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Research article

Diffusion tensor imaging parameters in differentiation recurrent breast cancer from post-operative changes in patients with breast-conserving surgery

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ABSTRACT

Aim of the work: To investigate mean diffusivity (MD) and fractional anisotropy (FA) measured by diffusion tensor imaging (DTI) as complementary tools to differentiate recurrent breast cancer from post-operative changes in patients with breast-conserving surgery (BCS).
Patients and Methods: Prospective study was conducted upon 30 patients with BCS that underwent DTI and dynamic contrast MR imaging. DTI was performed using an axial two-dimensional spin-echo echo-planar imaging sequence. The MD and FA of the lesions were calculated by 2 observers. A single pixel seed isotropic region of interest was placed in the solid part of the tumor on the axial color FA map guided by an enhanced part of the tumor. The final diagnosis was done by biopsy for all patients.
Results: The pathological examination proved to be recurrent breast cancer (n = 13) and post-operative changes (n = 17). Recurrent breast cancer had significantly lower MD (P = 0.001, 0.001) and higher FA (P = 0.003, 0.02) than in post-operative changes for both observers respectively. At ROC curve analysis of MD, the AUC was 0.86 and 0.85 by both observers. The threshed MD was (0.86, 0.85 × 10^{-3} mm^2/s) used for differentiation between entities revealed sensitivity (76.9%, 92.3%), specificity (82.4%, 64.7%) and accuracy (80%, 76.7%) of both observers respectively. At ROC curve analysis of FA, the AUC was 0.82 and 0.75 by both observers. The threshold FA (0.82, 0.75) was used for differentiation between entities revealed sensitivity (92.3%, 76.9%), specificity (70.6%, 70.6%) and accuracy of (80.0%, 73.3%) of both observers respectively. There was a strong positive correlation of MD (r = 0.86) and FA (r = 0.73) of both observers. Combined analysis of FA and MD used for differentiation between entities had AUC (0.90, 0.88) revealed sensitivity (92.3%, 92.3%), specificity (82.4%, 70.6%) and accuracy of (86.7%, 80.0%) for both observers respectively.
Conclusions: Combined analysis of MD and FA of DTI may play an important role as a non-invasive method for differentiation recurrent breast cancer from post-operative changes in patients with BCS.

1. Introduction

Breast-conserving surgery (BCS) is a preferred therapeutic procedure for early low-grade cancer breast because it has the same survival rates as mastectomy, and have a better cosmetic effect [1,2]. Local recurrence is the most important issue after BCS that related to presence of residual tumor cells and usually occur in the first 2–3 years after surgery [3,4]. Several changes occur after surgery and radiation therapy, which may cause difficulties in the image interpretation during the follow-up period [3–5]. Mammography, ultrasound and dynamic contrast MR imaging is used for assessment of patients after BCS, but they have low specificities in differentiating recurrent breast cancer from post-operative changes [5–8]. Dynamic contrast MR imaging is commonly used to detect occult breast cancer, regional axillary nodes, and determine the extent of breast cancer. Several studies reported the role of dynamic contrast MR imaging in staging of breast cancer and

Abbreviations: BCS, breast-conserving surgery; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; MD, Mean diffusivity; FA, fractional anisotropy

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assessment response to the neo-adjuvant chemotherapy [9–11]. MR breast imaging has been considered a surveillance modality for patients who underwent BCS [11]. One study reported that dynamic contrast MR imaging showed higher sensitivity (81.8%) than did mammography (18.2%) and ultrasound (18.2%) in differentiation between recurrent breast cancer and postoperative changes after BCS [13]. Another study added that higher parenchymal signal enhancement ratio around the tumor at preoperative dynamic contrast MR imaging and larger histologic tumor size are independent factors associated with worse free survival in patients after BCS [12].

