Original Article
Diagnostic performance of ADCs in different ROIs for breast lesions

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Abstract: Objective: The purpose of this study was to explore the diagnostic performance of apparent diffusion coefficient (ADC) values for breast lesions by different measuring methods and find out the optimum measuring method. Methods: ADC\textsubscript{W-mean} and ADC\textsubscript{W-min} were obtained by whole-measurement method, while ADC\textsubscript{mean} and ADC\textsubscript{min} were extracted by spot-measurement method. Four ADCs were analyzed by One-way ANOVA and Independent T-test. The diagnostic performances of these four ADCs were calculated by receiver operating characteristics (ROC) curves and the area under the curves (AUC) were compared through Z-test. Results: For the whole-measurement method, there were significant differences between malignant and benign lesions (ADC\textsubscript{W-mean}=1.014±0.197 for malignant, ADC\textsubscript{W-min}=1.650±0.348 for benign, F=37.511, P<0.001; ADC\textsubscript{W-min}=1.245±0.290 for benign, F=41.446, P<0.001), as well as the spot-measurement method (ADC\textsubscript{mean}=1.010±0.234 for malignant, ADC\textsubscript{min}=1.648±0.392 for benign, F=34.580, P<0.001; ADC\textsubscript{min}=0.817±0.203 for malignant, ADC\textsubscript{min}=1.411±0.357 for benign, F=40.039, P<0.001). The optimal diagnostic threshold of ADC\textsubscript{W-mean}, ADC\textsubscript{W-min}, ADC\textsubscript{mean}, and ADC\textsubscript{min} values were 1.223×10\textsuperscript{-3} mm\textsuperscript{2}/s, 0.897×10\textsuperscript{-3} mm\textsuperscript{2}/s, 1.315×10\textsuperscript{-3} mm\textsuperscript{2}/s, and 1.111×10\textsuperscript{-3} mm\textsuperscript{2}/s, respectively. ROC curves indicated that the AUC for ADC\textsubscript{W-min} (0.969) was statistically significant higher than the AUC for ADC\textsubscript{W-mean} (0.940; Z=2.473, P=0.013), ADC\textsubscript{mean} (0.919; Z=3.691, P<0.001), and ADC\textsubscript{min} (0.928; Z=3.634, P=0.000). The AUC for ADC\textsubscript{W-mean} was also significantly higher than the AUC for ADC\textsubscript{mean} (Z=2.863, P=0.004). Conclusion: The results provided evidence that the most reliable and accurate value in demonstrating the limitation of diffusion may be ADC\textsubscript{W-min}, and it has the highest diagnostic value in distinguishing breast lesions from malignant to benign.

Keywords: Diagnostic performance, apparent diffusion coefficient, breast lesions

Introduction

Worldwide, breast cancer is the most common disease among women. The incidence of breast cancer, which is a heterogeneous breast lesion with highly variable biological behavior, is higher than most of the other women’s malignant diseases. Its treatment and prognosis are much more different from those of breast benign lesion. Therefore, correct diagnosis of breast lesion is of great value in developing the therapy. With the highly development of magnetic resonance (MR) technology, MR imaging has been a promising modality in the differentiate breast lesions and evaluate local extent of lesions.

MR diffusion-weighted imaging (DWI) has been widely applied to the diagnosis of breast lesions. DWI is an essential imaging modality for diagnosis and management of breast lesions and is currently the only noninvasive technique used for detecting Brownian motion of bulk water molecules in vivo. It quantifies the limitation of Brownian motion on these molecules through apparent diffusion coefficient (ADC) values. The ADC values have relatively high sensitivity and specificity in cancer detection [1, 2]. However, the method of measurement on the ADC values is not constant. There is no uniform standard towards the choice of regions of interests (ROIs) when measuring the ADCs. Most of the literatures discuss about the factors affecting ADC values. To our knowledge, studies rarely measure the ADCs in different ROIs and evaluate its values in the diagnosis of breast lesions. The aim of this study is to investigate the diagnostic value of different measur-
ing methods on ADC values and try to obtain the best method in the differentiation of breast lesions.

