

Original Research

The Role of Diffusion Kurtosis MR Imaging in the Evaluation of Invasive Breast Cancer Classification and its Correlation with Prognostic Factors: A Prospective Study of Primarily Advanced Stage Cancers

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Abstract

Background: The present exploration is aimed to determine whether diffusion kurtosis imaging (DKI)-derived mean diffusivity (MD) and mean kurtosis (MK) are possible parameters for the invasive breast cancer grading and whether MD/MK is related to breast cancer clinical-pathologic factors including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and Ki-67. **Methods:** Tumors from 108 invasive breast carcinoma patients (45.6 ± 11.2 years old; range, 20–84 years), diagnosed by pathological examination between January 2016 and August 2017, were included. DKI data (with b values of 0, 1000, 2000 sec/mm^2) and MD/MK were measured. The expression of ER, PR, HER-2, and Ki-67 was evaluated by immunohistochemistry. **Results:** It was found that MD was significantly lower in grade III breast cancer than in grade II breast cancer (0.82 ± 0.21 vs 1.17 ± 0.24 , $p < 0.0001$), while MK was significantly higher in grade III breast cancer than that in grade II breast cancer (1.00 ± 0.31 vs 0.85 ± 0.21 , respectively; $p < 0.05$). In addition, MD was negatively associated with Ki-67 level ($r = -0.39$, $p < 0.05$), while MK was positively associated with Ki-67 level ($r = 0.56$, $p < 0.05$). Furthermore, MD was significantly increased in ER and PR positive expression group compared with ER and PR negative expression group, while there is no significant difference of MK in ER and PR positive expression group compared with ER and PR negative expression group. Additionally, there is no significant difference of MD and MK in HER-2 positive expression group compared with HER-2 negative expression group. **Conclusions:** These results demonstrate that DKI has value in the evaluation on the classification of invasive breast carcinoma. MD values were associated with breast cancer clinical-pathologic factors. DKI can provide useful information in the assessment of tumor proliferation activity.

Keywords: breast cancer; diffusion kurtosis imaging; magnetic resonance imaging; prognostic factors

1. Introduction

It has been shown that evaluation of the degree of malignancy of breast cancer contributes to the diagnosis and treatment of breast cancer patients. Conventional methods are not effective enough for evaluation of breast lesions [1–3]. Therefore, it is essential for radiologist to improve the accuracy of diagnosis and classification of breast cancer, especially in invasive breast cancer.

Magnetic resonance imaging (MRI) is extensively used to diagnose suspicious breast lesions [4–8]. Diffusion weighted magnetic resonance imaging (DWI) is also used to diagnose suspicious breast lesions. The conventional DWI model always assumes a Gaussian diffusion of water protons. Thus, the DWI signal mono exponentially decreases with increasing b value. However, water diffusion in the living tissues is restricted by tissue microstructure and a non-Gaussian distribution of water displacement profile was discovered in the presence of various barriers.

In 2005, Jensen *et al.* [9] reported a non-Gaussian diffusion-weighted model called diffusion kurtosis imaging (DKI). Compared to DWI in assessing extracellular water diffusion, DKI may improve the understanding of water diffusion characteristics of the local microenvironment by calculating and analyzing the coefficients of kurtosis and diffusion. Furthermore, it has been demonstrated that DKI may provide the non-Gaussian diffusion behavior in various tissues including liver [10,11], brain [12–14], and prostate [15–17]. Moreover, it has been shown that DKI may offer better characterization of tumors than traditional DWI [18,19].

The traditional DWI model is based on the Gaussian behavior of water diffusion, which makes the diffusion of water molecules without any restriction. However, in living tissues, diffusion is usually limited by tissue microstructure and shows non-Gaussian behavior. The DKI model can quantify the amount of water molecules deviating from the



normal distribution, which can reflect the subtle changes of human environment more truly and accurately. DKI imaging has two important parameters, mean diffusivity (MD) and mean kurtosis (MK). MD reflects the overall dispersion level and resistance of the molecule, and only represents the size of the dispersion. The larger the value, the stronger the diffusion ability of water molecules. MK is the most critical parameter of DKI technology, which is defined as the average value of diffusion kurtosis in all directions and is considered as an indicator of the complexity of tissue microstructure. The size of MK depends on the complexity of tissue microstructure in the region of interest. The more complex the structure (such as the lower differentiation degree of cancer cells and the higher cell density), the more significant the diffusion restriction of non-Gaussian water molecules and the larger the MK. If DKI parameters can precisely predict proliferative activity as well as histologic malignancy grade of breast cancers, it will be a great aid in making clinical decision. However, few studies have evaluated association between different clinical-pathologic risk factors of breast cancer and the DKI parameters [18–20]. In the present study, we aimed to evaluate the role of DKI in the diagnosis and characteristics of breast carcinoma. We also evaluated the relationship between breast cancer-associated pathologic factors and DKI parameters.