Diffusion weighted imaging (DWI) is a non-contrast technique based on the diffusion encoding in the three orthogonal directions that provides a quantitative isotropic diffusion parameter. It has evolved as a promising tool in the evaluation of breast cancer. DWI is used for characterization of the breast mass, staging of breast cancer, prediction the response of breast cancer to chemotherapy and differentiation of recurrence of breast cancer from post treatment changes [14–19]. Two studies discuss role of DWI in patients after BCS. One study reported that sensitivity and specificity for DWI in differentiating recurrent breast cancer from benign post-operative changes at cutoff point of 1.35 × 10-3cmm2/s were 100% and 94.7%, respectively [18]. Another study added that dynamic contrast MR imaging and DWI showed sensitivity (100%, 88.9%), specificity (93.9%, 87.9%), and accuracy (96.7%, 88.3%) respectively for detection of recurrence in patients underwent BCS [19].

Diffusion tensor imaging (DTI) detect more information about microstructure as it provides three- dimensional anisotropy diffusion parameters such as fractional anisotropy (FA) and mean diffusivity (MD) which reflects the average diffusion [16–20]. DTI model has added value in diagnosis and characterization of breast cancer. Recent studies are shown that DTI parameters are used for monitoring the patients with breast cancer after neo-adjuvant chemotherapy [21] and well correlated with a prognostic parameter of breast cancer [22–26]. Also, DTI parameters are helpful in detection [27,28], and characterization of breast cancer [29,30]. To our knowledge, this is the first study demonstrates differences in DTI parameters between breast cancer recurrence and post-operative changes in a patient with BCS.

1.1. Aim of work

To investigate MD and FA measured by DTI as complementary noninvasive tool to differentiate tumor recurrence from post-operative changes in patients with BCS.

2. Materials and methods

2.1. Patients

This prospective inter observational study was approved by our institutional review board, and informed consent was obtained from all patients before the study. The study was performed from June 2015 till April 2018 on women with pathologically proven breast cancer that underwent BCS (6 months till 6 years after BCS) presented with palpable lump or on their routine follow up. The study included 32 patients, 2 patients were excluded due to motion artifacts so total cases were 30 women, their ages ranged from 27 to 58 years. Histopathology was done for all patients either by tru cut (n = 27) or surgical biopsy (n = 3).

2.2. MR protocol

MR imaging was performed using a 1.5 T magnet (Acheiva; Philips Medical Systems, Best, Netherlands) with a breast coil. The MR examination was done between 7th -14th days of the menstrual cycle. The protocol was; axial T1-fast spin echo (TR = 512 ms, TE = 8 ms, FOV = 300-350 mm^2, slice thickness = 4 mm), axial T2-fast spin echo (TR = 3730 ms, TE = 120 ms, FOV = 300–350 mm, slice thickness 4 mm). Axial and coronal T2-inversion recovery (TR = 400 ms, TE = 65 ms, TI = 175, FOV = 300–350 mm, slice thickness = 4 mm). DTI was performed using an axial two-dimensional spin-echo echo-planar imaging sequence (*b* value = 0 and 1000s/mm^2, diffusion gradient directions = 12, TR = 6900 ms, TE = 90 ms, slice thickness = 5 mm with zero gap, number of excitations = 4, FOV = 380 × 285 mm^2, matrix = 144 × 192, acquisition time = 3 min, fat suppression: spectral adiabatic inversion recovery), Then post contrast study including 1 pre-contrast and 5 post-contrast series (1 mm slice thickness) each of them take about 2 min with 20 s delay from the basal scan.

2.3. DTI Post processing and image analysis

All DTI data were post-processed using extended workspace workstation release 2.6, Philips Medical Systems, Nederland and analyzed by two experienced women imaging radiologists (Z M, B D) since 10 and 12 years respectively. They independently reviewed the MR images and they were blinded to the clinical presentations and final pathological results. The slice with the maximum diameter of the lesion on dynamic contrast MR imaging was selected for the image analysis. A single pixel seed isotropic a region of interest was placed on the axial color FA map in the solid part of the tumor avoid the cystic and hemorrhagic parts of the lesion guided by an enhanced part of the tumor at dynamic contrast MR images. Care was taken to avoid the adjacent normal breast parenchyma and fat. The DTI parameters including MD and FA were automatically calculated.

