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The Role of Multidirectional Diffusion Weighted Imaging in the Diagnosis of Breast Carcinoma in Magnetic Resonance Imaging

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ABSTRACT

Background: Magnetic resonance imaging (MRI) is increasingly used in breast imaging. Diffusion imaging (DWI) is used in conjunction with contrast enhanced series. There is a signal difference between the stationary and moving water molecules in DWI, due to the fact that all molecules receive a first gradient pulse and then another pulse at the 180 degree-reverse direction of the first one. The stationary molecules have zero signal after the two of the pulses and show restriction (low signal). However, the moving molecule is not at the same location and escape from the 180 degree pulse with an energy in the end of the gradients. Multidirectional Diffusion-Weighted Imaging (MDDWI) gives information signifying water's capacity to move freely in a direction according to its physiological and pathological boundaries, which is referred to as fractional anisotropy (FA). This study aimed to determine the usefulness of FA maps in differentiating benign and malignant breast lesions.

Methods: The patients who had breast MRI including MDDWI series and went through pathological evaluation (79 patients with 86 lesions) were included in the study. The FA values were measured in addition to the conventional Diffusion-ADC values. Also, diffusion restriction and pathology results were noted. The lesion FA and ADC values, diffusion assessment, and pathology results were compared using the Student t-test.

Results: The patients were between 23 and 76 years and the mean age for benign lesions was 43.9, whereas it was 50.4 for the malignant lesions. Forty-five patients had benign and 41 had malignant lesions. The mean ADC values were significant between benign and malignant lesions (correspondingly; $1256.5x10^{-3}$ mm²/s. and $978.7x10^{-3}$ mm²/s.) The FASD value of each lesion was found to be significant for malignant lesions ($100x10^{-3}$), especially those with restricted diffusion. In addition, for lesions with restricted diffusion, the maximum FA ($75x10^{-3}$) and mean FA ($200x10^{-3}$) values were found to be significant for malignancy. A cut-off point of 500×10–3 of FA max was found to be a value that could be used to increase the specificity of suspicious lesions with restricted diffusion

Conclusion: Restricted diffusion is used as a supporting finding for biopsy indication, but due to its lower specificity DWI cannot be very helpful in increasing the specificity of conventional breast MRI. In the search of finding a tool to increase the specificity of breast MRI, FA values seem to have the potential in differentiating benign lesions.

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INTRODUCTION

Magnetic resonance imaging (MRI) is increasingly used for breast imaging. Dynamic contrast-enhanced imaging is the main sequence for determining breast cancer malignancy.[1,2,3] Diffusion imaging is also employed with dynamic series as a supportive sequence in the evaluation of breast lesions.[3,4,5] This gives information about water

molecules' movement ability in the tissue. The motion of water is restricted in tissues with more cellular components and cell membranes, like tumour tissues.[6]

Diffusion images-maps have found a wide daily usage in daily practice. Multidirectional diffusion-weighted imaging (MDDWI) - a kind of Diffusion Tensor Imaging- is a suitable diffusion sequence for investigating anisotropic diffusion in tissue, including the calculation of diffusion tensors.[7,8] With these sequences, we can have information about the diffusion ability of water molecules in the extracellular matrix of the tissue in all directions and this is known as fractional anisotropy (FA). Healthy tissues will have their preserved normal tissue alignment concordant with their anatomical and histological properties. If there is a pathology that will interfere with the healthy orientation of the tissue, the diffusion alignment of the tissue will be more anarchic.[9,10] Initially, this type of diffusion was used for brain lesions, but recently it has also been used for breast lesions.[11] Since the breast has a web-like trabecular structure, breast tissue has different diffusion properties in different directions.[2]

The anisotropy difference between normal tissue and malignant/benign lesions is a developing field of research.[3,4,6,7,9,12,13] There have been some studies with breast diffusion tensor imaging but the drawback of these studies is that they require post process evaluations. Thus, a practical way of using this information is required. FA maps are similar to the (trace and ADC) maps of Diffusion Weighted Imaging. The aim of the present study is to determine the effectiveness of FA maps in differentiating benign and malignant breast lesions in daily practice without using post-process evaluations.