2. Materials and Methods

2.1 Patients

This is a prospective study. Institutional review board has approved the investigation and written informed consent from patients were obtained. A total of 178 patients with suspected breast cancer who received treatment in our hospital from August 2015 to August 2018 were collected. According to the exclusion criteria, 60 cases of fibroma were removed, 7 cases of inflammatory pseudotumor were removed, and 3 cases of image artifacts were assessed for large impact. 108 female patients (mean of age = 45.6 ± 11.2 years; range of age = 20 to 84 years) were finally enrolled in the study. Inclusion criteria: (1) all patients were pathologically diagnosed as breast cancer; (2) all patients received conventional magnetic resonance imaging and multi-B value DKI sequences; (3) no biopsy, chemoradiotherapy before imaging examination; (4) breast lesions >1.0 cm in diameter. Exclusion criteria: (1) patients with other malignant tumors; (2) patients with contraindications to MRI examination; (3) the obtained image artifacts are large, which affects the evaluator; (4) patients with inconsistent clinical data.

2.2 MR Imaging Technique

A 3.0-T MR imager (Magnetom Skyra; Berlin, Germany) with a dedicated four-channel bilateral breast coil in the axial orientation was used to perform MR imaging examinations. T2-weighted images acquirement and dynamic contrast-enhanced T1-weighted MRI was conducted as described previously [21].

2.3 Clinical Pathological Examination

Lesion samples were obtained after breast MRI. The lesion was removed surgically. Or after local anesthesia, the lesion was obtained by ultrasound-guided needle biopsy. The tumors ($n = 108$) used in this study were defined as grade II and grade III, according to the formation of glandular ducts, nuclear shape and size and chromatin, chromatin increase and nuclear division, etc. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and Ki-67 antigens results were obtained from the cancer registry having been processed in pathology department.

Positive judgment of ER and PR: when calculating the proportion of positive cells in total cells, 0% is recorded as negative (–) if no positive cells are found; if the rate of positive cells $\geq 1\%$ but $< 10\%$ is recorded as weakly positive (1+); if the rate of positive cells $\geq 10\%$ but $< 30\%$ is recorded as positive (2+); if the rate of positive cells $\geq 30\%$ is recorded as strongly positive (3+). Criteria for positive determination and stratification of HER-2: ratio of positive cells $\leq 10\%$, incomplete and weak staining of cell membrane, denoted as negative (–); the proportion of positive cells was $> 10\%$, and the cell membrane showed incomplete and weak staining, which was denoted as weakly positive (1+). The proportion of positive cells $> 10\%$, incomplete and moderate intensity staining of cell membrane, or the proportion of positive cells $\leq 10\%$, complete and obvious staining of cell membrane, denoted as positive (2+); The proportion of positive cells was more than 10%, but the cell membrane showed complete and obvious staining, which was denoted as strongly positive (3+). Ki-67 positive determination criteria: calculate the proportion of positive cells in total cells, if the positive cell rate < 14 is denoted as negative (–), if the positive cell rate $\geq 14\%$ but < 30 is denoted as weakly positive (1+), if the positive cell rate $\geq 30\%$ but < 50 is denoted as positive (2+), if the positive cell rate $\geq 50\%$ is denoted as strongly positive (3+) [22,23]. In this study, it was only divided into negative and positive. The weakly positive, positive and strongly positive were all positive.

2.4 Statistical Analysis

Statistical analyses were implemented with SPSS software (version 20.0, Chicago, IL, USA). Continuous variables were reported as the mean \pm standard deviation or median with interquartile range (IQR). Categorical variables were reported as frequency and proportions. The independent-sample *t* test or Mann–Whitney U test was performed to compare the quantitative parameters and the chi-square test to compare the qualitative features. Kolmogorov Smirnov test was used to analyze whether each continuous variable conforms to the normal distribution, and the results are shown in Table 1. $p < 0.05$ was considered statistically significant. In addition, false negative results may result from poor test performance. Therefore, in the results where *p* value is greater than or equal to 0.05, we performed

