Original Article

Contribution of Diffusion-Weighted Imaging and Ultrasound Elastography to the Diagnosis of Breast Cancer

Meme Kanserinde Difüzyon Ağırlıklı Görüntüleme ve Ultrason Elastografinin Tanıya Katkıları

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ABSTRACT

Introduction: The firmness of breast lesions helps to differentiate malignant masses from benign masses. Tissue stiffness can be evaluated quantitatively and objectively by magnetic resonance imaging (MRI) and ultrasonography (USG) using the apparent diffusion coefficient (ADC) and ultrasound elastography techniques, respectively. We aimed to determine the strain ratio (SR) and ADC and their contribution to the diagnosis in malignant breast masses using US elastography and diffusion MR sequences.

Methods: Our study included 50 lesions in 50 female patients over 18 years of age who had invasive breast cancer proven histopathologically by tru-cut biopsy and had breast US elastography and breast MRI examinations before biopsy in the Radiology clinic archive. Sonoelastographic studies were performed with a 13-18 Mhz linear high resolution volumetric probe (Toshiba Aplio 400, Japan, 2014). Imaging and measurements were made by a single practitioner with 10 years of experience in breast radiology. ADC values were measured from different parts of the lesion, not including cystic, necrotic and hemorrhagic areas, using 10-40 mm^2 ROI on ADC maps and the lowest ADC value was selected.

Results: A significant correlation between the SR and sizes of the masses ($p<0.001$). A correlation between the mass ADC and the size was found to be inversely proportional to each other, but suggesting statistically low significance ($p<0.031$). The highest SR and ADC were 92.79 in a single case with mixed intracystic mucinous and ductal carcinoma and $1.49x10^{-3}$ mm^2/s in a single case with mucinous carcinoma, respectively.

Discussion and Conclusion: Sonoelastography and DWI are relatively new non-invasive methods with high sensitivity and specificity. The use of these methods together with basic methods in breast diseases increases the diagnostic performance in the differentiation of benign and malignant breast lesions.

Keywords: breast cancer, diffusion weighted imaging, US elastography

ÖZET

Giriş ve Amaç: Meme lezyonlarının sertliği, malign kitleleri benign kitlelerden ayırmaya yardımcı olur. Doku sertliği, sırasıyla görünür difüzyon katsayısı (ADC) ve ultrason elastografi teknikleri kullanılarak manyetik rezonans görüntüleme (MRG) ve ultrasongrafi (US) ile kantitatif ve objektif olarak değerlendirilebilir. Bu çalışmada US elastografi ve difüzyon MR sekanslarını kullanarak malign meme kitlelerinde strain ratio (SR) ve görünür difüzyon katsayısı değerlerinin (ADC) ve tanıya katkılarını belirlemeyi amaçladık.

Yöntem ve Gereçler: Çalışmamıza İstanbul Eğitim veAraştırma Hastanesi Radyoloji Kliniği'nde Kasım 2013-Nisan 2014 tarihleri arasında, tru-cut biyopsi ile histopatolojik olarak kanıtlanmış invaziv meme kanseri olan ve Radyoloji kliniği arşivinde, biyopsi ve tedavi öncesi meme US elastografi ve

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meme MRG incelemeleri bulunan 18 yaş üzeri 50 kadın olguda 50 lezyon dahil edildi. Sonoelastografik incelemeler 13-18 Mhz lineer yüksek rezolüsyonlu volümetrik prob ile gerçekleştirildi (Toshiba Aplio 400, Japan, 2014). Görüntüleme ve ölçümler 10 yıl meme radyoloji tecrübesi olan tek uygulayıcı tarafından yapılmıştır. MR görüntüleri pron pozisyonda, bilateral 16 kanallı phased-array meme koili kullanılarak 1.5-Tesla MR cihazı (Signa HDi; GE Healthcare, Milwaukee, WI) ile gerçekleştirilmiştir. ADC haritalarında 10-40 mm^2 ROI kullanılarak lezyonun farklı bölgelerinden, kistik, nekrotik ve hemorajik alanları içermeyecek şekilde ADC değerleri ölçüldü. Bu değerler arasından en düşük ADC değeri seçildi.

