Original Article

Diagnostic Values of Diffusion Tensor Parameters in 3 T Breast Magnetic Resonance Imaging: Differentiation of Breast Tumors from Bilateral Healthy Breast Parenchyma

ST Ozal, E Inci

Department of Radiology, Medical Sciences University, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Bakirkoy, Istanbul, Turkey

ABSTRACT

Purpose: Our aim is to search diagnostic value of diffusion tensor parameters in the breast cancer. **Materials and Methods:** We included 46 patients with contrast enhanced magnetic resonance imaging of the breast between the dates of July 2015 and December 2016. We measured fractional anisotropy (FA), apparent diffusion coefficient (ADC), relative anisotropy (RA) and volume ratio (VR) values of the malignant mass, ipsilateral and contralateral healthy breast parenchyma in each patient. **Results:** ADC and VR values of the malignant lesions were significantly lower than normal parenchyma ($P < 0.01$). FA values were statistically higher in masses than normal breast parenchyma ($P < 0.05$). RA values were statistically higher in the mass than ipsilateral breast parenchyma ($P < 0.01$) but not significantly different from in contralateral breast parenchyma ($P > 0.05$). Only ADC values were statistically lower in contralateral side than ipsilateral breast parenchyma ($P < 0.05$) other parameters showed no statistical significance between parenchymas. **Conclusion:** DTI findings, such as FA, ADC, RA and VR, provide significant contribution in differentiating cancer from healthy breast tissue.

KEYWORDS: *Breast cancer, diffusion tensor imaging, magnetic resonance*

INTRODUCTION

The most common type of cancer among women is breast cancer.[1] Magnetic resonance imaging (MRI) of the breast is a supplementary method in addition to mammography and breast ultrasonography.[2] The sensitivity of MRI is increased with the help of the new techniques such as diffusion weighted images (DWI) and diffusion tensor imaging (DTI). Both DWI and DTI are changes of movement in water diffusion. The causes of the changes were variations in the tortuosity and restriction of tissues.[3] At least six multiple directional diffusion gradients must be applied for DTI. DTI shows microstructural properties through anisotrophy parameters.[4] The most commonly used anisotropy indices are the fractional anisotropy (FA), apparent diffusion coefficient (ADC = same as the mean diffusivity [MD]), the relative anisotropy (RA), and the volume ratio (VR).[5]

Preliminary DTI studies of the normal breast[6,7] and breast lesions[8,9] have been reported. These studies indicated lower values of ADC[6,10] in cancerous lesions, as compared with normal breast tissue and benign lesions. The results regarding the diagnostic capacity of the FA index were inconclusive.[6,10] Only a few previous DTI studies with 3 T imaging analyzing the normal breast parenchyma[7] and breast lesions[9] were reported. Higher magnetic field imaging has the advantages of higher signal-to-noise ratio (SNR) which allows higher temporal and spatial resolution.[11]

The purpose of this study was to search anisotropy parameters in the bilateral healthy breast parenchyma and malign breast lesions with a 3-T imager and their ability to differentiate cancer from normal breast tissue.

Address for correspondence: Dr. ST Ozal, Department of Radiology, Medical Sciences University, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Bakirkoy, Istanbul, Turkey. E-mail: drstok_21@hotmail.com

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_222_17

We also searched the differences of the parameters between bilateral healthy breast parenchyma. To our knowledge, this is the first study to compare bilateral normal breast parenchyma to determine its value in predicting cancer side.

MATERIALS AND METHODS

Patient selection

The study was approved by the institution's Regional Committees for Medical and Health Research Ethics. We included 46 female patients with contrast-enhanced MRI of the breast between the dates of July 2015 and December 2016 in this retrospective study. In premenopausal women, the MRI examination was performed in the second week of the menstrual cycle to minimize enhancement of normal glandular tissue. In subjects with multiple lesions, only the largest lesion was included in the analysis. The histopathological diagnoses of the malignant lesions were invasive ductal carcinoma ($n = 39$), invasive lobular carcinoma ($n = 3$), mix type ($n = 3$), and mucinous carcinoma ($n = 1$). The size of the lesions varied from 8 to 49 mm with a mean ± SD of 29.26 ± 10.09 mm. Their ages ranged 33–77 years (mean 55.88 ± 10.92).