Table 1. Normally distributed results for each continuous variable by Kolmogorov Smirnov test.

| Parameter | | MD (10^{-3} mm ² /s) | | MK (10^{-3} mm ² /s) | |
|--------------------|-------------------|------------------------------------|----------------|------------------------------------|----------------|
| | | Statistic | <i>p</i> value | Statistic | <i>p</i> value |
| ER | Negative (n = 25) | 0.095 | 0.200 | 0.096 | 0.200 |
| | Positive (n = 83) | 0.086 | 0.196 | 0.088 | 0.168 |
| PR | Negative (n = 29) | 0.072 | 0.200 | 0.184 | 0.013 |
| | Positive (n = 79) | 0.063 | 0.200 | 0.086 | 0.200 |
| HER-2 | Negative (n = 70) | 0.115 | 0.022 | 0.067 | 0.200 |
| | Positive (n = 38) | 0.097 | 0.200 | 0.080 | 0.200 |
| Ki-67 | Low (n = 40) | 0.105 | 0.200 | 0.054 | 0.200 |
| | High (n = 68) | 0.089 | 0.200 | 0.064 | 0.200 |
| Grade II (n = 44) | | 0.122 | 0.098 | 0.094 | 0.200 |
| Grade III (n = 64) | | 0.091 | 0.200 | 0.128 | 0.011 |

Table 2. Clinical features and diffusion parameters between different grades of tumors.

| Characteristic | Grade II | Grade III | <i>p</i> value |
|------------------------------------|-------------|------------------|-----------------|
| Patient age | 46.5 ± 8.5 | 47.1 ± 9.2 | <i>p</i> > 0.05 |
| Menstrual status | | | <i>p</i> < 0.05 |
| Premenopausal (n = 63) | 32 | 31 | |
| Postmenopausal (n = 45) | 12 | 33 | |
| Lesion characteristics | | | |
| Size (cm) | 3.1 ± 0.93 | 3.5 ± 1.2 | <i>p</i> > 0.05 |
| Shape | | | <i>p</i> > 0.05 |
| Round | 4/44 | 6/64 | |
| Oval | 9/44 | 11/64 | |
| Irregular | 31/44 | 47/64 | |
| MD (10^{-3} mm ² /s) | 1.17 ± 0.24 | 0.82 ± 0.21 | <i>p</i> < 0.05 |
| MK | 0.85 ± 0.21 | 1.01 (0.85–1.16) | <i>p</i> < 0.05 |

Note: MD, mean diffusivity; MK, mean kurtosis.

a power analysis using the Student's *t* test. Below 0.20: the effect is too small; 0.20–0.50: small effect; 0.50–0.80: large effect; above 0.80: large effect.

3. Results

3.1 Basic Characteristics

Totally, 108 patients with breast tumors were included: 90 infiltrating ductal carcinomas, 2 *in situ* ductal carcinomas, 15 infiltrating lobular carcinomas, and 1 *in situ* lobular carcinoma. As shown in Table 2, there was a significant difference between grade II and Grade III tumors, depending on the patient's menstrual status. However, as shown in Table 2, there was no significant difference between Grade II and Grade III tumors, based on patient age and tumor size. TRA images, Dynamic contrast enhancement (DCE) maps, MD and MK maps, and the pathology images of a 34 years old woman with infiltrating ductal carcinomas in right breast were shown in Figs. 1,2.

3.2 MD and MK were Changed in Grade III Tumors in Comparison with Grade II Tumors

As shown in Table 1, MD values were significantly decreased in grade III tumors (0.82 ± 0.21 (10^{-3} mm²/s)) compared with grade II tumors (1.17 ± 0.24 (10^{-3} mm²/s)) (Fig. 3A). In contrast, MK values were significantly increased in grade III tumors (1.00 ± 0.31 (10^{-3} mm²/s)) compared with grade II tumors (0.82 ± 0.21 (10^{-3} mm²/s)) (Fig. 3B).