2.4. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22. The Kolmogorov-Smirnov test was used to test the normality of quantitative data. The FA and MD were non-parametric. Mann Whitney test was used to compare between the two studied groups as the data was non-parametric. The receiver operating characteristic (ROC) curve was used for detection of the validity (sensitivity, specificity, and accuracy) and the cut-off point of FA and MD and combined parameters in differentiating recurrence from post-operative changes. Spearman correlation was used to detect the interclass correlation beyond that expected by the chance between 2 observers. The *r* value between 0.61 and 0.80 represented good; and between 0.81 and 1.00 represented excellent. A (*P*) value less than 0.05 was considered to indicate a statistically significant difference.

3. Results

Thirteen cases were pathologically proven to be recurrent breast cancer (Fig. 1) and seventeen cases proved to be post-operative changes. Table 1 shows the MD and FA of recurrent breast cancer and post-operative changes of the studied cases. Table 2 shows the validity of FA and MD in diagnosing recurrent breast cancer for both observers in studied cases.

The median MD of recurrent breast cancer (0.84, 0.98 × 10^{-3} mm^2/s) were statistically lower (P = 0.001) than that of granulation tissue (1.46; 1.49 × 10^{-3} mm^2/s) by both observers respectively. There was strong positive significant correlation of MD between two observers for all patients (r = 0.86, p = 0.001), recurrence (r = 0.89, p = 0.001) and post-operative changes (r = 0.72, p = 0.001). At ROC curve analysis of MD, the AUC was 0.86 and 0.85 by both observers. The threshold MD was (0.86, 0.85 × 10^{-3} mm^2/s) used for differentiation between both entities revealed sensitivity (76.9%, 92.3%), specificity (82.4%, 64.7%) and accuracy (80%, 76.7%) of both observers respectively (Fig. 2).

The median FA were higher in recurrent cancers (0.49, 0.47) than post-operative changes (0.24, 0.24) with statistical significance (p = 0.003, 0.02) by both observers respectively. There was positive

