnormality (e.g. palpable lesion, nipple discharge). To that aim further imaging modalities are additionally implemented, the most important of which being ultrasound (US) and Magnetic Resonance Imaging (MRI) (Fig. 1). Breast US is the most usually implemented imaging modality to

Abbreviations: ADC, Apparent Diffusion Coefficient; ARFI, Acoustic Radiation Force Impulse; DCIS, Ductal Carcinoma In Situ; DWI, Diffusion Weighted Imaging; ECM, Extracellular Matrix; IC NST, Invasive Carcinoma of No Special Type; MRI, Magnetic Resonance Imaging; SWE, Shear Wave Elastography; SWV, Shear Wave Velocity; US, Ultrasound; VTIQ, Virtual Touch IQ.

* Corresponding author.
E-mail addresses: panagiotis.kapetas@meduniwien.ac.at (P. Kapetas), paola.clauser@meduniwien.ac.at (P. Clauser), ruxandra-iulia.milos@meduniwien.ac.at (R.-I. Milos), maria.bernathova@meduniwien.ac.at (M. Bernathova), thomas.helbich@meduniwien.ac.at (T.H. Helbich), pascal.baltzer@meduniwien.ac.at (P.A.T. Baltzer).

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further evaluate a mammographic or clinical breast abnormality. However, even when using established diagnostic criteria as described in the Breast Imaging Reporting and Data System (BI-RADS) lexicon [3], B-mode US shows an inherently low specificity [4], leading to a substantial number of unnecessary breast biopsies. These not only carry a psychological burden for the patient but also increase healthcare costs.

To increase the specificity of breast US, different modalities beyond the standard B-mode are additionally used. One of these is elastography, which is based on the evaluation of tissue stiffness [5]. Shear-wave elastography (SWE) has been developed in recent years. Here, an acoustic push pulse generates shear waves in the underlying tissue, which propagate perpendicularly to the US beam. Acoustic Radiation Force Impulse (ARFI) is a SWE imaging technique, where the propagation speed of the shear waves can be measured using a series of diagnostic pulses. Cancer-induced changes in tissue stiffness reflect changes in the extracellular matrix (ECM) and the cellularity of the tumour [6,7] and malignant breast lesions tend to be stiffer than benign ones or normal parenchyma. Since shear waves propagate faster in stiffer tissue, ARFI has been shown by several studies to be accurate in the identification of malignant breast lesions [8–10].

A further imaging modality often used in the assessment setting for the characterization of a known breast lesion is MRI. Standard breast MRI is based on the use of an intravenous contrast medium. However, not all enhancing lesions are malignant and often, benign lesions are classified as suspicious, especially by less experienced readers [11], resulting again in nonessential biopsy recommendations. In order to improve lesion characterization in breast MRI, several approaches have been implemented. One of the most widely used MRI techniques for this purpose is diffusion-weighted imaging (DWI). DWI is based on the measurement of the random (Brownian) movement of water molecules in tissue [12]. This movement is affected by the tumour cellularity and stromal characteristics [13,14]. The quantification of water molecule movement can be achieved by calculation of the apparent diffusion coefficient (ADC), for which different b-values (i.e. degrees of diffusion weighting) are used [15]. Breast cancer normally demonstrates a hindered diffusion of water molecules due to the interplay of increased cellularity and stromal desmoplastic reaction, resulting into low ADC values [16,17].

In this respect, both DWI and ARFI offer an insight into the microstructural tissue properties of tumours [7,18]. Additionally, both techniques provide numeric values of ADC or shear-wave-velocity (SWV) respectively, thus allowing for quantitative and reproducible results [8,19,20]. However, DWI is part of a costly and time-consuming MRI protocol, whereas ARFI only necessitates seconds of measurement on an US device. Moreover, US machines are ubiquitously available whereas MRI scanning capacities are limited, especially in developing parts of the world. Finally, some patients cannot receive an MRI examination due to contraindications, including non-compatible implants or claustrophobia. Due to a lack of empirical data, we aimed at comparing the diagnostic performance of DWI and ARFI elastography for breast lesions.

We hypothesized that ARFI and DWI provide largely redundant information regarding tumour characterization and the aim of this study was to evaluate the association between quantitative ARFI and DWI metrics and compare their diagnostic performance in an assessment setting.