3.3 Relationship of MD and MK with ER, PR, HER-2, and Ki-67

Then, the relationship of MD and MK with the expressions (positive and negative) of ER, PR, HER-2 and Ki-67 were analyzed. The routine HE staining and IHC staining of grade II tumors with ER (1+), PR (–), Ki-67 (3+, about 70%), and HER-2 (3+) was demonstrated in Fig. 4A. As shown in Fig. 4B,C, MD was negatively associated with Ki-67 level ($r = -0.39$, $p < 0.05$), while MK was positively associated with Ki-67 level ($r = 0.56$, $p < 0.05$). As shown in Table 3, MD was significantly decreased in high Ki-67 level group compared with low Ki-67 level group, while MK was significantly increased in high Ki-67 level group

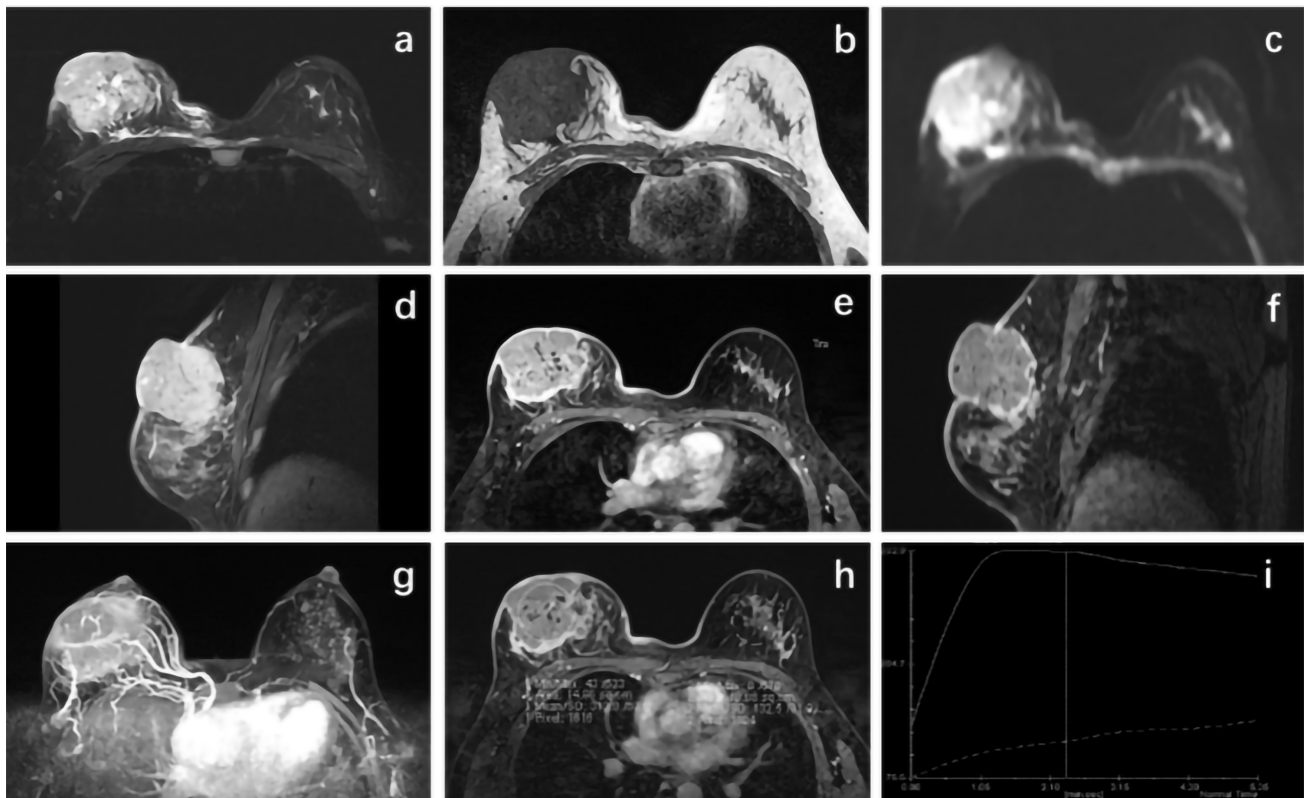


Fig. 1. Transverse (TRA) images showing the pathology and dynamic contrast enhancement (DCE) of a 34 years old woman with right breast infiltrating ductal carcinomas. T2-weighted TRA short TI inversion recovery (STIR) image (a) T1-weighted TRA image (b), T1-weighted TRA image (c), DWI TRA image (d), T1-weighted TRA contrast image (e), and T1-weighted SAG contrast image (f) of a 34 years old woman with infiltrating ductal carcinomas in right breast. In the upper outer quadrant of the right breast, there was an irregular mass surrounded by disorder structures, and an irregular nodular shadow below the mass. The lesion showed strong enhancement. Dynamic contrast enhancement (DCE) of a 34-year old woman with infiltrating ductal carcinomas in right breast. The DCE maps (g), enhancement maps (h) and contrast enhancement curves (i) of maximum intensity projection (MIP) of a 34-year old woman with infiltrating ductal carcinomas in right breast.

compared with low Ki-67 level group. MD was significantly increased in ER and PR positive expression group compared with ER and PR negative expression group, while there is no significant difference of MK in ER and PR positive expression group compared with ER and PR negative expression group. Additionally, there is no significant difference of MD and MK in HER-2 positive expression group compared with HER-2 negative expression group.

