RESEARCH

Prediction of local breast cancer recurrence after surgery: the added value of diffusion tensor imaging

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Abstract

Background: There is considerable overlap between benign postoperative changes and recurrent breast cancer imaging features in patients surgically treated for breast cancer. This study aims to evaluate the value of adding multiple diffusion tensor imaging (DTI) parameters, including mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity, (AD), and relative anisotropy (RA) in differentiating breast cancer recurrence from postoperative changes in patients who were surgically treated for breast cancer and to also evaluate the role of these parameters in characterizing the different pathologies seen in the postoperative breast.

Results: This is a prospective study that was performed on female patients who were surgically treated for breast cancer. The study was done on 60 cases having 77 breast lesions. (Sixty-two of them were described as mass lesions and 15 of them were described as non-mass enhancement on MRI.) Among analyzed DTI parameters, MD showed the highest sensitivity (97.1%), specificity (88.1%), and accuracy (92.2%) in predicting recurrent breast cancer. FA, AD, and RD showed sensitivity (77.1%, 85.7%, and 88.6%) and specificity (83.3%, 83.3%, and 73.8%) in predicting recurrent breast cancer, respectively. The median MD values were lower in grade III recurrent breast cancers when compared to its values in recurrent grade II breast cancers and recurrent DCIS (0.6×10^{-3} mm^2/s vs. 0.8×10^{-3} mm^2/s and 0.9×10^{-3} mm^2/s), respectively. FA also showed median values in grade III recurrent breast cancer higher than its values in grade II recurrent breast cancer and recurrent DCIS (0.6 vs. 0.5 and 0.39), respectively. The sensitivity, specificity, PPV, NPV, accuracy, F1 score, and MCC of DCE-MRI alone versus DCE-MRI plus combined DTI parameters were 88.6% versus 100%, 88.1% versus 90.5%, 86.1% versus 89.7%, 90.2% versus 100%, 88.3% versus 94.6%, 87.3% versus 94.6%, and 76.5% versus 90.1%, respectively.

Conclusions: DTI may play an important role as a complementary method to discriminate recurrent breast cancer from postoperative changes in patients surgically treated for previous breast cancer.

Keywords: Breast, DTI, Postoperative, MRI, Cancer, Recurrence

Background

Imaging of cases with palpable masses after mastectomy is challenging secondary to postoperative changes [1, 2]. There is considerable overlap between recurrent breast cancer imaging features and benign postoperative changes in patients surgically treated for breast cancer [3, 4].

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Mammography remains the standard tool used for postoperative screening of patients who underwent breast conservation therapy [5, 6]. Although the use of breast MRI has increased over the past few years in patients who were surgically treated for breast cancer, controversy remains regarding its use as a screening tool for those patients [7, 8].

Recently many studies reported that DCE-MRI showed much higher sensitivity than mammography in the characterization of postoperative breast masses [1, 7]. Although high sensitivity, dynamic contrast-enhanced breast MRI lacks high specificity and so causes many false-positive results [9, 10]. So, recognizing recent MRI techniques that complement DCE-MRI improving its specificity without lowering its sensitivity is a demanding field of active research [11].

DWI is an emerging MRI tool that has shown the promising results to decrease the false-positive rate and the number of unnecessary biopsies when used as a complementary tool to conventional DCE-MRI [11–13]. DTI represents a DWI extension that can add information about the directionality of water molecules' diffusion [14]. DTI technique differs from simple DWI in that it uses additional gradients to detect diffusion in at least six directions. Many quantitative parameters can be driven by DTI including MD (Mean Diffusivity), AD (Axial Diffusivity), RD (Radial Diffusivity), FA (Fractional Anisotropy), and RA (Relative Anisotropy) [15–17].

In diffusion tensor imaging, three eigenvalues are generated using matrix diagonalization which are $ƛ1$, $ƛ2$, and $ƛ3$. These eigenvalues describe the magnitude of water molecules' diffusion in three different directions (one direction parallel to the axial direction of the voxel $\{ƛ1\}$ and two directions perpendicular to it $\{ƛ2$, and $ƛ3\}$) [15, 17]. Mean diffusivity (MD) is the average diffusion of the previously described three eigenvalues $\{(λ1+λ2+λ3)/3\}$ [18]. The average diffusion of $ƛ2$ and $ƛ3$ eigenvalues $\{(λ2+λ3)/2\}$ is defined as radial diffusivity (RD). Axial diffusivity (AD) represents the diffusion in an axial direction within the voxel $\{λ1\}$ [17]. Fractional anisotropy (FA) and relative anisotropy (RA) represent diffusion anisotropy indices which are calculated by combinations of the terms of the three eigenvalues [15].

DTI parameters have been used in breast imaging to increase specificity in the characterization of breast masses, it also can be used to give an idea about tissue cellularity and to track the mammary ductal network [9, 12, 15, 19]. Although there is an established role of DWI in differentiating benign from malignant breast masses, there are conflicting results regarding the role of DTI parameters [11, 12]. Many studies have reported that malignant tumors have lower MD values than benign lesions [6, 11, 12]. Some studies have reported FA values

to be higher in malignant breast lesions compared to benign ones, secondary to the differences in their microstructures, while others found no significant value of adding FA parameter to the DCE studies [5, 11, 12, 16].

This study aims to determine whether DTI can add value when used as a complementary tool to DCE-MRI in differentiating breast cancer recurrence from postoperative changes in patients who were surgically treated for breast cancer and to also evaluate the role of these parameters in differentiating between different pathologies seen in the postoperative breast.

