



## Breast Imaging

## Diagnostic performance of quantitative diffusion tensor imaging for the differentiation of breast lesions at 3 T MRI

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## ABSTRACT

**Background:** Conventional breast magnetic resonance imaging (MRI), including dynamic contrast-enhanced MR mammography, may lead to ambiguous diagnosis and unnecessary biopsies.

**Purpose:** To investigate the contribution of quantitative diffusion tensor imaging (DTI) in the discrimination between benign and malignant breast lesions at 3 T MRI.

**Material and methods:** The study included a total of 86 lesions (44 benign and 42 malignant) in 58 women (34 with malignant lesions, 23 with benign lesions and 1 with both types of lesions). All patients were examined on a 3 T MRI scanner. Fractional Anisotropy (FA), Mean Diffusivity (MD), Apparent Diffusion Coefficient (ADC), as well as eigenvalues ( $\lambda_1, \lambda_2, \lambda_3$ ) were calculated and compared between benign and malignant lesions using two different software packages (GE Functool and ExploreDTI).

**Results:** Malignant lesions exhibited significantly lower ADC values compared to benign ones ( $ADC_{mal} = 1.06 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $ADC_{ben} = 1.54 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $p\text{-value} < 0.0001$ ). FA measurements in carcinomas indicated slightly higher values than those in benign lesions ( $FA_{mal} = 0.20 \pm 0.07$ ,  $FA_{ben} = 0.15 \pm 0.05$ ,  $p\text{-value} = 0.0003$ ). Eigenvalues  $\lambda_1, \lambda_2, \lambda_3$ , showed significantly lower values in malignant tumors compared to benign lesions and normal breast tissue. ROC curve analysis of ADC and DTI metrics demonstrated that ADC provides high diagnostic performance ( $AUC = 0.944$ ) while, MD and  $\lambda_1$  showed best discriminative results ( $AUC = 0.906$ ) for the differentiation of malignant and benign lesions in contrast to other DTI parameters.

**Conclusion:** The addition of eigenvalue analysis improves DTI's ability to differentiate between benign and malignant breast lesions.

## 1. Introduction

Breast cancer is the most commonly diagnosed cancer among women and constitutes the second leading cause of cancer deaths [1]. Even though the breast cancer incidence rate has been increased over the last two decades, the mortality rate has been substantially declined from 1989 to 2014, reaching a reduction of 38% according to the American Cancer Society [2]. Hence, early detection plays a critical role in the determination of treatment options and the effectiveness of the selected treatment approach.

The predominant techniques currently used in breast cancer detection and diagnosis are mammography and ultrasonography, but despite

their wide use, their sensitivity and specificity remain in some cases insufficient [3].

Breast MRI is an imaging tool with highest sensitivity for breast cancer detection [4,5], especially for invasive ductal cancer, extremely dense [6] and heterogeneously dense breast tissue on mammography [7], and has gained clinical acceptance for a range of clinical indications, such as supplemental screening and pre-operative assessment of breast cancer [8].

More specifically, Dynamic Contrast-Enhanced MRI (DCE-MRI) has become an asset for the detection and characterization of breast cancer, which however indicates a high false-positive rate, often leading to unnecessary biopsies [9] and shows moderate specificity (range

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37%–97%) [10].

Diffusion Weighted Imaging (DWI), on the other hand, has shown promising results to overcome the above limitation. DWI is a form of MR imaging based upon measuring the random Brownian motion of water molecules within a voxel of tissue, which is restricted by the various tissue components. A basic parameter that can be measured using DWI is the Apparent Diffusion Coefficient (ADC) and represents the magnitude of diffusion (of water molecules) within tissue. Consequently, ADC can provide details regarding the microstructure and the tissue cellularity [11].

Diffusion tensor imaging (DTI) is a MRI technique that enables the measurement of the restricted diffusion of water in a tissue and the characterization of water motion in more detail. Furthermore, it provides the measure of directionality - diffusion anisotropy in addition to ADC.

In particular, the average of the ADC values along the three orthogonal directions is known as Mean Diffusivity (MD), while another DTI parameter, Fractional Anisotropy (FA), is a scalar value between zero and one which describes the degree of anisotropy of a diffusion process.

A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted along all other directions. Moreover, the evaluation of the eigenvalues ( $\lambda_1, \lambda_2, \lambda_3$ ) may enable the characterization of diffusion in three dimensions calculating the degree of anisotropic water diffusion in the tissue.

There is a large body of literature investigating the potential of ADC [4,12–14] and DTI [7,15–18] for the differentiation of breast lesions confirming lower ADC values in malignant tumors compared to normal breast tissue and benign lesions.

The purpose of this study was to examine the ability of DTI parameters and more specifically the 3D anisotropic diffusion (eigenvalues) to discriminate between benign and malignant breast lesions, by comparison to ADC. Moreover, DTI metrics were calculated using two different software packages for DTI data analysis, GE Functool (GE Healthcare, Milwaukee, USA) and ExploreDTI (developed by A. Leemans) in order to estimate software dependency on eigenvalue evaluation.

## 2. Material and methods

### 2.1. Patients

In this study, 58 women were included, ranging in age from 31 to 79 years (mean  $\pm$  SD, 53  $\pm$  13 years).

This was a retrospective study, approved by the local Institutional Review Board and informed consent was obtained from all participants. Breast MRI was performed in patients with suspicious BI-RADS 3 (Breast Imaging-Reporting and Data System) to BI-RADS 5 lesions detected on mammography and/or ultrasonography prior to any type of biopsy.

Each breast MRI scan, completed bilateral coverage, revealed at least one contrast-enhancing lesion and was accompanied by the corresponding pathology report derived from core needle biopsy or surgical excision.

The exclusion criteria for participation in the study were: receiving neoadjuvant chemotherapy or radiation therapy, having any metallic clips from previous surgical procedures and having general contraindications to MRI or to the administration of contrast agents.

All patients underwent the same protocol including conventional breast MRI, DWI and DTI.

All breast lesions included were confirmed histologically.