4. Discussion

Traditional breast cancer screening, classification and diagnosis have always relied on X-ray imaging and ultrasound. However, with the progress of the times, the accuracy and sensitivity of traditional diagnostic techniques are increasingly high, and the traditional diagnosis is faced with great challenges [18]. For radiologists, it is necessary to improve the accuracy of breast cancer diagnosis and pathological grading. Accurate description of breast tumor types and degree of malignancy is conducive to the formulation of treatment plans and improvement of treat-

ment outcomes. DKI, with its non-invasive imaging function, can provide valuable information about water diffusion characteristics in tumor microenvironment for diagnosis. In the present project, we investigated the association between DKI-derived parameters MD and MK with tumor grade and the expression of breast cancer-related proteins including Ki-67, ER, PR, and HER-2. Our results show that MD was obviously lower in grade III breast cancer than that in grade II breast cancer, while MK was prominently higher in grade III breast cancer than that in grade II breast cancer. MD was negatively correlated with Ki-67 level, while MK was positively associated with Ki-67 level. In addition, MD was positively associated with the level of ER and PR, but not HER-2. A study has found that the MD value of benign breast lesions is higher than that of malignant breast lesions, while the MK value of malignant breast lesions is significantly higher than that of benign breast lesions. The MD and MK values of benign breast lesions are significantly different from those of malignant breast lesions, and only the MK value is statistically different between fibroadenoma

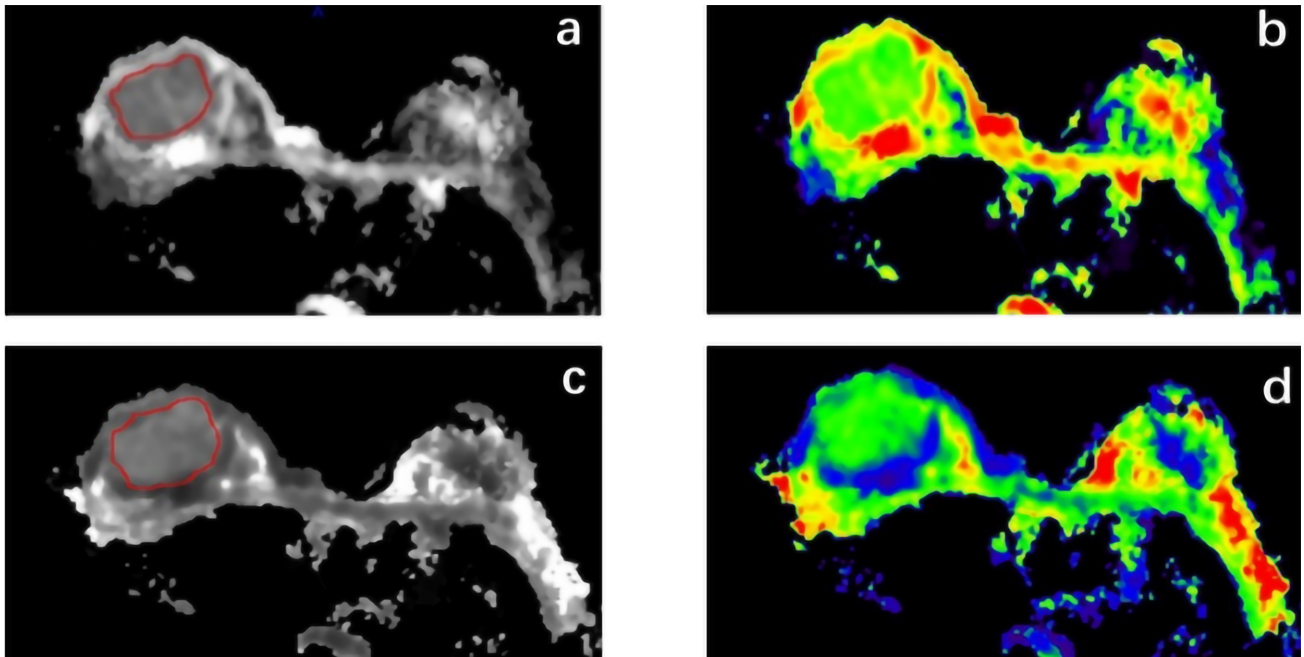


Fig. 2. MD and MK maps of a 34-years old woman with infiltrating ductal carcinomas in right breast. MD images showed that the lesion was slightly hypointense. MK image shows slightly hyperintense lesion. MD map (a), MK maps (b), MD pseudo color map (c), MK pseudo color map (d) of a 34-years old woman with infiltrating ductal carcinomas in right breast.