Methods
Study population
This study is a prospective study that was performed from October 2018 to January 2022 on women with a previous history of breast cancer who underwent breast surgery including (breast conservative therapy, unplanned mastectomy, and modified radical mastectomy) with the time interval between the surgery and the postoperative MRI ranging from 6 months to 10 years. Patients included in this study underwent MRI as they complain of a palpable breast mass. The study included 62 patients, we excluded 2 cases due to motion artefacts so the total number of included cases was 60 cases, 10 patients with multiple lesions ($N=27$), and 50 patients with a single lesion ($N=50$), so the total number of breast lesions were 77 breast lesion. Patient ages ranged from 30 to 68 years. This study was approved by our institutional review board. Informed consent was obtained from all patients.

MR acquisition
MRI was performed using a 1.5T magnet (Ingenia; Philips Medical Systems, Best, the Netherlands). Patients lie in a prone position with their breasts suspended in a breast coil. The imaging protocol consisted of a conventional dynamic contrast-enhanced breast MRI and DTI.

The conventional MRI protocol included Axial T1-FSE (TR=487 ms, TE=8 ms, FOV=300–350 mm^2, slice thickness=3 mm), Axial T2-FSE (TR=3730 ms, TE=120 ms, FOV=300–350 mm, slice thickness 4 mm), and Axial T2-inversion recovery STIR (TR=3083 ms, TE=65 ms, TI=175 ms, FOV=300–350 mm, slice thickness=3 mm).

The dynamic contrast-enhanced study was done in the axial plane including 1 pre-contrast and 5 post-contrast series (1 mm slice thickness) time of acquisition of each of them is about 2.5 min with a delay from the basal scan of 20 s.

DTI was performed before the contrast-enhanced study by using an axial 2D echo-planar imaging technique. We selected a b value of 0 and 1000 s/ mm^2, fat suppression was done using spectral adiabatic inversion

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recovery, TR = 4000 ms, TE = 101 ms, diffusion gradient directions = 12, FOV = 380 × 285 mm², slice thickness = 2.5 mm with no inter-slice gap, matrix = 256 × 256, NOE = 4, acquisition time = 4 min.

DTI post-processing and image interpretation

DTI data were post-processed using (extended MR 130 Workspace 2.6.3.5, Philips Medical Systems, Netherlands). DTI parametric colored maps were automatically generated for mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), fractional anisotropy (FA), and relative anisotropy (RA).

Two experienced women imaging radiologists with 12 and 10 years' experience independently reviewed the MR images while they were blinded to the final pathological results. FA and MD parametric maps were overlaid on DCE-MRI images, which were used as a reference to define the lesion allowing accurate ROI placement. Other DTI parametric maps including AD, RD, and RA were not been able to be overlaid on a reference image so the ROI was put on the color map alone. A free-hand ROI was drawn to include the largest solid area of the lesion in a single slice, excluding the necrotic, hemorrhagic, and cystic areas.

Final diagnosis

Our standard of reference was the histopathological results. The type of biopsy was determined according to the results of MRI imaging. Tru-cut biopsy was done using a 14–16 gauge core needle if the patient was diagnosed to have recurrent breast carcinoma, traumatic fat necrosis, or postoperative granulation tissue based on MRI. FNAC was performed when the lesion was diagnosed as postoperative collection or seroma based on MRI (Figs. 1, 2).

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Spearman's correlation was used to assess the association between two quantitative data. Kruskal–Wallis *H*-test was used to compare non-normally distributed quantitative data between more than two groups. A cutoff value of a continuous variable that can differentiate between two conditions was made by using ROC curve analysis. The results of any of used tests were considered significant if the *P* value was 0.050. Measures of diagnostic performance were done by using an online calculator (Online Confusion Matrix) (https://onlineconfusionmatrix.com). Sensitivity = TP/(TP + FN), Specificity = TN/(FP + TN), PPV = TP/(TP + FP), NPV = TN/(TN + FN), Accuracy = (TP + TN)/(TP + FP + TN + FN),

F1 score = 2TP/(2TP + FP + FN), and MCC = (TP * TN − FP * FN) / sqrt((TP + FP) * (TP + FN) * (TN + FP) * (TN + FN)).

Results

Our study included 77 breast lesions that were detected by breast MRI from which 62 lesions were described as mass lesions (37 of them were pathologically proven as postoperative changes and 25 of them were pathologically proven as recurrence breast cancer) and 15 cases were described as non-mass enhancement (5 lesions of them were pathologically proven as postoperative changes and 10 lesions of them were pathologically proven as recurrence breast cancer) depending on the dynamic contrast-enhanced study.

Dynamic contrast-enhanced MRI criteria that were most encountered in recurrent breast cancer lesions presented as a mass were low T1 SI, high STIR SI, heterogenous enhancement, and washout curve as summarized in Table 1. Regarding lesions presented as a non-mass enhancement (NME), recurrent breast cancers were mostly presented as clumped or clustered NME with regional distribution and plateau curve as described in Table 2.

The mean MD, AD, and RD values for recurrent breast cancer were significantly lower than their values in postoperative changes. The cutoff values used to differentiate both entities were 1.18×10^{-3} mm²/s for MD (*P* value < 0.001, 95% CI 0.85–0.98), 1.95×10^{-3} mm²/s for AD (*P* value < 0.001, 95% CI 0.78–0.94), and 1.5×10^{-3} mm²/s for RD (*P* value < 0.001, 95% CI 0.735–0.91).

Recurrent breast cancer showed statistically higher mean FA and RA values than postoperative changes. FA cutoff value was 0.39 (*P* value < 0.001, 95% CI 0.73 to 0.91) while RA cutoff value was 0.27 (*P* value 0.533, 95% CI 0.425–0.656) to differentiate both entities.

MD was the best discriminative parameter when compared to other DTI parameters as shown in Table 3. At ROC curve analysis, MD cutoff value showed sensitivity (97.1%) specificity (88.1%), and AUC (0.934) for predicting recurrent breast cancer. However, AD and RD cutoff values showed sensitivity (85.7%, 88.6%) specificity (83.3%, 73.8%), and AUC (0.875, 0.836) for predicting recurrent breast cancer, respectively (Fig. 3a). FA cutoff value showed much lower sensitivity (77.1%) specificity (83.3%), and AUC (0.835) for predicting recurrent breast cancer (Fig. 3b). RA showed poor performance in the differentiation between recurrent breast cancers and postoperative changes (Fig. 3b).