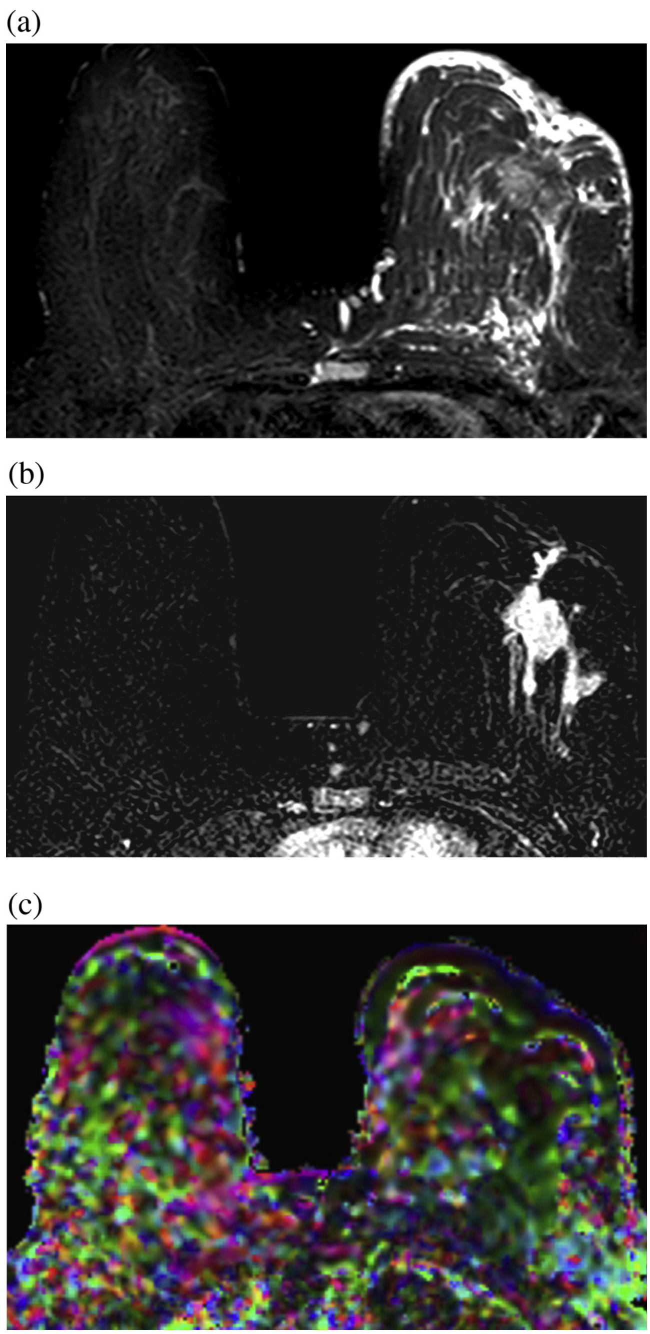

Fig. 1. Recurrent invasive ductal carcinoma: (A) STIR image shows irregular spiculated hyperintense mass is seen in the left breast parenchyma. (B) Dynamic contrast-enhanced image shows intense heterogeneously enhancing mass. (C) Color FA map shows the mass with calculated MD value of 1.03 and 0.97 X10^{-3} mm^2/s and FA value of 0.67 and 0.60 by both observers respectively.

Table 1
Median, minimum and maximum MD (X10^{-3} mm^2/s) and FA of recurrent breast cancer and post-operative changes by both observers.

	Recurrent cancer (n = 13)	Post-operative changes (n = 17)	P value
MD	0.84 (0.32-1.35)	1.46 (0.35-214)	0.001
(1st observer)	0.98 (0.27-1.50)	1.49 (0.43-1.97)	0.001
(2nd observer)			
FA	0.49 (0.21-0.92)	0.24 (0.11-0.56)	0.003
(1st observer)	0.47 (0.19-0.81)	0.24 (0.14-0.67)	0.02
(1st observer)			

Table 2
Validity of FA and MD in detection recurrent breast cancer by both observers.

	AUC	Cut off	Sensitivity (%)	Specificity (%)	Accuracy (%)
MD	0.86	≤1.11	76.9	82.4	80.0
(1sr observer)	0.85	≤1.43	92.3	64.7	76.7
(2nd observer)					
FA	0.82	≥0.47	92.3	70.6	80.0
(1sr observer)	0.75	≥0.40	76.9	76.6	73.3
(2nd observer)					
Combined FA &MD	0.90		92.3	82.4	86.7
(1st observer)	0.88		92.3	70.6	80.0
(2nd observer)					

significant correlation of FA between two observers for all patients ($r = 0.73$, $p = 0.003$), recurrence ($r = 0.77$, $p = 0.002$) and post-operative changes ($r = 0.55$, $p = 0.023$) for post-operative changes). At ROC curve analysis of FA, the AUC was 0.82 and 0.75 by both observers. The threshold FA (0.47, 0.40) was used for differentiation between entities revealed sensitivity (92.3%, 76.9%), specificity (70.6%, 70.6%) and accuracy of (80.0%, 73.3%) for both observers respectively (Fig. 2).

At ROC curve, the combined analysis of FA and MD used for differentiation between both entities had AUC (0.90, 0.88) revealed sensitivity (92.3%, 92.3%), specificity (82.4%, 70.6%) and accuracy of (86.7%, 80.0%) for both observers respectively (Fig. 3).

4. Discussion

The main findings in this work that FA and MD parameters of DTI can differentiate recurrent breast cancer from post-operative changes in patients with BCS. The recurrence shows higher FA and lower MD compared than post-operative changes. The MD and FA are statistically different between recurrent breast cancer and post-operative changes with a strong inter-observer agreement of both parameters.