Patients with a clinicoradiologic indication for histopathologic examination underwent a biopsy within a week after MRI examination, for a reliable radiologic–pathologic correlation.

Pregnant or lactating patients, patients with a breast lump smaller than 0.5 cm or greater than 5 cm, patients with type A (predominantly fatty parenchyma) breast pattern in mammography, patients with a history of neoadjuvant chemotherapy or radiotherapy, patients with a history of operation from the breast, bilateral breast masses, with carcinoma *in situ* only, with benign lesions, and/or with motion artifacts excluded from the study.

Breast magnetic resonance imaging protocol

All breast MRI held at 3 T MR (Verio, Siemens Healthcare, Erlangen, Germany) in the prone position by using breast coils (Breast matrix, Siemens Healthcare, Erlangen, Germany). Prior to the MRI examination, an intravenous (IV) catheter was inserted in the left or right arm. The first taken breast MRI sequence in our institute was axial turbo spin echo inversion recovery fat-sat T2-weighted sequence (TR 3570 ms, TE 70 ms, FOV 340 × 340 mm, matri × 358 × 448, slice thickness 4 mm with no intersection gap, NE × 2). Then, DTI sequence was performed by using an axial two-dimensional diffusion weighted echo planer imaging sequence (TR 4400 ms, TE 69 ms, slice thickness 3 mm with zero gap, NE × 4, FOV 340 × 340 mm, matri × 512 × 128) and the diffusion gradients were applied in six directions with $b = 0$ and

1000 s/mm². Finally, a dynamic contrast-enhanced sequence containing an axial T1-weighted 3D fast-spoiled gradient-recalled echo sequence (TR 4.15 ms, TE 1.5 ms, FOV 360 × 360 mm, matri × 288 × 320, slice thickness 1.5 mm) was performed. One precontrast acquisition and four postcontrast acquisitions were performed before and after IV administration of Gd-DTPA (Omniscan GE) with a dose of 0.1 mmol/kg, using an automated pump at a rate of 2 ml/s, followed by 20 ml of saline flush, at 2 ml/s.

Diffusion tensor imaging data postprocessing and analysis

Diffusion tensor data were post-processed and analyzed on the MRI Syngo station (Siemens Healthcare) using the Neuro 3D toolbox (Siemens Healthcare, Erlangen, Germany). All images were assessed retrospectively by over 5-year-experienced breast MRI radiologist (S. T. O.) blinded to histopathological findings.

For the measuring of DTI, region of interest (ROI) had 7–9 pixels. By browsing the contrast-enhanced subtraction images, the slice showing the lesion's maximum diameter was determined and then the same slice was found in the axial DTI map. The mostly contrast-enhanced and diffusion-restricted areas of the tumors were chosen for DTI [Figure 1]. The areas for DTI for ipsilateral breast parenchyma were chosen dense parenchymal regions far from the malign mass. For the contralateral breast, dense parenchymal areas of the symmetrical region of the breast mass were chosen [Figure 2]. We did not measure DTI from the cystic-necrotic and calcific areas of the mass. No measurements from the parenchymas were done for the predominantly fatty parenchyma. Three measurements were done from every region and the mean of these values was recorded. These values are FA, ADC, VR, and RA.

Statistical analysis

Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) program was used for the statistical analysis. Kolmogorov–Smirnov test was used for the assessment of study data for conformity for a normal distribution in addition to descriptive statistical methods (such as mean, standard deviation, median, ratio). Paired sample *t*-test was used for the normally distributed intragroup comparisons. Results were evaluated at 95% confidence interval and $P < 0.05$ level.