2. Material and methods

2.1. Patients

This was an IRB-approved, retrospective, cross-sectional study. Due to its retrospective nature, the necessity for informed consent was waived by the local IRB. A breast imaging fellow (S.V.), under the supervision of an experienced breast radiologist (P.K., 11 years of experience), searched the local PACS database to identify all patients who underwent a breast US examination which included ARFI imaging and a breast MRI between June 2013 and October 2016. In order to be included in the analysis, following criteria needed to be met: female gender; patient age $\geq 18$ years; time difference between the US and the MRI examination of no more than 3 weeks; a DWI sequence of adequate quality included in the MRI protocol; calculation of an ADC map; a BI-RADS 3–5 breast lesion visible on both US and the ADC map; quantitative measurement of the maximum SWV ($SWV_{\text{max}}$) on the ARFI image; histopathological verification of the lesion with an image-guided biopsy.
or surgery. Patients were excluded if the lesion had already been biopsied prior to one of the two examinations. Out of overall identified 320 patients, 60 (median age 50 years, age range 30–84 years) met the inclusion and exclusion criteria and were included in this study. Fig. 2 shows the study inclusions and exclusions.

2.2. Ultrasound examinations

All examinations were performed in the Breast Imaging Division of the Department of Biomedical Imaging and Image-guided Therapy of BLINDED FOR REVIEW using the same Siemens Acuson S3000 device (Siemens Healthineers, Mountain View, CA, USA) by one out of a pool of five experienced breast radiologists (P.K., P.C., R.-I.M., M.B., P.A.T.B.; experience 5–17 years). All of them had an experience in the use of elastography in clinical routine for at least one year. A linear 9L4 transducer was used for the ARFI examinations.

All ARFI examinations were performed using the Virtual Touch IQ (VTIQ) technology, which is based on the generation of pushing pulses from the transducer that induce longitudinal shear waves in the examined tissue. The propagation speed of the shear waves can be locally measured using a $2 \times 2$ mm quantification ROI. Image acquisition does not rely on manual pressure from the examiner and is performed by applying minimal pre-compression [8,21]. Placement of the quantification ROI at the tumour area, which is perceived by the examiner to be the stiffest in the color-coded elastogram, enables measurement of the $SWV_{max}$ of the tumour. We chose to include patients examined only until October 2016 in order to make sure that a subsequent software update would not influence the measurements acquired.

Fig. 2. Flowchart showing patient inclusions and exclusions.
2.3. MRI examinations

Our hospital is a tertiary assessment centre - therefore some of the MRI examinations had been performed locally and some in other referring institutions. Different 1.5 T and 3 T MRI scanners and variable DWI sequences had been used; however, all scans had been performed according to international guidelines (EUSOBI, EUSOMA) [22,23]. DWI sequences with at least two different b values (e.g. 0 and 800 or 1000 sec/mm²) had been acquired in all included examinations and an apparent diffusion coefficient (ADC) map had been calculated, according to the equation:

\[ \text{ADC} = \ln(S_1/S_2)/(b_2 - b_1) \]

with \( b_1 \) being the minimum b value, \( b_2 \) the maximum, \( S_1 \) the signal intensity at \( b_1 \) and \( S_2 \) the signal intensity at \( b_2 \).

2.4. Data acquisition

Only one lesion was included for each patient. All ARFI examinations were reviewed by a dedicated breast radiologist (P.K.), who identified the lesion laterality, location and size and recorded its SWV max. The MRI examinations were subsequently reviewed by a breast imaging fellow (S.V.), who, knowing the previously mentioned lesion characteristics, identified the lesions on the ADC map and manually drew a ROI to measure their mean ADC values. The size of the ROI could vary between 3 and 6 mm², according to the lesion size. Both reviewers were blinded to the findings of the other modality and the pathologic results of each lesion.

2.5. Histopathological examination

All lesions underwent US-guided biopsy with a 14G biopsy system (BIP-HistoCore®; BIP Medical, Tuernefeld, Germany). The histopathological biopsy results were used as the standard of reference, unless the patient received an excisional biopsy due to a lesion of uncertain malignant potential. In the latter case, the postsurgical histopathological result served as the reference standard.

