Original Article

Sub-classification of BI-RADS by MRI dynamic enhanced vascular imaging and diffusion weighted imaging

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Abstract: Aims: To promote the classification of BI-RADS by MRI dynamic enhanced vascular imaging and diffusion weighted imaging (DWI). Methods: A total of 143 patients with 150 breast lesions (confirmed by operation or biopsy) received dynamic contrast enhancement and DWI. The cut-off of the receiver operating characteristics curve was the threshold of apparent diffusion coefficient. BI-RADS Category four breast lesions were subdivided by combining Fischer’s scoring system and DWI. The BI-RADS-MRI 4A, 4B and 4C were defined as BI-RADS-MRI 4A(-), 4A(+), 4B(-), 4B(+), 4C(-), and 4C(+) by combining the enhanced 3D maximum intensity projection images of MRI. The positive predicted value of each category of lesions was analyzed and clinical treatment strategies for the lesions were determined accordingly. Results: Among the 150 breast lesions, there were 62 BI-RADS-MRI 4 lesions. The positive predicted values of 4A, 4B and 4C lesions were 7.7%, 52.4% and 89.3%, respectively. Those values of the 4A(-), 4A(+), 4B(-), 4B(+), 4C(-) and 4C(+) lesions were 0, 50%, 33.3%, 66.7%, 66.7% and 100%, respectively. Accordingly, new sub-classification could be as follows: 4A(-) could be re-classified as the 3rd class of lesions and avoided unnecessary puncture biopsy of 11 benign cases; 4C(+) re-classified as the 5th class of lesions, 4A(+) and 4B(-) re-classified as the 4B class of lesions, and 4B(+) and 4C(-) re-classified as the 4C class of lesions. Conclusions: DWI can be used to subdivide BI-RADS-MRI four classes of lesions and combining the MRI dynamic enhanced vessel imaging and the sub-classification improves the accuracy of BI-RADS classification.

Keywords: Breast MR imaging, contrast-enhanced MRI, diffusion-weighted imaging, breast biopsy

Introduction

Breast magnetic resonance imaging (MRI) is the most sensitive approach to detect mammary cancer; however, the diagnostic specificity is low, and the false positive rate is high, which further results in the over treatment of breast lesions and high puncture biopsy rate [1-4]. BI-RADS is the most widely used guide for describing and categorizing these abnormalities. The BI-RADS Category 4 is defined as a lesion that is suspicious for malignancy, with a malignancy possibility of 2-95% [5]. There are high overlaps between benign and malignant lesions, which are the most important cause of the high puncture biopsy rate. Reasonably sub-classification of the 4 classes of lesions in BI-RADS-MRI will be helpful for the choice of correct clinical diagnostic plan, reduction of the puncture biopsy rate. Many studies [5, 6] reported that BI-RADS Category 4 could be subdivided into 4A, 4B and 4C with mammography and sonography. Category 4A has low suspicion for malignancy (> 2% but ≤ 10% likelihood of malignancy). Category 4B is moderate suspicion for malignancy (> 10% but ≤ 50% likelihood of malignancy), and Category 4C is high suspicion for malignancy (> 50% but ≤ 95% likelihood of malignancy). No sub-categorization has been established for suspicious abnormalities found with MRI, because it is unclear whether particular imaging characteristics will provide enough information for the sub-classification. Diffusion weighted imaging (DWI) with the advantage of simplicity, is considered as a useful adjuvant method for the enhanced characterization of breast lesions. Studies [7-11] have reported the raising diagnostic specificity of breast disease based on DWI. However, effective stan-
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...are still missing, and how to sub-classify the 4 classes of lesions in BI-RADS-MRI still needs to be investigated.