Table 4 shows the pairwise correlation between the different studied DTI parameters.

Regarding the correlation of DTI parameters with tissue cellularity, the median MD values were lower

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Table 1 Comparison between dynamic contrast enhanced MRI criteria of postoperative changes vs. recurrent breast cancer presented as mass lesions (*N* = 62)

Characteristic	Postoperative changes (*N* = 37)	Recurrent breast cancer (*N* = 25)	*P* value
Mass shape			**0.002**
Irregular	24 (64.9%) a	9 (36%) b	
Rounded	3 (8.1%) a	12 (48%) b	
Oval	10 (27%) a	4 (16%) a	
Mass margin			0.067
Speculated	2 (5.4%) a	3 (12%) a	
Smooth	10 (27%) a	12 (48%) a	
Irregular	25 (67.6%) a	10 (40%) b	
T1 SI			**0.004**
Mixed	13 (35.1%) a	2 (8%) b	
Low	19 (51.4%) a	23 (92%) b	
Intermediate	3 (8.1%) a	0 (0%) a	
High	2 (5.4%) a	0 (0%) a	
T2 SI			**0.005**
Mixed	17 (45.9%) a	2 (8%) b	
Low	8 (21.6%) a	13 (52%) b	
Intermediate	7 (18.9%) a	7 (28%) a	
High	5 (13.5%) a	3 (12%) a	
STIR SI			**< 0.001**
Mixed	16 (43.2%) a	0 (0%) b	
Low	7 (18.9%) a	5 (20%) a	
High	14 (37.8%) a	20 (80%) b	
Mass enhancement pattern			**< 0.001**
No	1 (2.7%) a	2 (8%) a	
Marginal	21 (56.8%) a	2 (8%) b	
Homogeneous	11 (29.7%) a	10 (40%) a	
Heterogeneous	4 (10.8%) a	11 (44%) b	
Dynamic curve			**< 0.001**
No	1 (2.7%) a	2 (8%) a	
Progressive	22 (59.5%) a	1 (4%) b	
Plateau	11 (29.7%) a	6 (24%) a	
Washout	3 (8.1%) a	16 (64%) b	

Bold values represent significant *P* values

Data are *N* (%). Tests of significance is Fisher's exact test. Comparisons of column proportions are in letters, similar letters = insignificant difference, and different letters = significant difference. Significant *P* values (< 0.05)

Table 2 Comparison between dynamic contrast enhanced MRI criteria of postoperative changes versus recurrent breast cancer presented as non-mass enhancement (NME) (*N* = 15)

Characteristic	Postoperative changes (*N* = 5)	Recurrent breast cancer (*N* = 10)	*P* value
NME distribution			0.790
Regional	3 (60%)	7 (70%)	
Linear	1 (20%)	2 (20%)	
Focal	1 (20%)	0 (0%)	
Diffuse	0 (0%)	1 (10%)	
NME pattern			**0.005**
Homogeneous	3 (60%) a	1 (10%) b	
Heterogeneous	2 (40%) a	0 (0%) b	
Clustered ring	0 (0%) a	2 (20%) a	
Clumped	0 (0%) a	7 (70%) b	
Dynamic curve			**0.030**
Progressive	3 (60%) a	0 (0%) b	
Plateau	1 (20%) a	7 (70%) a	
Washout	1 (20%) a	3 (30%) a	

Bold values represent significant *P* values

Data are *N* (%). Test of significance is Fisher's exact test. Comparisons of column proportions are in letters, similar letters = insignificant difference, and different letters = significant difference. Significant *P* values (< 0.05)

recurrent breast cancers and recurrent DCIS (0.6 vs. 0.5 and 0.39), respectively (Fig. 4).

The median MD value for traumatic fat necrosis was 1.4×10^{-3} mm^2/s while in granulation tissue it was 1.6×10^{-3} mm^2/s which was much higher than their corresponding value in recurrent DCIS and recurrent breast cancers (*P* value < 0.001). Both traumatic fat necrosis and granulation tissue showed equal median AD and RD values (2.3×10^{-3} mm^2/s and 1.8×10^{-3} mm^2/s), respectively, which were higher than corresponding values in recurrent DCIS and recurrent breast cancers (*P* value < 0.001). On analyzing FA, its value in traumatic fat necrosis was 0.29 while in granulation tissue it was 0.23. Both entities showed lower FA values than recurrent DCIS and recurrent breast cancers (*P* value < 0.001) (Fig. 4).

Table 5 shows that adding DTI parameters to dynamic contrast-enhanced MRI improves the diagnostic performance in discriminating recurrent breast cancer from postoperative changes.

Discussion

The main finding of this study is that DTI parameters can increase both sensitivity and specificity of DCE-MRI in predicting recurrent breast cancer. Overall, malignancies exhibited lower MD, AD, and RD, and higher FA and RA values when compared to their values in benign lesions [9, 11, 20]. Among the DTI parameters, MD contributed

in aggressive highly cellular grade III recurrent breast cancers when compared to its values in recurrent grade II breast cancers and recurrent DCIS (0.6×10^{-3} mm^2/s vs. 0.8×10^{-3} mm^2/s and 0.9×10^{-3} mm^2/s), respectively. FA also showed median values in grade III recurrent breast cancers higher than its values in grade II

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Table 3 Diagnostic performance of DTI parameters in discriminating recurrent breast cancer from postoperative changes