RESULTS

Comparison of diffusion tensor imaging measurements between carcinoma and contralateral breast parenchyma

FA, ADC, RA, and VR values of the lesions and the contralateral breast parenchyma were shown in Table 1.
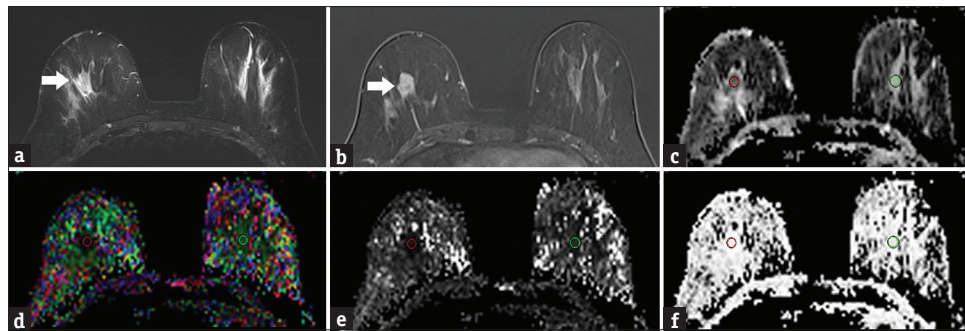
Figure 1: T2WI, contrast-enhanced T1WI, and DTI images of a 38-year-old woman with invasive ductal carcinoma in the right breast. The figures are the axial images of T2WI (a), contrast-enhanced T1WI (b), ADC map (c), FA map (d), RA map (e), and VR map (f). The ADC, FA, RA, and VR of tumor tissue diffusion parameters are calculated with ROIs on the contrast-enhancing areas of the mass with reference to the postcontrast image, and on the contralateral breast fibroglandular parenchyma. Arrows (a and b) show tumor. T2WI = T2-weighted image; T1WI = T1-weighted image; ADC = apparent diffusion coefficient; FA = fractional anisotropy; RA = relative anisotropy; VR = volume ratio; DTI = diffusion tensor imaging; ROI = region of interest
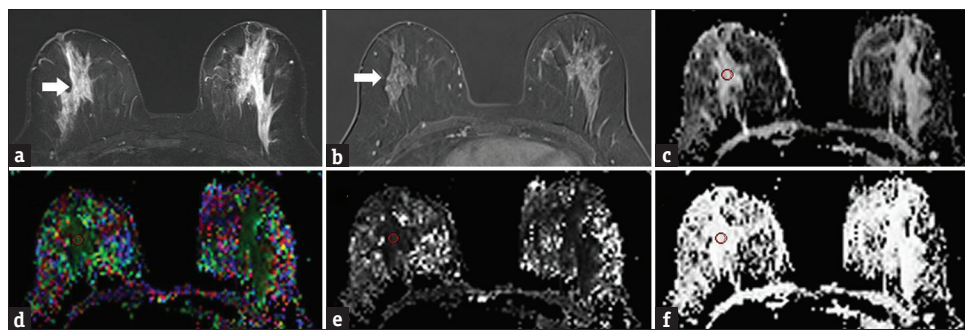
Figure 2: T2WI, contrast-enhanced T1WI, and DTI images of a 38-year-old woman with invasive ductal carcinoma in the right breast. The figures are the axial images of T2WI (a), contrast-enhanced T1WI (b), ADC map (c), FA map (d), RA map (e), and VR map (f). The ADC, FA, RA, and VR diffusion parameters are calculated with ROIs on the ipsilateral breast fibroglandular parenchyma with reference to the postcontrast image. Arrows (a and b) show normal breast parenchyma. T2WI = T2-weighted image; T1WI = T1-weighted image; ADC = apparent diffusion coefficient; FA = fractional anisotropy; RA = relative anisotropy; VR = volume ratio; DTI = diffusion tensor imaging; ROI = region of interest
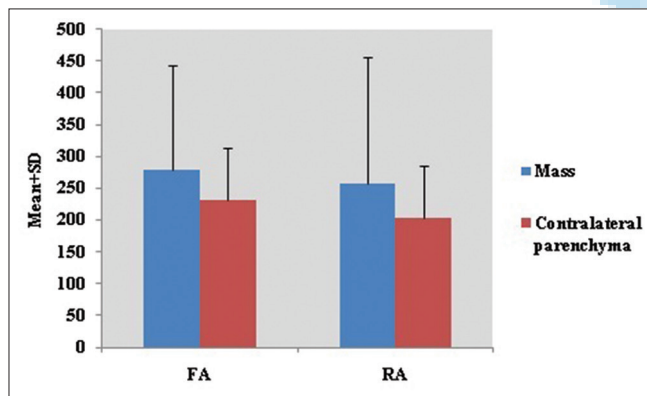