Dynamic contrast-enhanced MRI (CE-MRI) 3D vascular subtraction could reflect the blood supply of tumors, clearly show the anatomic structure and spatial distribution of blood vessels in breast, and explain the vascular abnormality and microcirculation characteristics of lesion areas [12-14]. Thus, it has great significance in breast disease diagnosis. The purpose of this paper is to investigate whether Fischer’s scores combined with DWI are adequate for sub-dividing BI-RADS category 4 in accordance with the BI-RADS criteria. We also sought to further classify the 4A, 4B and 4C categories and to increase the classification accuracy of BI-RADS through combining the dynamic CE-MRI blood vessel imaging.

Materials and methods

Patients

A total of 150 patients with breast lesions who received breast MRI examination between June 2013 and March 2016 in the hospital were recruited. All the patients received puncture biopsy and the diagnosis of the breast lesions was further confirmed by operation and pathology. The exclusion criteria were as follows: without a DWI sequence and those in which movement and field inhomogeneity artifacts presented diagnostic difficulties to the reviewers; lesions considered foci or not consistently depicted by DWI; lesions without pathologic evaluation. Among them, 7 patients with insufficient fat saturation and rendering DWI images non-diagnostic were excluded from further evaluation. Finally, 143 patients were involved in the study. All patients were female with an average age of 46 years old, ranging from 28 to 82 years old. Among them, 73 patients had mammary cancer (77 lesions in total), and 70 were benign (73 lesions in total). Thus, there were a total of 150 lesions including 115 mass-like enhancement and 35 non-mass-like enhancement lesions. No patient had received any medical treatment before the MRI examination, and the operation and puncture biopsy were performed within 2 weeks after the MRI examination. Prior written and informed consent was obtained from every patient and the study was approved by the ethics review board of Taishan Medical University.

Magnetic resonance imaging (MRI)

All patients received breast MRI scan, multi-phase dynamic enhanced scan and DWI examination before operation. A 1.5 T HDx type superconducting MR imaging system (GE Healthcare, US) and 4-channel special surface coil (GE Healthcare, US) for mammary gland were used for the MRI scan.

The multi-phase dynamic enhanced scan was performed after the fat suppression T2WI and DWI examination. In the DWI examination, the single shot echo technique was used, with repetition time (TR) of 8400 ms, echo time (TE) of 93.8 ms, a parallel acquisition factor of 2, b value of 0.800 s/mm², a matrix of 128 mm × 128 mm and the number of excitation (NEX) of 2. Fat-suppression used T2WI: Fast spin echo (FSE) A sequence. In chemical frequency, fat saturation was selected, and TR was 4660 ms, TE was 89.2 ms, matrix was 320 mm × 256 mm, and NEX was 2. Axial scan was used for both the DWI sequence and T2WI sequence, and the position was identical, with a visual field of 320 mm × 320 mm, a layer thickness of 4 mm, an interval of 1 mm, and 32 layers to cover the whole breast. The VIBRANT sequence was used in dynamic enhanced scan, which is a three dimensional disturbed phase gradient echo sequence, with TR of 4.7 ms, a matrix of 320 mm × 320 mm, a layer thickness of 1.0 mm. The scan covered breast and axilla. The 12 periods of scan were performed with each period lasting 41 s. The first period of scan was pre-scan, and then 0.1 mmol/kg contrast medium gadopentetate meglumine was injected through the elbow vein group with a flow rate of 2 mL/s. The same sequence and parameter as the above dynamic enhanced scan were used for TIWI.

Post-imaging process and analysis

All captured images were transferred to an ADW4.3 workstation (Advantage Windows version 4.3, GE Healthcare, US) and processed. The Regions of Interests (ROIs) were placed in the most obvious area in the dynamic enhanced curve test. The test was performed in triplicate, and the worst curve was chosen as the dynamic enhanced time-signal intensity curve (TIC) of...
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lesions. The early intensity rate of the second period of enhanced scan was also calculated. The after-subtraction images of the second period of enhanced scan were 3D MIP reconstructed, and the number of the mammary vessels of two sides was counted. The vessel length ≥ 3 cm and the maximum diameter ≥ 2 mm were used as the selection criteria. If the difference between the counts of two sides of mammary vessels was no less than 2, the asymmetry of mammary blood supply was considered increased [10]. The condition of the blood vessels around the lesion was observed. If there were one or more blood vessels entering the lesion, the adjacent blood vessel sign was determined as positive [11]. The location of ROIs measured by the apparent diffusion coefficient (ADC) value was determined based on the image of the dynamic enhancement test. The ADC values of the lowest three ROIs were selected, and the average value was calculated. The morphological characteristics of lesions were determined based on the dynamic enhanced images. All the characteristics of lesions and data were captured after the consultation of two doctors with many years of breast MRI experience.