### 2.2. Image acquisition

MR images were acquired on a 3.0 T MRI scanner (GE Healthcare, Signa HDx, Milwaukee, WI, USA) with patients placed in the prone

position, using a dedicated phased array 8-channel breast coil. The final imaging protocol consisted of a conventional MRI protocol, DWI and DTI.

Each conventional MRI examination included scanning of the two breasts. Breast DCE-MRI protocol consisted of axial T2-weighted fast spin echo sequence (T2-FSE), (repetition time/echo time (TR/TE) 3600/100 ms, slice thickness 4.0 mm and spacing 0 mm), axial short inversion recovery sequence (STIR), (repetition time/echo time (TR/TE) 3875/90 ms, slice thickness 4.0 mm and spacing 0 mm), 3D T1-weighted vibrant dynamic sequence with fat-suppression (flip angle 10° and isotropic voxel 1 mm<sup>3</sup>) which was applied before and five times after the intravenous (IV) injection of the contrast agent (gadolinium) with a 10 second timing delay, using an automatic injector system.

The DWI protocol consisted of a DWI sequence which was acquired before IV injection of the contrast medium with the following characteristics: repetition time (TR) 6000 ms, echo time (TE) 63.80 ms, slice thickness 4.0 mm, spacing 0 mm, flip angle 90° and b-value 850 s/mm<sup>2</sup>. The selected matrix size was 256  $\times$  256.

Diffusion tensor imaging (DTI) was performed using an axial echo planar imaging (EPI) sequence with repetition time (TR) 6000 ms, echo time (TE) 63.70 ms, slice thickness 4.0 mm, spacing 0 mm and flip angle 90°. The number of the diffusion directions was 6 and the diffusion weighting (b-value) was set to 0 and 600 s/mm<sup>2</sup>. DTI images were acquired before the gadolinium-contrast medium injection.

An indicative example of the aforementioned protocol with DTI parametric analysis is depicted in Fig. 1.

### 2.3. Data analysis

Data analysis and diffusion measurements were performed using the vendor's software package for DTI analysis GE Functool (GE Healthcare, Milwaukee, USA) and ExploreDTI which is a graphical toolbox, developed by Alexander Leemans, for exploratory diffusion tensor MRI [19].

GE Functool toolbox is used for advanced processing of 3D datasets for multiple MR applications including perfusion, spectroscopy and diffusion tensor imaging studies. The pre-processing stage comprised EPI and eddy current distortion correction. During the basic analysis of diffusion data, DTI scalars such as Fractional Anisotropy (FA) and Mean Diffusivity (MD) were produced, while DTI parametric maps were generated for the extraction of eigenvectors  $u_1, u_2, u_3$  and eigenvalues  $\lambda_1, \lambda_2, \lambda_3$ .

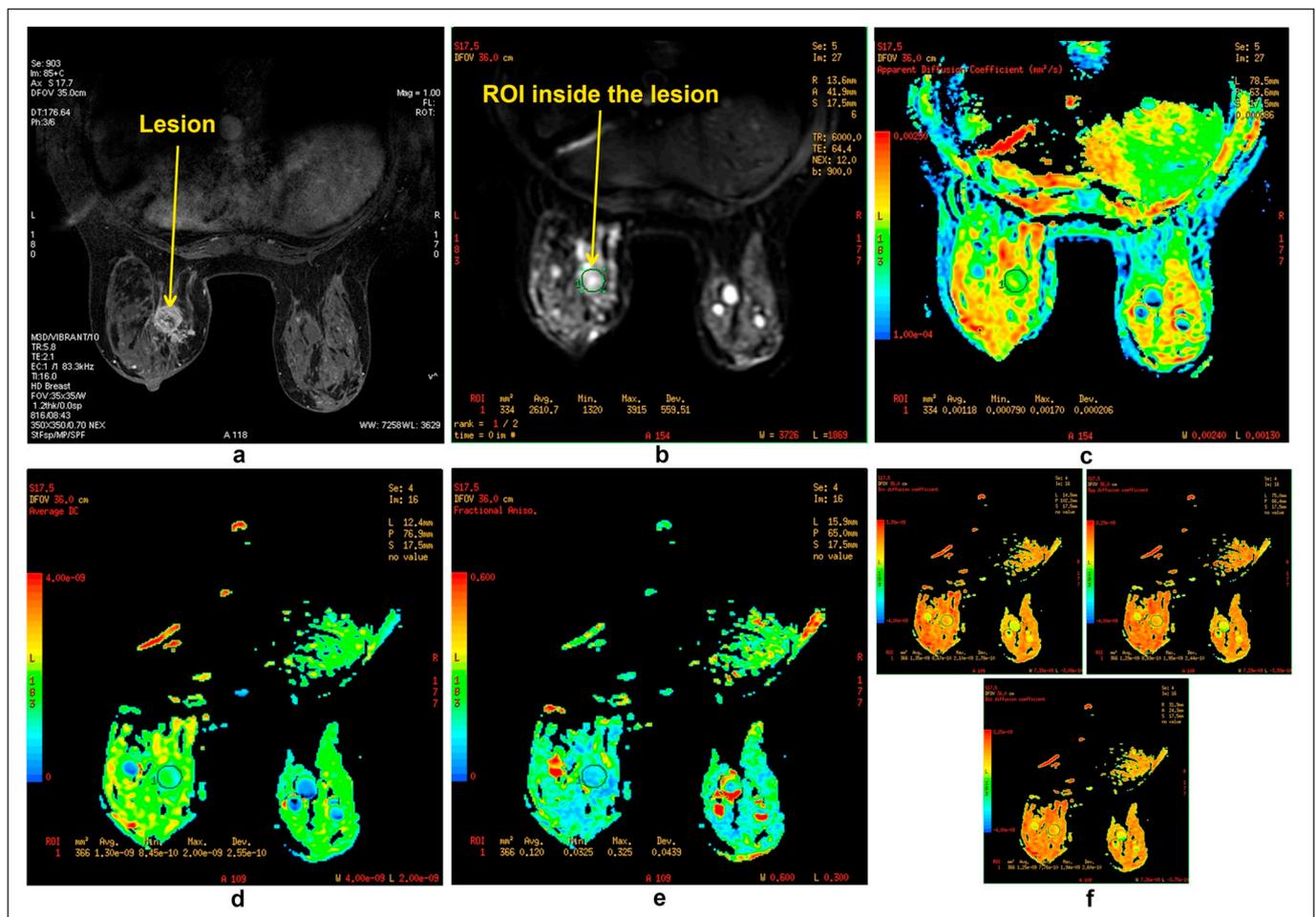
The eigenvectors and eigenvalues were calculated after completing and diagonalizing the symmetrical diffusion tensor, Eq. (1).