Feature	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	Accuracy (%)	F1 score (%)	MCC (%)
MD ≤ 1.18	97.1	88.1	0.934	87.2	97.4	92.2	91.9	84.9
AD ≤ 1.95	85.7	83.3	0.875	81.1	87.5	84.4	83.3	68.8
RD ≤ 1.5	88.6	73.8	0.836	73.8	88.6	80.5	80.5	62.4
FA ≥ 0.39	77.1	83.3	0.835	79.4	81.4	80.5	78.3	60.6
RA ≥ 0.27	31.4	83.3	0.542	61.1	59.3	59.7	41.5	17.4

AUC = Area under the ROC curve, PPV = positive predictive value. NPP = negative predictive value Accuracy = (TP + TN)/(all Positive + all Negative). F1 = 2TP/ (2TP + FP + FN). MCC = Matthews Correlation Coefficient = TP*TN − FP*FN / sqrt (TP + FP) *(TP + FN) *(TN + FP) *(TN + FN)). MD, AD and, RD cutoff values were given in × 10^{−3} mm²/s
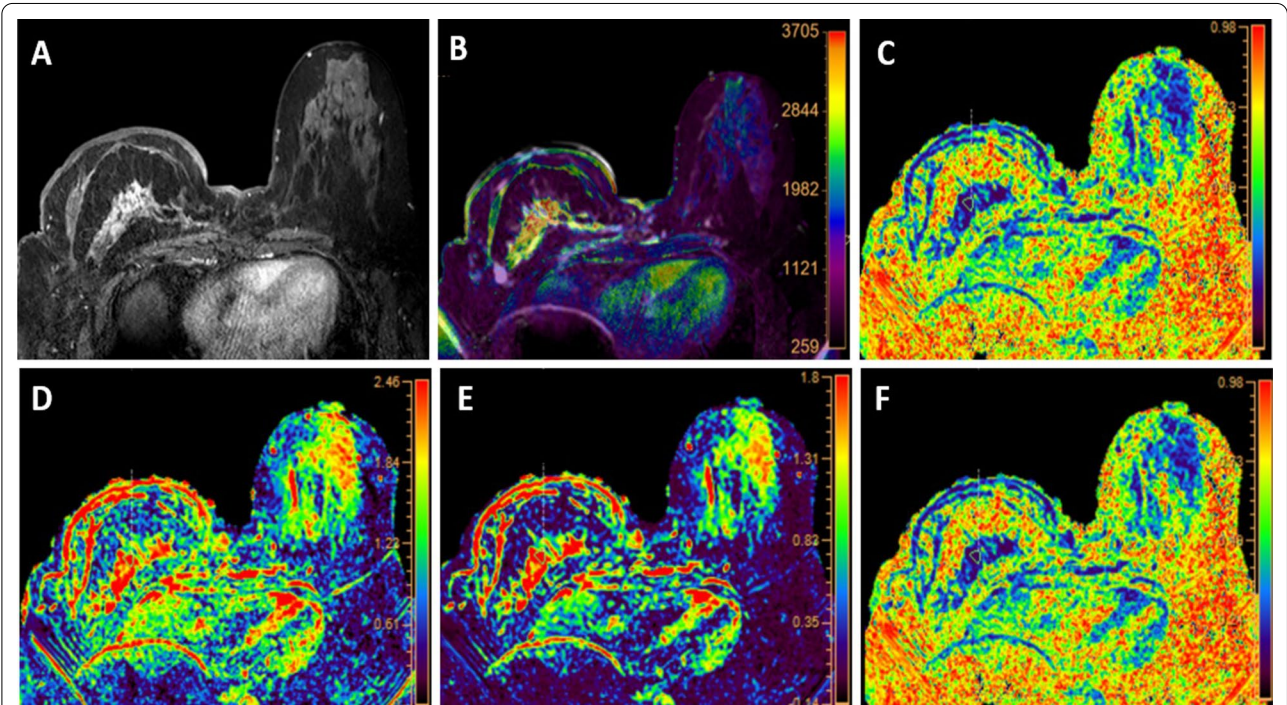
Fig. 1 A 60-year-old female with previous right BCT 3 years ago for grade II IDC. **A** DCE-MRI shows regional clumped NME in the upper inner quadrant of the right breast. **B** Fused DCE-MRI and DTI images used for ROI placement. Parametric color maps of DTI **C** FA, **D** AD, **E** RD, and **F** RA were generated and analyzed. ROI is placed within the lesion borders to calculate all the DTI parameters. MD = 0.7 × 10^{−3} mm²/s. FA = 0.4, AD = 1 × 10^{−3} mm²/s, RD = 1.2 × 10^{−3} mm²/s, and RA = 0.2. The lesion was recurrent grade II IDC on histopathological analysis

most significantly to the overall diagnostic performance [11, 18].

MD represents the average diffusion of water molecules that resembles unrestricted isotropic diffusion [18]. In this study, MD showed excellent performance in differentiating recurrent breast cancer from postoperative changes. On analyzing MD values in this study, it showed significantly lower values in recurrent breast cancer compared to its values in postoperative changes. Previous studies reported lower values of MD in malignant breast lesions (ranging from $1 \times 10^{−3}$ mm²/s to $1.4 \times 10^{−3}$ mm²/s) compared to benign breast lesions (ranging from $1.5 \times 10^{−3}$ mm²/s to $1.8 \times 10^{−3}$ mm²/s) [9, 11, 15]. This can be explained by barriers and multiple compartments seen in the malignant masses that restrict the free motion of a water molecule [9].