MATERIALS AND METHODS

Subjects

The participants included patients with BIRADS 4, and 5 scores based on MRI who had MDDWI and pathology results. Breast MRI images of all patients who presented with suspicious masses and had MDDW imaging were reviewed. Ninety patients underwent imaging; 11 were excluded because their pathology results could not be reached. Finally, 86 biopsy proven lesions from 79 patients were included in the study.

The Ethical Board approval was taken from our University's Ethical Committee with an approval number of 11.15.2017/215. The study was performed in the Ankara Ataturk Training and Research Hospital as a retrospective study. The identifiers of the patients were kept in minimum and were not shared.

Techniques

The MRI images were obtained with a 3T MRI system (Magnetom Skyra; Siemens Healthcare, Erlangen, Germany), and an 18-channel breast coil (Siemens A 3T Tim Coil, Siemens Healthcare, München, Germany) was used. After positioning the patient on the table in prone position, all images were obtained in parallel imaging (GeneRalized Autocalibrating Partially Parallel Acquisition-Integrated Parallel Acquisition Techniques-GRAPPA-IPAT) mode. Axial fat-saturated turbo spin echo T2 images were obtained with the Turbo Inversion Recovery Magnitude (TIRM) sequence with a slice thickness of 4mm. The following additional parameters were employed: repetition time (TR) of 3500ms, echo time (TE) of 69ms, inversion time (TI) of 230ms, average of 2, distance factor of 10% and acquisition matrix of 384×307. Non-fat saturated T1 images were obtained with a slice thickness of 4mm, distance factor of 10%, field of view (FOV) of 380, TR of 548, average TE of 12 and acquisition matrix of 448×358.

Diffusion imaging was carried out via MDDWI with six gradient directions. B-values of 50, 400 and 800 were used. The TR was 4200ms, TE was 64ms, slice thickness was 5mm and FOV was 340mm; the distance factor was 10%, and the acquisition resolution was 200×120. The fat saturation was accomplished using the Spectral Attenuated Inversion Recovery (SPAIR) sequence with a strong fat-saturation mode. The diffusion trace images, apparent diffusion coefficient (ADC) maps and FA maps were retrieved from the MDDW images. Dynamic images were obtained with one pre-contrast and five post-contrast SPAIR fat saturated T1 images. The TR value was 4.51ms, TE was 1.61ms, flip angle was 10 and average slice thickness was 1mm; and there were 25ms between each phase of the dynamic imaging. The acquisition time for each phase was 1min and 1s. The acquisition matrix was 448×300, voxel size was 0.8×0.8×1.1mm, and acquisition was 1.13×0.76×1.63mm. For the contrast media, either gadobutrol (Gadovist®, Bayer Schering Pharma, Berlin, Germany) or gadoterate meglumine (Dotarem®, Guerbet, Villepinte, France) was used at 0.1mmol/kg, with an infusion rate of 4ml/s via electronic infuser (Med-tron AG Accutron, Saarbrücken, Germany). Subtraction images were obtained by subtracting the pre-contrast image from each phase of the dynamic images.

Data collection

The images were interpreted by a radiologist of seven years of breast imaging experience in a blinded manner to evaluate the pathology results of the lesions.

The lesions were identified with the subtracted dynamic contrast-enhanced images. For each lesion, the lesion diameters were measured. The kinetic curve

types were recorded. Free-hand region of interest (ROI) drawings were generated on the restricted area of the lesions on ADC maps if possible, or on the trace maps if the lesion did not show restricted diffusion with the help of the subtracted contrast-enhanced images. The mean ADC values were recorded, and restricted diffusion was noted visually.