$$\bar{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \xrightarrow{\text{diagonalization}} \lambda_1, \lambda_2, \lambda_3, \mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3 \quad (1)$$

In order to measure the aforementioned DTI parameters inside the lesion and in the contralateral normal tissue, the placement of Regions of Interest (ROIs) is required.

Two radiologists with 20 years of experience in the interpretation of breast MRI images, were blinded to the pathologic findings and histological information of the participants and manually delineated free-hand ROIs around the lesions. The ROI was placed carefully within the lesion borders excluding cystic, necrotic or hemorrhagic areas. Overall there was minimal interobserver variability. In case of disagreement, interobserver differences were resolved by consensus review.

ExploreDTI on the other hand is a graphical toolbox, for the exploration of diffusion (tensor) MRI and fiber tractography [18]. DTI pre-processing was performed again consisting of subject motion, EPI and eddy current distortion correction with reorientation of the b-matrix. Subsequently, DTI data sets were reprocessed and all DTI parameters were computed since the selected ROI was manually located inside the lesion and in the physiological breast tissue by the radiologist. In contrast to GE Functool, ExploreDTI displays directly the



**Fig. 1.** An example of DTI parametric analysis in a 43-year-old patient with a malignant lesion. (a) Post contrast T1-weighted image shows a lesion with heterogeneous internal enhancement. (b) Parametric maps of DWI, (c) ADC, (d) Average DC, (e) Fractional Anisotropy and (f) eigenvalues  $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$  where generated and analyzed. A ROI is placed within the lesion borders to calculate all the DWI and DTI parameters.

calculated DTI metrics based on ROI Statistics.

### 2.4. Statistical analysis

Statistical analysis was performed using SPSS (IBM Corp., Endicott, NY, USA). Descriptive statistics consisted of means and standard deviations for ADC, FA, MD and  $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$  measurements. Non-parametric Mann-Whitney *U* tests were used to evaluate the significance in the ADC and DTI metrics between malignant and benign breast lesions, while the Wilcoxon signed rank test was used between the affected (benign or malignant) and the contralateral areas.

Receiver-operating characteristic (ROC) curve analysis based on logistic regression models was performed to assess the diagnostic performance of ADC and DTI parameters, while the statistical significance was set at  $p = 0.05$ .

### 3. Results

Fifty-eight women aged 31–79 years (mean  $\pm$  SD,  $53 \pm 13$  years) participated in this study. Out of a total of 86 lesions identified on MRI, 44 (51%) were benign and 42 (49%) were malignant, while the mean ROI size was  $127.59 \text{ mm}^2$  for benign lesions and  $228.82 \text{ mm}^2$  for malignant lesions respectively. The lesion size was 1.7 cm on average (range, 0.6–5.1 cm) for benign lesions and 2.8 cm on average (range, 0.7–9.0 cm) for malignant lesions.

### 3.1. DWI

ADC was measured for each patient, and for all breast lesions and contralateral normal breast parenchyma. The mean ADC value of malignant and benign lesions was  $1.06 \times 10^{-3} \pm 0.24 \text{ mm}^2/\text{s}$  and  $1.54 \times 10^{-3} \pm 0.22 \text{ mm}^2/\text{s}$  respectively, while the mean ADC value of the normal tissue was  $1.77 \times 10^{-3} \pm 0.20 \text{ mm}^2/\text{s}$  (Table 1). Concerning the characterization of breast lesions, ADC measurements in malignant lesions indicated lower values ( $p < 0.0001$ ) compared to benign lesions and normal breast tissue.

### 3.2. DTI analysis and comparison of different evaluation software (GE Functool and ExploreDTI)

DTI data analysis was performed using both GE Functool and ExploreDTI software packages and produced results regarding the FA,

**Table 1**

ADC mean values ( $\pm$  SD) for malignant and benign lesions, and contralateral normal area.

	Malignant	Benign	Contralateral normal tissue	p-Value
ADC ( $\times 10^{-3} \text{ mm}^2/\text{s}$ )	$1.06 \pm 0.24$	$1.54 \pm 0.22$	$1.77 \pm 0.20$	$< 0.0001$

*p* values represent Mann-Whitney *U* test for the comparison of the ADC values between malignant and benign breast lesions.

**Table 2**  
MD and FA mean values ( $\pm$  SD) for malignant and benign lesions, and contralateral normal area using GE Functool and ExploreDTI.

	Malignant	Benign	Contralateral normal tissue	p-Value
MD <sub>Functool</sub> ( $\times 10^{-3}$ mm <sup>2</sup> /s)	1.25 $\pm$ 0.31	1.70 $\pm$ 0.24	1.99 $\pm$ 0.24	< 0.0001
MD <sub>ExploreDTI</sub> ( $\times 10^{-3}$ mm <sup>2</sup> /s)	1.22 $\pm$ 0.26	1.80 $\pm$ 0.25	1.96 $\pm$ 0.20	< 0.0001
FA <sub>Functool</sub>	0.20 $\pm$ 0.07	0.15 $\pm$ 0.05	0.17 $\pm$ 0.06	0.0003
FA <sub>ExploreDTI</sub>	0.18 $\pm$ 0.08	0.13 $\pm$ 0.06	0.16 $\pm$ 0.05	0.001

p values represent Mann-Whitney U test for the comparison of the MD and FA between malignant and benign breast lesions.

