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Ultrasound shear-wave elasticity and magnetic resonance diffusion coefficient show strong inverse correlation in small fibroadenomas

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ABSTRACT

Objective: Stiffness of breast lesions helps distinguish malignant from benign solid masses. Stiffness can be quantitatively measured by magnetic resonance and ultrasound imaging using apparent diffusion coefficient (ADC) and shear-wave elastography (SWE) techniques, respectively. This study aims to analyze correlations between SWE and ADC in biopsy-proven small fibroadenomas.

Patients and Methods: Shear-wave elastography and ADC measurements of 50 fibroadenomas were evaluated retrospectively. Mean patient age was 41±13 years (range 27-63). All lesions had maximum diameters of ≤20 millimeters. Correlations between intralesional ADC, lesion-parenchyma ADC ratio, intralesional SWE, SWE heterogeneity index and lesion volume were analyzed.

Results: Mean values of lesions were as follows: ADC=1.71±0.22 x10-3mm2/s, ADC ratio=1.04±0.09, maximum SWE=73.4±28.8 kPa, minimum SWE=43.9±21.8 kPa and SWE heterogeneity index =29.4±12.7 kPa. There was a strong inverse correlation between fibroadenoma ADC and SWE values (rho = – 0.746, p <0.01). Significant correlations were also found between fibroadenoma volume and ADC (rho = – 0.525, p <0.05) and SWE (rho = 0.840, p <0.01).

Conclusion: Apparent diffusion coefficient and SWE values show strong inverse correlation in small fibroadenomas. If proven threshold values for lesion characterization are revealed, ultrasonographic SWE and diffusion-weighted MRI have potential to be used interchangeably.

Keywords: Apparent diffusion coefficient, Fibroadenoma of breast, Magnetic resonance imaging, Ultrasound shear-wave elastography

1. INTRODUCTION

Stiffness of breast lesions helps distinguish malignant from benign solid masses. Tissue stiffness can be quantitatively and objectively assessed by magnetic resonance and ultrasound imaging using apparent diffusion coefficient (ADC) and shear-wave elastography (SWE) techniques, respectively. Diffusion-weighted magnetic resonance imaging (DW-MRI) is based on random diffusivity principle of water molecules. Diffusivity is impeded within dense and highly cellular tissues and can be quantitatively measured as ADC values. Ultrasound SWE, on the other hand, uses acoustic energy pulses to generate shear waves causing transient displacements in tissue which are then measured as shear moduli as absolute measures of tissue elasticity. Both techniques have previously been proven to be useful adjuncts in determining malignancy risk of large solid breast masses [1, 2]. This study, on the other hand, aims to analyze correlations between SWE and ADC in a rather overlooked category of breast lesions, namely biopsy-proven small fibroadenomas.

2. PATIENTS and METHODS

Approval for the study was obtained from the Ethics Committee of Marmara University, School of Medicine with the decision numbered 2018.478. A total of 50 consecutive female patients with biopsy proven solitary fibroadenomas of maximum diameter ≤20 millimeters within a one year period, from May 2018 till May 2019, were included after consenting to usage of relevant medical information in written form during follow-up clinical visits. Routine pre-biopsy diagnostic magnetic resonance and ultrasound studies were reviewed for ADC and SWE measurements.

Diagnostic breast MRI were realized using a 1.5 Tesla scanner (Optiva, General Electrics, USA) with the patient in prone position and both breasts in bilateral 16-channel phased array dedicated breast coils. DW-MRI examination was performed using a pre-contrast axial single-shot echo planar imaging (EPI) sequence with fat suppression and b values of 0, 400, and 800 s/mm^2. TR/TE was 6055/69 ms and FOV was 350 mm. A 3.5 mm slice thickness and

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a matrix of 128x96 was employed. ADC maps were automatically calculated by MRI scanner. ADC measurement of lesions were performed using specialized software (AW Volume Share, version 5, General Electrics, USA) by manually placing region of interest (ROI) on the largest cross-section of lesions (Figure 1). ADC values were recorded in units of mm^2/s and control ADC measurements from contralateral breast parenchyma were also made in order to obtain a lesion to parenchyma ADC ratio.