Figure 3: Comparison of FA and RA values between breast cancers and normal contralateral breast parenchyma. FA = Fractional anisotropy; RA = relative anisotropy

FA values were statistically higher in masses than contralateral breast parenchyma ($P < 0.05$) [Figure 3]. ADC values were statistically lower in masses than contralateral breast parenchyma ($P < 0.01$) [Figure 4]. Although the RA values of masses are higher than contralateral side, there was no statistically meaningful difference for RA values between two of them ($P > 0.05$). VR values were statistically lower in masses than contralateral breast parenchyma ($P < 0.05$).

Comparison of diffusion tensor imaging measurements between carcinoma and ipsilateral breast parenchyma

FA, ADC, RA, and VR values of the lesions and the ipsilateral breast parenchyma were shown in Table 2. FA values were statistically higher in the mass than ipsilateral breast parenchyma ($P < 0.01$) [Figure 5]. ADC values were statistically lower in the mass than ipsilateral breast parenchyma ($P < 0.01$) [Figure 6]. RA values were statistically higher in the mass than ipsilateral breast parenchyma ($P < 0.01$). VR values were statistically lower in the mass than ipsilateral breast parenchyma ($P < 0.01$).

Comparison of diffusion tensor imaging measurements between normal ipsilateral and contralateral breast parenchyma

FA, ADC, RA, and VR values of the lesions and the ipsilateral breast parenchyma were shown in Table 3. There was no statistically meaningful difference for FA values between ipsilateral and contralateral breast
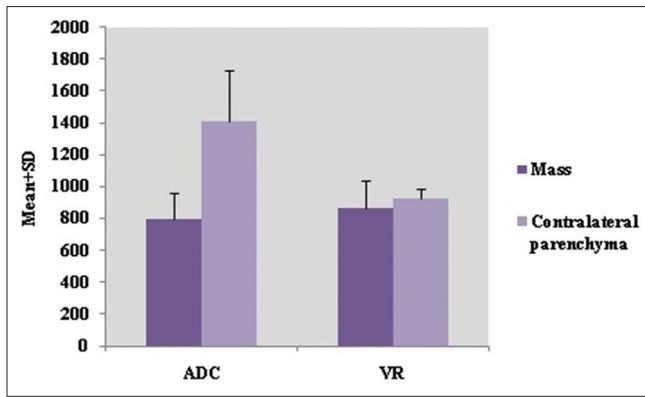
Figure 4: Comparison of ADC and VR values between breast cancers and normal contralateral breast parenchyma. ADC = Apparent diffusion coefficient; VR = volume ratio
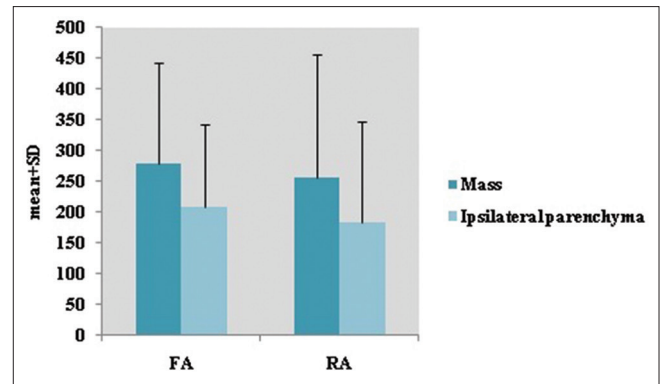