MD and eigenvalues  $\lambda_1, \lambda_2, \lambda_3$  (Table 2). DTI parameters were calculated for each patient and for all breast lesions and contralateral normal breast parenchyma.

Results derived from GE Functool: The MD mean values for malignant lesions, benign lesions and normal tissue were  $1.25 \times 10^{-3} \pm 0.31$  mm<sup>2</sup>/s,  $1.70 \times 10^{-3} \pm 0.24$  mm<sup>2</sup>/s and  $1.99 \times 10^{-3} \pm 0.24$  mm<sup>2</sup>/s respectively, while the corresponding FA mean values were  $0.20 \pm 0.07, 0.15 \pm 0.05$  and  $0.17 \pm 0.06$ .

Results derived from ExploreDTI: The MD mean values calculated for malignant lesions, benign lesions and normal tissue were  $1.22 \times 10^{-3} \pm 0.26$  mm<sup>2</sup>/s,  $1.80 \times 10^{-3} \pm 0.25$  mm<sup>2</sup>/s and  $1.96 \times 10^{-3} \pm 0.20$  mm<sup>2</sup>/s respectively, while the corresponding FA mean values were  $0.18 \pm 0.08, 0.13 \pm 0.06$  and  $0.16 \pm 0.05$ .

As depicted in Fig. 2, for both methods MD showed lower values when measured in malignant lesions, in contrast to benign lesions and exhibited significant differences,  $p < 0.0001$ . Regarding FA mean values, the p-value was calculated 0.0003 (GE Functool) and 0.001 (ExploreDTI).

Mean  $\lambda_1, \lambda_2$  and  $\lambda_3$  values were calculated for malignant and benign lesions and for contralateral normal tissue using both GE Functool and ExploreDTI software packages (Table 3). Statistical analysis of the primer eigenvalue  $\lambda_1$  exhibited significant lower values for malignant lesions, where benign and normal tissues appeared to have high  $\lambda_1$  values.

More specifically,  $\lambda_1$  values derived from GE Functool were

$1.43 \times 10^{-3} \pm 0.28$  mm<sup>2</sup>/s,  $1.91 \times 10^{-3} \pm 0.24$  mm<sup>2</sup>/s and  $2.22 \times 10^{-3} \pm 0.24$  mm<sup>2</sup>/s respectively.  $\lambda_2$  and  $\lambda_3$  showed the same tendency towards lower values for carcinomas ( $1.29 \pm 0.28$  mm<sup>2</sup>/s and  $1.12 \pm 0.29$  mm<sup>2</sup>/s respectively) compared to benign breast lesions ( $1.70 \pm 0.21$  mm<sup>2</sup>/s and  $1.56 \pm 0.23$  mm<sup>2</sup>/s). p-Values were calculated lower than 0.05 ( $< 0.0001$ ) for each eigenvalue. Statistical analysis of the maximal anisotropy indices ( $\lambda_1$ – $\lambda_3$ ) indicated same mean values for carcinomas and benign lesions ( $0.35 \pm 0.21 \times 10^{-3}$  mm<sup>2</sup>/s) ( $p = 0.682$ ).

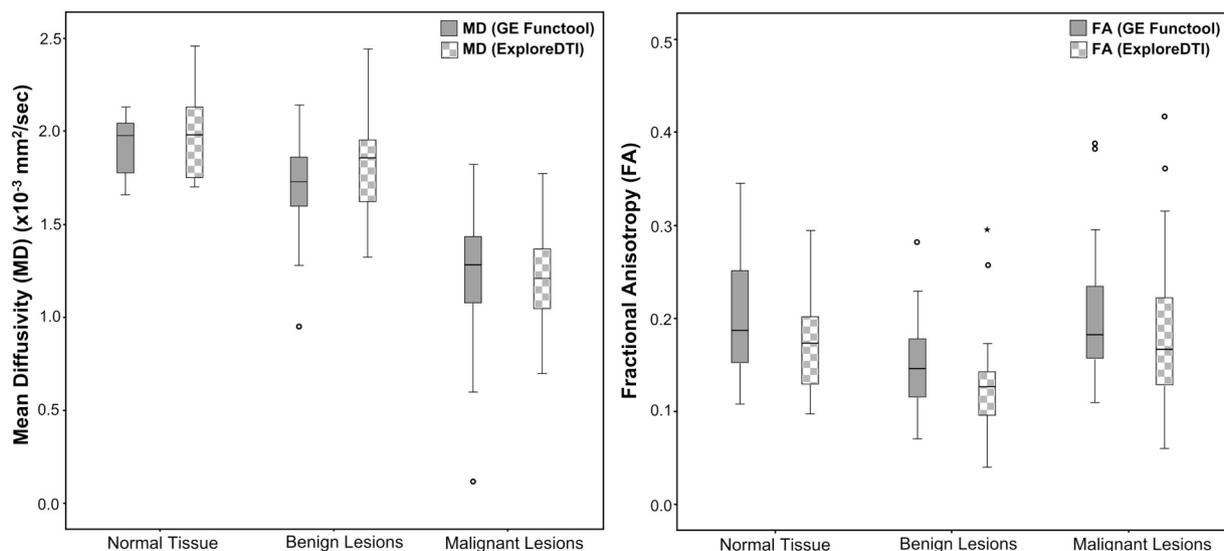
ExploreDTI results accord with those derived from GE Functool as depicted in Fig. 3. The mean  $\lambda_1$  for carcinomas, benign lesions and normal tissue was:  $1.45 \times 10^{-3} \pm 0.25$  mm<sup>2</sup>/s,  $2.08 \times 10^{-3} \pm 0.34$  mm<sup>2</sup>/s and  $2.03 \times 10^{-3} \pm 0.75$  mm<sup>2</sup>/s ( $p < 0.0001$ ). The value of maximal anisotropy indices ( $\lambda_1$ – $\lambda_3$ ) was  $0.45 \times 10^{-3} \pm 0.20$  and  $0.53 \times 10^{-3} \pm 0.33$  for malignant and benign lesions, respectively. However, the p-value of ( $\lambda_1$ – $\lambda_3$ ) failed to reach statistical significance ( $p = 0.338$ ).