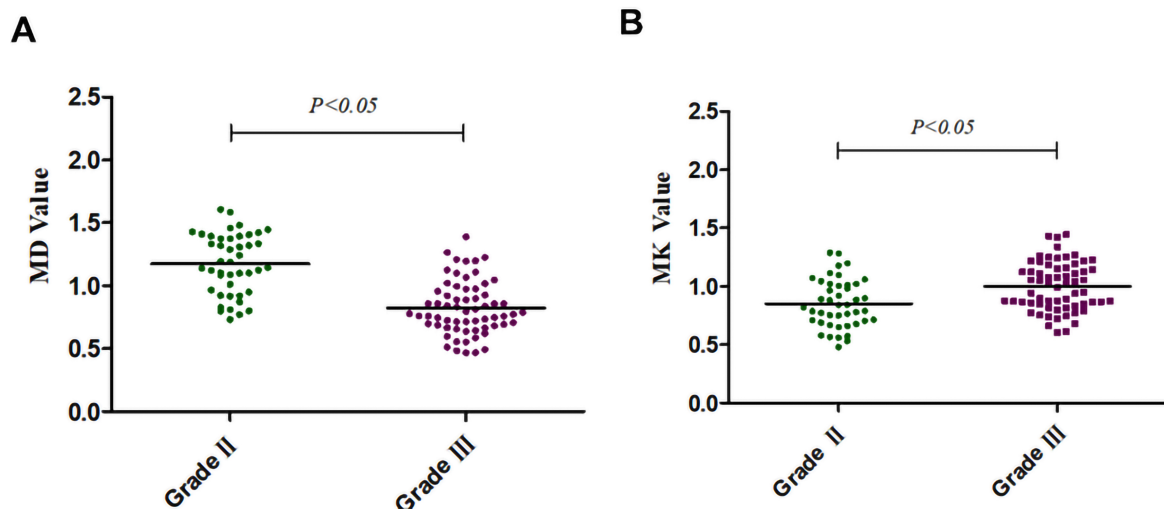


Fig. 3. Different MD and MK in grade II and grade III breast cancer patients. Summarized data showing MD values (A) and MK values (B) in grade II and grade III breast cancer patients.

and fibrocystic breast lesions [18]. Therefore, the results of this study and previous studies show that DKI may serve as a useful tool in the diagnosis for breast cancer.

Firstly, our study focused on two main parameters: MD and MK, which was calculated by DKI model. Diffusivity is the diffusion coefficient with correction of non-Gaussian bias, and Kurtosis quantifies the deviation of tissue diffusion from a Gaussian pattern [15]. The present study demonstrated that MD was significantly decreased, while MK was significantly increased in grade III patients in contrast to grade II patients. It has been well accepted that

DKI, a non-invasive functional imaging technique, could help us to figure out the properties of water diffusion in microenvironment of tumors. This finding is consistent with a previous study demonstrating that high-grade tumors are identified with evident variation of nuclear pleomorphic and high mitotic counts and without tubule and gland formation [24]. Indeed, DKI could provide us with the characteristics of tissue water diffusion [9,25]. Specifically, the characterization of the water diffusion of the microenvironment can help us to understand the pathological status of breast lesions. Because of a reduction of the extracellular

