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FULL PAPER

Preoperative predicting malignancy in breast mass-like lesions: value of adding histogram analysis of apparent diffusion coefficient maps to dynamic contrast-enhanced magnetic resonance imaging for improving confidence level

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Objective: This study aims to find out the benefits of adding histogram analysis of apparent diffusion coefficient (ADC) maps onto dynamic contrast-enhanced MRI (DCE-MRI) in predicting breast malignancy.

Methods: This study included 95 patients who were found with breast mass-like lesions from January 2014 to March 2016 (47 benign and 48 malignant). These patients were estimated by both DCE-MRI and diffusion-weighted imaging (DWI) and classified into two groups, namely, the benign and the malignant. Between these groups, the DCE-MRI parameters, including morphology, enhancement homogeneity, maximum slope of increase (MSI) and time-signal intensity curve (TIC) type, as well as histogram parameters generated from ADC maps were compared. Then, univariate and multivariate logistic regression analyses were conducted to determine the most valuable variables in predicting malignancy. Receiver operating characteristic curve analyses were taken to assess their clinical values.

Results: The lesion morphology, MSI and TIC Type ($p < 0.05$) were significantly different between the two

groups. Multivariate logistic regression analyses revealed that irregular morphology, TIC Type II/III and ADC_{10} were important predictors for breast malignancy. Increased area under curve (AUC) and specificity can be achieved with Model 2 (irregular morphology + TIC Type II/III + $ADC_{10} < 1.047 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) as the criterion than Model 1 (irregular morphology + TIC Type II/III) only (Model 2 vs Model 1; AUC, 0.822 vs 0.705; sensitivity, 68.8 vs 75.0%; specificity, 95.7 vs 66.0%).

Conclusion: Irregular morphology, TIC Type II/III and ADC_{10} are indicators for predicting breast malignancy. Histogram analysis of ADC maps can provide additional value in predicting breast malignancy.

Advances in knowledge: The morphology, MSI and TIC types in DCE-MRI examination have significant difference between the benign and malignant groups. A higher AUC can be achieved by using ADC_{10} as the diagnostic index than other ADC parameters, and the difference in AUC based on ADC_{10} and ADC_{mean} was statistically significant. The irregular morphology, TIC Type II/III and ADC_{10} were significant predictors for malignant lesions.

INTRODUCTION

Among all cancers in females, breast cancer has become the most serious “killer” because of its highest morbidity.¹ Thus, it will be crucial to perform early detection, accurate diagnosis and efficient treatment to the patients. Dynamic contrast-enhanced MRI (DCE-MRI), reputed for its high sensitivity, free of ionizing radiation damage, high resolution of soft tissue and multidimensional imaging,²

is acknowledged as one of the most important clinical methods for the examination of breast lesions and treatment evaluation. However, its clinical limitation in cancer diagnosis is also noticed owing to the low specificity, which may lead to unnecessary biopsy.³ Furthermore, DCE-MRI may bring to the patients side effects from the contrast media. Recent studies of diffusion-weighted imaging (DWI) for quantitatively characterizing *in vivo* movement

of water molecules reflects the tissue physiology or pathological status.^{4,5} Accordingly, the possibility may also exist that DWI will be helpful in improving the specificity of DCE-MRI for cancer diagnosis and staging.

Although malignant breast lesions usually present high-signal intensity on DWI, apparent diffusion coefficient (ADC) value showed a substantial overlap between benign and malignant breast lesions, limiting its clinical value for individual patients.⁶ On the other hand, histogram analysis of the ADC map on the basis of pixel distribution has currently been proven useful in differentiating and grading lesions as well as in predicting the treatment response in various organs by providing quantitative information about lesion heterogeneity.^{7,8}

Thus, the objective of the study was to evaluate the benefits in combining histogram analysis of ADC maps with DCE-MRI in the discrimination of malignant and benign breast lesions.