### 3.3. Comparison of ADC and DTI parameters

The mean ADC value of all malignant breast masses (using GE Functool) was  $1.06 \times 10^{-3} \pm 0.24$  mm<sup>2</sup>/s, significantly lower than the ADC of benign lesions ( $1.54 \times 10^{-3} \pm 0.22$  mm<sup>2</sup>/s,  $p < 0.0001$ ). ADC measurements in the contralateral normal tissue indicated even higher values,  $1.77 \times 10^{-3} \pm 0.20$  mm<sup>2</sup>/s.

MD and  $\lambda_1, \lambda_2, \lambda_3$  values were significantly lower in malignant compared to benign lesions ( $p < 0.0001$ ), while malignant masses showed significantly higher values of FA ( $0.20 \pm 0.07$ ) compared to benign masses ( $0.15 \pm 0.05, p = 0.0003$ ). On the other hand, the maximal anisotropy indices ( $\lambda_1$ – $\lambda_3$ ) exhibited no significant difference between benign and malignant lesions ( $p = 0.682$ ).

The evaluation of ADC and DTI parameters as discriminators of benign and malignant tissues was performed utilizing receiver operating characteristic (ROC) curve analysis. According to the ROC analysis depicted in Fig. 4, ADC produced an AUC of 0.944, with sensitivity of 85% and specificity of 84.4%, while MD and  $\lambda_1$  constituted the best discriminative DTI parameters with the same AUC, 0.906. Fractional Anisotropy showed a lower AUC of 0.729 with 65.8% sensitivity and 67.4% specificity and ( $\lambda_1$ – $\lambda_3$ ) an even lower AUC of 0.512. ROC curve analysis of MD combined with FA depicted in Fig. 5, demonstrated an AUC of 0.910, which remains lower compared to the diagnostic performance of the ADC.



**Fig. 2.** Box-plots showing the MD and FA measurements in normal tissue, benign and malignant lesions respectively and the comparison between the two software (GE Functool and ExploreDTI).

**Table 3**  
Eigenvalues and maximal anisotropy indices with their corresponding SD and comparison results between malignant, benign, and contralateral normal area.

	DTI metrics	Malignant	Benign	Contralateral normal tissue	p-Value
GE Functool ( $\times 10^{-3} \text{ mm}^2/\text{s}$ )	$\lambda_1$	$1.43 \pm 0.28$	$1.91 \pm 0.24$	$2.22 \pm 0.25$	$< 0.0001$
	$\lambda_2$	$1.29 \pm 0.28$	$1.70 \pm 0.21$	$1.98 \pm 0.24$	$< 0.0001$
	$\lambda_3$	$1.12 \pm 0.29$	$1.56 \pm 0.23$	$1.78 \pm 0.26$	$< 0.0001$
	$\lambda_1-\lambda_3$	$0.35 \pm 0.21$	$0.35 \pm 0.21$	$0.44 \pm 0.16$	0.682
ExploreDTI ( $\times 10^{-3} \text{ mm}^2/\text{s}$ )	$\lambda_1$	$1.45 \pm 0.25$	$2.08 \pm 0.34$	$2.03 \pm 0.75$	$< 0.0001$
	$\lambda_2$	$1.21 \pm 0.25$	$1.76 \pm 0.24$	$1.74 \pm 0.65$	$< 0.0001$
	$\lambda_3$	$1.00 \pm 0.30$	$1.54 \pm 0.28$	$1.41 \pm 0.64$	$< 0.0001$
	$\lambda_1-\lambda_3$	$0.45 \pm 0.20$	$0.53 \pm 0.33$	$0.62 \pm 0.43$	0.338

p values represent Mann-Whitney U test for the comparison of  $\lambda_1, \lambda_2, \lambda_3$  between malignant and benign breast lesions.

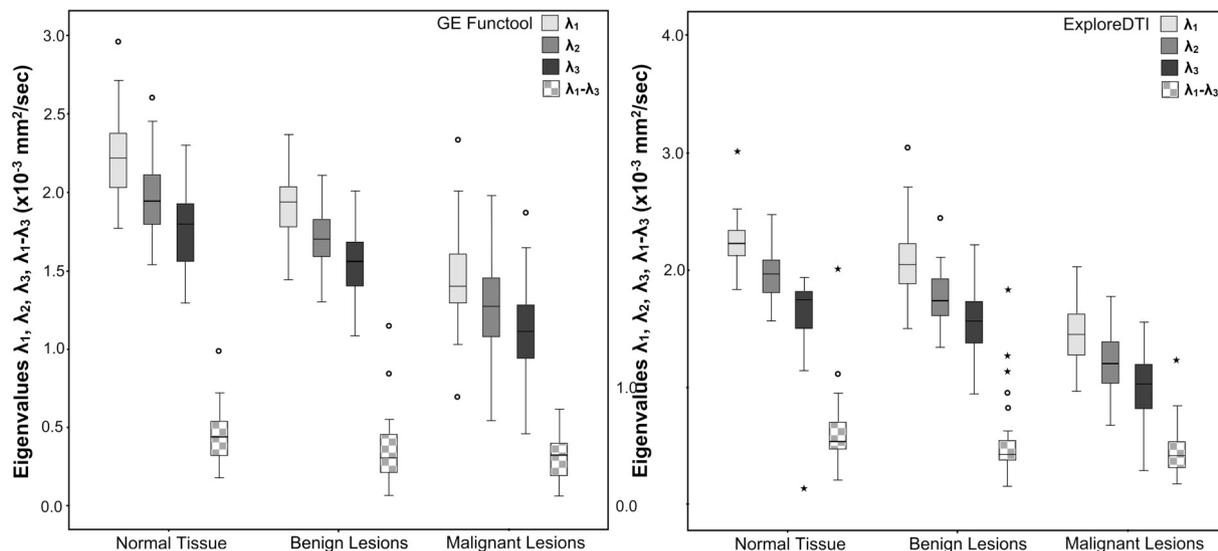


Fig. 3. Box-plots showing (a) eigenvalues  $\lambda_1, \lambda_2, \lambda_3$  and (b)  $\lambda_1-\lambda_3$  measurements in normal tissue, benign and malignant lesions using both analysis software.