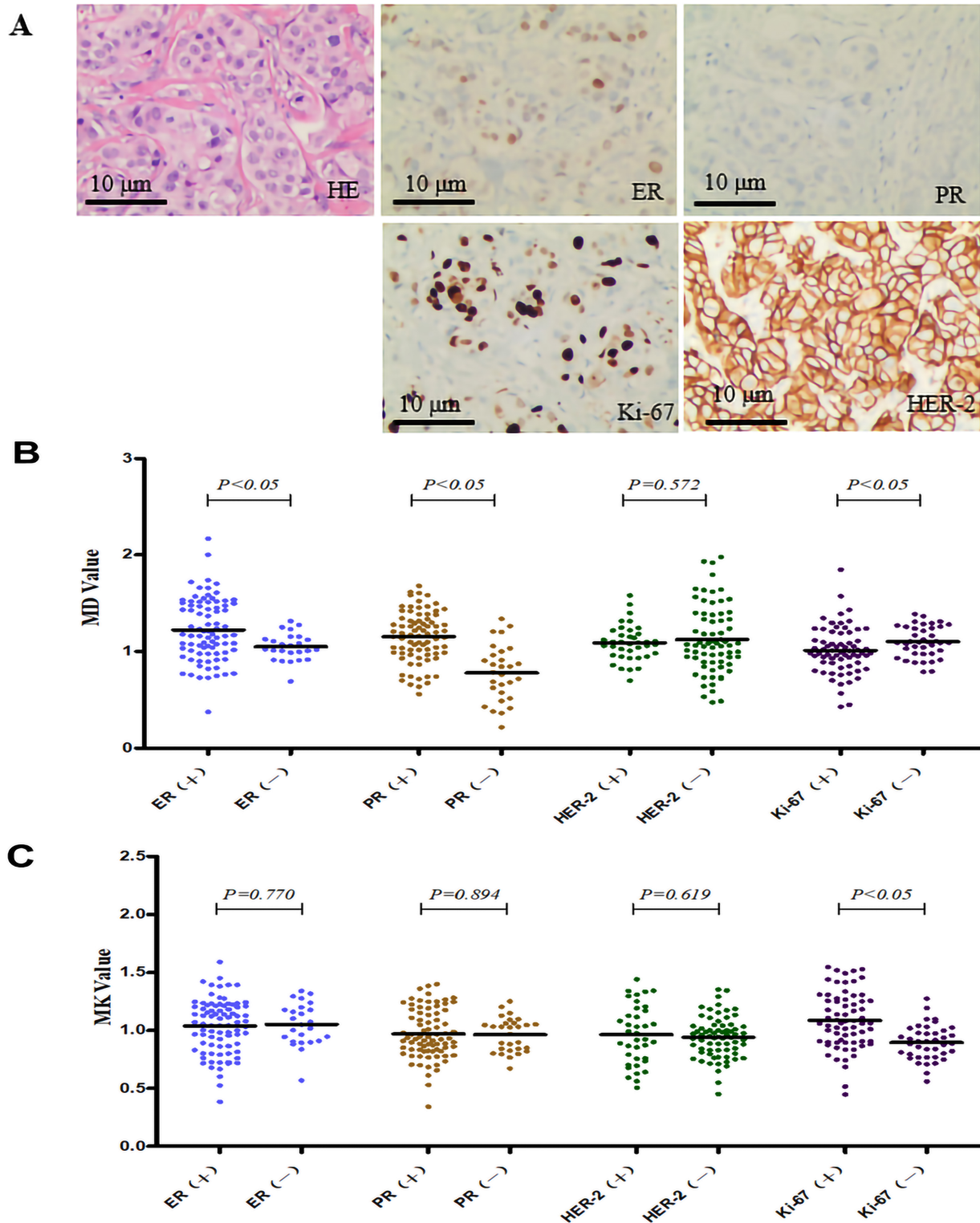


Fig. 4. Correlation of MD and MK with the expression of ER, PR, and Ki-67. (A) The pathological images 200 \times showing a right breast grade II cancer patient with routine HE staining, ER (1+), PR (-), Ki-67 (3+, about 70%), and HER-2 (3+). (B,C) Correlation of MD and MK with the expression of ER, PR, HER-2, and Ki-67.

space, cell proliferation in high-grade tumor is promoted, and motion of water molecules is restricted. The cellular density is much higher in high-grade tumors than that in low-grade tumors. These changes suggest that tissue com-

plexity was increased at the microstructural level in grade III tumors and exhibited higher kurtosis and lower diffusivity. Therefore, this study suggests that the change in tissue complexity at the microstructure level results in higher

Table 3. Comparison of clinic pathologic variables with MD and MK values.