In this study, the MD of recurrent breast cancer is significantly lower than that of post-operative changes by both observers. The MD reflects the average diffusion that resembles free and unrestricted isotropic diffusion of water protons. In fact, the barriers and various compartments in the tissues restrict the free displacement of the water molecules, and this explains lower MD in recurrent breast cancer compared to benign post-operative changes [20–22]. Previous studies reported lower values of MD in breast cancer compared with benign lesions [29,30]. Few studies added that tumors with reduced MD have poor prognostic features, such as larger tumor size, high histological grade and/or the presence of axillary node metastasis. These tumors are expected to have disorganized and disrupted microstructures due to the blockage of the branching ductal network by proliferative tumor cells, resulting in a decrease in the magnitude and directionality of the water diffusion in breast tissues [22–26]. One study reported that the MD of the residual glioma is significantly lower ($P = 0.001$) than that of post-radiation changes in the brain [31]. Other study on brain tumor demonstrated that pseudo-tumor progression after treatment of glioblastoma exhibits higher MD than tumor progression, partly due to extent of the cellular death and vascular changes [32]. Another studies in head and neck cancer added that there is a significantly lower MD and higher FA ($P = 0.001$) between residual head and neck squamous cell carcinoma and post-radiation changes with excellent intra-reader agreement between both readings ($K = 0.958$) [33,34].

In this study, the FA of recurrent breast cancer is significantly higher than that of post-operative changes by both observers. FA measured by DTI reflect the water diffusion action in the three orthogonal directions, so it may be possible that diffusion of water molecules is enhanced in a certain directions and reduced in others where there are highly cellular, disorganized microstructures of the malignant tumors. Thus, it leads to

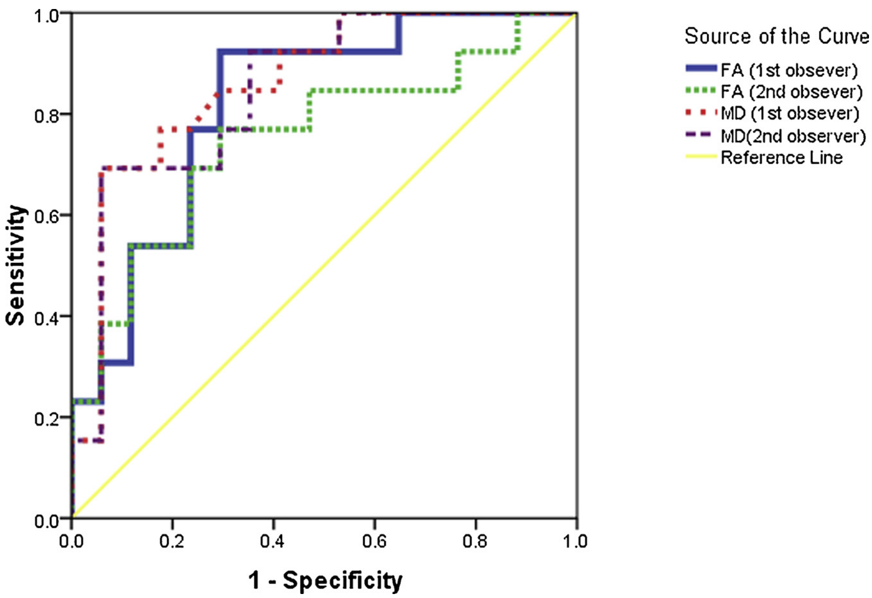

Fig. 2. ROC of MD and FA parameters for differentiation recurrent breast cancer from post-operative changes. The AUC of MD is 0.86 and 0.85 and for FA is 0.82 and 0.75 by both observers respectively. The threshed MD was (0.86, 0.85 X10^{-3} mm^2/s) used for differentiation between entities revealed accuracy (80%, 76.7%) of both observers respectively. The threshed FA (0.82, 0.75) was used for differentiation between entities revealed an accuracy of (80.0%, 73.3%) for both observers respectively.

asynchronous changes in the three orthogonal eigenvectors in each pixel of DTI resulting in an increase of the FA of the recurrent breast cancers when compared to benign post-operative changes [20–24]. One study reported that a rising tendency of the FA with an increase the grade of breast cancer [26]. Another study added that lower FA both in an ER-negative group compared with an ER-positive group and in a high Ki-67 group compared with a low Ki-67 group. These results suggested that microstructural changes, caused by aggressive breast cancers may be reflected by pronounced changes in the diffusion anisotropy. The reduction in the anisotropic movement of the water molecules in the breast cancers with ER-negative and high Ki-67 due to presence of these microstructural changes [23]. Parameters of DTI including FA and MD are used to enable differentiation of the responder from non-responder to the neo-adjuvant chemotherapy in patients with breast cancer [22].