METHODS AND MATERIALS

Study population

This retrospective study was approved by the institutional review board, and the requirement for informed consent was waived. From January 2014 to March 2016, 166 patients were enrolled in the study upon the following criteria: (1) breast MRI was performed on the same 3.0 T MRI scanner to evaluate the suspected lesions discovered by ultrasonography and/or mammography; (2) DWI sequence was performed with b -values of 50 and 800 s mm⁻²; (3) patients did not accept any biopsy, chemotherapy or other interventions before MRI examination; (4) final histopathological results were acquired by surgery or core needle biopsy at The First Affiliated Hospital of Nanjing Medical University not more than 1 month after MRI. Among these 166 patients, 35 were excluded for having non-mass-like enhanced lesions, 15 were excluded for having lesions with the largest diameter less than 1 cm and 21 for poor image quality on DWI. Finally, the remaining 95 patients (mean age, 44.1 ± 11.4 years; range, 25–92 years) constituted the study population. The study cohort was composed of 47 benign and 48 malignant lesions. The detailed histopathological information of the two groups are described in Table 1.

MRI techniques

MRI was obtained using a bilateral eight channel phased-array breast coil with the patient in the prone position. Images were acquired with a 3.0 T system (MAGNETOM Trio, Siemens, Germany) following such sequences: (1) an axial turbo spin-echo T_2 weighted imaging sequence with repetition time/echo time (TR/TE), 5000/61 ms; field-of-view (FOV), 320 × 320 mm; matrix size, 576 × 403; slice thickness, 4 mm; (2) a DWI sequence, readout-segmented echo-planar imaging, with b -values, 50 and 800 s mm⁻²; TR/TE, 5400/86 ms; FOV, 360 × 180 mm; matrix size, 192 × 82; and slice thickness, 4 mm. Five readout segments were acquired for readout-segmented echo-planar imaging. ADC maps were calculated automatically by using MRI software from the DWI; (3) the dynamic series, consisting of a three-dimensional transverse fast low angle shot T_1 weighted sequence with fat suppression; TR/TE, 4.23/1.57 ms; FOV, 340 × 340 mm; flip angle, 10; matrix size, 448 × 296; slice thickness, 0.9 mm; and pixel resolution, 1.1 × 0.8 × 0.9 mm. Gadopentetate dimeglumine (Magnevist; Bayer Healthcare, Berlin, Germany) was injected intravenously as a bolus (0.1 mmol kg⁻¹ body weight) by a power injector at 3.0 ml s⁻¹, followed by a 20 ml saline flush after pre-contrast acquisitions. The images were obtained in five post-contrast acquisitions with no gap centered at 20 s within total 5 min and 41 s. (4) finally, the sagittal T_2 weighted imaging sequence with fat suppression, TR/TE, 3000/72 ms; FOV, 340 × 340 mm; matrix size, 269 × 384; and slice thickness, 4.0 mm.

Imaging processing

Two radiologists (YNJ and JJJ) with over 10 years experience in breast lesions diagnosis, analysed the MRI images without any information about clinical finding and final diagnosis. The lesion morphology (regular 0 and irregular 1) and enhancement homogeneity (homogeneous 0 and heterogeneous 1) were observed on the DCE-MRI images. For the patient with multiple lesions, only the largest one was selected. The DCE-MRI data were post-processed with the mean-curve software on syngoMMWP VE40B workstation. Region of interest (ROI) was drawn with a diameter of 5–10 mm² on the most enhanced region of the lesion, without any cystic, haemorrhagic or necrotic area. The time-signal intensity curve (TIC) was generated from the selected ROI, on

Table 1. Demographic and histological information of two groups

Demographic data	Benign group ($n = 47$)	Malignant group ($n = 48$)	p -value
Age (years)	42.7 ± 10.24	45.5 ± 12.43	0.235
Maximum diameter (cm)	2.29 ± 1.29	2.76 ± 1.38	0.092
Histological results	Fibroadenomas (27)	Invasive ductal carcinomas (34)	–
	Benign phyllodes tumour (5)	Invasive lobular carcinoma (3)	
	Fibrocystic changes (3)	Ductal carcinomas <i>in situ</i> (6)	
	Hyperplasias (2)	Mucinous carcinomas (3)	
	Sclerosing adenoses (4)	Eczematoid carcinoma (1)	
	Intraductal papillomas (4)	Sarcomatoid cancer (1)	
	Granulomatous lobular mastitis (2)		