| Parameter | MD (10^{-3} mm ² /s) | MK |
|-------------------|------------------------------------|------------------|
| ER | | |
| Negative (n = 25) | 1.05 ± 0.14 | 1.05 ± 0.18 |
| Positive (n = 83) | 1.22 ± 0.32 | 1.04 ± 0.23 |
| <i>p</i> value | 0.010 | 0.770 |
| power value | - | 0.961 |
| PR | | |
| Negative (n = 29) | 0.78 ± 0.29 | 1.03 (0.83–1.06) |
| Positive (n = 79) | 1.15 ± 0.26 | 0.97 ± 0.21 |
| <i>p</i> value | 0.000 | 0.917 |
| power value | - | 0.957 |
| HER-2 | | |
| Negative (n = 70) | 1.07 ± 0.49 | 0.94 ± 0.18 |
| Positive (n = 38) | 1.09 ± 0.18 | 0.96 ± 0.25 |
| <i>p</i> value | 0.997 | 0.619 |
| power value | 0.915 | 0.936 |
| Ki-67 | | |
| Low (n = 40) | 1.10 ± 0.16 | 0.90 ± 0.15 |
| High (n = 68) | 1.01 ± 0.24 | 1.09 ± 0.24 |
| <i>p</i> value | 0.040 | 0.000 |

Note: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2; MD, mean diffusivity; MK, mean kurtosis.

MK values and lower MD values in the tissues of grade 3 breast cancer cases compared with grade 2 breast cancer cases. In addition, Spearman correlation analysis results in this study showed that MD value was negatively correlated with the pathological grade of breast cancer, while MK value was positively correlated with the pathological grade, which proved that DKI had a certain guiding value in evaluating the degree of breast cancer lesions.

It has been reported that high Ki-67 level represents high recurrence ratio and low survival rate [26–29], and detection of Ki-67 positivity is helpful in evaluating prognosis of breast cancer patients. The results of this study showed that MD value was negatively correlated with Ki-67 expression, while MK value was positively correlated with Ki-67 expression. Our result is consistent with previous studies demonstrating that MK was positively correlated with histological grade and Ki-67, while MD was negatively correlated with histological grade and Ki-67 [19]. This may be caused by that tumor tissue becomes more complex due to tumor cell proliferation and vascular hyperplasia. The positive association between MK value and Ki-67 and the negative association between MD value and Ki-67 in advanced tumors may have certain value to evaluate the tumor grade in response to tumor proliferative activity, and provide the basis for later treatment.

In addition to Ki-67 factor, ER, PR and HER-2 are also widely used prognostic markers of breast cancer, and there are many studies related to imaging. And ER and

PR are widely used markers in determining therapeutic response to hormone therapies [20,30–32]. The results of this study showed that there were significant statistical differences in MD values between negative and positive expression groups of ER, PR and Ki-67 factors, but no statistical differences between negative and positive expression groups of HER-2 factors. MK showed statistically significant difference only between the negative and positive expression groups of Ki-67 factor, but no statistically significant difference between the negative and positive expression groups of ER, PR and HER-2 factor. The results with no significant difference were tested by the T-test of efficacy analysis, and the effect values were all greater than 0.9. Therefore, *p* value greater than or equal to 0.05 was the true negative result. In addition, in the current study, MD was positively correlated with ER, PR positive expression, indicating that diffusion kurtosis MRI could be of interest to discriminate hormone receptor-positive breast cancers. However, the present study has a few limitations. When we do magnetic resonance imaging of breast, we first judge the condition of breast cancer by using the T2WI image, and then decide whether to use the longer DKI scanning sequence or not. The lack of experienced doctor's guidance caused the omission of some cases. In order to improve the systematicness and scientificity of this study, attention should be paid to the collection and study of early and small cases in the future.

5. Conclusions

In summary, this exploration shows the quantitative analysis of DKI parameters has great value in the evaluation on the classification of invasive breast carcinoma. DKI can provide help in characterization and diagnosis of breast lesions. However, further studies are needed to further explore the value of DKI in breast carcinoma with larger sample size.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YG did data collection, data collation and manuscript writing. NW did the sorting of patient data, statistical analysis and manuscript revision. GYH reviewed the draft and checked the results of the data analysis. XMW did had a hand in revising the first draft and designing of the work. CHH examined the overall framework of the manuscript and the interpretation of data for the work. JS verified the study design and involved in drafting the manuscript. WGT analyzed the data and revised it critically for important intellectual content. LY did was involved in the collection of patient image information and involved in drafting the

manuscript. XXM did was involved in delineating the extent of the lesion and involved in drafting the manuscript. QQW was involved in image acquisition and image processing and revised in drafting the manuscript. MZ determined the method and purpose of the research, constructed the overall framework of the research, and provided the research funding. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee. The ethics approval number is 073. Written informed consent from patients were obtained.

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Conflict of Interest

The authors declare no conflict of interest.

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