Materials and methods

Patients

This study was approved by the Institution Review Board of Guangxi Medical University and an informed consent was obtained from each patient. Two hundred patients (with 248 lesions) were consecutively recruited from March 2011 to March 2013 at the Affiliated Cancer Hospital of Guangxi Medical University (Nanning, People’s Republic of China). Two hundred patients (mean age, 46.81 years; range, 17–80 years) with breast lesions were underwent preoperative breast MRI with DWI. Among these patients, only one was male, and the others were female. All of them had met the following criteria: (a) Without any biopsy or interventional therapy or medical treatment performed on breast lesions before the MR imaging scan; (b) The breast lesions were confirmed by histopathological examination of specimens obtained by excision biopsy, core biopsy, or fine-needle aspiration.

MRI imaging protocol

MR imaging was performed with a 1.5 Tesla (T) clinical MR imaging system (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) equipped with a dedicated eight-channel phased array breast coil in the prone position. A transverse T2-weighted TIRM pulse sequence was performed with 5600/59/180 (repetition time/echo time/inversion time) ms, a 4 mm section thickness, a 0.8 mm intersection gap, a field of view of 34×34 cm, a matrix of 314×320. A transverse T1-weighted FLASH pulse sequence was performed with 8.6/4.7 (repetition time/echo time[TR/TE]), a 1 mm section thick-
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 ness, a 0.2 mm intersection gap, a field of view of 32×32 cm, a matrix of 323×448. DWI MR images were acquired in the axial planes by using an echo-planar imaging sequence, parallel imaging with sensitivity encoding (acceleration factor of two), fat suppression (in a spectral selective attenuated inversion-recovery sequence), volume shimming, b values of 0 and 800 s/mm², TR/TE/TI=5800/86/180 ms, a 6 mm section thickness, a 0.2 mm intersection gap, a field of view of 32×32 cm, and a matrix of 323×448. The ADC maps were created automatically by the system from the trace-weighted images with b values of 0 and 800. ADC values were calculated according to the following formula: ADC=-(1/b) ln (S2/S1), where the S2 and S1 are the signal intensities at b value of 800 and 0, respectively.

ROI measurement

ADC values were measured according to two distinct regions of interests (ROI) measurement methods: (1) whole-measurement, (2) spot-measurement. For the whole-measurement method, ROIs were freehanded along the border of tumor on ADC figures in order to cover the entire lesion areas, while the obviously necrotic, liquefactive, hemorrhagic, cystic, or calcified areas were excluded (based on T1WI, T2WI, and dynamic contrast-enhanced MRI figures)[3-5]. Mean ADC (ADC_{W-mean}) and minimum ADC (ADC_{W-min}) values of ROIs were figured out. For the spot-measurement method, ROIs were randomly drawn to extract three circles with 5-10 mm in diameter in different positions of lesions, while the areas with obvious necrosis, liquefactions, hemorrhage, cystic, or calcification were excluded (based on T1WI, T2WI, and dynamic contrast-enhanced MRI figures)[6-10]. Mean ADC (ADC_{mean}) and minimum ADC (ADC_{min}) values were also calculated (Figures 1-3). These measurements were completed by two experienced radiologists (Dong Xie, with 20 years of experience in reading breast MRI;

Figure 2. Pathological of fibroadenoma in left breast. A. Was for the Whole-measurement method (ADC_{W-mean} =1.5×10^{-3} \text{ mm}^2/\text{s}; ADC_{W-min} =1.189×10^{-3} \text{ mm}^2/\text{s}). B. Was for the spot-measurement method (ADC_{mean} =1.498×10^{-3} \text{ mm}^2/\text{s}; ADC_{min} =1.46×10^{-3} \text{ mm}^2/\text{s}). C. Was Photomicrograph (hematoxylin-eosin staining, original magnification 100×) method.
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Guanqiao Jin, with 15 years of experience in reading breast MRI) who were blinded to the pathological diagnosis and clinical examinations.

Statistical analysis

Results were expressed as mean ± standard deviation (X±SD). Four ADCs for distinguishing breast lesion from benign to malignant were analyzed by One-way ANOVA and Independent T-test with SPSS 16.0 software. The diagnostic performances of four ADC values (ADC_W, ADC_W_min, ADC_W_mean, and ADC_W_min) were calculated by receiver operating characteristics (ROC) curves and the area under the curves (AUC) were compared through Z-test using MedCalc V13.0.2.0 software. When Youden index reached the highest point, sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) were calculated. A p-value of less than 0.05 was judged as statistically significant.