Bulgular: Kitlelerin SR değerleri ile boyutları arasında birbiriyle doğru orantılı ve istatistiksel olarak orta derecede anlamlı ilişki izlenmektedir ($p<0.001$). Kitle ADC değeri ile boyut arasında ise birbiriyle ters orantılı ancak istatistiksel olarak düşük anlamlılık düşündüren korelasyon bulundu ($p<0.031$). Kitle ADC ve SR değerleri arasında anlamlı korelasyon izlenmedi ($p>0.05$). En yüksek SR değeri, mikst intrakistik müsinöz ve invazif duktal karsinom tanılı tek olguda 92.79 ve en yüksek ADC değeri ise müsinöz karsinom tanılı tek olguda $1.49x10^{-3}$ mm^2/s olarak elde edilmiştir.

Tartışma ve Sonuç: Ultrason Elastografi ve difüzyon ağırlıklı görüntüleme yüksek duyarlılık ve özgüllüğü olan invazif olmayan nisbeten yeni yöntemlerdir. Bu yöntemlerin meme hastalıklarında temel yöntemler ile birlikte kullanılması benign ve malign meme lezyonun ayrımında diagnostik performansı artırmaktadır.

Anahtar Kelimeler: meme kanseri, difüzyon ağırlıklı görüntüleme, US elastografi

Introduction

Breast cancer is currently the most frequently diagnosed cancer in women and the leading cause of cancer death worldwide [1]. Early and reliable diagnosis is the most effective method of reducing breast cancer-related deaths [2]. Although the early diagnosis rates of breast cancer increase with the widespread use of mammography (MG) and ultrasonography (US), these examinations may be insufficient to differentiate benign and malignant breast lesions. Therefore, magnetic resonance imaging (MRI) is increasingly used as a complementary and problem-solving method [2,3].

The firmness of breast lesions helps to differentiate malignant masses from benign masses. Tissue stiffness can be evaluated quantitatively and objectively with MRI and USG using the apparent diffusion coefficient (ADC) and ultrasound elastography techniques, respectively [4]. Previously, both techniques have been proven to be non-invasive imaging techniques that are beneficial in determining the malignancy risk of breast masses [5].

Diffusion-weighted imaging (DWI) is an MRI technique based on thermal energy-induced random motion (Brownian motion) of water molecules in biological tissues, and its quantitative parameter is ADC. In malignant tissue, low ADC values are expected due to the relatively reduced extracellular space due to increased cellularity, limited fluid diffusion, and increased nucleus/cytoplasm ratio. In many studies comparing ADC in malignant and benign lesions of the breast, significantly lower ADC values and diffusion restriction were observed in malignant lesions [6,7].

Elastography is a non-invasive imaging method used in combination with US. In elastography, the strain (elasticity) map of the compressed tissues is created. The basis of this technique is that tumor tissues are harder than normal tissues due to desmoplastic reaction and fibrosis, and hard tissues are more resistant to compression. Harder areas are seen in darker and blue tones on the strain map [8,9]. One of the elastography methods is the measurement of strain ratio, which is a semi-quantitative value. In this method, the average stiffness index of the mass, normal

glandular tissue or breast adipose tissue (strain index) is obtained by the device and the mass stiffness index is compared with the stiffness indices of the normal glandular tissue or breast adipose tissue with a special software. This ratio obtained is the strain ratio (SR) [8,10].

In this study, we aimed to determine the contribution of SR and ADC values to the diagnosis of malignant breast masses using US elastography and DWI methods.

Material and Method

Approval for the study was obtained from the Ethics Committee of Istanbul Training and Research Hospital, with the decision numbered 468.

Patient Selection

Our study was conducted in İstanbul Training and Research Hospital Radiology Clinic between November 2013 and April 2014. 50 lesions in 50 female patients with invasive breast cancer proven histopathologically by tru-cut biopsy and who had breast US elastography and breast MRI examinations were included. All of the MRI examinations were obtained before biopsy and treatment. A voluntary consent form was obtained from all patients.

Ultrasonographic B-mode and Elastography Evaluation

Ultrasonographic examinations were performed with a 13-18 Mhz linear high resolution volumetric probe (Toshiba Aplio 400, Japan, 2014). Imaging and measurements were made by a single practitioner with 10 years of experience in breast radiology. In the examination, all quadrants of the breast were scanned in different planes. The dimensions of the detected masses were measured and their longest diameters were included in the study.