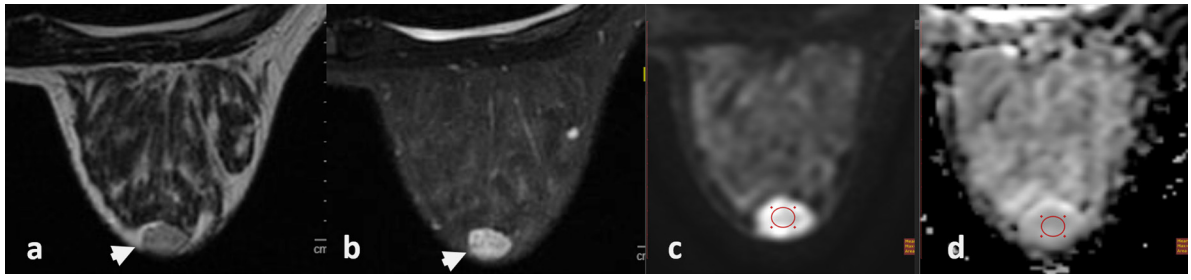

Figure 1. *A 27-year-old female presenting with enlarging periareolar mass. (a) T2-weighted axial and (b) Fat-saturated T2-weighted axial images delineate a well-circumscribed oval retroareolar lesion (arrowheads). (c) Diffusion-weighted imaging and (d) corresponding Apparent Diffusion Coefficient maps show restricted water diffusion within the lesion. ADC measurements are performed using a free-hand elliptical ROI (ovals).*

Pre-biopsy SWE of lesions was performed using a 12-16 MHz linear probe and a dedicated ultrasound system (Logic S8, General Electrics, USA) by a single operator who had over 15 years of experience in breast imaging and previous practice of SWE in different patient populations. Sonoelastographic measurements were made with the transducer held perpendicular to the skin while applying minimal pressure during one single breath-hold. A standard circular ROI of $2.25mm^2$ area was used and intralesional maximum and minimum elasticity (E_{max} and E_{min}) were measured in units of kilopascals (kPa) (Figure 2). Lesion volume was calculated using formula for spheroid volume, i.e. $V = 4/3 \times \pi \times r1 \times r2 \times r3$; and SWE heterogeneity indices (HI) were calculated according to formula $HI = E_{max} - E_{min}$.

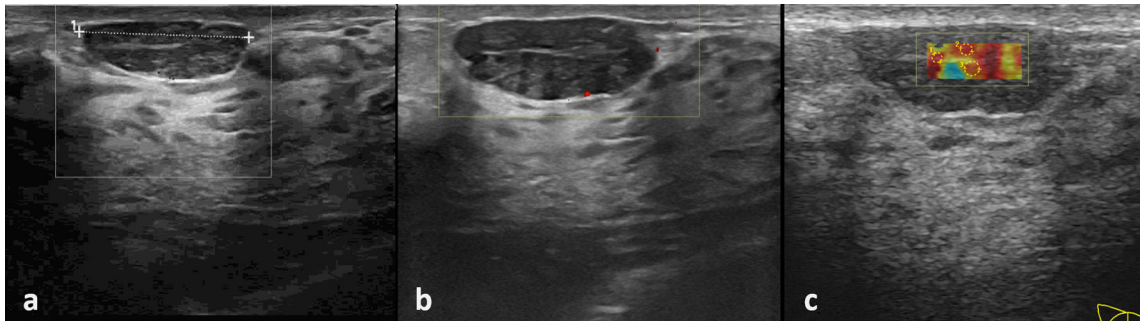

Figure 2. *(a) Ultrasound image of retroareolar mass of the same patient. (b) Lesion had interval enlargement within one-year clinical follow-up, and was therefore sampled. Pathological diagnosis was consistent with fibroadenoma. (c) Shear-wave elastography of the lesion.*