In this study, combined data analysis of DTI parameters increased performance of DTI in differentiation between recurrence and post treatment changes. One study reported that combined analysis of FA and MD parameters is used for characterization of the salivary gland tumors with an accuracy of 86% [35]. Another study added that combined ASL and DTI metrics of the enhanced lesion and related edema are used for differentiation of the residual/recurrent gliomas from post-radiation changes [31].

The merits of DTI are fast, non-invasive, non-ionizing radiation, and don't need injection of the contrast medium, repeated safely, and can give a quantitative value. The challenges of DTI of the breast are technical limitations, such as echo-planar imaging-related artifacts, susceptibility artifacts, motion artifacts, imperfect fat suppression, and low signal-to-noise ratio and spatial resolution of DTI than that of dynamic contrast MR imaging [35–37].

There are some limitations to this study. The main limitation of this study is small number of patients; a multicenter study upon a larger number of patients is required to be more preciously show the diagnostic value of DTI parameters in BCS. Second, this study used only DTI in assessment of patients with BCS. Multi-parametric MR imaging of DTI with MR spectroscopy, arterial spin labeling and dynamic contrast MR imaging [38–42] will improve the results in the future. Third, this study was done using 1.5 T scanner machine, further studies at higher 3

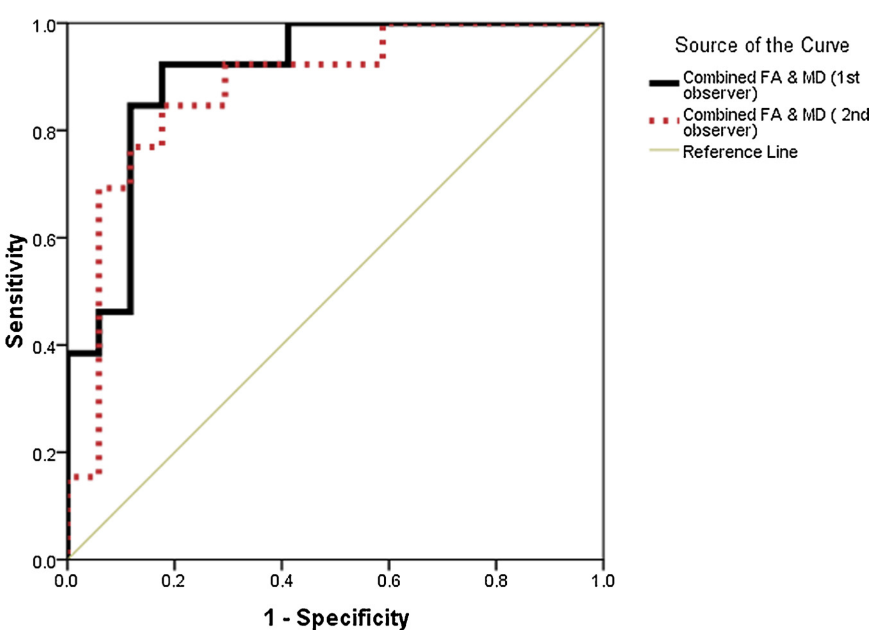

Fig. 3. ROC of combined MD and FA parameters for differentiation recurrent breast cancer from post-operative changes. The combined analysis of FA and MD used for differentiation between entities had AUC (0.90, 0.88) revealed sensitivity (92.3%, 92.3%), specificity (82.4%, 70.6%) and accuracy of (86.7%, 80.0%) for both observers respectively.

Tesla scanner using advanced multichannel coils increase the resolution of DTI images and improve diagnostic performance of DTI in assessment of patients after BCS [43].

5. Conclusion

We concluded that combined analysis of MD and FA of DTI may play an important role as a non-invasive method for differentiation recurrent breast cancer from post-operative changes in patients after BCS.

Conflict of interest

The authors have no conflicts of interest. This includes financial or personal relationships that inappropriately influence (bias) his or her actions.

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