The same ROI of ADC maps were copied and pasted to the FA maps of MDDW images. The minimum, maximum and mean FA values, as well as the standard deviation of the FA values (FA min, FA max, FA lesion, FA SD), in the ROI area were recorded. A similar-sized ROI was drawn on the normal breast tissue of the same breast on both the ADC and FA maps. If sufficiently normal fibroglandular tissue on the same breast was absent, the contralateral normal fibroglandular tissue was measured. The differences in the mean FA values of the lesions and normal tissue were recorded.

The patients' pathology results were searched. After biopsy, if the patient went through mastectomy, we used the pathology results of the mastectomy specimens to get a more accurate diagnosis. If there had been no mastectomy operation, the biopsy results were used. Fifty-one of the lesions were biopsied using tru-cut biopsy, while 17 were carried out by excisional biopsy via ultrasound or the mammography-guided wire localisation method. For 17 patients, the mastectomy specimen results were obtained. One of the biopsies was a fine-needle aspiration biopsy.

Statistical analysis

The lesions were grouped as malignant and benign in all cases. A Levene test was performed for evaluation of the distribution, and the groups were compared with an independent *t*-test regarding their FA properties, ADC values and restricted diffusion ratios and differences of the FA values of the lesions and normal tissue. In addition, the FA values were clustered into six groups, with increasing intervals of 50.

Lesions with restricted diffusion were divided into two groups as malignant and benign according to their pathological results. The groups' distributions were analysed regarding their FA values and compared with an independent *t*-test. Lesion kinetic curve types were compared with pathology results using Mann-Whitney U test.

RESULTS

Eighty-six BIRADS 4 or 5 lesions of 79 patients in whom pathological confirmation had been performed were studied. The patient characteristics are described below.

Age

The patients were 23–76 years old, with an average age of 46.96 years. The mean ages of the patients were 43.9 and 50.4 years for the benign and malignant groups, respectively. There was a statistically significant difference for age between the benign and malignant groups (P=0.009).

Pathology results

Forty-five lesions were benign, while 41 were malignant. Four lesions were high-grade ductal carcinoma in situ, one with accompanying microinvasion and one with accompanying lobular carcinoma-in situ. Twenty-eight lesions were invasive ductal carcinoma, 6 were lobular and 2 included both ductal and lobular components. Two patients had signet cell variant carcinoma and one had medullar carcinoma.

Size

The average sizes of the lesions were 22×14mm for benign lesions and 34×24mm for malignant lesions. There was a significant relationship between the size of the lesions in the long and short axes (P=0.005 and P=0.000) and malignancy. In addition, the short axis diameter was found to be related to malignancy in lesions with restricted diffusion (P=0.013).

Kinetics

The kinetic curve type was found to be related to malignancy, showing a higher possibility of malignancy as the curve type increased (P=0.001). This finding was evident in both the diffusion-restricted group and all study patients' group.

DWI

The mean ADC value of the benign lesions was 1.256×10^{-3}mm²/s, while that of the malignant lesions was 0.978×10^{-3} mm²/s. There was a significant difference between these two groups, as determined by an independent t-test (P=0.0005). The mean ADC value was also significant for the lesions with visually restricted diffusion in terms of malignancy (P=0.03; ADC=1.163×10^{-3}mm²/s for benign, 0.958mm²/s for malignant lesions). Visual assessment of diffusion restriction was also significant for malignancy (P=0.003). Restricted diffusion was seen in 57% of benign and 92% of malignant BIRADS 4 and 5 lesions.

The ADC values were also evaluated for the patients' normal tissues. Interestingly, the ADC values of the normal tissue were found to be related to malignancy in the group with diffusion-restricted lesions (P=0.02).

FA measurements

The mean FA value of the benign lesions was 201×10^{-3}, while that of the malignant lesions was 219×10^{-3}. Higher FA values were found to be related to malignancy in the diffusion-restricted group (P=0.05). When the FA records were divided into six groups with intervals of 50, it was found that increased FA values were related to malignancy more strongly in the diffusion restricted group (P=0.038) but was not significant for all the lesions. For the restricted lesions, an FA value of 200×10^{-3} had a specificity of 73%, while an FA value of 250×10^{-3} had a specificity of 85% (Figure 1).