Results

Eighty-five benign breast lesions were confirmed by pathology: 49.41% (42/85) were diagnosed as cyclomastopathy, 25.88% (22/85) were fibroadenoma, 5.88% (5/85) were benign phyllodes tumor, 4.71% (4/85) were cyclomastopathy accompanied with infection, 3.53%
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Table 1. Histopathological diagnoses of breast lesions

<table>
<thead>
<tr>
<th>Histological findings</th>
<th>Number of lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td>85</td>
</tr>
<tr>
<td>cyclomastopathy</td>
<td>42 (49.4)</td>
</tr>
<tr>
<td>fibroadenoma</td>
<td>22 (25.9)</td>
</tr>
<tr>
<td>benign phylloides tumor</td>
<td>5 (5.9)</td>
</tr>
<tr>
<td>cyclomastopathy accompanied with infection</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>granulomatous mastitis</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>fibroadenoma accompanied with infection</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>breast tuberculosis</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>intraduct papilloma</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>chronic suppurative mastitis</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>gynecomastia</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>163</td>
</tr>
<tr>
<td>invasive ductal carcinoma</td>
<td>142 (87.1)</td>
</tr>
<tr>
<td>ductal carcinoma in situ</td>
<td>12 (7.3)</td>
</tr>
<tr>
<td>invasive lobular carcinoma</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>mucinous carcinoma</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>tubular carcinoma</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>malignant phylloides tumor with rhabdomyosarcoma</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>papillary carcinoma</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

(3/85) were granulomatous mastitis, 2.35% (2/85) were fibroadenoma accompanied with infection, 2.35% (2/85) were breast tuberculosis, 2.35% (2/85) were chronic suppurative mastitis, 2.35% (2/85) were intraduct papilloma, and 1.18% (1/85) were gynecomastia. Among one hundred and sixty-three lesions of malignant breast lesions, 87.12% (142/163) were invasive ductal carcinoma, 7.36% (12/163) were ductal carcinoma in situ, 1.84% (3/163) were invasive lobular carcinoma, 1.23% (2/163) were mucinous carcinoma, 1.23% (2/163) were tubular carcinoma; 0.61% (1/163) were malignant phylloides tumor with rhabdomyosarcoma, and 0.61% (1/163) were papillary carcinoma (Table 1).

For the whole-measurement method, there were significant differences between malignant and benign lesions (ADC<sub>W-mean</sub> = 1.014±0.197 for malignant, ADC<sub>W-mean</sub> = 1.650±0.348 for benign, F=37.511, P<0.001; ADC<sub>W-min</sub> = 0.627±0.144 for malignant, ADC<sub>W-min</sub> = 1.245±0.290 for benign, F=41.446, P<0.001), as well as the spot-measurement method (ADC<sub>mean</sub> = 1.010±0.234 for malignant, ADC<sub>mean</sub> = 1.648±0.392 for benign, F=34.580, P<0.001; ADC<sub>min</sub> = 0.817±0.203 for malignant, ADC<sub>min</sub> = 1.411±0.357 for benign, F=40.039, P<0.001) (Table 2; Figure 4). When their Youden index reached the highest points, the optimal diagnostic threshold of ADC<sub>W-mean</sub>, ADC<sub>W-min</sub>, ADC<sub>mean</sub>, and ADC<sub>min</sub> values were 1.223×10⁻³ mm²/s, 0.897×10⁻³ mm²/s, 1.315×10⁻³ mm²/s, and 1.111×10⁻³ mm²/s, respectively. The corresponding SE, SP, PPV, and NPV values were 89.4%, 89.0%, 94.2%, and 81.7% for ADC<sub>W-mean</sub>, 89.7%, 97.5%, 98.7%, and 86.5% for ADC<sub>W-min</sub>, 84.7%, 91.4%, 95.2%, and 75.7% for ADC<sub>mean</sub>, and 82.4%, 95.1%, 97.1%, and 73.6% for ADC<sub>min</sub>. ROC curves indicated that the AUC for ADC<sub>W-min</sub> (0.969) was statistically significant higher than the AUC for ADC<sub>W-mean</sub> (0.940; Z=2.473, P=0.013), ADC<sub>mean</sub> (0.919; Z=3.691, P=0.000), and ADC<sub>min</sub> (0.928; Z=3.634, P=0.000). The AUC for ADC<sub>W-mean</sub> was also significantly higher than the AUC for ADC<sub>mean</sub> (Z=2.863, P=0.004) (Table 3; Figure 5).

