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FULL PAPER

Diffusion tensor imaging of breast lesions: evaluation of apparent diffusion coefficient and fractional anisotropy and tissue cellularity

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Objective: To investigate the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) measured by diffusion tensor imaging (DTI), tissue cellularity and their relationship in breast malignant/benign lesions.

Methods: 88 patients with 88 breast lesions who underwent DTI and dynamic contrast-enhanced MR scanning between November 2013 and December 2014 were retrospectively analyzed. The diagnosis was confirmed pathologically. ADC and FA values as well as histopathological cellularity of different pathological types of lesions were analyzed and compared statistically. The Pearson's correlation between cellularity and ADC and FA was calculated.

Results: There were 59 cases of breast cancer and 29 cases of benign lesions included in the study. ADC values of breast cancers were statistically lower than that of benign lesions ($p < 0.001$). FA and cellularity were higher in cancers than in benign lesions with statistical significance ($p < 0.05$ and $p < 0.001$, respectively). The mean FA values

in the patients with invasive ductal carcinoma (IDC) were higher than that in the patients with ductal carcinoma *in situ* (DCIS) without statistical difference ($p > 0.05$). The ADC and the cellularity in the IDC of grade III were statistically lower ($p < 0.05$) and higher ($p < 0.05$) than that in the DCIS and IDC of grade I–II, respectively. ADC was negatively correlated to cellularity ($r = -0.8319$, $p < 0.001$) and FA was positively correlated to cellularity ($r = 0.4231$, $p < 0.001$).

Conclusion: ADC and FA values were statistically different between benign and malignant breast lesions and were significantly correlated to tissue cellularity. ADC and FA may help to discriminate malignant from benign breast lesions and to predict cellularity. ADC is helpful in the prediction of the grade of breast cancer.

Advances in knowledge: ADC and FA values were statistically different between benign and malignant breast lesions and were significantly correlated to tissue cellularity.

INTRODUCTION

The incidence of breast cancer in the world has been growing in recent years. Breast cancer has become the fastest growing tumour and is the main cause of cancer-related deaths among females.^{1,2} MRI, especially dynamic contrast-enhanced (DCE)-MRI, is increasingly regarded as a promising modality in breast cancer diagnosis owing to its high sensitivity in the detection of breast cancer^{3,4} and its ability to show vascularity.⁵ It is reported that DCE-MRI with its high contrast resolution provided a high sensitivity (90%) in the detection of breast cancer. However, its specificity (72%) is lower than its sensitivity, and discriminating malignant from benign lesions is still a clinical issue. Recently, diffusion-weighted imaging (DWI), which tracks water molecule diffusion in the tissue and provides

information about the integrity of the cell membrane, has been considered as a useful adjunct method for DCE-MRI and is widely used in cancer detection, characterization and differentiation between malignant and benign lesions. Combined with DCE, DWI scans have significantly elevated the specificity and accuracy in the diagnosis of breast cancer compared with DCE-MRI alone.^{4,6}

Based on DWI, diffusion tensor imaging (DTI) could detect more information about the microstructure.⁷ DTI could provide not only the average apparent diffusion coefficient (ADC), but also three-dimensional anisotropy diffusion parameters such as fractional anisotropy (FA). The DTI model has shown value in the diagnosis of breast cancer.^{8,9}

DTI has been increasingly applied in breast lesions, and it has been shown that both ADC and FA were helpful in breast cancer detection and characterization.^{9,10} But, there is no report concerning the correlation between metrics of DTI and histology, such as cell density, in breast tumours in literature. The purpose of the present study was to evaluate the ADC and FA measured by DTI, tissue cellularity and their relationship in breast malignant/benign lesions. The demographic data, ADC, FA, histopathological results etc. of the patients were collected and analyzed statistically.