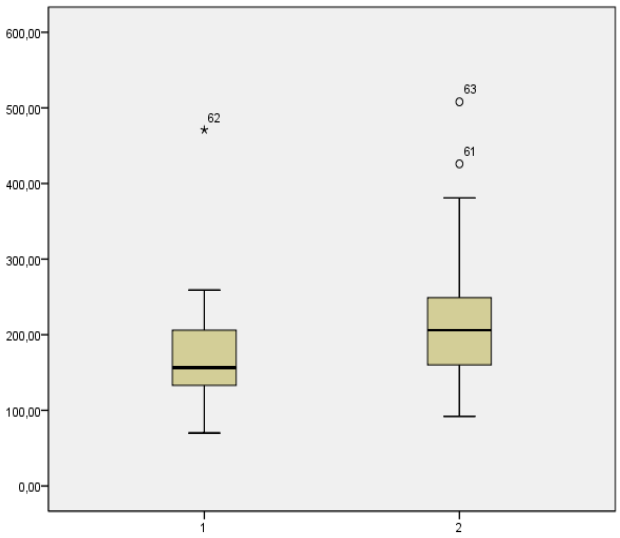

Figure 1. Lesions with restricted diffusion; FA values according to pathology (1: Benign, 2: Malignant). FA values are multiplied with 10^{-3}. Star is a lesion of atypical ductal hyperplasia with a FA value of 471×10^{-3}.

The FASD value was found to be more significantly correlated with malignancy for the patients with restricted diffusion (P = 0.003). It was found that an FASD of 77.5×10^{-3} was the cut-off value for differentiating malignancy, with a sensitivity of 75% and specificity of 62%. An FASD value higher than 100×10^{-3} revealed 80% specificity for malignancy in the restricted diffusion lesions (Figure 2).

The mean value of FA min of the benign lesions was 62; for malignant lesions, it was 88. It was found that having a higher FA min value was related to malignancy (P=0.037).

For the lesions with restricted diffusion, the mean FA max values were 405×10^{-3} for benign lesions and 645×10^{-3} for malignant lesions (Figure 3). These values were significantly higher in the malignancy group in lesions with restricted diffusion (P<0.001). Tables 1 and 2 summarise the results.