Discussion

Nowadays, DWI is the only image technology for detecting Brownian motion of bulk water molecules in vivo, which is used to quantify water diffusion by ADC values. It has been widely applied to the diagnosis of benign and malignant lesions [11-13]. However, the measurement methods of ADCs were different [14-19]. Recently, many studies were published to assess the diagnostic performances of DWI in benign and malignant breast lesions [1, 2,
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14-24]. Some studies had found that ADCs had relatively high sensitivity and specificity in distinguishing malignant and benign lesions [1, 2]. Others had indicated that the pathologic basis of DWI were cell density, nucleus cytoplasm ratio, extracellular volume, and membrane integrity [1-2, 14-24]. However, the measurement methods of ADC values were inconstant. Moreover, different sizes of ROIs would result in different sensitivity and specificity of ADCs. Therefore, we performed this study to assess two measurement (whole-measurement and spot-measurement) methods of ADC values and the diagnostic performance of ADCs (ADC$_{W\text{-}\text{mean}}$, ADC$_{W\text{-}\text{min}}$, ADC$_{\text{mean}}$, and ADC$_{\text{min}}$).

The results of our study showed that the optimal diagnostic threshold ADC$_{W\text{-}\text{mean}}$, ADC$_{W\text{-}\text{min}}$, ADC$_{\text{mean}}$, and ADC$_{\text{min}}$ values were $1.223 \times 10^{-3}$ mm$^2$/s, $0.897 \times 10^{-3}$ mm$^2$/s, $1.315 \times 10^{-3}$ mm$^2$/s, and $1.111 \times 10^{-3}$ mm$^2$/s, respectively. The corresponding AUC values were 0.919, 0.928, 0.940, and 0.969, respectively. The diagnostic performance of ADCs (ADC$_{W\text{-}\text{mean}}$ and ADC$_{W\text{-}\text{min}}$) in the whole-measurement method was significantly higher than that of ADCs (ADC$_{\text{mean}}$ and ADC$_{\text{min}}$) in the spot-measurement method, especially ADC$_{W\text{-}\text{min}}$ value. However, several factors should be mentioned: (1) ADCs obtained from the spot-measurement method can be affected by different observer. (2) The size and number of ROIs obtained from the spot measurement were highly dependent on methods of ROI analysis [9, 11]. Therefore, ADCs obtained from the whole-measurement method are more reproducible than those obtained from the spot measurement.

It is known that different growth mode and growth speed of breast tumor cells can result in different extracellular volumes and nucleus cytoplasm ratios [1, 2, 9, 14-19]. It was hard to select intratumor highest cellular zone which was influenced by window level and width. Therefore, we can not assess the diagnostic strength of ADC$_{\text{min}}$ and ADC$_{\text{mean}}$ because it was liable to be subjective.

However, the whole-measurement method could avoid some subjective factors during the measurement process, and provide the objective, reliable, and well repeatable ADC$_{W\text{-}\text{mean}}$ and ADC$_{W\text{-}\text{min}}$ values of breast lesions by Siemens workstation. Due to the factor that malignant breast lesions show pathologic heterogeneity frequently, the presence of anaplasia, such as fibrosis and tiny liquefactive necrosis, may affect ADC values, especially maximum ADC. In addition, mucinous carcinoma often includes intratumoral mucin pool with a lower cell density [9, 25], and the highest cellular zone were usually the rim of tumor [9, 25]. Due to all these factors, ADC$_{W\text{-}\text{min}}$ can reflect well the pathologic features of tumor. Thus, we considered that ADC$_{W\text{-}\text{min}}$ value as an optimal DWI single parameter in distinguishing breast lesions from benign to malignant.