Figure 5: Comparison of FA and RA values between breast cancers and normal ipsilateral breast parenchyma. FA = Fractional anisotropy; RA = relative anisotropy
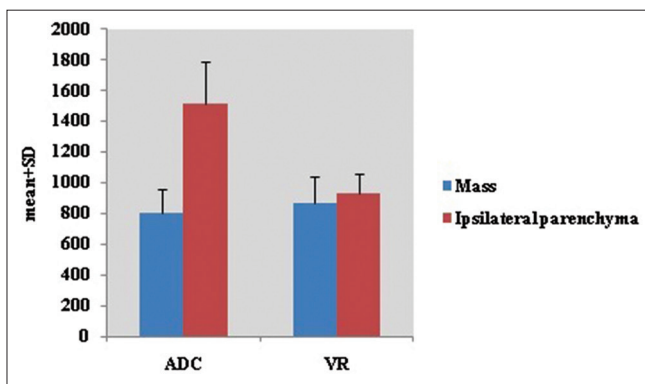

Figure 6: Comparison of ADC and VR values between breast cancers and normal ipsilateral breast parenchyma. ADC = Apparent diffusion coefficient; VR = volume ratio
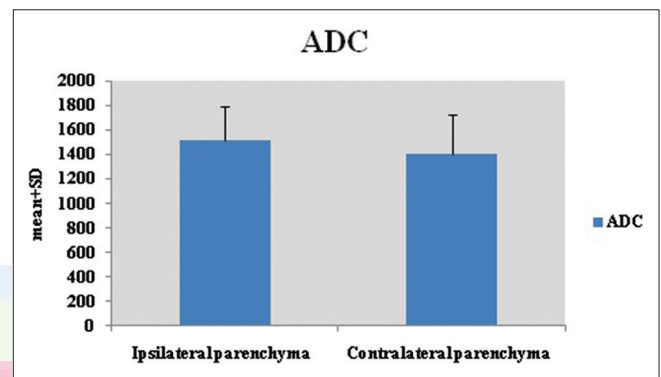

Figure 7: Comparison of ADC values between normal ipsilateral and contralateral breast parenchyma. ADC = Apparent diffusion coefficient

Table 3: Diffusion parameters in normal ipsilateral and contralateral breast parenchyma

	Ipsilateral parenchyma		Contralateral parenchyma		P
	Mean±SD	Median	Mean±SD	Median	
FA	207,52±135,04	178	230,27±84,17	220	0,233
ADC	1515,41±272,05	1501	1407,98±322,11	1371	0,014*
RA	183,39±162,62	149,5	202,26±82,77	185	0,412
VR	929,41±129,49	962	921,44±62,68	941	0,643

Paired samples *t*-test. **P<0,05. Mean ± SD values for FA, ADC, RA and VR are given in ×10⁻³mm²/s

Table 1: Diffusion parameters in breast masses and in the normal contralateral breast parenchyma

	Mass		Contralateral parenchyma		P
	Mean±SD	Median	Mean±SD	Median	
FA	278,22±164,94	251	230,27±84,17	220	0,044*
ADC	799,80±157,32	843	1407,98±322,11	1371	0,000**
RA	256,82±199,79	209	202,26±82,77	185	0,061
VR	866,78±169,76	925	921,44±62,68	941	0,024*