**4. Discussion**

DCE-MRI has been established as a powerful asset for the detection and diagnosis of breast cancer [20]. There is a direct correlation between DCE-MRI and the vascularity of tumors, but there appears to be no evidence to link this technique with tumor cellularity [21].

However, despite its high sensitivity in detecting breast lesions, the main weakness of breast DCE-MRI remains its low specificity.

The utilization of diffusion MR imaging enhances the characterization of breast lesions, as it investigates tissue microstructure [22]. ADC constitutes the basic parameter of diffusion-weighted imaging and reflects the magnitude of diffusion of water molecules within tissue.

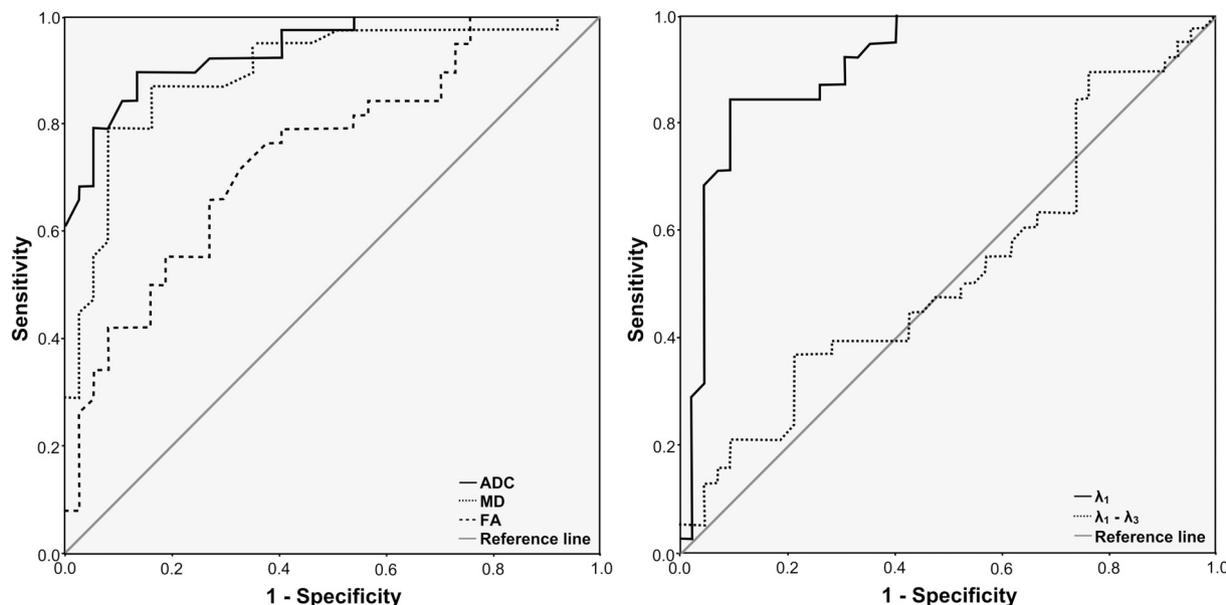


Fig. 4. ROC curves of (a) ADC, MD and FA and (b)  $\lambda_1$  and  $(\lambda_1-\lambda_3)$  for differentiation of malignant and benign breast lesions.

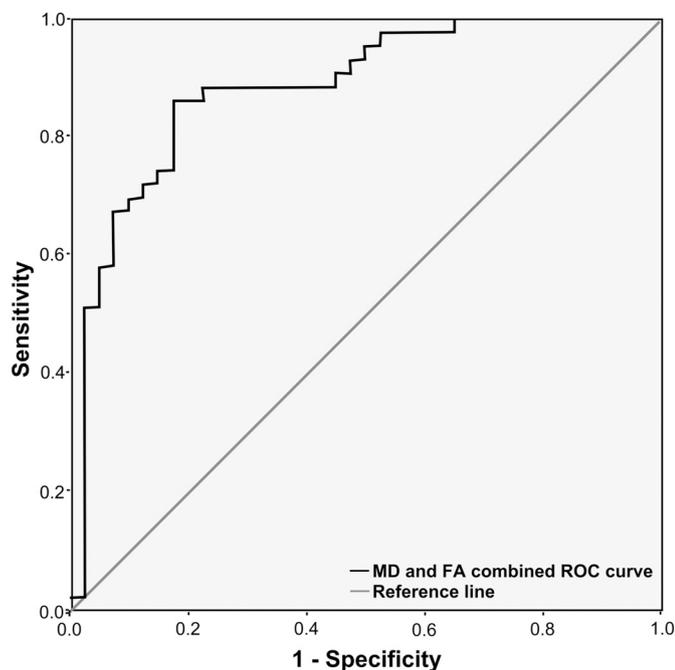


Fig. 5. Combined ROC curve of MD and FA for differentiation of malignant and benign breast lesions.

Typically, it can be measured by placing a freehand ROI inside the lesion borders excluding hemorrhagic, necrotic and cystic areas [23]. Nevertheless, the higher cell density of malignant masses compared to benign lesions or normal tissue and the narrow extracellular space, restrict the movement of water molecules and hence result in lower ADC values [23]. There are a large number of studies which confirm the significantly lower ADC values in malignant versus benign lesions [12–14,24]. A recent study of Akin et al. [25], showed statistically significant differences between the ADC values of malignant and benign breast lesions with a very high AUC value of 0.945. In our study, ADC measurements in malignant lesions indicated significantly lower values ( $p < 0.0001$ ) compared to benign lesions and normal breast tissue, while the ROC curve analysis proved its high diagnostic performance (AUC = 0.944) with 85% sensitivity and 84.4% specificity. The mean ADC values in cancer and benign tissue were  $1.06 \times 10^{-3} \pm 0.24 \text{ mm}^2/\text{s}$  and  $1.54 \times 10^{-3} \pm 0.22 \text{ mm}^2/\text{s}$  respectively and are similar to those of previously published studies such as Costantini et al. [26], Nakajo et al. [27] and Razek et al. [28], who revealed an association between tumor grade and ADC values, and Belli et al. [29] who concluded that breast cancers with lower ADC values may be more aggressive and have a higher metastatic potential.