Strain US elastography was performed in cases with a mass detected in B-mode US examination, by applying a one-second interval, repetitive compression at constant power, perpendicular to the lesion. Images with the same morphology and wave spectrum at least 5 times were analyzed. After the elastographic images were obtained, the strain values of the mass and adjacent adipose tissue were measured numerically with the ROIs placed on a static elastographic image, and the strain ratio (SR) values were obtained automatically by the device. Considering the color map obtained, the hardest areas without cystic, necrotic and calcification areas were selected for ROIs placed in the mass.

MRI Technique

MR images were performed in prone position with a 1.5-Tesla MR device (Signa HDi; GE Healthcare, Milwaukee, WI) using bilateral 16-channel phased-array breast coils. A standard protocol including contrast and diffusion-weighted imaging (DWI) sequences was used in all examinations. For DWI sequence, fat-suppressed pre-contrast axial single-shot echo planar imaging (EPI) sequence with b values of 0 and 800 s/mm^2 was used. Automatically generated ADC maps from DWIs with a special software were created on the GE advantage workstation (Figure 1). ADC values were measured by manually placing 20-40 mm^2 ROIs (region of interest) from different regions of the lesions on these maps, not including cystic, necrotic and hemorrhagic areas. Among these values, the lowest ADC values were selected.

Statistical Method

Descriptive statistics were presented as mean, standard deviation, and percentage. The mean of the two groups was compared with the t-test for independent groups. The mean of more than two groups was compared with one-way anova comparison methods. In the statistical evaluation, the correlation of the distribution of quantitative variables with each other and categorical features with each