METHODS AND MATERIALS

Patients

This study was approved by the ethics committee of the hospital, and signed informed consents were obtained from all patients. The clinical data of the patients with breast lesions who underwent DTI and DCE MR scanning between November 2013 and December 2014 were retrospectively analyzed. The inclusion criteria were: lesions were confirmed by contrast-enhanced MRI and clearly identified on ADC and FA maps; biopsy or surgery was performed within 30 days after MRI; and the patient with a benign or malignant histopathological result. The exclusion criteria were: patients with a history of surgery, radiotherapy or chemotherapy to treat breast cancer. There were 103 suspected cases and they were intended to undergo breast MRI. Among the 103 cases, 3 cases had undergone biopsy before MRI examination; 8 cases were not diagnosed pathologically; and 4 cases had a small lesion (the diameter of the tumour was <1 cm). Therefore, 15 cases were excluded in this study.

MR protocol

All the patients were examined in the prone position with head first on the 1.5-T MRI system (AVANTO; Siemens Healthcare, Erlangen, Germany) using a dedicated bilateral breast matrix coil of four channels (Breast matrix, Siemens Healthcare, Erlangen, Germany). The routine axial turbo spin-echo inversion recovery sequence with fat-suppressed T_2 weighted image [repetition time (TR) 5800 ms, echo time (TE) 56 ms, field of view (FOV) 275×275 mm, matrix 314×320 , slice thickness 6 mm without intersection gap, number of excitations 2] was performed after tomography, followed by a DTI sequence. DTI was performed using an axial two-dimensional diffusion-weighted echoplanar imaging sequence (TR 6900 ms, TE 90 ms, slice thickness 5 mm with zero gap, number of excitations 4, FOV 380×285 mm, matrix 144×192 , acquisition time 3 min and 11 s, fat suppression: spectral adiabatic inversion recovery), and the diffusion gradients were applied in six directions with $b = 0$ and $b = 1000 \text{ s mm}^{-2}$.

Finally, the DCE sequence, an axial T_1 weighted three-dimensional fast spoiled gradient-recalled echo sequence (TR 4.19 ms, TE 1.22 ms, FOV 340×340 mm, matrix 448×340 , slice thickness 0.9 mm, acquisition time 6 min and 42 s, fat suppression: Q-fat sat.), was obtained. One pre-contrast acquisition and five post-contrast acquisitions were performed before and after the rapid bolus injection of gadolinium diethylenetriaminepentaacetic acid (Omniscan™; GE Healthcare, Princeton, NJ) at a dose of 0.1 mmol kg^{-1} through an in-dwelling i.v. catheter in the back of the hand.

DTI data post-process and analysis

All DTI data were post-processed on the MR Syngo station (Siemens Healthcare, Erlangen, Germany) using the Neuro3D

toolbox and analyzed by two experienced MRI physicians blinded to the histopathological results. The slice with the maximum diameter of the lesion in DCE images and the corresponding slice in the axial ADC map were used. The region of interest (ROI) in the ADC map corresponding to the hyperintensity in DCE images was drawn along the margin of the lesions avoiding the haemorrhagic, cystic and calcific areas. It was considered as haemorrhagic when there was a high signal and no intensification on the T_1 weighted image sequence. It is regarded as cystic when the ADC value is above $2.0 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and there is no intensification. The large calcification could be easily confirmed. A large calcification was suspected when there was no intensification in the different phases of the DCE image and there were spots with a very low signal on the ADC map. Those spots were excluded from the ROI. Then, the DTI parameters including ADC and FA were automatically calculated. Each lesion was measured three times by each of the two physicians independently. The average values were used.

Tissue cellularity analysis

All histopathological specimens were reviewed by an experienced pathologist who was blinded to the results of DTI/MRI. The samples at the centre of the breast lesions were used. After haematoxylin–eosin staining and zooming to $200\times$, five FOVs without necrosis, cystic areas or large blood vessels were photographed randomly. Histopathological photos were imported to a computer station and analyzed using Adobe Photoshop v. 8.0 (Adobe Systems Inc., San Jose, CA) for cellularity calculation. Colour pictures were transformed into black-and-white ones, and the nucleus showed as black points. Cellularity was defined as the total area of nucleus divided by that of FOV, with reference to the previous study.¹¹ The average cellularity of the five FOVs was used as the final result. Breast cancers were graded according to the Scarff–Bloom–Richardson breast cancer-grading system.¹²

Statistical analysis

Statistical analysis was performed using SPSS® v. 19.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) and Medcalc v. 11.4.2.0 (Medcalc Software, Mariakerke, Belgium). The differences of ADC, FA and cellularity between breast cancer and benign lesions and the differences among the different grades of breast cancers were compared using the Kruskal–Wallis test. Pearson's correlation analysis was used to evaluate the correlation between ADC, FA and tissue cellularity. p -value <0.05 was considered to be statistically significant.