Regarding the studies which investigated the role of diffusion tensor imaging in the differentiation of breast lesions, the results of MD and  $\lambda_1$  measurements indicated lower values of both MD [4,18,30–32] and  $\lambda_1$  [30–32] in malignant tumors compared to benign lesions. In the present analysis, our results were consistent with those of previous studies, as they showed significantly lower MD,  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$  values ( $p < 0.0001$ ) of breast cancer in contrast with benign breast masses. After ROC curve analysis, MD and  $\lambda_1$  produced the same high AUC of 0.906 and hence we concluded that MD and  $\lambda_1$  constitute the best discriminative DTI parameters (82.5% sensitivity and 81.4% specificity) for the discrimination of breast lesions.

On the other hand, the results concerning the diagnostic utility of DTI anisotropy indices remain conflicting. Baltzer et al. [4,17], Jiang et al. [33] and Teruel et al. [30] showed higher FA values in breast cancer, while Partridge et al. [17], Cakir et al. [34] and Eyal et al. [31] reported no significant difference between benign and malignant lesions. Furman-Haran et al. [35] reported that ( $\lambda_1$ – $\lambda_3$ ) may contribute in

the discrimination of malignant and benign breast tumors. According to our findings, carcinomas showed significantly higher values of FA ( $0.20 \pm 0.07$ ) compared to benign tumors ( $0.15 \pm 0.05$ ,  $p = 0.0003$ ) and its ROC curve had an AUC of 0.729. On the contrary, ( $\lambda_1$ – $\lambda_3$ ) exhibited no statistically significant difference between benign and malignant lesions ( $p = 0.682$ ). ROC curve analysis revealed an AUC of 0.512, which indicates a performance similar to random predictions and represents a parameter with no discriminatory power.

When the diagnostic performance of MD and FA were compared with ADC, the AUC of the combined curve (0.910) did not exceed the AUC of the ADC (0.944), however the combination of MD and FA may provide complementary information for the differentiation between benign and malignant lesions. Onaygil et al. [32] showed that anisotropic parameters using a binary logistic regression model including DCEMRI and DTI increase the specificity of DCE-MRI from 83.0% to 93.6% without decreasing the 100.0% sensitivity.

The evaluation of software dependency on the calculation of quantitative DTI parameters using the two software packages, GE Functool and ExploreDTI, demonstrated a satisfactory agreement of the derived values. The only exception was that the eigenvalue difference ( $\lambda_1$ – $\lambda_3$ ), calculated by ExploreDTI, showed a slightly lower value in malignant tumors compared to benign tumors ( $0.45 \pm 0.20$  and  $0.53 \pm 0.33$ , respectively) coming closer to the hypothesis of Furman-Haran et al. [35] regarding the maximal anisotropy index ( $\lambda_1$ – $\lambda_3$ ) nevertheless without a statistically significant confirmation.

One of the limitations of this study was the size of the population. Undoubtedly, a larger group of participants is required to elucidate the diagnostic role of DTI in the discrimination of breast tumors and to draw safe conclusions. Another limitation is the partial volume effect which can lead to errors in measurements, especially in case of small lesions, where two or more tissue compartments exist within the same voxel [36].

In addition, the average lesion size in this study was 1.7 cm and 2.8 cm for benign and malignant lesions, respectively, which can be considered large, resulting in quite high specificity. Nevertheless, in case of small lesions ( $< 1$  cm), future improvements in DWI and DTI may allow higher spatial resolution and hence a more accurate assessment. Regarding the selection and the placement of the ROIs, they were determined manually for each lesion. An automated segmentation software could facilitate the data analysis and lead to less biased results.

Lastly, it has to be noted that the implementation of DTI as a routine protocol can be limited by several technical issues associated with the inhomogeneity and fat suppression ability as well as the EPI related artifacts.

In conclusion, quantitative DTI may improve the specificity of conventional 3.0 T breast MRI for the differentiation of malignant and benign breast lesions, and can be considered a feasible addition as an adjunct tool in the clinical routine.

## References

- [1] DeSantis CE, Ma J, Sauer AG, et al. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* 2017;67:439–48.
- [2] American Cancer Society. *Cancer facts & figures 2017*. Atlanta: American Cancer Society; 2017.
- [3] Nissan N, Furman-Haran E, Feinberg-Shapiro M, et al. Tracking the mammary architectural features and detecting breast cancer with magnetic resonance diffusion tensor imaging. *J Vis Exp* 2014;94:52048.
- [4] Baltzer PAT, Schäfer A, Dietzel M, et al. Diffusion tensor magnetic resonance imaging of the breast: a pilot study. *Eur Radiol* 2011;21:1–10.
- [5] Peters NH, Borel Rinkes IH, Zuithoff NP, et al. Meta-analysis of MR imaging in the diagnosis of breast lesions. *Radiology* 2008;246:116–24.
- [6] Sardanelli F, Giuseppetti GM, Panizza P, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. *AJR Am J Roentgenol* 2004;183:1149–57.
- [7] Wiederer J, Pazahr S, Leo C, et al. Quantitative breast MRI: 2D histogram analysis of diffusion tensor parameters in normal tissue. *MAGMA* 2014;27:185–93.
- [8] Partridge SC, Nissan N, Rahbar H, et al. Diffusion-weighted breast MRI: clinical applications and emerging techniques. *J Magn Reson Imaging* 2017;45:337–55.