Paired samples *t*-test. *P<0,05, **P<0,01. Mean ± SD values for FA, ADC, RA and VR are given in ×10⁻³mm²/s

Table 2: Diffusion parameters in breast masses and in the normal ipsilateral breast parenchyma

	Mass		Ipsilateral parencyma		P
	Mean±SD	Median	Mean±SD	Median	
FA	278,22±164,94	251	207,52±135,04	178	0,001**
ADC	799,80±157,32	843	1515,41±272,05	1501	0,000**
RA	256,82±199,79	209	183,39±162,62	149,5	0,002**
VR	866,78±169,76	925	929,41±129,49	962	0,002**

Paired samples *t*-test. **P<0,01. Mean ± SD values for FA, ADC, RA and VR are given in ×10⁻³mm²/s

parenchyma ($P > 0.05$). ADC values were statistically lower in contralateral side than ipsilateral breast parenchyma ($P < 0.05$) [Figure 7]. There was no statistically meaningful difference for RA and VR values between two breast parenchymas ($P > 0.05$).

DISCUSSION

DTI is a new supplementary method for breast imaging nearby dynamic contrast-enhanced MRI.[12] DTI provides us 3D diffusion model for many organs. Because the number of diffusion gradients used in DTI is much more

than that used in DWI, a specific 3D ellipsoid tensor unit can be uniquely determined in each pixel, within which the diffusion ability in any direction can be accurately calculated. By measuring the anisotropic diffusion in different tissues, DTI can give us more detail about microstructure and pathophysiology than DWI and could be helpful to describe different lesions. There were many studies by using DTI in different organs such as brain, prostate, and kidney.[13-16]

The breast is different from the other organs. Its anatomy is mixed up fatty and fibroglandular elements. The fibroglandular tissue is divided by many lobes. The sizes and shapes of the lobes are not uniform. Each lobe has its own mammary tree and associated lobules forming the glandular tissue. These structures are surrounded by connective-fibrous tissue.[17]

Diffusion of water molecules in the mammary ducts and lobules shows a specific example of restricted and anisotropic movement. The movement is in parallel to the walls of the ducts and lobules; the diffusion is close to that of free diffusion. However, diffusion in the directions perpendicular to the walls is restricted by the walls. The walls are composed of two layers of cell and basement membrane. For this reason, the diffusion in the ductal/glandular system is relatively fast and anisotropic. On the other hand, the diffusion in the fibrous tissue surrounding the ducts is fast and isotropic, because water content is high. Cell density in this tissue is low also. In the malignancy condition, water movement is restricted. The reason of this condition is obliteration of the ducts and lobules by malignant cells. The result is lower diffusion coefficients and movement.[18-20]

It could be possible to measure and quantify anisotropic water diffusion in restricted environments by using DTI.

The majority of published DWI breast studies and DTI studies have been conducted with 1.5 T. We did this study at 3 T. The advantages of 3-T field are higher temporal and spatial resolution due to higher SNR. The disadvantages are much more chemical shift and susceptibility artifacts and field inhomogeneity. For the disadvantages using of parallel imaging techniques, additional shimming and optimization of the center frequency might be helpful.[11]

Analyzing the normal breast, Partridge *et al.*[6] in a 1.5-T DTI study found mean MD (ADC) and FA values of 1.77 ± 0.29 and 0.30 ± 0.05 mm^2/s, respectively, for *b* value of 1000 s/mm^2. With the same *b* value, Tagliafico *et al.*[7] found mean MD and FA values of 1.92 ± 0.30 and 0.32 ± 0.09 mm^2/s, respectively, in a 3-T DTI study, with MD measurements reportedly being more reproducible than FA. In our study,