2.6. Statistical analysis

Statistical analysis was performed using the MedCalc 20 (MedCalc Software bvba, Ostend, Belgium, 2013) and SPSS 20.0.0 (IBM Corp, Armonk NY, 2012) software. The Kolmogorov-Smirnov test was used to evaluate the distribution of all variables. The diagnostic performance of both ARFI imaging and DWI was assessed using receiver operating characteristics (ROC) curve analysis and the DeLong’s test was used to compare the resulting ROC curves. Sensitivity, specificity, positive and negative likelihood ratios were calculated for each modality. A cut-off value providing a sensitivity of >90% and thus effectively ruling out malignancy was selected for the further analysis and the McNemar test was used to compare sensitivities and specificities of the two modalities. Uni- and multivariate logistic regression with forward feature selection were used to evaluate independent predictors of malignancy. The correlation between the SWV max and ADC values was assessed by the Spearman’s rank correlation coefficient (\( \rho \)). Regression analysis and Bland Altman plots were used to evaluate the potential for interchangeable value prediction between the two modalities. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Out of all 60 lesions (median size 16 mm, size range 5–55 mm), 16 were benign (median size 15 mm, size range 7–50 mm) and 44 malignant (median size 17 mm, size range 5–55 mm). The most usual benign lesions were fibrocystic change (5 patients) and papilloma (3 patients), while the most usual malignancy was invasive carcinoma of no special type (IC NST-28 patients). Table 1 shows an overview of all pathologic results.

3.2. Diagnostic performance of ARFI elastography

The area under the ROC curve (AUC) of quantitative ARFI elastography for the differentiation of benign and malignant lesions was 0.822 (95% CI 0.700–0.906, p-value <0.001). At a SWV max cut-off value of 2.33 m/s, sensitivity, specificity, positive and negative likelihood ratios were 95.5%, 43.8%, 1.66 and 0.16. Table 2 provides more details regarding the diagnostic performance of DWI with ADC measurements. Fig. 3 shows the US (a-b) and MRI (c-d) examinations of a patient with a malignant lesion.

3.3. Diagnostic performance of DWI

Quantitative DWI with ADC mapping demonstrated an AUC of 0.871 (95% CI 0.759–0.943, p-value <0.001). The corresponding sensitivity, specificity, positive and negative likelihood ratios at an ADCmean cut-off value of 1081 * 10⁻⁶ mm²/s were 93.2%, 43.8%, 1.66 and 0.16. Table 2 provides more details regarding the diagnostic performance of DWI with ADC measurements. Fig. 3 shows the US (a-b) and MRI (c-d) examinations of a patient with a malignant lesion.

3.4. Comparison of the diagnostic performances of ARFI and DWI

Both modalities showed a high diagnostic performance as measured by the AUC and the difference between them was not statistically significant (p-value = 0.48). There was also no statistically significant difference between the sensitivities and specificities of ARFI elastography and DWI (corresponding p-values 0.73 and 0.63). The comparison of the AUCs of both modalities is demonstrated in Fig. 4.

3.5. Correlation of ARFI elastography with DWI and association with malignancy

The Kolmogorov-Smirnov test showed that the SWV max and ADCmean values did not follow a normal distribution, thus their correlation was evaluated using the Spearman’s rank correlation coefficient (\( \rho \)). The two modalities demonstrated a significant (p-value = <0.001) albeit moderate negative correlation (\( \rho = –0.501 \)).

In the univariate analysis, high SWV max in ARFI elastography and low ADCmean values in DWI were both significantly associated with the presence of malignancy (corresponding p-values were 0.001 and <0.001).

Multivariate logistic regression demonstrated only ADCmean Values to be independently associated with malignancy (OR = 0.988, 95 %CI = 0.981–0.995, p-value = <0.001).

3.6. Prediction of ADC values based on SWV measurements

Regression analysis was performed to predict ADCmean values based on SWVmax measurements and revealed the equation “ADCmean = 1094.25 + (–26.56 × SWVmax)” (p-value = <0.001). The corresponding coefficient of determination (R²) was 0.242 and the adjusted R² was 0.229, proving the value of the prediction model. This was further validated by a Bland Altman plot, which demonstrated no systematic difference between the predicted and the actual ADCmean values as well as narrow limits of agreement of <30% (Fig. 5).