Data in parentheses indicate the number of the corresponding patients in our study.

which maximum slope of increase (MSI) was also obtained. There are three TIC types including: Type I (assigned as “0”), continuously rising curve with $SI_{\text{slope}} > 10\%$; Type II (assigned as “1”), flat type, $-10\% \leq SI_{\text{slope}} \leq 10\%$; Type III (assigned as “1”), continuous descend type with $SI_{\text{slope}} < -10\%$. Here SI_{slope} is defined as the slope of signal intensity with its formula as $SI_{\text{slope}} = [(SI_{\text{tail}} - SI_{\text{peak1}})/SI_0] \times 100\%$,⁹ and SI_{tail} stands for the signal intensity at the last time point; SI_{peak1} refers to the maximum signal strength during the first two post-contrast phases; SI_0 is the signal intensity of the pre-contrast phase. MSI was calculated following formula $MSI = [(SI_{\text{peak}} - SI_0) \times 100\%]/T_{\text{peak}}$, where SI_{peak} means the highest signal intensity after enhancement and T_{peak} equals to the time from contrast arrival to peak (counted in seconds).

For quantitative assessment of the DWI, all data were transferred in digital imaging and communications in medicine format and post-processed offline with in-house software (FireVoxel; CAI²R, New York University, NY). ADC map was constructed using a monoexponential fitting model. Following DCE-MRI, all ROIs were drawn on an encompassed lesion area, including necrotic, cystic and haemorrhagic parts and were selected slightly smaller than the real lesion to minimize the influence of partial volume effect. Moreover, ADC histograms were achieved by the whole-lesion volume. Histogram analysis described the statistical information. Then, the multiparametric measurements of ROIs in each slice of the lesion foci were summed up to drive the voxel-by-voxel values for histogram analysis. The histogram parameters for each ROI were analysed with commercially available software (SPSS v. 19.0, Chicago, IL). The ADC histograms were plotted with its *x*-axis showing diffusivity, with a bin size of $1 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, and its *y*-axis standing for the percentage of lesion volume (frequency in each bin/total number of voxels analysed).

Based on the whole-lesion approach ROI, the parameters derived from ADC histogram analysis included ADC_{mean} , standard deviation (SD), skewness, kurtosis, ADC_{min} , ADC_{max} , ADC_{10} , ADC_{20} , ADC_{25} , ADC_{30} , ADC_{40} , ADC_{50} , ADC_{60} , ADC_{70} , ADC_{75} , ADC_{80} and ADC_{90} . Under each percentile, a certain amount of observations were calculated. Skewness tells the asymmetry of the pixel distribution. It will be positive if more values gather at left side of the mean value, and negative if more values at right side. While kurtosis measures the peakedness of the distribution. The higher the kurtosis is, a sharper peak the histogram has. In a normal distribution case, skewness should be 0 and kurtosis be 3.

To evaluate the intrareader reproducibility, the MRI images were processed again by the first reader after an interval of at least 4 weeks. The average of two measurements by the first reader was adopted for statistical analysis.

Statistical analysis

Statistical analysis was conducted using software packages (SPSS v. 19.0, Chicago, IL; and MedCalc, v. 12.7, Mariakerke, Belgium). Numeric data were averaged over all patients, expressed as mean $\pm$ SD and then tested by Kolmogorov–Smirnov test for normally distributed analysis. Univariate analysis was first performed on

each qualitative and quantitative variable to determine their ability of predicting a malignant breast lesion. The frequency distribution of each qualitative MRI feature was compared by χ^2 test between the two groups. If the sample size in the subgroup was too small, then Fisher exact test was conducted instead. The difference of quantitative parameters between the two groups was compared with that of the unpaired Student's *t*-test. Then, multivariate logistic regression analysis was introduced to determine the most valuable variables for predicting breast malignancy. Moreover, multiple receiver operating characteristic (ROC) curves were drawn to illustrate and compare the value of identified risk variables in predicting malignancy. Sensitivity and specificity were performed with the threshold criterion defined as the maximum value of Youden index (Youden index = sensitivity + specificity – 1).