Many studies reported a cutoff value for MD used to differentiate benign from malignant breast lesions this cutoff value range from 1 to $1.26 \times 10^{−3}$ mm²/s [11, 14, 20]. Our cutoff value for MD agreed well with those reported in the literature. In this study the cutoff value of MD used to discriminate recurrent breast cancer from postoperative changes was $1.18 \times 10^{−3}$ mm²/s (*P* value < 0.001 and AUC of 0.934). This result correlated

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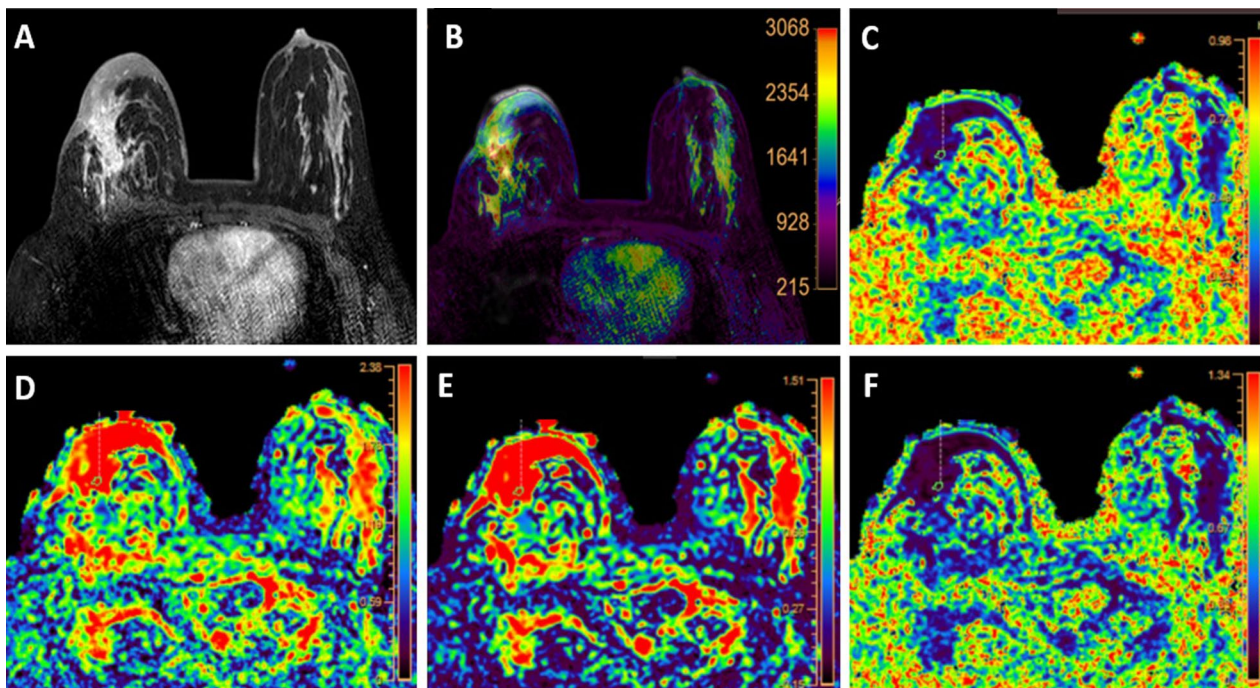
Fig. 2 A 39-year-old patient with a history of right BCT 9 months ago for grade II IDC. **A** DCE-MRI shows regional heterogeneous NME in the upper outer quadrant of the right breast. **B** Fused DCE-MRI and DTI images used for ROI placement. Parametric color maps of DTI **C** FA, **D** AD, **E** RD, and **F** RA were generated and analyzed. ROI is placed within the lesion borders to calculate all the DTI parameters. MD $= 1.7 \times 10^{-3}$ mm^2/s, FA $= 0.3$, AD $= 2.9 \times 10^{-3}$ mm^2/s, RD $= 2.5 \times 10^{-3}$ mm^2/s and RA $= 0.1$. The lesion was pathologically proven to be granulation tissue
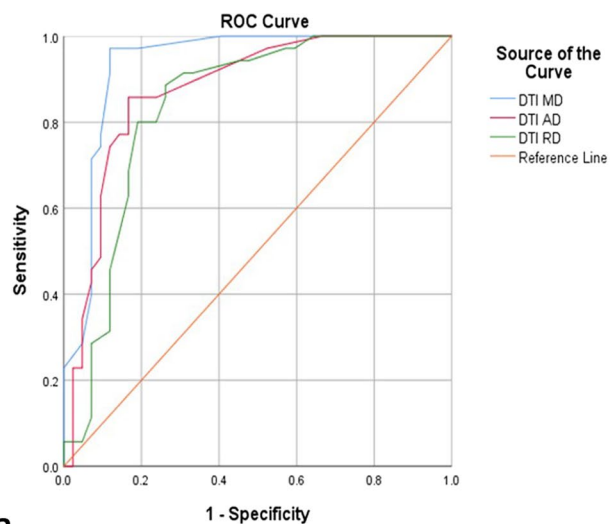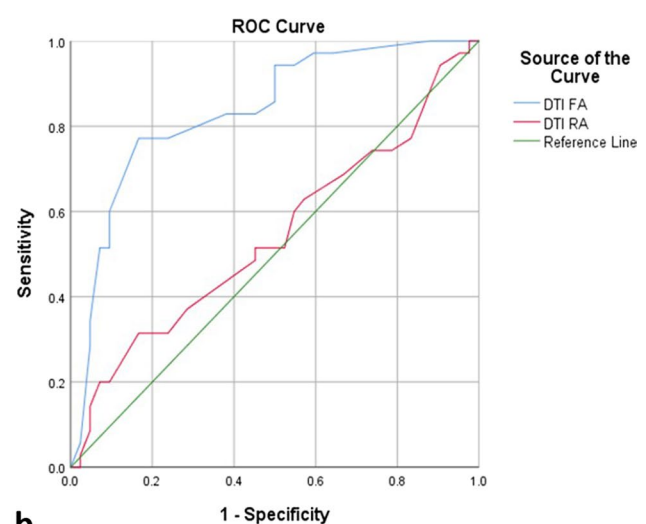
Fig. 3 ROC curves showed that MD had the highest sensitivity, specificity, and AUC when compared to AD and RD (**a**) and FA showed higher sensitivity, specificity, and AUC than RA (**b**)

with the results of one study in which two observers used a cutoff value of 1.1×10^{-3} mm^2/s and 1.43×10^{-3} mm^2/s showing *P* value (0.001, 0.001) and AUC (0.86, 0.85), respectively, to differentiate the two entities [18].