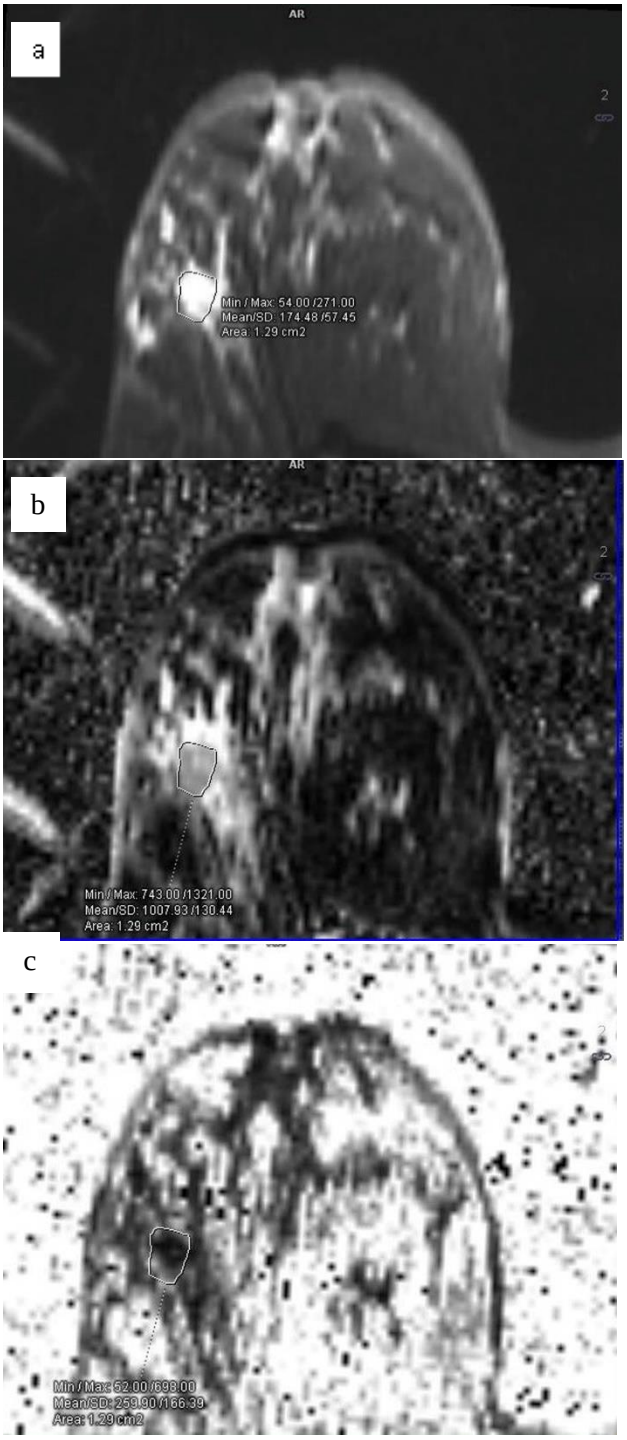

Figure 2. Invasive ductal carcinoma, Grade2. **2a.** Diffusion Trace Image, **2b.** ADC map, **2c.** FA map. On the left breast, there is a 15x13 mm diffusion restricted, type 2 enhancing mass. FA is 256, FASD is 167.

Multiparametric MRI with and without FA

The positive predictive value of multiparametric MRI of radiologically suspicious lesions was 47.6% (41 malignancy out of 86 MRI lesions).

The sensitivity of diffusion restriction was 92.5%, specificity was 42.2%, and the positive predictive value (PPV) of diffusion restriction was 58.7, whereas the negative predictive value (NPV) of diffusion restriction was 90.5% (Table 3).

Table 1. Group Statistics for Restricted Diffusion Group

	Pathology	Mean	Std	P value
age	1	42.5	13.3	0.01*
	2	50.2	9.6	
size long axes (mm)	1	23.9	19.8	0.064
	2	33.2	18.9	
size short Axes (mm)	1	15.4	10.7	0.011*
	2	23.0	11.8	
ADC (mm^2/s)	1	1163.3	284.9	0.003*
	2	958.7	186.6	
ADC normal tissue (mm^2/s)	1	1723.2	354.9	0.020*
	2	1506.8	349.4	
FA	1	179.3	76.8	0.050**
	2	221.8	91.1	
FASD	1	78.1	48.7	0.016*
	2	110.5	54.1	
FA min	1	71.3	45.7	0.614
	2	64.9	53.4	
FA max	1	405.0	219.9	<0.001*
	2	645.5	276.4	
FA normal tissue	1	167.5	80.7	0.064
	2	212.8	101.5	

Pathology 1=benign, Pathology 2=malignant
* Significant with 95% confidence interval
**P=0.038 for grouped FA values.
ADC and FA values are multiplied by 10^{-3}

Table 2. Group Statistics for all BIRADS 4&5 Lesions

	Pathology	Mean	Std.	P value
age	1	43.8	12.9	0.009*
	2	50.3	9.2	
size long axes (mm)	1	22.4	19.4	0.004*
	2	34.3	18.4	
size short axes (mm)	1	14.1	11.3	<0.001*
	2	23.5	11.4	
ADC (mm^2/s)	1	1256.5	303.5	<0.001*
	2	978.7	212.3	
ADC normal tissue (mm^2/s)	1	1524.4	464.7	0.767
	2	1497.7	341.4	
FA	1	201.6	95.1	0.373
	2	219.9	92.7	
FASD	1	88.9	54.9	0.083
	2	109.9	54.7	
FA Min	1	88.0	62.0	<0.001*
	2	61.5	53.0	
FA Max	1	538.2	593.9	0.324
	2	640.1	280.8	
FA normal tissue	1	208.4	136.5	0.99
	2	208.4	99.0	

Pathology 1=benign, Pathology 2=malignant,
*significant with 95% confidence interval
ADC and FA values are multiplied by 10^{-3}.