Sub-classification of BI-RADS-MRI 4

BI-RADS-MRI classification of breast diseases was performed based on the Fischer scoring criteria [15]. Score 0-1 was classified as the BI-RADS-MRI 1st class, score 2 as the 2nd class, score 3 as the 3rd class and score 4-5 as the 4th class. If the Fischer’s score is 4 and the ADC value is more than the optimal diagnostic threshold, the disease is classified into BI-RADS-MRI 4A class. If the Fischer’s score is 5 and the ADC value is not more than the optimal diagnostic threshold, the disease is classified into BI-RADS-MRI 4C class. If the Fischer’s score is 4 and the ADC value is not more than the optimal diagnostic threshold, or if the Fischer’s score is 5 and the ADC value is more than the optimal diagnostic threshold, the disease is classified into the BI-RADS-MRI 4B class (Table 1). If there is no increase of the asymmetry of blood supply and no adjacent blood vessel sign, the lesions of BI-RADS-MRI 4A, 4B and 4C classes are further defined as BI-RADS-MRI 4A(-), 4B(-) and 4C(-); otherwise, they are defined as BI-RADS-MRI 4A(+), 4B(+) and 4C(+).

Table 1. Criteria for the sub-classification of 4 classes of lesions in BI-RADS-MRI

<table>
<thead>
<tr>
<th>Fischer Score</th>
<th>4A</th>
<th>4B</th>
<th>4B</th>
<th>4C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC value (× 10^{-3} mm^2/s)</td>
<td>&gt; 1.1</td>
<td>≤ 1.1</td>
<td>&gt; 1.1</td>
<td>≤ 1.1</td>
</tr>
</tbody>
</table>

Figure 1. The ROC curve of the ADC values for the diagnosis of benign and malignant breast lesions.

Results

ROC curves of ADC

To determine the optimal diagnosis threshold of the ADC value, the ROC analysis was performed. Based on the analysis of the ROC
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Table 2. The positive predicted value of each sub-class of the BI-RADS-MRI 4 classes

<table>
<thead>
<tr>
<th>Sub-classification</th>
<th>Benign</th>
<th>Malignant</th>
<th>Positive predicted value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4A</td>
<td>12</td>
<td>1</td>
<td>7.7%</td>
</tr>
<tr>
<td>4B</td>
<td>10</td>
<td>11</td>
<td>52.4% (29.8%-74.3%)</td>
</tr>
<tr>
<td>4C</td>
<td>3</td>
<td>25</td>
<td>89.3% (71.3%-97.8%)</td>
</tr>
<tr>
<td>4A(-)</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4A(+)</td>
<td>1</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>4B(-)</td>
<td>6</td>
<td>3</td>
<td>33.3% (7.5%-70.1%)</td>
</tr>
<tr>
<td>4B(+)</td>
<td>4</td>
<td>8</td>
<td>66.7% (34.9%-90.1%)</td>
</tr>
<tr>
<td>4C(-)</td>
<td>3</td>
<td>6</td>
<td>66.7% (29.9%-92.5%)</td>
</tr>
<tr>
<td>4C(+)</td>
<td>0</td>
<td>19</td>
<td>100%</td>
</tr>
</tbody>
</table>

Note: Because the case numbers of 4A, 4A(-), 4A(+) and 4C(+) classes were small, the 95% confident interval of their positive predicted value were unable to calculate.