The inter- and intrareader reproducibility of quantitative and qualitative parameter measurement was evaluated using the intraclass correlation coefficient (ICC) with 95% CI or κ analysis, respectively. Intrareader reproducibility was computed from the two measurements of reader 1, while interreader reproducibility was computed from the first measurement of reader 1 and the measurement of reader 2. The κ value and ICC range from 0 to 1.00. Value closer to 1.00 means better reproducibility. Specifically, value ≤ 0.40 means poor agreement; $0.41 \leq \text{value} \leq 0.60$ indicates moderate agreement; $0.61 \leq \text{value} \leq 0.80$ denotes good agreement; and $0.81 \leq \text{value} \leq 1.00$ signifies excellent agreement. A two-sided *p* value of less than 0.05 was taken to exhibit statistical significance.

RESULTS

The morphology, MSI and TIC types in DCE-MRI examination showed great difference between the benign and malignant groups ($p < 0.05$). However, no significant difference was observed in their enhancement patterns ($p > 0.05$) (Table 2). On DWI, we found that malignant lesions showed remarkably lower values than benign ones on the following parameters, ADC_{mean} , ADC_{min} , ADC_{10} , ADC_{20} , ADC_{25} , ADC_{30} , ADC_{40} , ADC_{50} , ADC_{60} , ADC_{70} , ADC_{75} , ADC_{80} and ADC_{90} , but higher kurtosis. Comparison of histogram parameters between the two groups is shown in Table 3.

By using ADC_{10} as the diagnostic index, a higher area under curve (AUC) can be achieved than by other ADC parameters. Moreover, the difference of AUC based on ADC_{10} and ADC_{mean} was statistically significant (AUC, 0.933 vs 0.879; $p < 0.001$). Considering the problem of collinearity, only one quantitative histogram parameter, ADC_{10} , which demonstrated a highest AUC, was adapted into multivariate logistic regression analysis together with morphology, TIC and MSI. Multivariate logistic regression analysis results showed that irregular morphology, TIC Type II/III and ADC_{10} were significant predictors for malignant lesions. The representative cases are shown in Figures 1 and 2.

Using the ROC curve analysis, we found that $ADC_{10} = 1.047 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ would be the optimal threshold value in differentiating breast malignant lesions from benign ones when it is set as the only differentiating index. Therefore, upon this result and former

Table 2. Comparison of DCE-MRI parameters for benign and malignant lesions

Parameters		Benign group (<i>n</i> = 47)	Malignant group (<i>n</i> = 48)	<i>p</i> -value	<i>K</i> -value
Morphology	Regular	23	9	0.002	0.813
	Irregular	24	39		
Enhancement homogeneity	Homogeneous	14	8	0.150	0.697
	Heterogeneous	33	40		
TIC type	I	22	5	0.000	0.895
	II, III	25	43		
MSI	Mean ± SD	2.078 ± 1.296	2.861 ± 1.274	0.004	-

DCE-MRI, dynamic contrast-enhanced MRI; MSI, maximum slope of increase; TIC, time-signal intensity curve.

multivariate logistic regression analysis result, we established two diagnostic models (Model 1, irregular morphology and TIC Type II/III; Model 2, irregular morphology, TIC Type II/III and $ADC_{10} < 1.047 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). We noticed that higher AUC and specificity can be achieved by using Model 2 than Model 1 (Model 2 vs Model 1; AUC, 0.822 vs 0.705; sensitivity, 68.8 vs 75.0%; specificity, 95.7 vs 66.0%). And their AUC difference was statistically significant ($p = 0.001$). Detailed ROC curves are shown in Figure 3.