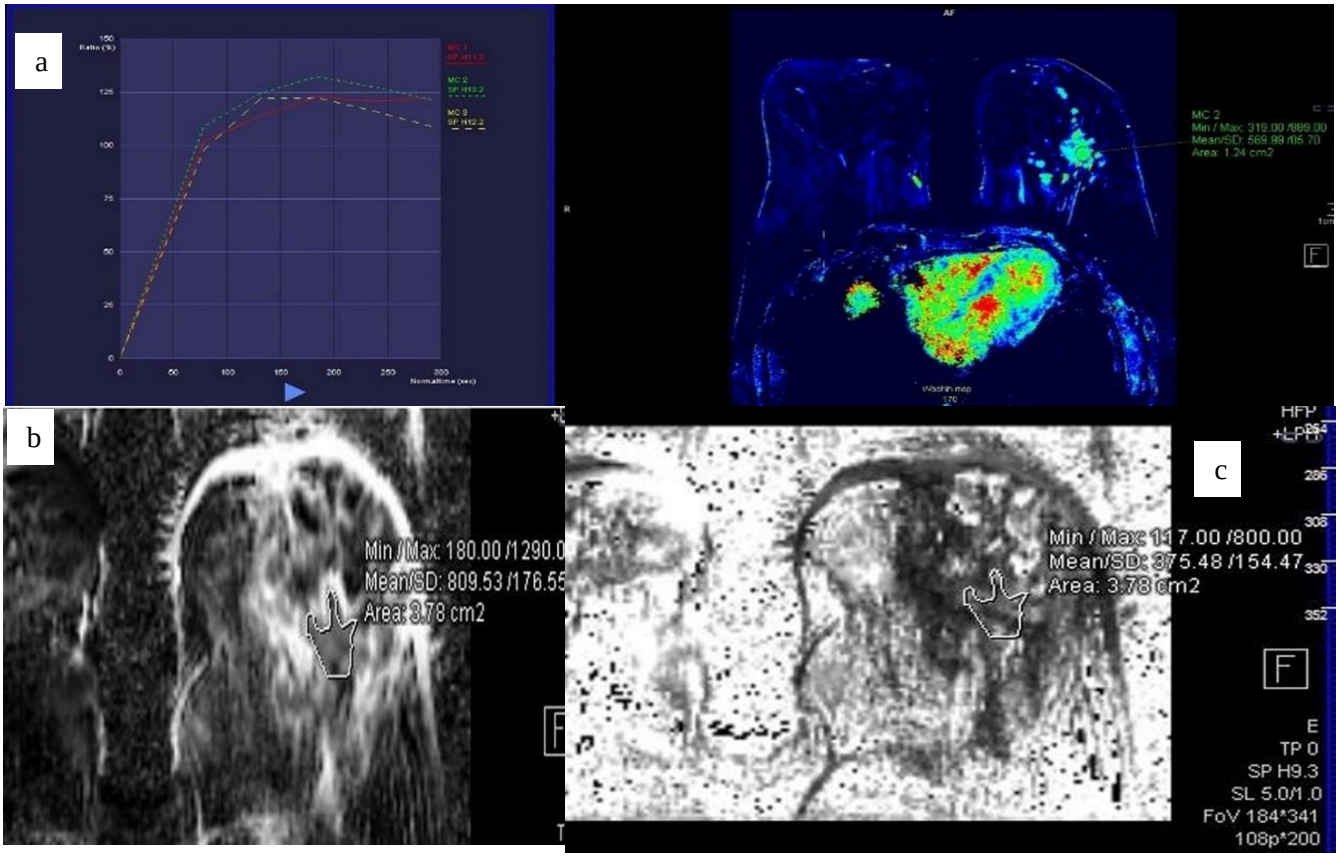

Figure 3. Invasive lobular carcinoma Grade 2.
3a. Lesion shows Type 3 kinetics on dynamic imaging. **3b.** ADC map. Lesion has restricted diffusion.
3c. FA maps show high FA value, 375 and heterogeneity in FA; FASD154. Fa min 117, FA max 800.