To determine whether the combination of dynamic CE-MRI blood vessel imaging and DWI is adequate for the sub-categorization of BI-RADS category 4, the positive predicted values of each sub-classification was performed. The 150 cases of lesions, 62 cases belonged to the BI-RADS-MRI 4 class, in which 13 cases were 4A class (12 cases were benign and 1 case was malignant), 21 cases were 4B class (10 cases were benign and 11 cases were malignant), and 28 cases were 4C class (3 cases were benign and 25 cases were malignant). The positive predicted values of the 4A, 4B and 4C classes were 7.7%, 52.4% and 89.3%, respectively (Table 2). After a further sub-classification, it was determined that 11 cases belonged to the 4A(-) class, and all cases were benign; 2 cases belonged to the 4A(+) class, in which one was benign and the other was malignant; 9 cases belonged to the 4B(-) class, in which 6 cases were benign and 3 cases were malignant; 12 cases belonged to the 4B(+) class, in which 4 cases were benign and 8 cases were malignant; 9 cases belonged to the 4C(-) class, in which 3 cases were benign and 6 cases were malignant; 19 cases belonged to the 4C(+) class, and all cases were malignant. The positive predicted values of the 4A(-), 4A(+), 4B(-), 4B(+), 4C(-) and 4C(+) classes were 0, 50%, 33.3%, 66.7%, 66.7% and 100%, respectively (Table 2). Accordingly, the 4A(-) class could be considered as the 3rd class of lesions, so the 11 benign cases would not receive the puncture biopsy (Figure 2). The 4A(+), 4B(+) and 4C(-) classes of lesions could be recognized as the 4B class of lesions (Figure 3), and the 4B(+), 4C(-) classes of lesions could be recognized as the 4C class of lesions (Figure 4). The 4C(+) class could be considered as the 5th class of lesions (Figure 5). This indicates that sub-classification of BI-RADS-MRI 4 with the MRI dynamic enhanced vessel imaging and DWI is reasonable, which will be helpful for the choice of proper clinical treatment plan.

Discussion

Breast MRI is highly sensitive in showing lesions, and has great advantages in discovering multiple malignant lesions of one or two breasts. However, the high sensitivity may lead to the over-treatment of lesions [1-4]. MR-guided biopsy is considered as a fast, safe and accurate method. However, CE-MRI of the breast may lead to false-positive results up to 74.1% [1, 16, 17]. This fact increases the demand for improved differentiation between benign and malignant lesions to reduce unnecessary biopsies, and to raise the overall accuracy of breast CE-MRI. Recently, many researches have shown that combination of DWI and CE-MRI could decrease the false positive rate of breast MRI diagnosis and increase the diagnostic accuracy [1, 18-20]. However, how to effectively combine the two methods still lacks standards to be followed.

The malignant probability of the BI-RADS 4 classes of lesions of breast diseases falls between 2% and 95% [5], so there will be unavoidable unnecessary puncture biopsies on many benign cases if it is operated on all the 4 classes of lesions. Besides, the negative result of puncture biopsy always baffles clinical doctors to determine further treatment plan.
Figure 2. The sub-classification of the breast cancer of a 43 years old female, whose pathological result was fibroadenoma in the right breast. A: Dynamic contrast enhanced (DCE) MRI showed irregular nodules in the right breast, and the edge was clear with homogeneous enhancement. B: The TIC curve showed the shape of flatbed, and the early enhancement rate was 198%. C and D: The Fischer score was assigned as 4 and the ADC value was $1.60 \times 10^{-3}$ mm$^2$/s, and the lesion was classified into the BI-RADS-MRI 4A class. E: No increased asymmetric blood supply and adjacent blood vessel sign was observed, and the lesion was classified into the BI-RADS-MRI 4A(-) class and treated as the BI-RADS 3rd class lesion.
that missed diagnosis of breast cancer cannot be avoided. In mammography and sonography, there are already standards for the sub-classification of BI-RADS 4, including 4A, 4B and 4C. The malignant probability of the 4A class of lesions falls between 2% and 10% [5, 6]. If the biopsy of the 4A class of lesions is benign, routine follow-up or six months follow-up can be prescribed. The malignant probability of the 4B class of lesions falls between 10% and 50% [5, 6]. If the result of puncture biopsy of the 4B lesions is exclusively typical benign, observation is sufficient. However, if the result is papillary tumor or atypical hyperplasia, then further biopsy is necessary. The malignant probability of the 4C class of lesions falls between 50% and 95% [5, 6, 21]. For the cases that the result of puncture biopsy is benign, consultation with the pathology department and further analysis are needed [21, 22]. However, no standards exist for the sub-classification of BI-RADS 4 categories of lesions in breast MRI. To our knowledge, this work is the first sub-classification for BI-RADS-MRI 4 categories based on DWI.