Good or excellent inter- and intrareader agreements were obtained during the assessment of DCE-MRI and the measurements of histogram parameters. Detailed κ values for the inter-reader agreement of qualitatively DCE-MRI assessment are shown in Table 2. Detailed inter- and intrareader ICCs for the

quantitative measurements of MSI derived from DCE-MRI and histogram parameters derived from ADC maps are shown in Table 4.

DISCUSSION

Our study demonstrated that irregular morphology, TIC Type II/III and ADC_{10} were significant predictors for malignant breast lesions. Histogram analysis of the ADC maps might provide added value in clinical diagnosis, especially when specificity is concerned. To our knowledge, this study is at first time trying to assess the added value of histogram analysis of ADC maps in distinguishing malignant breast lesions from benign ones.

DCE-MRI, one of the most important and effective methods for breast lesions examination,^{10,11} provides plenty of morphological

Table 3. Difference of histogram parameters between benign and malignant lesions

Parameters	Benign group	Malignant group	<i>t</i> -value	<i>p</i> -value
ADC_{mean}	1.486 ± 0.245	1.140 ± 0.188	7.696	0.000
SD	0.161 ± 0.056	0.197 ± 0.077	-2.665	0.009
Skewness	0.447 ± 0.612	0.635 ± 0.630	-3.918	0.084
Kurtosis	3.276 ± 1.144	4.064 ± 1.361	-3.056	0.003
ADC_{min}	1.046 ± 0.295	0.690 ± 0.207	6.790	0.000
ADC_{max}	1.849 ± 0.255	1.752 ± 0.305	1.682	0.096
ADC_{10}	1.279 ± 0.251	0.903 ± 0.137	9.033	0.000
ADC_{20}	1.351 ± 0.251	0.982 ± 0.158	8.548	0.000
ADC_{25}	1.384 ± 0.251	1.008 ± 0.166	8.595	0.000
ADC_{30}	1.409 ± 0.253	1.030 ± 0.173	8.503	0.000
ADC_{40}	1.455 ± 0.253	1.071 ± 0.178	8.517	0.000
ADC_{50}	1.495 ± 0.258	1.113 ± 0.186	8.263	0.000
ADC_{60}	1.535 ± 0.259	1.167 ± 0.207	7.646	0.000
ADC_{70}	1.574 ± 0.258	1.223 ± 0.227	7.033	0.000
ADC_{75}	1.594 ± 0.256	1.255 ± 0.237	6.694	0.000
ADC_{80}	1.622 ± 0.254	1.297 ± 0.250	6.295	0.000
ADC_{90}	1.682 ± 0.244	1.403 ± 0.260	5.388	0.000

ADC, apparent diffusion coefficient; ADC_n , *n*th percentile value of cumulative ADC histogram; SD, standard deviation. Except *t*-value and *p*-value, data are reported as mean ± SD. The unit for ADC value is $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

Figure 1. Images of a 43-year-old female diagnosed with invasive ductal carcinoma in the left breast. (a) Dynamic contrast-enhanced image (one slice) shows intensely enhancing mass lesion with irregular morphology. (b) Obtained TIC shows a washout pattern. (c) Corresponding colour map for pixel-by-pixel ADC values of the entire lesion delineated with freehand ROI is obtained on diffusion-weighted image ($b = 800 \text{ s mm}^{-2}$). (d) Histogram of the entire lesion constructed from SPSS shows a large portion of pixels with low ADC values and $\text{ADC}_{10} = 0.689 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

information and reflects their haemodynamic characteristics.^{12,13} Specially, the model-based analysis of DCE-MRI can reveal more specific information about the true vascular physiology. However, such a compartment modelling analysis requires very high temporal resolution but sacrificing the spatial resolution. And its modelling process requires dedicated software. Furthermore, its sensitivity to the noise of data and fitting instabilities also leads to relatively low interreader reproducibility. All these drawbacks have limited its application in daily clinical setting. In response to this, many semi-quantitative approaches have been described and are now in relatively common use in clinical settings. We hypothesize that this analysis can provide valuable data to differentiate malignant lesions from benign ones.