Table 4 Correlation between different DTI parameters

Variable	MD	AD	RD	FA	RA
MD	–	0.687 (**< 0.001**)	0.728 (**< 0.001**)	− 0.807 (**< 0.001**)	− 0.330 (**< 0.001**)
AD	0.687 (**< 0.001**)	–	0.872 (**< 0.001**)	− 0.552 (< 0.001)	− 0.188 (0.101)
RD	0.728 (**< 0.001**)	0.872 (**< 0.001**)	–	− 0.650 (**< 0.001**)	− 0.511(**< 0.001**)
FA	− 0.807 (**< 0.001**)	− 0.552 (< 0.001)	− 0.650 (**< 0.001**)	–	0.399 (**< 0.001**)
RA	− 0.330 (0.003)	− 0.188 (0.101)	− 0.511(**< 0.001**)	0.399 (**< 0.001**)	–

Bold values represent significant *P* values

Data are Spearman's correlation coefficient *P* value

Fig. 4 Box-plot for DTI parameters showing that the median MD, AD, and RD values were higher in DCIS than granulation tissue and traumatic fat necrosis. However, they were lower in DCIS than in grade II and grade III IDC. The median FA values were significantly higher in both grade II and grade III IDC versus both granulation tissue and traumatic fat necrosis
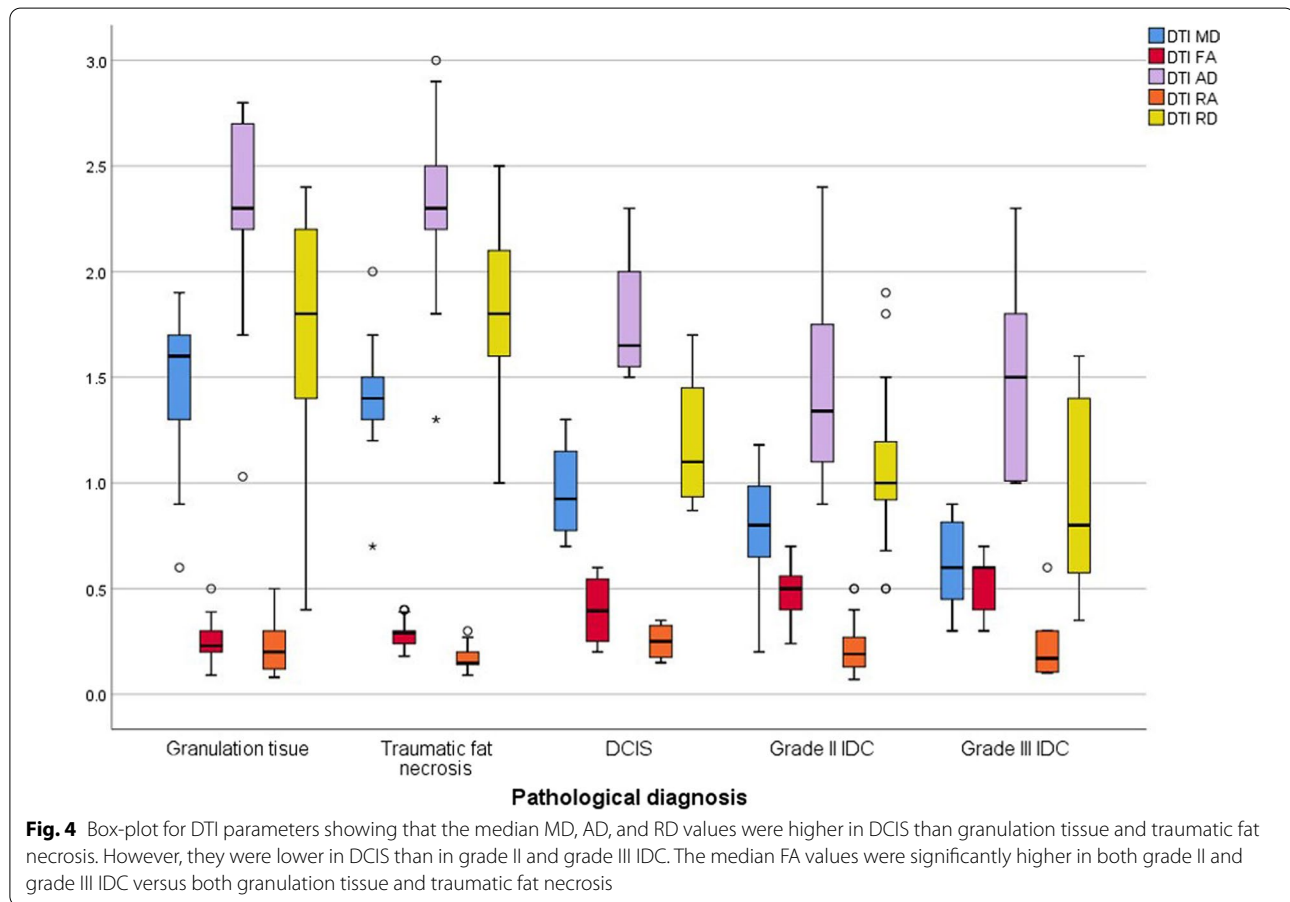
In this study, MD showed the highest sensitivity and specificity when compared to other DTI parameters in the characterization of postoperative breast lesions. Our results were comparable to a previous study which reported that MD cutoff value $(1.24 \times 10^{-3}$ mm^2/s) showed sensitivity (95.6%), specificity (93.6%), PPV (93.5), and NPV (95.7%) in predicting malignant breast masses [15]. However, our results showed higher sensitivity and specificity when compared to the results of one study which evaluated DTI parameters in differentiating benign from malignant breast lesions. In the previously mentioned study, they used a cutoff MD value of 1×10^{-3} mm^2/s showing a sensitivity (90%), specificity (63%), and accuracy (53%) in predicting malignant breast lesions [14]. In contrast to our study, O. Cakir et al. reported higher MD sensitivity (100%) and much lower specificity (40%) in predicting malignant breast lesions [16].