RESULTS

A total of 88 patients (27–69 years, median 45 years) with 29 benign lesions and 59 breast cancers were included in the study (Table 1). The lesion size was 3.4 ± 1.7 cm on an average (range, 1.0–7.1 cm). In terms of morphology, there were 65 cases of mass including 51 cases of breast cancer and 14 cases of benign lesions; there were 23 cases of non-mass enhancement, including 8 cases of breast cancer and 15 cases of benign lesions. 64 cases were premenopausal and 24 cases were postmenopausal. The excellent images of DTI and DCE and the pathological pictures were achieved in all patients. The diagnosis was confirmed by surgery (Figure 1). There were 29 cases of benign lesions and 59 cases of breast cancer.

Table 1. The histologic results of 88 breast lesions

Histologic type	n/%
Breast cancer	59/67%
Invasive carcinoma	45
Grade I	9
Grade II	6
Grade III	30
DCIS	14
Benign	29/33%
Fibroadenomas	12
Fibrocystic changes	5
Adenosis	9
Sclerosing adenosis	3

DCIS, ductal carcinoma *in situ*.

Apparent diffusion coefficient, fractional anisotropy and cellularity values in breast cancers and benign lesions

ADC values of breast cancers were statistically lower than that of benign lesions ($p < 0.001$). FA and cellularity were higher in cancers than in benign lesions with statistical significance ($p < 0.05$ and $p < 0.001$, respectively) (Table 2).

As for breast cancer, there were 14 cases of ductal carcinoma *in situ* (DCIS) and 45 cases of invasive ductal carcinoma (IDC) including grade I (9 cases), grade II (6 cases) and grade III (30 cases), according to the Scarff–Bloom–Richardson breast cancer-

grading system.¹² The cellularity in the IDC of grade III was higher than that in the DCIS and IDC of grade I–II with statistical difference ($p < 0.05$), indicating a high proliferation activity in grade I–II and a higher proliferation activity in grade III. The mean ADC in the IDC of grade III was statistically lower ($p < 0.05$) than that in the DCIS and IDC of grade I–II. The statistical significance of ADC values among the three groups suggests a negative relationship between the ADC values and the proliferation activity. ADC might be used to predict the cellularity and the proliferation activity of the breast. A further non-parameter test showed that the mean FA values in the patients with IDC were higher than that in the patients with DCIS without statistical difference ($p > 0.05$) (Table 3), indicating that FA might be unable to predict the cellularity of the breast.

Correlation between apparent diffusion coefficient, fractional anisotropy and cellularity in breast lesions
Pearson's correlation analysis showed that both ADC and FA in breast cancer and benign lesions had significant association with cellularity, which is shown in Figure 2. ADC was negatively correlated to cellularity ($r = -0.8319$, $p < 0.001$; breast cancer group: $r = -0.7191$, $p < 0.001$; benign lesion group: $r = -0.7741$, $p < 0.001$), while FA was positively correlated to cellularity ($r = 0.4231$, $p < 0.001$; breast cancer group: $r = 0.3811$, $p < 0.01$; benign lesion group: $r = 0.3854$, $p < 0.05$).

DISCUSSION

In the present study, the results showed that ADC and FA values were statistically different between benign and malignant breast lesions. ADC was also statistically different in the different grades of breast cancers. Besides, ADC and FA in breast lesions were significantly correlated to tissue cellularity.