4. Discussion

The results of this study show that there is a significant negative correlation between the US-acquired SWVmax and MRI-acquired ADCmean values of breast lesions. Since both modalities have a similar
Table 1
Detailed pathologic results of all included patients. na: not applicable.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Benign Lesions</th>
<th>Malignant Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td>n (16)</td>
<td>Median size (mm)</td>
</tr>
<tr>
<td>Fibrocystic change</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Papilloma</td>
<td>4</td>
<td>14.5</td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Scar</td>
<td>2</td>
<td>8.5</td>
</tr>
<tr>
<td>Invasive carcinoma NST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive mucinous carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic neuroendocrine carcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Diagnostic performance of Acoustic Radiation Force Impulse (ARFI) elastography and z (DWI). A cut-off value providing a sensitivity of >90% has been chosen for the analysis. Sensitivity, specificity and the corresponding 95% confidence intervals (CI) are given in %. SWV_{max} = maximum shear wave velocity, ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristic curve, LR = likelihood ratio.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Quantitative parameter</th>
<th>AUC 95% CI</th>
<th>Cut-off</th>
<th>Sensitivity 95% CI</th>
<th>Specificity 95% CI</th>
<th>+LR 95% CI</th>
<th>-LR 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARFI elastography</td>
<td>SWV_{max}</td>
<td>0.822</td>
<td>&gt;2.33 m/s</td>
<td>95.5</td>
<td>84.5-99.4</td>
<td>19.8-70.1</td>
<td>1.70</td>
<td>1.1-2.6</td>
</tr>
<tr>
<td>DWI</td>
<td>ADC</td>
<td>0.871</td>
<td>≤1081 * 10^{-6} mm²/s</td>
<td>93.2</td>
<td>81.3-98.6</td>
<td>43.8</td>
<td>19.8-70.1</td>
<td>1.66</td>
</tr>
</tbody>
</table>

Fig. 3. 52 year old female presenting with a palpable lump in the right breast. B-mode US (a.) demonstrates a non-circumscribed, complex cystic and solid lesion with posterior enhancement, which was classified as BI-RADS 4. The lesion shows a high stiffness in ARFI elastography, with a SWV_{max} of 9.22 m/s (b.). On MRI, the lesion shows an intense enhancement after administration of contrast medium (c.). The lesion (inside the red circle) demonstrates a restricted diffusion, which in the ADC map corresponds to an ADC_{mean} value of 772 * 10^{-6} mm²/s (d.). US-guided biopsy proved a grade 2, luminal B IC NST.

accuracy for the differentiation of benign from malignant lesions, application of ARFI elastography may be used for the characterization of a sonographically evident breast lesion with achieving the same diagnostic certainty as a DWI-including protocol of an additional MRI examination, thus improving the immediate patient management.

Contrary to screening, the assessment setting is associated with the characterization of a known breast lesion. Within the scope of an assessment examination, a breast radiologist is often confronted with the question whether a biopsy of the lesion is necessary or not. Image-guided biopsies are generally considered a safe and accurate way of tissue acquisition for breast lesions [24-26]. However, they carry both a substantial psychological burden for the patient as well as a financial cost for the healthcare system [27]. At the same time they are time consuming and, as any interventional technique, carry the potential of complications, although usually minor [28]. Thus, a central goal of breast imaging in the assessment setting is to improve breast lesion...
Weighted Imaging. be safely used for the further characterization of BI-RADS 4 breast findings at conventional imaging [30]. While this indication of breast setting as a high sensitivity needs to be retained, so that no significant number of cancer cases will be overlooked.

Although current guidelines discourage the use of MRI to avoid biopsy of a conventionally suspicious (BI-RADS 4) lesion [22,23,29], a recent survey by the European Society of Breast Imaging (EUSOBI) demonstrated that breast MRI is usually performed in the assessment setting as a “problem-solving” modality for patients with inconclusive findings at conventional imaging [30]. While this indication of breast MRI is still controversial, Strobel et al [31] demonstrated that MRI can be safely used for the further characterization of BI-RADS 4 breast lesions. A more recent meta-analysis came to similar conclusions regarding non-calcified breast lesions [32]. Still, although MRI examinations are often used in everyday routine for this indication, they are costly, have limited availability and, most important in our clinical practice, necessitate additional scheduling, which leads to a delay in patient management.

Quantitative DWI with ADC calculation is an established modality included in multiparametric breast MRI protocols for the characterization of breast lesions and identification of unequivocally benign ones [16], thus obviating a substantial number of unnecessary biopsies [33,34]. In line with previous research, application of a cut-off value of 1081 × 10^-6 mm²/s in our patient cohort could obviate more than 40% of all biopsies with benign results, maintaining a high sensitivity of 93.2%.

On the other hand, ARFI is a type of US SWE technique, which provides information regarding tissue stiffness. It is performed during the US examination and leads to an increase of the specificity of B-mode US. Thus, it also has the potential to significantly reduce the number of unnecessary biopsy recommendations caused by false-positive B-mode results [35-37]. In our study, using a threshold of 2.33 m/s could correctly classify more than 40% of biopsied benign lesions as such, rendering their histologic work-up unnecessary. At the same time, the corresponding sensitivity of 95.5% resulted in the correct identification of the vast majority of malignancies, proving its clinical value in an assessment setting.