FA is the most studied DTI parameter aside from MD, and while some studies have reported higher FA in malignant lesions compared with benign ones [5, 12, 13] others have found no significant difference [16]. The analysis in our study showed that the mean FA was statistically

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Table 5 Diagnostic accuracy of DCE-MRI lone versus DCE-MRI with DTI in predicting recurrent breast cancer:

Measurement	DCE MRI alone (%)	DCE MRI with DTI (%)
Sensitivity	88.6	100
Specificity	88.1	90.5
Positive predictive value	86.1	89.7
Negative predictive value	90.2	100
Accuracy	88.3	94.8
F1 score	87.3	94.6
MCC	76.5	90.1

Accuracy = (TP + TN) / (all Positive + all Negative). F1 = 2TP/s(2TP + FP + FN). MCC = Matthews Correlation Coefficient = TP*TN − FP*FN / sqrt((TP + FP) *(TP + FN) *(TN + FP) *(TN + FN))

higher in recurrent breast cancer compared to its values in postoperative changes. This result agreed with Razek et al., study that reported higher FA values of recurrent breast cancer detected after conservative breast therapy compared to their corresponding values in postoperative changes [18]. Moreover, our results also were comparable to one study that reported higher FA values in malignant breast lesions (0.28 ± 0.15) compared to benign ones (0.23 ± 0.13) (*P* value 0.007) [11].

In our study, the FA cutoff value to differentiate recurrent breast cancer from postoperative changes was 0.39 (P value < 0.001). At ROC curve analysis of FA, its cutoff value for differentiation of both entities showed sensitivity (77.1%), specificity (83.3%), PPV (79.4%), NPV (81.4%), and AUC (0.835). Those results were comparable to one study which reported a relatively lower cutoff FA value (0.2) used to differentiate benign from malignant breast masses and they reported that this cutoff value showed sensitivity (81%), specificity (51%), and accuracy (33%) for predicting breast cancer [14]. Our results were also comparable to Razek et al., results who reported FA cutoff value slightly higher than ours (0.47 by one observer and 0.4 by another observer) to differentiate recurrent breast cancer from postoperative changes, they reported sensitivity (92.3%, 76.9%), specificity of (70.6%, 76.6%), and accuracy of (80% and 73%) for both observers, respectively [18]. However, O. Cakir et al. found that FA values were not discriminative and showed no statistical significance [16].

Axial diffusivity (AD (represents the diffusion of a water molecule in the axial direction (Λ1) [17] While, radial diffusivity (RD) is the average of Λ2 and Λ3 eigenvalues [15]. Luo et al., studied 266 cases and reported that AD and RD values were lower in malignant lesions when compared to benign ones with AUC (0.73 and 0.74) for AD and RD, respectively [11]. Eyal et al., also reported

lower values of Λ1, Λ2, and Λ3 in malignant breast lesions compared to benign lesions and normal breast tissue [21]. Our results strongly agreed with the previously mentioned studies, according to our study, AD and RD showed very good performance in discriminating recurrent breast cancers from postoperative changes.

In our study, the AD cutoff value of 1.95×10^{-3} mm^2/s showed sensitivity (85.7%), specificity (83.3%), PPV (81.1%), and NPV (87.5%) for predicting recurrent breast cancer. One study, which was carried out on 92 primary diagnosed breast lesions, reported a slightly lower AD cutoff value (1.59×10^{-3} mm^2/s.) to discriminate benign from malignant breast lesions. The above-mentioned study reported comparable AD sensitivity (97.8%), specificity (87.2%), PPV (88%), NPV (97.6%), and accuracy (92.3%) for predicting malignant breast lesions [15].

According to our results, a cutoff value of 1.5×10^{-3} mm^2/s for RD showed an AUC (0.836), sensitivity (88.6%), specificity (73.8%), PPV (73.8%), and NPV (88.6%%) for predicting recurrent breast cancer. Our results agreed well with one study that reported RD cutoff value close to ours (1.12×10^{-3} mm^2/s), they reported a comparable AUC (0.968), comparable sensitivity (95.6%), slightly higher specificity (93.6%), slightly higher PPV (93.5%), and comparable NPV (95.7%) in differentiating benign from malignant breast lesions [15].

In a meta-analysis of 73 studies that were searched from January to March 2018, Baxter et al., evaluated the diagnostic performance of DTI parameters in 6791 breast lesions and reported that AD (Λ1) had the best performance among other studied DTI parameters with sensitivity, specificity, and AUC (93%, 90%, and 0.94), respectively, compared to MD sensitivity, specificity, and AUC (90%, 78%, 0.92), respectively [9]. Another meta-analysis of 16 studies included 1636 patients and supported that result with AUC (0.97) for AD compared to AUC (0.92 and 0.92) for MD and FA, respectively [22]. Those meta-analysis studies lacked statistical power due to the relatively small number of included studies and lack of DTI method standardization. In contrast to the above-mentioned studies, we found that AD had the second-best performance among DTI parameters after MD producing an AUC (0.875 vs. 0.934) for AD and MD, respectively. Onaygil et al., reviewed a total of 105 breast lesions using a 3T MRI machine and agreed well with our findings as they reported AD AUC (0.95) which is slightly lower than MD (0.969) [15].

In our study, RA showed poor performance in discriminating recurrent breast cancer from postoperative changes with an AUC (0.542) and accuracy (59.7%). This result correlated with one study that reported that RA showed the worst performance among DTI parameters with an AUC (0.761) and accuracy (70.6%) [15].