When the FA value of 200×10^{-3} was considered as a cut-off value for the lesions with restricted diffusion, the sensitivity of FA was 51.3%, the specificity was 73%, the PPV was 73% and the NPV was 51%.

FA max value of 500×10^{-3} was taken as a cut-off value of malignancy, for diffusion restricted lesions; the sensitivity was 64.8%, specificity was 69.2%, PPV was 75% and NPV was 58%. Table 3 summarizes the effect of different FA values on both the patients and on diffusion restricted lesions.

Table 3. DWI and FA data for all and diffusion restricted lesions

	Measurement	Sensitivity	Specificity	PPV	NPV
Diffusion restricted lesions	FA (200×10^{-3})	51.3%	73%	73%	51%
	FA_{max} (500×10^{-3})	64.8%	69.2%	75%	58%
	FASD (100×10^{-3})	54.2%	76.9%	76%	55.5%
All lesions	Diffusion restriction	92.5%	42.5%	58.7%	90.5%
	FA_{min} (75×10^{-3})	30%	46.6%	36.3%	45.2%

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FA, FA_{max} and FASD values with the cut-off points in diffusion restricted lesions. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of diffusion restriction and minimum FA values for all BI-RADS 4 and 5 patients.

DISCUSSION

Diffusion imaging of breast tissue is widely used in addition to contrast-enhanced dynamic breast MRI, with an apparent complementary relationship to this imaging.[10] It is known that diffusion restriction is an indicator of malignant, highly cellular tissue.[14] However, it is also known that the results from diffusion imaging of tissue are different from those obtained from in vivo models, which include internal structural membranes and limitations in some directions.[15] Using more recently developed techniques, not only the free water diffusion of the tissues, but also the diffusion values in different directions can be learned. Diffusion tensor imaging and three-dimensional (3D) post-processing evaluations are used for searching for the relationship between the heterogeneous diffusion directions–FA and the pathology of the lesions.[16] Previous studies have employed different measurement models and calculations of DTI of breast lesions, but the evaluations require of the use of multiple parameters and post-processing.[9,17,18] Multidirectional diffusion imaging uses diffusion imaging in at least six directions, as in DTI, and it gives FA maps – in addition to diffusion trace images and ADC maps – but it does not require post-process applications.[19] Measuring the lesion with a ROI on FA maps does not bring an additional burden to the daily usage of DWI.

Restriction of diffusion is known to be a criterion for differentiating malignant lesions from benign ones.[20] This study also revealed that ADC values are lower in malignant lesions: The mean ADC value for malignant lesions was $0.978\times10^{-3}mm^2/s$, while that of benign lesions was $1.256\times10^{-3}mm^2/s$. There was a significant difference between these two groups, as determined by an independent t-test (P=0.0005).

These values are lower than those reported in studies performed with patient groups including BIRADS scores other than 4 and 5 ($1.25\times10^{-3}mm^2/s$ for malignant and $1.74\times10^{-3}mm^2/s$ for benign lesions)[4], but higher than the study of Arponent *et al.*[21], which was performed on patients with biopsy indications with 3T MRI ($0.61\times10^{-3}mm^2/s$ for malignant, $1.1\times10^{-3}mm^2/s$ for benign lesions). The mean ADC value was also significant for the lesions with visually restricted diffusion in terms of malignancy (P=0.003; ADC=$1.163\times10^{-3}mm^2/s$ for benign, $0.958\times10^{-3}mm^2/s$ for malignant lesions). Visual assessment of diffusion restriction was also significant for malignancy (P=0.003). Restricted diffusion was seen in 57% of benign and 92% of malignant BIRADS 4 and 5 lesions. There is no strict ADC value for differentiating between malignant and benign breast lesions in the literature, but every centre can find its own values for malignancy.