Important differences have been noticed in the MSI, morphology and TIC type of the lesion between the benign and malignant groups of all the dynamic parameters in this study. Multivariate logistic regression analysis showed that only the morphology and TIC type were significant predictors for malignant lesions. It has been found that malignant cells are at rapid growth and unequal speeds, resulting in the irregular shape of the lesion due to the stretching of the marginal tissues; while benign lesions are slow-growing, acquiring a regular shape.^{14,15} The TICs of malignant breast masses on DCE-MRI are mostly of Type II or III, while benign ones are mostly of Type I. The pathological basis of this

phenomenon lies in angiogenesis. Higher vascular permeability and arteriovenous shunt of malignant tumours, induced by its higher microvessel density and immature vascular endothelial, lead to the fast entry of the contrast agent into the interstitial tissue of the tumour.^{12,16} As a result, the TICs of malignant tumours are of Type II or III. While MSI was not included in the multivariate logistic regression analysis. It indicates the speed of the lesion enhancement and reflects tissue physiology indirectly because of the correlation with the expression of vascular endothelial growth factor receptor 2. Higher density tumour vessels may contribute to higher MSI in malignant lesions. On the other hand, some benign lesions may have similar effect in promoting angiogenesis like inflammatory ones.¹⁷ They may exhibit good blood supply, and accordingly a quick increase in the amount of signal enhancement as in malignant lesions.

In our study, whole-lesion ROI approach was used to assess heterogeneity during image post-processing, while previous studies only used one or several selected ROIs during histogram analysis.^{18–20} This whole-lesion approach would decrease the effect of sampling bias and improve the measurement reproducibility, which is good for the clinical application of histogram analysis.^{21,22} Accordingly, its procedure would be more objective. The ADC values of malignant breast lesions are significantly lower than that of benign ones because of

Figure 2. Images of a 42-year-old female diagnosed with fibroadenoma in the right breast. (a) Dynamic contrast-enhanced image (one slice) shows intensely enhancing mass lesion with regular morphology. (b) Obtained TIC shows a persistent pattern. (c) Corresponding colour map for pixel-by-pixel ADC values of the entire lesion delineated with freehand ROI is obtained on diffusion-weighted image ($b = 800 \text{ s mm}^{-2}$). (d) Histogram of the entire lesion constructed from SPSS shows a large portion of pixels with high ADC values and $\text{ADC}_{10} = 1.208 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

Figure 3. ROC curves of using two different diagnostic models of differentiating benign and malignant breast lesions. AUC, area under curve; ROC, receiver operating characteristic.

Table 4. Inter- and Intrareader ICCs for measurements of MSI and histogram parameters

Parameters	Interreader ICC	Intrareader ICC
MSI	0.846 (0.783–0.884)	0.892 (0.809–0.914)
ADC _{mean}	0.892 (0.794–0.941)	0.911 (0.805–0.955)
SD	0.876 (0.742–0.916)	0.899 (0.809–0.956)
Skewness	0.863 (0.754–0.933)	0.906 (0.793–0.951)
Kurtosis	0.834 (0.764–0.977)	0.913 (0.773–0.964)
ADC _{min}	0.882 (0.754–0.940)	0.901 (0.815–0.935)
ADC _{max}	0.844 (0.749–0.896)	0.899 (0.715–0.934)
ADC ₁₀	0.856 (0.796–0.974)	0.902 (0.843–0.941)
ADC ₂₀	0.838 (0.723–0.867)	0.873 (0.749–0.896)
ADC ₂₅	0.855 (0.785–0.906)	0.889 (0.751–0.907)
ADC ₃₀	0.832 (0.737–0.856)	0.909 (0.888–0.944)
ADC ₄₀	0.834 (0.733–0.924)	0.903 (0.854–0.964)
ADC ₅₀	0.829 (0.766–0.898)	0.878 (0.751–0.907)
ADC ₆₀	0.854 (0.731–0.911)	0.868 (0.772–0.893)
ADC ₇₀	0.831 (0.783–0.894)	0.921 (0.885–0.948)
ADC ₇₅	0.848 (0.773–0.890)	0.901 (0.833–0.940)
ADC ₈₀	0.893 (0.794–0.909)	0.904 (0.876–0.942)
ADC ₉₀	0.820 (0.796–0.923)	0.849 (0.759–0.897)