Figure 1. Diffusion tensor imaging maps and histopathological result of a 47-year-old patient with invasive ductal carcinoma in the left breast. (a) The post-contrast T_1 weighted image (T1WI). The invasive carcinoma was significantly enhanced after gadolinium diethylenetriaminepentaacetic acid injection on the T1WI. (b) The apparent diffusion coefficient (ADC) map (curve) and (c) the fractional anisotropy (FA) map: the carcinoma showed a lower ADC [$0.87 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ in (b)] and FA [0.18 in (c)] values than the adjacent tissue and the normal tissue in the contralateral breast. (d) The histopathological result is shown (haematoxylin-eosin; 200 $\times$).

Table 2. The comparison of apparent diffusion coefficient (ADC), fractional anisotropy (FA) and cellularity between breast cancers and benign lesions

Histologic type	<i>n</i>	ADC ($\times 10^{-3} \text{mm}^2 \text{s}^{-1}$)	FA	Cellularity (%)
Benign lesions	29	1.47 ± 0.35	0.17 ± 0.05	18.6 ± 8.7
Breast cancers	59	0.93 ± 0.25	0.19 ± 0.05	30.0 ± 7.5
χ^2		36.815	4.316	24.502
<i>p</i> -value		0.000	0.038	0.000

The mean ADC values of breast cancer and the cellularity in the two groups were in accordance with the previous studies.^{8,13} The results also showed that ADC values of breast cancers were statistically lower than that of benign lesions ($p < 0.001$). However, there are some overlaps between benign and malignant diseases in our study and previous literature, which may influence the diagnosis and differentiation of breast cancers. In our study and previous literature, the typical ADC value was $1.0\text{--}2.1 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$ for benign lesions and it was $0.56\text{--}1.71 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$ for breast cancers. Some benign lesions such as fibrocystic disease and intraductal papilloma may have a low ADC.¹⁴ In our study, nearly half of the fibroadenomas had low ADC values ranging from 0.96 to $1.26 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$; four fibroadenomas and two sclerosing adenosis had ADC values $< 1.0 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$. Woodhams et al¹⁴ reported that nearly half of the fibrocystic diseases showed low ADC values, which may mimic breast cancers, while the five cases with fibrocystic disease in our study did not show a low ADC.

Although several studies^{9,10,15} have shown that FA is very helpful in the detection and diagnosis of breast cancer, and the combination of ADC and FA increases the diagnostic accuracy of breast cancer, the role of FA in the prediction of malignancy still remains controversial. In our study, the mean FA value of breast cancers was significantly higher than that of benign lesions, which is in accordance with the result of Baltzer et al¹⁰ but contrary to that of Cakir et al.⁸ As our study showed, there seemed to be a rising tendency in FA values with the increase of malignancy and grade of breast tumours (Table 3); but, the FA values between DCIS and IDC had no statistical difference. It suggests that the difference in the FA among different kinds of breast lesions may be small and FA alone is unable to distinguish different grades of breast tumours.

Breast cancer has a higher cellularity than benign lesions in our study. And the degree of cellularity in grade III IDC is higher than that in grade II IDC and DCIS. Probably the diffusion of water molecules was significantly decreased in the tumour which had smaller intracellular space and extracellular clearance.¹¹ Maybe, this is the main reason for the reduced ADC values in high-grade breast cancers. It may be more complicated why the FA elevated with the increase of cell density. As FA reflects the water diffusion activity in three orthogonal directions, it is possibly due to that the diffusion of water molecules is enhanced in certain directions while reduced in others in the more disordered microstructures of higher grade tumours. Thus, it leads to asynchronous changes in the three orthogonal eigenvectors in each pixel of DTI and the increase in FA.¹⁶

In our study, ADC had a negative correlation with the cellularity of breast lesions, which is consistent with the study of breast mucinous carcinoma by Woodhams et al.¹⁷ Besides, in the previous meta-analysis,¹⁸ 28 of the included 30 studies showed that there is a strong negative correlation between ADC and cellularity. The relationship between FA and cellularity has not been reported in the breast, but it has been reported in brain tumours. Kinoshita et al¹⁶ found that FA values of malignant brain tumours were positively correlated with cell density, and Stadlbauer et al¹⁹ also showed similar results in gliomas. FA was found to positively correlate with cellularity in the present study, and FA values in IDC were slightly higher than that in DCIS and benign lesions without statistical difference. Therefore, ADC and FA may help to differentiate benign and malignant lesions and to predict the grade of breast cancer, which is also meaningful in guiding clinical practices, such as breast lesion characterization, biopsy and assessing the response of breast tumour after neoadjuvant chemotherapy.