Statistical Analyses

Statistical analyses were performed using a commercially available software package (SPSS Advanced Statistics module, version 21.0, IBM, USA) and potential correlations among ADC measurements, i.e. intralesional ADC and lesion-to-parenchyma ADC ratio (ADC_{ratio}), and SWE values, namely E_{max}, E_{min} and HI, were sought. Correlation strength was categorized based on Spearman's correlation coefficient obtained from analyses (Table I). The Mann-Whitney U test was used to compare continuous data between groups. The results were evaluated at a 95% confidence interval. $p < 0.05$ was considered significant.

Table I. *Strength of linear relationship corresponding to correlation coefficient value (Spearman's rho).*

Correlation coefficient value (rho=)	Strength of correlation
0.80 – 0.99	Very Strong
0.60 – 0.79	Strong
0.40 – 0.59	Moderate
0.01 – 0.39	Poor

3. RESULTS

Patient ages ranged from 27 to 63 years (mean 41±13 years). Mean lesion volume was 735 mm^3 while median volume was

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434 mm^3 and volumes ranged from 113 to 3751 mm^3. Mean ADC of lesions was 1.71±0.22 $x10^{-3}$ mm^2/s (range 1.37 to 2.11 $x10^{-3}$ mm^2/s). Mean lesion to normal parenchyma ADC ratio was 1.04±0.9 and ranged from 0.90 to 1.21. Mean elasticity measurements of lesions were as follows: E_{max}=73.4±28.8 kPa (range 41-133 kPa), E_{min}=43.9±21.8 kPa (range 15-84 kPa) and HI=29.4±12.7 kPa (range 12-61 kPa).

A strong inverse correlation was found between ADC and E_{max} of fibroadenomas (rho = – 0.746, p <0.01) (Figure 3). Additionally, there were a strong inverse correlation among mean ADC and E_{min} (rho = – 0.661, p=0.003) and a moderate inverse correlation between ADC and HI (rho = – 0.538, p=0.001). ADC_{ratio} and E_{max} had a moderate inverse correlation (rho = – 0.525, p <0.01) (Figure 4). There were no statistically significant correlations among ADC_{ratio} and E_{min} or HI (rho = – 0.335, p=0.013 and rho = – 0.248, p=0.071, respectively).

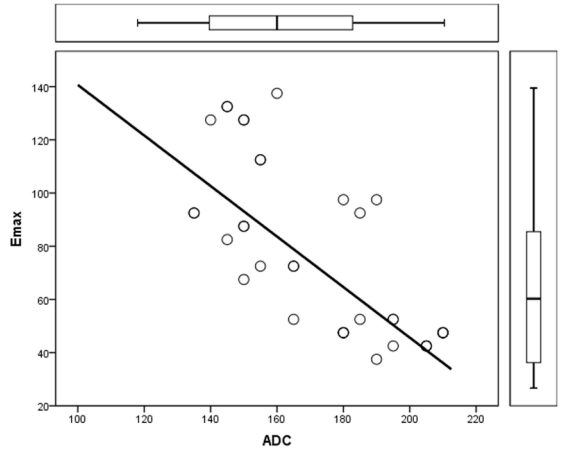

***Figure 3**. A strong inverse correlation was found between apparent diffusion coefficient (ADC) and maximal elasticity (Emax) of fibroadenomas (Spearman's rho = – 0.746, p <0.01). ADC is presented in units of $x10^{-5}$ mm^2/s.*