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Regarding accuracy, our study revealed that MD showed the highest accuracy (92.2%) in discriminating recurrent breast cancer from postoperative changes compared with other DTI parameters (80.5% for FA, 84.4% for AD, 80.5% for RD, and 59.7% for RA). This finding was supported by a previous study that reported MD accuracy of 94.5% compared to 92.3% for AD, 70.6% for FA, and 70.6% for RA in discriminating benign from malignant breast lesions [15]. However, Tsougos et al. reported equal accuracy of MD and AD (AUC of 0.906) which was higher than FA accuracy (AUC of 0.729) [20]. Other studies showed higher AD accuracy than MD [9, 22].

One study reported high pairwise correlations of MD with axial ($r = 0.81$) and radial ($r = 0.95$) diffusivity while they reported a high negative correlation between MD and FA ($r = -0.51$) [11]. Our results also agreed well with the previously mentioned results as on analyzing the pairwise correlation of DTI parameters in our study we found that the pairwise positive correlation of MD with AD ($r_s = 0.687$) and RD ($r_s = 0.728$) was high as well as its negative correlation with FA ($r_s = -0.807$).

Many studies reported that MD and FA can contribute to reveal the microstructure of breast tissue and therefore differentiate between different grades of breast cancers as well as differentiating invasive breast cancer from carcinoma in situ [11, 12, 23–25]. This study agreed well with the above-mentioned studies as it showed the ability of DTI parameters to correlate with tissue cellularity. The median MD in our study was lower in aggressive high cellular grade III recurrent breast cancer when compared to its values in recurrent grade II breast cancer and recurrent DCIS. However, the median FA values in grade III recurrent breast cancer were higher than their values in grade II recurrent breast cancer and recurrent DCIS. A similar result was reported by one study which was done on 88 breast masses, they reported lower MD values and higher FA values in highly cellular high grades of breast cancer compared with less cellular lower grades [12]. This result was supported by one study that reported an MD value for DCIS of 1.28 versus 1.03 for invasive breast cancer (P value = 0.001), they also reported much lower FA values than ours, they reported an FA value of 0.13 for DCIS vs 0.16 for invasive breast cancer (P value = 0.288) [23]. Another study reported that FA was significantly lower in DCIS compared to invasive breast cancer (0.22 vs. 0.30) (P value = 0.026) [11].

In our study, the addition of combined DTI parameters to dynamic contrast MRI increased sensitivity from 88.6 to 100%, specificity from 88.1 to 90.5% accuracy from 88.3 to 94.8% in predicting recurrent breast cancer. Our results agreed with one study which reported that the adding of MD to DCE MRI increased the accuracy of differentiating benign from malignant breast lesions from 91.3% with using DCE alone to 94.5% with using DCE plus MD and the adding of FA to DCE increased accuracy from 91.3% with using DCE alone to 96.7% with using DCE with FA [20]. Another study reported comparable results as they reported an AUC of 0.76 by using DCE MRI alone vs an AUC of 0.81 by using DCE MRI plus DTI in discriminating benign from malignant breast lesions [11].

This study is a prospective study in which the interpreting radiologists analyzed multiple quantitative DTI parameters and they were blinded to the final pathological results. There are several strengths of our study. To our knowledge, our study contains the largest prospective cohort of cases to date who have undergone breast DTI for differentiating recurrent from postoperative changes. Our study also assessed multiple DTI parameters not only the most commonly studied MD and FA. Another point of strength is that we correlated the results of different DTI parameters with grades of recurrent breast cancer.

There are also many limitations to our study. First, although our study contains the largest number of postoperative breast DTI patients to date, it was done at a single institution, which may affect the generalizability of the results. Undoubtedly, a larger number of cases are needed to establish a final diagnostic role of DTI in the postoperative breast. Second, this study was done using a 1.5T MRI machine, further studies at higher field 3 Tesla MRI using advanced multichannel coils may improve the diagnostic performance of DTI. Third, the partial volume and motion artefacts may lead to measurements errors, especially in small lesions. Future improvements in the DTI technique may allow higher spatial resolution and more accurate measurements.

Conclusions

We concluded that DTI parameters including MD, AD, RD, and FA may play an important role as a complementary method for differentiation of recurrent breast cancer from postoperative changes in patients surgically treated for previous breast cancer.

Abbreviations

DCE-MRI: Dynamic contrast-enhanced MRI; DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; DTI: Diffusion-tensor imaging; MD: Mean diffusivity; FA: Fractional anisotropy; RA: Relative anisotropy; RD: Radial diffusivity; AD: Axial diffusivity; STIR: Short TI inversion recovery sequence; T1WI: T1-weighted image; T2WI: T2-weighted image; MRI: Magnetic resonance imaging; PPV: Positive predictive value; NPV: Negative predictive value; FSE: Fast spin echo; FOV: Field of view; TI: Inversion time; NOE: Number of excitation; TR: Repetition time; TE: Echo time; ms: Millisecond; mm: Millimeter; DCIS: Duct carcinoma in situ; ROC: Receiver operating curve; ROI: Region of interest; AUC : Area under the curve; MCC: Matthews correlation coefficient; CI: Confidence interval; TP: True positive; TN: True negative; FP: False positive; FN: False negative; BCT: Breast conservative therapy; NME: Non-mass enhancement.

Availability of data and material
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The study was approved by our institution's ethics committee (Mansoura Faculty of Medicine Institutional Research Board) (ethics committee reference number is MD.20.08.355), A written informed consent was obtained from all patients included in the study.

Consent for publication
The participants in the study were informed and consented to the possibility of research publication. Authors hereby transfer, assign or otherwise convey all copyright ownership to the EJRNM if such work is published in that journal.

Competing interests
The authors declare that they have no conflict of interest.

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