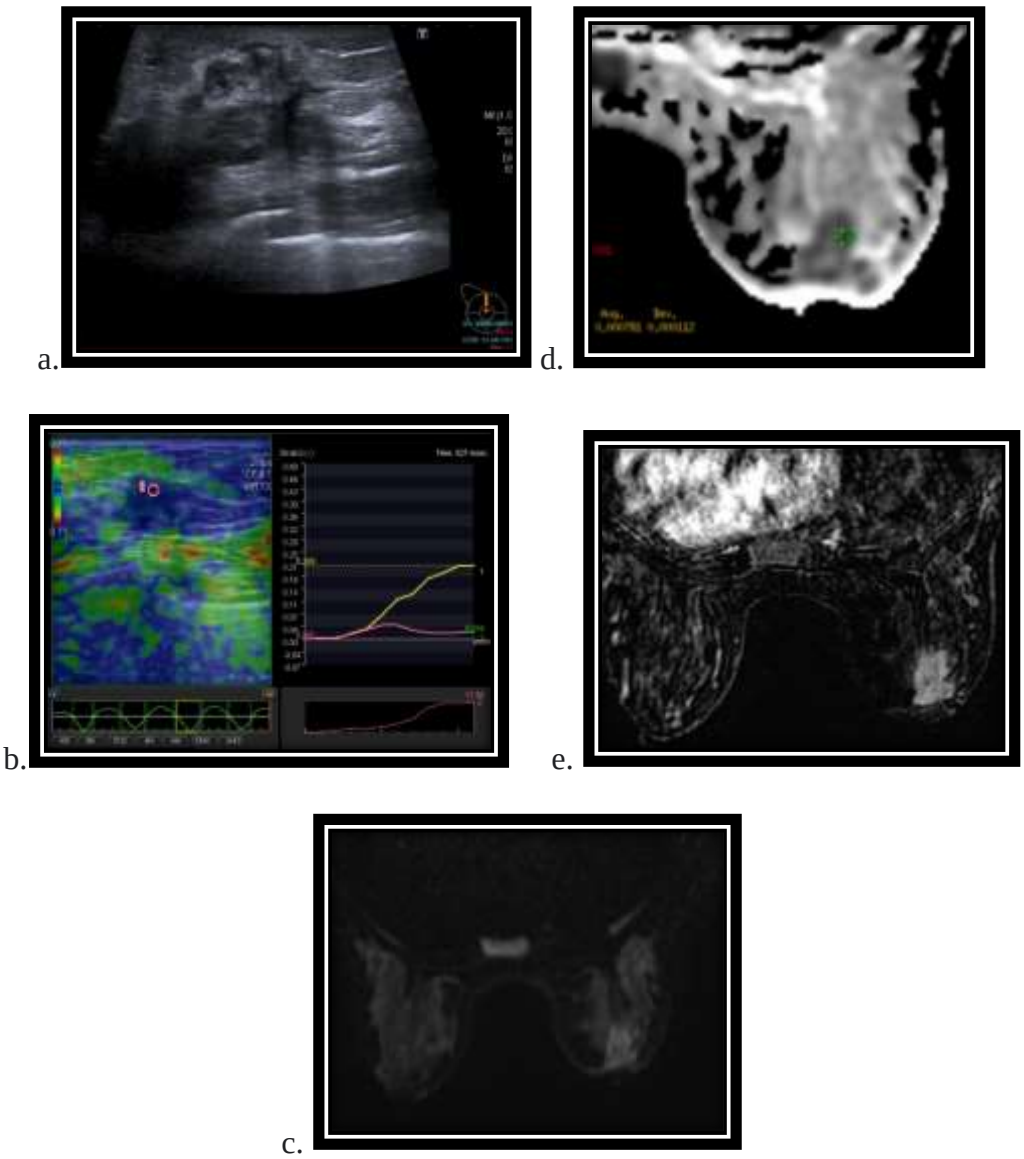

Figure 1. Retroareolar area of the right breast with gray scale USG (a) with irregularly defined lobulated contour, (b) SR value of 11.55 on US elastography, diffusion restriction on DWI (c), peripheral hypointensity on ADC map (d) and dynamic Contrast-enhanced examination (e) reveals a mass lesion with heterogeneous contrast-enhancing malignant character.

other was calculated using the Pearson test. Statistical analyzes were performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) package program. The significance level was accepted as 0.05 in all tests.

Results

A total of 50 patients and 50 lesions were included in the study. The ages of the cases were between 21 and 89, and the mean age was calculated as 53.38±13.2.

In the evaluation of the localization of the lesions, 20 lesions (40%) were located in the right breast and 30 lesions (60%) were located in the left breast.

In the evaluation made according to the localization of the lesions in the breast, quadrant localization; Each breast was divided into five quadrants and a retroareolar area. The distribution of the lesions according to their localization is given in Table 1.

Table 1. Distribution of lesions by localization

Localization	n	%
Upper outer quadrant	22	44.0
Lower outer quadrant	8	16.0
Upper medial quadrant	10	20.0
Lower medial quadrant	5	10.0
Retroareolar region	5	10.0
Total	50	100.0

Table 2. Descriptive statistical data of the size, strain ratio and ADC values of the lesions

	n	min	max	median	SD
Size (mm)	50	8.00	80.00	23.48	12.73
SR	50	4.42	92.79	20.60	20.21
ADC value (10^{-3} mm^2/s)	50	0.24	1.49	0.82	0.26

min:minimum, max:maximum, SD:standart deviation

Table 3. Data on the evaluation of the relationship between patient age, lesion dimensions and strain ratios with Pearson's test

		Age	Size	Strain ratio
Size (mm)	r	0.052		
	p	0.722		
	N	50		
Strain ratio	r	0.133	0.594	
	p	0.356	<0.001	
	N	50	50	
ADC value (10^{-3} mm^2/s)	r	0.055	-0.305	-0.154
	p	0.702	0.031	0.287
	N	50	50	50

ductal carcinomas (with no subcategories specified), one mixed invasive cribriform carcinoma and invasive tubular carcinoma, one mixed intracystic mucinous carcinoma and invasive ductal carcinoma, one mixed invasive ductal and invasive mucinous carcinoma, and one mucinous (N=50).

Descriptive statistical data of the size, strain ratio and ADC values of the lesions are given in Table 2.

The relationships between patient age, lesion sizes, strain ratios and ADC values were evaluated with the Pearson test, and the data are shown in Table 3.

A directly proportional and statistically moderately significant ($p<0.001$) (Figure 2) relationship is observed between the SR values and sizes of the masses. A correlation was found between the mass ADC value and the size, which was inversely proportional to each other, but was statistically insignificant ($p<0.031$). Bilateral relationships between age and strain ratio and between age and ADC value were not significant (Table 3). No statistically significant correlation was found between strain ratio and ADC value ($p>0.05$). Comparisons were made by side with the t-test to determine the connections between independent groups, but no statistically significant difference was found between the right and left sides.