ADC, apparent diffusion coefficient; ADC_n, *n*th percentile value of cumulative ADC histogram; ICC, intraclass correlation coefficient; MSI, maximum slope of increase; SD, standard deviation. Data in parentheses are 95% CI.

the hypercellularity, enlarged nuclei and reduced extracellular space as stated in several previous studies.^{23,24} Our study found similar results. Furthermore, we noticed that malignant lesions showed a higher kurtosis value than benign ones. To our knowledge, kurtosis is an important index that reflects the degree of lesion heterogeneity. In addition, the most distinctive feature of invasive ductal carcinomas is heterogeneity, which is composed of invasive cancer nests, stroma, intraleisional fibrosis or necrosis and intraductal components. Naturally, the malignant breast lesions would have a higher kurtosis than benign ones.

The ADC₁₀ values performed better than ADC_{mean} in differentiating benign lesions from malignant ones, and it achieved the highest AUC. The AUC between ADC₁₀ and ADC_{mean} was significantly different, and we adopted ADC₁₀ only into the multivariate logistic regression analysis. For this reason, we considered that low percentile ADC values would correspond well with the densely packed solid component of the lesion tissue. Within lesions with heterogeneous cellularity, focal areas of invasive components can be greatly represented by ADC₁₀ rather than by ADC_{mean}. Moreover, ADC₁₀ may best represent the most aggressive component of lesion. In lesions densely packed with malignant cells, more pixels display low ADC values. Several previous studies also indicated that low percentile of ADC value demonstrated better performance in differentiating or grading lesions than the high percentile of ADC value.²⁵ However, Suo et al demonstrated that ADC_{min} was the independent predictor of breast malignancy. This result did not correspond with our findings. The difference may owe to the fact that the ADC_{min} was easily influenced by the outlier data generated from noise, artefact and the surrounding structure in mass margin.²⁶ While ADC₁₀ reflected features of the lesion more stably. Moreover, heterogeneous inclusion of histological types of breast cancer in different studies can also cause different outcomes. Naturally, the low percentile ADC values would demonstrate better performance than high percentile ADC values.

By combining DCE-MRI features (irregular morphology, TIC Type II/III) with ADC₁₀, higher AUC and specificity can be obtained than by using the DCE-MRI features alone. The statistically significant difference in AUC and the excellent specificity would enhance our confidence for predicting malignant lesions, which is crucial for making the pretreatment plan and the communication between doctors and patients.

Several limitations exist in our study. First, most lesions in our study were fibroadenomas or invasive ductal carcinomas. This factor may influence the significance of the present results. Second, patients with breast lesions less than 1 cm in size were excluded. We believe higher spatial resolution will be available for accurate assessment on small lesions in the future as DWI techniques improves. Third, non-mass-like enhanced breast lesions were excluded in our study because normal parenchymal tissue can be easily interfused when measuring the ADC values which may cause ADC values of non-mass-like lesions falsely higher than those of mass-like lesions. Finally, DWI was achieved at *b*-values of 50 and 800 s mm⁻² in our study. The conventional ADC value generated

from monoexponential model is influenced by the effects of diffusion and perfusion. Multiple b -values combinations may be more valuable because it can provide more accurate data about signal decay, emphasizing perfusion or diffusion effect.

In conclusion, our results indicated that irregular morphology, TIC Type II/III and ADC_{10} were significant predictors for malignant breast lesions. Histogram analysis of the ADC map

can provide added diagnostic value in predicting malignant breast lesions, especially in improving the specificity.

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