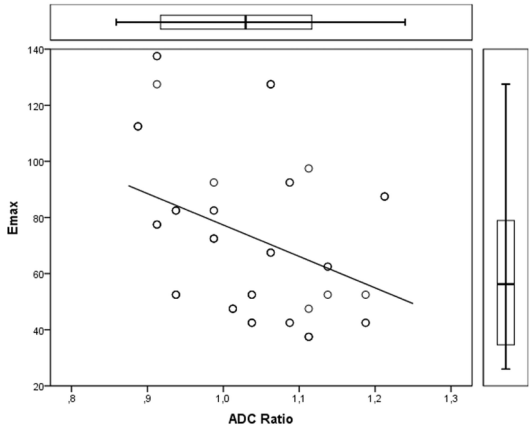

***Figure 4.** Lesion to parenchyma ratio of apparent diffusion coefficient (ADC_{ratio}) and maximal elasticity (E_{max}) of fibroadenomas had a moderate inverse correlation (Spearman's rho = – 0.525, p <0.01). E_{max} is presented in units of kPa.*

ADC had a moderate inverse correlation with fibroadenoma volume (Spearmans rho = – 0.520, p<0.001) (Figure 5). There was no statistically significant correlations among ADC_{ratio} and fibroadenoma volume (p=0.12). On the other hand, fibroadenoma volumes were positively and strongly correlated with SWE measurements; Spearman's rho were 0.840, 0.680 and 0.745 for E_{max}, E_{min} and HI, respectively (p<0.001 in all analyses) (Figure 6).

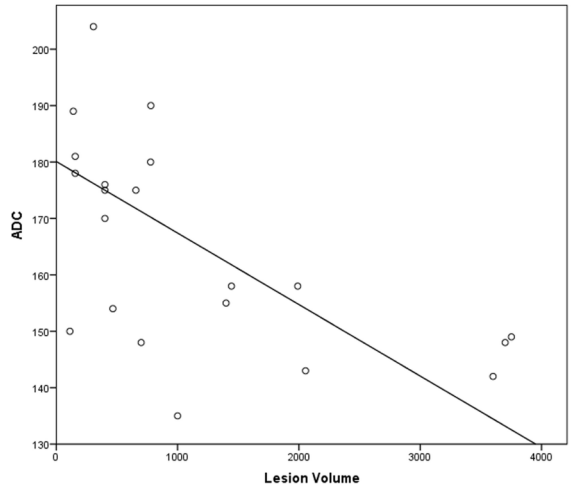

***Figure 5.** Apparent diffusion coefficient (ADC) showed a moderate inverse correlation with fibroadenoma volume (Spearman's rho = – 0.520, p<0.001). Volumes are presented in units of mm^3 and ADC in units of $x10^{-5}$ mm^2/s.*

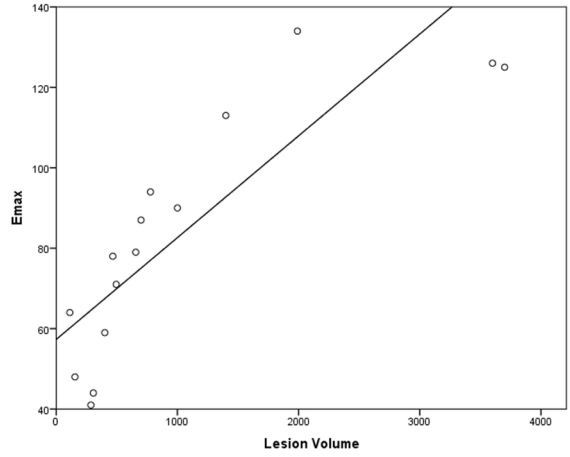

***Figure 6.** Lesion volumes were positively and strongly correlated with maximal elasticity (Emax) measured in fibroadenomas (Spearman's rho=0.840, p<0.001). Volume is presented in units of mm^3 whereas E_{max} is in units of kPa.*

There was no statistically significant correlation between patient age and SWE or ADC measurements of fibroadenomas (p = 0.23 and p = 0.47, respectively).