Both DWI and ARFI elastography inherently offer an insight into microstructural tissue properties. However, the exact tumoral characteristics, leading to alterations of diffusivity or stiffness have not been completely elucidated up to now. Tumourcellularity appears to be weakly-to-moderately inversely correlated to ADC values [38]; however, tumour cells are typically softer than normal cells [7]. It appears that other factors, such as changes in the tumoral extracellular matrix (ECM) may also play a substantial role [7,18]. Fibrosis e.g. is known to lead to both a restricted diffusion [39] as well as an increase in tissue stiffness [40]. This last correlation has also been demonstrated for fibrotic breast lesions [41]. These changes of the ECM are dynamic processes based on alterations of its chemical composition and spatial arrangement of its components and lead to tumour-associated desmoplasic reaction, which in turn affects different cell behaviours [42,43].

Since both modalities are influenced by and reflect extracellular tissue properties, our goal was to investigate whether the diagnostic information they provide is similar or independent from each other. In this study, ARFI and DWI demonstrated a comparably high diagnostic performance, with corresponding AUCs of 0.822 and 0.871. Neither the differences between the AUCs nor between sensitivities and specificities of the two modalities were statistically significant. At the same time, the results of the multivariate logistic regression showed that the combination of both did not improve the performance of each single modality, proving that the diagnostic information of ARFI and DWI is practically redundant for the characterization of breast lesions. Thus, ARFI elastography can be safely used to evaluate equivocal breast lesions with the potential to avoid further imaging used for breast lesion characterization, such as DWI. Moreover, the prompt availability of an ARFI examination facilitates the decision as to whether to perform a biopsy or not for sonographically evident lesions. DCIS is known to demonstrate higher ADC values as compared to invasive cancers [44,45], which is also confirmed by our results. On the other hand, 2 small invasive carcinomas were false negative in ARFI: a grade 2, Luminal A IC NST of 10 mm and a grade 1, Luminal B IC NST of 5 mm (Fig. 6). This is also in line with previous literature demonstrating that small lesion size is a factor, which often leads to false
negative results in SWE [46,47].

To our knowledge, this is the first study directly comparing the diagnostic performance of quantitative ARFI elastography and DWI for the evaluation of breast lesions. Rafaelsen et al. [48] evaluated ARFI and DWI in patients with rectal cancer and identified a strong inverse correlation between the two ($r = -0.65$, $p < 0.0001$). Our results are in line with this study, demonstrating a linear relationship between SWV and ADC measurements.

Latif et al. [49] compared strain elastography and quantitative DWI for the evaluation of enlarged axillary lymph nodes. In this study, the sensitivity and accuracy of DWI were slightly higher as compared to elastography, while the specificity was the same. However, the authors of this study did not perform a correlation analysis between the two modalities. On the other hand, Matsubayashi et al. [41] investigated the correlation between strain elastography and MRI findings, including, among others, ADC values in fibrotic breast lesions. The authors could demonstrate a significant correlation between the elasticity score and the ADC of breast lesions; however, in their study, ADC did not correlate with the degree of fibrosis, as opposed to other reports. In another study, Satake et al. [50] evaluated strain elastography and DWI for the characterization of BI-RADS 4 and 5 breast lesions. In their multivariate analysis, only the elasticity score was predictive of malignancy for BI-RADS 4 lesions, which seemingly contradicts our results. Due to the lack of data it cannot be concluded whether this difference is due to patient selection, technical differences or underlying biological phenomena.

The main limitation of our study was the relatively small patient number, which was due to its retrospective nature and the necessity for patients to have undergone both an US examination including ARFI elastography and an MRI of the breast including a DWI measurement in a small time frame. Obviously, a prospective study with a larger number of patients would be necessary to verify our results and establish cut-off values, ideally in a multicentric setting using several US devices. Moreover, since our hospital is a tertiary breast assessment centre, the number of benign lesions in the study population is relatively low. Finally, we did not perform an exact radiologic-pathologic correlation of the intralesional areas demonstrating stiffness or diffusivity alterations with the corresponding histopathological slices.

In conclusion, there is a significant correlation between quantitative findings of ARFI elastography and DWI in breast lesions. Thus, ARFI elastography has the potential to be used for the characterization of a sonographically evident breast lesion achieving similar diagnostic certainty as a DWI-including protocol of an additional "problem-solving" MRI examination, improving the immediate patient management in the assessment setting.

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CRediT authorship contribution statement

Panagiotis Kapetas: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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