Several limitations should be mentioned in this study. First of all, microcalcification which should be excluded was hardly found out by naked eyes in the whole-measurement method. However, ADC values of microcalcification are relatively lower than those diagnosed as malignant lesions, which was consistent with the conclusions that most of the microcalcification took place in malignant breast lesions [26-28]. Secondly, there was lack of statistical significance between ADC$_{\text{min}}$ and ADC$_{W\text{-}\text{mean}}$ (Z=

Figure 4. Box plots graphs of parameters obtained in different ADCs measurement methods demonstrate a significant difference (P<0.05) between benign and malignant lesions. ○= outlier, *= extreme value.
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Table 3. Receiver operating characteristics (ROC) analysis and area under the curve (AUC) for each ADC parameter

<table>
<thead>
<tr>
<th>ADC Parameter</th>
<th>Cutoff level ($\times 10^{-3}$ mm$^2$/s)</th>
<th>SE (%)</th>
<th>SP (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUC</th>
<th>p value $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC$_{W\text{-mean}}$</td>
<td>1.223</td>
<td>89.4% (146/163)</td>
<td>89.0% (76/85)</td>
<td>94.2% (146/155)</td>
<td>81.7% (76/93)</td>
<td>0.940</td>
<td>0.013</td>
</tr>
<tr>
<td>ADC$_{W\text{-min}}$</td>
<td>0.897</td>
<td>91.8% (150/163)</td>
<td>97.5% (83/85)</td>
<td>98.7% (150/152)</td>
<td>86.5% (83/96)</td>
<td>0.969</td>
<td></td>
</tr>
<tr>
<td>ADC$_{\text{mean}}$</td>
<td>1.315</td>
<td>84.7% (138/163)</td>
<td>91.4% (78/85)</td>
<td>95.2% (138/145)</td>
<td>75.7% (78/103)</td>
<td>0.919</td>
<td>0.000</td>
</tr>
<tr>
<td>ADC$_{\text{min}}$</td>
<td>1.111</td>
<td>82.4% (134/163)</td>
<td>95.1% (81/85)</td>
<td>97.1% (134/138)</td>
<td>73.6% (81/110)</td>
<td>0.928</td>
<td>0.000</td>
</tr>
</tbody>
</table>

$^a$The best-performance cutoff was selected for optimal threshold when Youden index reached the highest point on the ROC curves. $^b$Statistically significant difference was compared with the AUC of the ADC$_{W\text{-mean}}$ parameter. The AUC for the ADC$_{W\text{-mean}}$ was statistically significantly higher than the AUC for the ADC$_{\text{mean}}$ (Z=2.863, P=0.004). That was no significantly between the AUC for the ADC$_{\text{mean}}$ and the AUC for the ADC$_{W\text{-mean}}$ (Z=1.247, P=0.213), the AUC for the ADC$_{\text{min}}$ and the AUC for the ADC$_{W\text{-mean}}$ (Z=1.069, P=0.285).

Figure 5. ROC of parameters obtained in different ADCs measurement methods for distinguishing breast Lesions from benign to malignant.

1.247, P=0.213), ADC$_{\text{mean}}$ (Z=1.069, P=0.285).
The reasons might be as follows: (1) no grouping was made based on lesions size, (2) four ADC values were similar when lesion’s diameter was small than 10 mm, and (3) the real extent of lesion was hard to evaluate due to diffuse cancer cells infiltrating the fat tissue [3]. Therefore, an accurate measurement method of ADCs with small error is needed to be exploited. Thirdly, this study was mainly investigated whether different measurement methods of ROIs had influence on ADCs. While, we did not explore whether different b values or equipments provided by different manufacturers, which may have some influence on the results [29, 30]. Therefore, further studies are needed to analyze the influence of different b values or equipments on ADCs.

Conclusions

ADCs obtained by the whole-measurement method are more accurate in reflecting the limitation of Brownian motion on water molecules than that of the spot-measurement method. All in all, our results provided evidence that the most reliable and accurate value in demonstrating the limitation of diffusion may be ADC$_{W\text{-min}}$ and it has the highest diagnostic value in distinguishing breast lesions from malignant to benign.

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Disclosure of conflict of interest

None.

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References


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