4. DISCUSSION

This study demonstrated a strong inverse correlation among ADC and SWE measurements of biopsy-proven small fibroadenomas, implying that ultrasound SWE has potential to be used interchangeably with diffusion-weighted MRI of such masses. ADC and SWE measurements also had significant correlation with lesion size, but not with patient age.

A previous study also showed significantly correlated lesion elasticity and ADC values. ADC values of malignant lesions was reported to be significantly lower than those of benign masses (0.94 versus 1.31 $x10^{-3}$ mm^2/s) and elasticity of lesions were also correlated with fibrosis grade histologically [3]. Our study population, comprising solely small biopsy-proven fibroadenomas, had comparable ADC measurements ranging from 1.37 to 2.11 $x10^{-3}$ mm^2/s. There were no correlation between patient age and fibroadenoma stiffness in another study [4]. This was also concordant with results of our study.

In our study, lesion volume was significantly correlated with both ADC and SWE measurements. This was in accordance with a previous study which also demonstrated that size of tumor was correlated with its stiffness. In the mentioned study, mean elasticity of larger cancers, i.e. those with diameter >15 mm, was 167 kPa whereas it was 109 kPa for smaller malignancies [5]. In regard to fibroadenomas, a prior study proposed that major predictor of a lesion's stiffness was its size and thus different SWE thresholds were required for malignancy differentiation in lesions of differing sizes [4]. Another study proposed cut-off SWE values of 65 and 75 kPa for small and larger lesions, respectively [6]. This proposal is, on the other hand, not in accord with our study in which maximal elasticity of small fibroadenomas ranged from 41to 133 kPa with a mean elasticity of 73.4±28.8 kPa.

SWE has proven to increase accurate characterization of lesions. In fact, stiffness of large and symptomatic breast masses are more easily assessed with SWE when compared to clinically occult lesions [2, 7]. But, on the other hand, utility of SWE in assessment of malignity has certain caveats. Benign breast masses generally have lower SWE measurements than malignant lesions. But, still there is a wide grey-zone between these proposed cut-off values for benignity and malignancy. In a large cohort, SWE measurements of less than 80 kPa indicated benignity with a specificity of 80% and 120 kPa was proposed as malignancy threshold [8]. Furthermore, there is no widely accepted elasticity threshold for malignancy detection yet. Due to histologic characteristics of certain neoplasms, there is significant overlap of elasticity of malignant and benign lesions. Several studies have indeed proposed very different cut-off values for malignancy [5, 9-11]. Most breast cancers are stiff and have mean elasticity over 50 kPa at SWE. Cancers falsely cleared as benign by SWE are mostly small lesions, i.e. less than 10mm in diameter, and low grade. Pure ductal carcinomas in situ are constitutionally softer than invasive cancers. Thus, a small and soft mass as shown by SWE may as well be an early cancer; so in such cases, it is advisable to use the biopsy option more liberally [12].

Another potential limitation SWE in differentiation of malignancy is that SWE may not be able to calculate lesion elasticity accurately in certain occasions. This occurs due to extremely diminished tissue deformation as seen in large and rigid infiltrative cancers which result in falsely low measurements because ultrasound cannot penetrate such highly attenuating scirrous tissues. This condition has potential to be confused as a low reading due to a lesion's benignity [2, 12]. In such cases, diffusion MRI and ADC mapping is indeed more valuable.

In conclusion ADC and SWE measurements have strong inverse correlation in small fibroadenomas which implies, in select cases, a potential of ultrasonographic SWE to be used interchangeably with diffusion-weighted magnetic resonance imaging.

Compliance with Ethical Standards

Ethical Approval: Approval for the study was obtained from the Ethics Committee of Marmara University, School of Medicine with the decision numbered 2018.478. Written informed consent was obtained from all patients.

Financial Support: No disclosures.

Conflict of Interest: The authors declare that they have no conflicts of interest concerning this article.

Author contributions: Both authors were actively involved in data collection, analysis, and the writing of the manuscript.

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