Table 3. The comparison of apparent diffusion coefficient (ADC), fractional anisotropy (FA) and cellularity among different grades of breast cancers

Tumour grade	<i>n</i>	ADC ($\times 10^{-3} \text{mm}^2 \text{s}^{-1}$)	FA	Cellularity (%)
DCIS	14	1.04 ± 0.31	0.18 ± 0.03	26.0 ± 8.1
Grade I-II IDC	15	1.00 ± 0.33	0.20 ± 0.05	28.0 ± 8.7
Grade III IDC	30	0.85 ± 0.14	0.20 ± 0.05	32.9 ± 5.2
χ^2		7.616	1.750	8.243
<i>p</i> -value		0.022	0.417	0.016

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma.

Figure 2. The correlation between the apparent diffusion coefficient (ADC), fractional anisotropy (FA) and cellularity in breast lesions: (a) the ADC was negatively correlated to cellularity ($r = -0.8319$, $p < 0.001$) and (b) the FA was positively correlated to cellularity ($r = 0.4231$, $p < 0.001$).

However, there are still several studies that disagreed with ours. Yoshikawa et al²⁰ studied the association between ADC and cellularity in breast cancer and found that the mean ADC value for breast cancer did not significantly correlate with cancer cellularity. Jenkinson et al²¹ found similar results in oligodendroglial tumour. This might be due to the following reasons. First, ADC and FA, especially ADC, are influenced by b -values. At lower b -values, the diffusion in the intravascular compartment will be larger, which means that lower b -values will generate higher ADC values and *vice versa*.²² As for FA, previous studies^{23,24} indicated that the influence on FA from b -values $>400 \text{ s mm}^{-2}$ are negligible. In our study, we used a b -value of 1000 s mm^{-2} to minimize the influence of microperfusion on ADC and FA. Although one study²⁵ showed that the minimum apparent diffusion coefficient ($\text{ADC}_{\min}$) at a b -value of 4000 s mm^{-2} was associated with tumour cellularity more significantly than $\text{ADC}_{\min}$ at a b -value of 1000 s mm^{-2} in brain tumours, no similar studies in the breast have been reported; extremely high b -values in the breast will reduce the signal of the breast tissue and lesions. Therefore, no b -values $>1000 \text{ s mm}^{-2}$ were used in our study. Second, ROI is another influencing factor because of the heterogeneity of the breast tissue.^{23,26,27} As for cellularity, tumour cells are not homogeneously distributed in the whole tumour. As is always the case, the ROIs in ADC and FA maps cannot be precisely corresponded to the FOVs for calculating the cellularity in the specimens; it will influence the

evaluation of the correlation between ADC, FA and cellularity. However, these factors are difficult to control. Therefore, in the present study, we measured only the significantly enhanced parenchyma in breast lesions, avoiding the haemorrhagic, cystic and calcific areas to reduce the influence.

In the present study, we did not assess the influence of the variability of the signal-to-noise ratio or noise level on the spread of values for the parametric maps. Fat suppression has much more influence in a fattier breast than in a dense breast according to our clinical practice experience. Fat might make the scattered small glands unclear. In the present study, the different fat contents among the patients did not affect the recognition and measurement on the parametric maps. When measuring ADC and FA, the ROI was slightly smaller than the size of the tumour in order to reduce the influence of the surrounding tissues of the tumour, especially the fat.

There are several limitations in our study, such as the small sample size and its retrospective nature. Besides, the accordance between ROIs in DTI maps and FOVs in histopathological pictures needs to be improved further for a precise measurement and evaluation. In conclusion, ADC and FA of DTI could be used as significant factors to discriminate malignant from benign breast lesions. Besides, ADC and FA in breast lesions are suggested to be indicative factors of tissue cellularity.

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