In Figure 3, the distribution of ADC values according to the number of cases is shown in the form of histogram graph. For example, the lowest ADC value of $0.24x10^{-3}$ includes 2% of the cases. The highest ADC value was obtained as $1.49x10^{-3}$ mm^2/s in a single case with mucinous carcinoma.

Discussion

Breast cancer is the second most common type of cancer in all humans, after lung cancer, and the most common in women. Although breast MRI has a sensitivity of 89-100% in detecting invasive breast cancers, its specificity is around 72% [11].

Other advantages of DWI over contrast-enhanced MRI are that it can show microscopic cellular changes with high sensitivity without the need for contrast material, it provides numerical information about cellularity, and the scanning time is short [12]. While normal tissue shows intense signal loss on DWI, these areas appear bright because tumor cells restrict the movement of

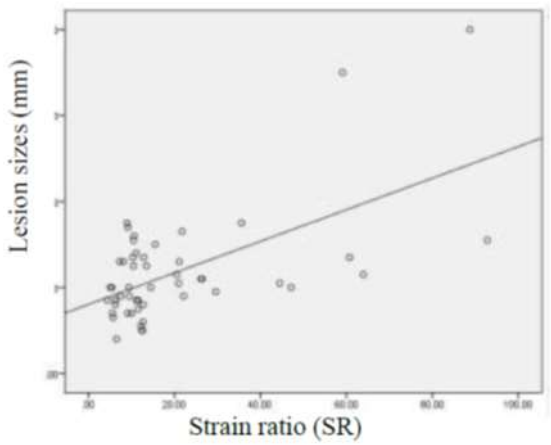

Figure 2. Scatterplot showing the relationship between SR values and sizes of the masse

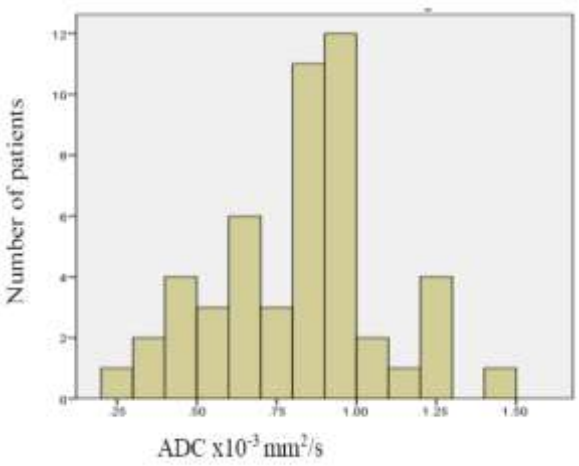

Figure 3. Histogram graph showing the distribution of mass ADC values according to the number of cases

molecules. DWI is basically obtained by adding the diffusion weight gradient known as the "b value" to the T2-weighted images. T2-weighted signal effect is more prominent in examinations performed with low b value (T2 shine through effect). Although the diffusion weight is more pronounced in the examinations used with a high b value, the are lower signal-noise (SNR) ratios. This affects the image quality [9,12,13].

The ADC value is the measurable numerical equivalent of the diffusion of water molecules in the tissues and can be represented as an ADC map showing the ADC of each voxel in each slice based on DWI. There is an inverse ratio between the ADC value and the cellular density of malignant breast masses. Lower ADC values were found in malignant breast masses with high cellularity [9].

The inclusion of DWI in breast MRI protocols is becoming widespread all over the world. DWI using ADC mapping can detect breast cancer with sensitivity up to 96% and specificity up to 100%. The main goal in the use of DWI is to distinguish between benign and malignant lesions in order to prevent unnecessary breast biopsies [14].

Being sensitive to tissue microstructure and cellularity, DWI provides quantitative information that can be used for lesion characterization. It has also been shown in multicenter studies that improved lesion characterization reduces the number of unnecessary biopsies [15]. Another factor affecting the ADC is the 'b value' used during shooting. The microperfusion effect of the tissue affects the ADC value and leads to higher values in the shots made using a low b value. However, there is no consensus in the literature on which b value is more suitable for breast diffusion studies.

Pereira et al. [12] reported that ADC values measured with 0 and 750 b values were slightly more reliable than other b values in the differentiation of malignant and benign breast masses. In our study, the b values used in DWIs were 0 and 850 s/mm^2.