- [9] Suo S, Zhang K, Cao M, et al. Characterization of breast masses as benign or malignant at 3.0 T MRI with whole-lesion histogram analysis of the apparent diffusion coefficient. *J Magn Reson Imaging* 2016;43:894–902.
- [10] Salem DS, Kamal RM, Mansour SM, et al. Breast imaging in the young: the role of magnetic resonance imaging in breast cancer screening, diagnosis and follow-up. *J Thorac Dis* 2013;5(Suppl. 1):S9–18.
- [11] Yoshikawa MI, Ohsumi S, Sugata S, et al. Relation between cancer cellularity and apparent diffusion coefficient values using diffusion-weighted magnetic resonance imaging in breast cancer. *Radiat Med* 2008;26:222–6.
- [12] Sahin C, Aribal E. The role of apparent diffusion coefficient values in the differential diagnosis of breast lesions in diffusion-weighted MRI. *Diagn Interv Radiol* 2013;19:457–62.
- [13] Kul S, Cansu A, Alhan E, et al. Contribution of diffusion-weighted imaging to dynamic contrast-enhanced MRI in the characterization of breast tumors. *AJR Am J Roentgenol* 2011;196:210–7.
- [14] Baltzer A, Dietzel M, Kaiser CG, et al. Combined reading of contrast enhanced and diffusion weighted magnetic resonance imaging by using a simple sum score. *Eur Radiol* 2016;26:884–91.
- [15] Nissan N, Furman-Haran E, Shapiro-Feinberg M, et al. Diffusion-tensor MR imaging of the breast: hormonal regulation. *Radiology* 2014;271:672–80.
- [16] Tagliafico A, Rescinito G, Monetti F, et al. L'imaging con tensore di diffusione nello studio della mammella normale: Riproducibilit  dell'anisotropia frazionaria derivante dalla DTI e dal coefficiente apparente di diffusione con una risonanza magnetica da 3.0 T. *Radiol Med* 2012;117:992–1003.
- [17] Tsougos I, Svolos P, Kousi E, et al. The contribution of diffusion tensor imaging and magnetic resonance spectroscopy for the differentiation of breast lesions at 3 T. *Acta Radiol* 2014;55:14–23.
- [18] Partridge SC, Ziadloo A, Murthy R, et al. Diffusion tensor MRI: preliminary anisotropy measures and mapping of breast tumors. *J Magn Reson Imaging* 2010;31:339–47.
- [19] Leemans A, Jeurissen B, Sijbers J, et al. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. *Proc 17th Sci Meet Int Soc Magn Reson Med*. 17. 2009. p. 3537.
- [20] Turnbull LW. Dynamic contrast-enhanced MRI in the diagnosis and management of breast cancer. *NMR Biomed* 2009;22:28–39.
- [21] Kuhl CK, Mielcareck P, Klaschik S, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology* 1999;211:101–10.
- [22] Partridge SC, DeMartini WB, Kurland BF, et al. Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value. *AJR Am J Roentgenol* 2009;193:1716–22.
- [23] Park GE, Kim SH, Kim EJ, et al. Histogram analysis of volume-based apparent diffusion coefficient in breast cancer. *Acta Radiol* 2017;58:1294–302.
- [24] El Khouli RH, Jacobs MA, Mezban SD, et al. Diffusion-weighted imaging improves the diagnostic accuracy of conventional 3.0-T breast MR imaging. *Radiology* 2010;256:64–73.
- [25] Akın Y, Uğurlu MÜ, Kaya H, et al. Diagnostic value of diffusion-weighted imaging and apparent diffusion coefficient values in the differentiation of breast lesions, histopathologic subgroups and correlation with prognostic factors using 3.0 Tesla MR. *J Breast Health* 2016;12:123–32.
- [26] Costantini M, Belli P, Rinaldi P, et al. Diffusion-weighted imaging in breast cancer: relationship between apparent diffusion coefficient and tumour aggressiveness. *Clin Radiol* 2010;65:1005–12.
- [27] Nakajo M, Kajiya Y, Kaneko T, et al. FDG PET/CT and diffusion-weighted imaging for breast cancer: prognostic value of maximum standardized uptake values and apparent diffusion coefficient values of the primary lesion. *Eur J Nucl Med Mol Imaging* 2010;37:2011–20.
- [28] Razeq AAKA, Gaballa G, Denewer A, et al. Invasive ductal carcinoma: correlation of apparent diffusion coefficient value with pathological prognostic factors. *NMR Biomed* 2010;23:619–23.
- [29] Belli P, Costantini M, Bufi E, et al. Diffusion magnetic resonance imaging in breast cancer characterisation: correlations between the apparent diffusion coefficient and major prognostic factors. *Radiol Med* 2015;120:268–76.
- [30] Teruel JR, Goa PE, Sjobakk TE, et al. Diffusion weighted imaging for the differentiation of breast tumors: from apparent diffusion coefficient to high order diffusion tensor imaging. *J Magn Reson Imaging* 2016;43:1111–21.
- [31] Eyal E, Shapiro-Feinberg M, Furman-Haran E, et al. Parametric diffusion tensor imaging of the breast. *Invest Radiol* 2012;47:284–91.
- [32] Onaygil C, Kaya H, Ugurlu MU, et al. Diagnostic performance of diffusion tensor imaging parameters in breast cancer and correlation with the prognostic factors. *J Magn Reson Imaging* 2017;45:660–72.
- [33] Jiang R, Ma Z, Dong H, et al. Diffusion tensor imaging of breast lesions: evaluation of apparent diffusion coefficient and fractional anisotropy and tissue cellularity. *Br J Radiol* 2016;89:20160076.
- [34] Cakir O, Arslan A, Inan N, et al. Comparison of the diagnostic performances of diffusion parameters in diffusion weighted imaging and diffusion tensor imaging of breast lesions. *Eur J Radiol* 2013;82:e801–6.
- [35] Furman-Haran E, Grobgeld D, Nissan N, et al. Can diffusion tensor anisotropy indices assist in breast cancer detection? *J Magn Reson Imaging* 2016;44:1624–32.
- [36] Alexander AL, Hasan KM, Lazar M, et al. Analysis of partial volume effects in diffusion-tensor MRI. *Magn Reson Med* 2001;45:770–80.