Interestingly, the normal fibroglandular tissue ADC values were found to be lower in patients with malignant lesions that exhibited restricted diffusion. This can be a reason why having dense breast tissue – which can cause lower diffusion values – is a risk factor for breast carcinoma.[22] However, further studies with MRI are required to confirm this.

There are studies supporting[3,18], and bracketing off FA[17,23], for finding breast cancer on MRI. In this study, the mean FA values of the lesions were not found to contribute to the diagnosis of breast cancer. However, minimum FA value of the lesions was higher in malignant lesions demonstrating a higher anisotropy in cancer tissue. When BIRADS 4 and 5 lesions with restricted diffusion were studied, it was found that the mean FA and FA max of malign lesions had a higher significance than those for all the BIRADS 4 and 5 lesions. In addition, the FASD value was found to be significantly higher in malignant lesions.

Other studies have shown that standard deviation on DWI can give information about malignancy.[24] This result suggests that the FA values of malignant lesions are more heterogeneous than those of benign lesions, which recalls the anarchic distribution of cancer cells. There are studies supporting the idea that higher FA values would support the suspicion of malignancy.[13,3,9] This finding is important because DWI is used as an additive method to the DCE sequences, and having a restricted diffusion supports the idea of malignancy. In this selective group, the FA, FASD and FA_{max} values seem to have merit in supporting DWI.

In this study patients had biopsy indications (BI-RADS 4a, 4b, 4c and 5) and 41 of the 86 of the lesions were malignant with a PPV of 47.6%. It is known that breast MRI has high sensitivity (over 90%) but relatively lower specificity (around 72%).[25] The high sensitivity and lower specificity of breast MRI may result in high false positive breast biopsies if it is not used with correct indications. DWI is used as an additional data source for supporting dynamic breast MRI. Diffusion restriction was found to have 92.5% sensitivity whereas 42.2% specificity in this study. Restricted diffusion is used as a supporting finding for biopsy indication. But due to its lower specificity, DWI cannot be very helpful in increasing the specificity of conventional breast MRI. In search of finding a tool to increase the specificity of breast MRI, FA values seems to have a potential in differentiating benign lesions. When the BI-RADS 4 and 5 lesions with restricted diffusion were evaluated, FA, FASD and FA max values increased the specificity of multiparametric breast MRI as summarised in Table 3.

Larger lesions in both long and short axis were found to be related to malignancy. However, it is interesting that the short axis was more strongly related to malignancy than the long axis was. This finding is due to the fact that, on ultrasound, solid lesions with a vertical orientation are suspicious, but oval-shaped lesions are generally considered benign.[26] The relation between short axis size and malignancy was also maintained for the BIRADS 4 and 5 diffusion-restricted lesions, but the long axis diameter was not related to malignancy in this subgroup.

This study had several limitations. These included the small sample size and lack of representation of the different breast cancer subtypes. BIRADS 4 subgroups could be evaluated with a larger patient group.

CONCLUSION

In this study, it is considered that using FA maps – obtained in the daily practice without an additional post-processing workload – can contribute to the diagnosis of malignant breast lesions. With the FA maps, the FA, FASD and FAmax values can give information about the lesions. Using these parameters can be helpful, especially in BIRADS 4 and 5 lesions with restricted diffusion, for differentiating malignant versus benign lesions.

CONFLICTS OF INTEREST

There is no conflict of interest to declare.

FUNDING

This research has not used any research fund.

ETHICAL CONSIDERATIONS

The protocol of the study has been approved by the Ethical Board of Yildirim Beyazit University, University with an approval number of 11.15.2017/215.

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Nothing.

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