It has been reported in the literature that malignant breast masses have lower ADC values compared to benign masses [9,12]. Chen et al. [16], in their meta-analysis study including 13 studies, reported that the mean ADC values of malignant breast masses varied between 0.87 and 1.36×10^{-3} mm^2/s, and the mean ADC values of benign breast lesions varied between 1.00 and 1.82×10^{-3} mm^2/s.

In our study, Kitajima et al. study [17], a low significant and inversely proportional correlation was found between mass ADC value and size ($p<0.031$). However, a study of Partridge et al. [18], using b values 0 and b 600 s/mm^2, reported that the size of the lesion had no effect on the ADC value.

Guo et al. [19], found that lesions with an ADC value of $1.30x10^{-3}$ mm^2/s and less were considered breast cancer, the sensitivity of DWI was reported as 93%, specificity 88%, and overall accuracy 91%. In our study, when the threshold value was $1.30x10^{-3}$ mm^2/s, 98% (n=49) of the masses were classified as malignant. The only case in our study that remained above this threshold value was mucinous carcinoma, and the ADC value was measured as $1.49x10^{-3}$ mm^2/s. Because mucinous cancers contain low cellularity and mucin islets, they show less diffusion restriction and higher ADC values compared to other malignant breast masses [20]. A study of Satake et al. [9] with 115 BIRADS (Breast Imaging-Reporting and Data System) category 4 and 5 breast masses, reported that the ADC value of mucinous cancer masses were greater than the threshold value and this finding is compatible with our study.

In the literature, the mean ADC value of malignant breast masses has been defined in many different studies: $0.75x10^{-3}$ mm^2/s [7], $0.907x10^{-3}$ mm^2/s (masses diagnosed only with invasive ductal carcinomas) [21], $0.97x10^{-3}$ mm^2/s [22], $1.09x10^{-3}$ mm^2/s [23]. In our study, the mean ADC value of malignant lesions was calculated as $0.82x10^{-3}$ mm^2/s. Considering that almost all of the lesions in our study were invasive ductal carcinoma, this value is compatible with the literature.

Itoh et al. [24] reported that there is a good correlation between real-time US elasto-graphy and histological analysis, and that this method has high sensitivity and specificity in the differentiation of benign and malignant masses.

Different SR values have been reported in the literature to differentiate benign and malignant masses. Mousa et al. [25], Zhi et al. [26] and Ueno et al. [27] reported the SR threshold value as 3.6, 3.05 and 4.8 in their study, respectively.

With all of the SR threshold values mentioned above, 100% of the masses in our study were classified in the malignant category, which is consistent with these studies. We think that these differences in SR values are due to the different pressures of the practitioners, the reference strain index being fibroglandular tissue or fatty tissue, the depth of the reference ROI and the difference in USG devices.

In many studies in the literature, it has been reported that there is a significant difference between the mean SR values of malignant and benign breast masses. Kim et al. [28] evaluated 157 lesions with US elastography, and reported the mean SR value of malignant lesions as 5.69±1.63 and benign lesions as 2.69±1.40. In our study, the mean SR value of malignant masses was 20.6±20.2, which is higher than literature. This may be because of the absence of in situ ductal or lobular carcinom cases in our study, unlike other studies.

In our study, it was shown that the SR values of the masses increased in direct proportion to their size. In parallel with our findings, in a multicenter study conducted with 1562 cases, it was shown that the stiffness of fibro-adenomas and malignant tumors was correlated with increasing lesion size, but there was no correlation between size and stiffness in other solid and cystic lesions of the breast and in-situ ductal cancers [29]. There are few studies in the literature evaluating the relationship between SR values and mass sizes in malignant masses.

The use of strain elastography as an elastography technique in our study can be considered as a limitation in terms of practitioner dependency, but we think that we

minimized this limitation by performing all measurements by a single practitioner with 10 years of breast radiology experience. In recent years, studies comparing the effectiveness of shear wave elastography and strain elastography with simultaneous applications have also shown that these elastography techniques have similar diagnostic performance [30,31]. In addition, the relatively small number of samples is among the limitations of our study.

Conclusion

US elastography and DWI are new non-invasive methods with high sensitivity and specificity. The use of these methods together with basic methods in breast diseases increases the diagnostic success in the differentiation of benign and malignant breast lesions.

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