mean ADC and FA of DTI were ipsilateral breast parenchyma FA value $207.52 \pm 135.04 \times 10^{-3}$ mm^2/s, ADC value $1515.41 \pm 272.05 \times 10^{-3}$ mm^2/s, RA value $183.39 \pm 162.62 \times 10^{-3}$ mm^2/s, and VR value $929.41 \pm 129.49 \times 10^{-3}$ mm^2/s, respectively, and contralateral breast parenchyma FA value $230.27 \pm 84.17 \times 10^{-3}$ mm^2/s, ADC value $1407.98 \pm 322.11 \times 10^{-3}$ mm^2/s, RA value $202.26 \pm 82.77 \times 10^{-3}$ mm^2/s, VR value $921.44 \pm 62.68 \times 10^{-3}$ mm^2/s, respectively, for *b* value of 1000 s/mm^2.

Baltzer *et al.*[21] in a study of DTI at 1.5 T with the *b* value of 0–1000 s/mm^2 found that the diffusion direction was mainly anterior–posterior in the breast parenchyma, whereas the lesions showed no predominant direction. The malignant lesions showed a lower ADC and FA, with the ADC being more discriminative. In our study, the mass FA value was found $278.22 \pm 164.94 \times 10^{-3}$ mm^2/s, ADC value $799.80 \pm 157.32 \times 10^{-3}$ mm^2/s, RA value $256.82 \pm 199.79 \times 10^{-3}$ mm^2/s, and VR value $866.78 \pm 169.76 \times 10^{-3}$ mm^2/s, respectively.

All four anisotrophy parameters in the mass were statistically different from ipsilateral breast parenchyma. Also, we compared these values with contralateral breast parenchyma. FA, ADC, and VR values in the mass were significantly different from contralateral breast parenchyma. Although the RA values of masses are higher than contralateral side, there was no statistically meaningful difference for RA values between two of them ($P > 0.05$). We compared the values of bilateral breast parenchymas. ADC values were high in the ipsilateral breast parenchyma. This may be due to edematous changes in the ipsilateral breast parenchyma.

Several studies have demonstrated that ADC and FA are lower in breast cancers compared with normal breast tissue and benign lesions.[8,9] But all the lesions in our study are malign. So, we could not compare the benign and malign lesions. Instead, we searched the differences between two breast parenchymas.

Recently, some authors worked on DTI of breast. Partridge *et al.*[8] found that diffusion anisotropy was lower in malign masses than normal parenchyma, but there was not any meaningful difference for FA values. Baltzer *et al.*[21] made a study at 1.5 T MRI. They found lower FA values as well as lower ADC values in the malign masses than normal glandular tissue. Their *b* values were of 0–1000 s/mm^2. They found that the diffusion in the mass showed no direction instead of anteroposterior diffusion of normal tissues.

One study made by Eyal *et al.*[9] searched the effectiveness of DTI at 3 T. They used *b* value of 0–700 s/mm^2 and found lower values of orthogonal diffusion coefficients, $\lambda 1$, $\lambda 2$, $\lambda 3$, and maximal anisotropy

index $\lambda 1$–$\lambda 3$, in malign masses in the breast than physiologic glandular tissue. According to this study, the maps of $\lambda 1$ is a good parameter for differentiating cancer from normal tissue. The $\lambda 1$–$\lambda 3$ was a secondary diagnostic parameter. The sensitivity of this parameter was high sensitivity, specificity was not as high as sensitivity.

The edema in the breast with a malign mass could alter ADC values. This fact may be the reason of changes in ADC values between two breasts.

Our study has some limitations, one of them is we have not got any benign lesion. The other limitation is in some studies, they used $b700$ value. But we used only $b0$ and 1000 like in most of the studies. We have got only 46 patients. We did not compare the results with histopathologic types. If we would have larger numbers of patients, we could arrange the values according to histopathological findings.

Conclusion

DTI is a useful method in differentiation of malign masses from normal parenchyma. The lower ADC values in the contralateral breast parenchyma is a new finding in the literature. This finding can be used in the evaluation of bilateral breast parenchyma in order to determine cancer side.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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