Assigning the Fisher score as 4, if the ADC value supports benign lesions, the lesions are defined as the 4A class lesions. A lower Fischer score and higher ADC value indicate a very high
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In this study, there were 13 BI-RADS-MRI 4A lesions, in which 12 were benign and only one was malignant, and the positive predicted value was 7.7%. Assigning the Fischer score as 5, if the ADC value supports malignant, the lesions are defined as the 4C class lesions. A higher Fischer score and lower ADC value indicate a very high probability of malignant lesions. In this study, there were 28 BI-RADS-MRI 4C class lesions, in which 25 were malignant and 3 were benign, and the positive predicted value was 89.3%. The other 4 categories of lesions were defined as 4B class. In this study, there were 21 BI-RADS-MRI 4B class lesions, in which 11 were malignant and 10 were benign, and the positive predicted value was 52.4%. This result was a little higher than previous reports [5, 6, 21], which might be caused by the high sensitive nature of breast MRI, but it has no influence on the guidance of clinical treatment choice. Basically, the sub-classification method proposed in this paper is in accordance with the reported BI-RADS 4 sub-classification standards [5, 21, 22]. At the same time, this method is simple and practical, easy to operate, and convenient for widespread clinical application.

In this study, there were 62 lesions belonging to the BI-RADS-MRI 4 classes, in which 25 cases were benign. Puncture biopsy or surgery was operated on all the cases. If the benign lesions in the BI-RADS-MRI 4 classes can be detected by MRI, the unnecessary puncture biopsy rate would be dramatically reduced. Combined with MRI dynamic blood vessel imaging, the BI-RADS-MRI 4A, 4B and 4C class lesions were further sub-classified. If there is no asymmetry incensement or adjacent blood vessel sign, the lesions are classified into negative classes indicated as BI-RADS-MRI 4A(-), 4B(-) and 4C(-); otherwise, they were classified as positive classes indicated as BI-RADS-MRI 4A(+), 4B(+) and 4C(+). In this study, the 4A(-) lesions were...
all benign. If all these lesions were classified into the 3rd class, 44% (11/25) of the benign lesions could avoid unnecessary puncture biopsy.

Several studies indicated that the false negative rate of breast MRI guided puncture biopsy was 0%-17% [20, 23-28]. Therefore, in clinical analysis, the result of puncture biopsy should be combined with the test of iconography in order to avoid missed diagnosis, and BI-RADS-MRI classification with higher accuracy is demanded. In this study, the 27 4C(+) lesions were all malignant, and could be classified as the 5th class. For the 4C(+) class, surgery or biopsy can be performed. If the result of the puncture biopsy is benign, excision biopsy should be positively performed to avoid missed diagnosis of breast cancer. For there were only two cases of 4A(+) lesions, they were categorized into 4B(-) class and analyzed. If the positive predicted value is 33.3%, the lesions can be treated as BI-RADS 4B class. If the positive predicted value of the 4B(+) and 4C(-) lesions is 66.7%, the lesions can be treated as BI-RADS 4C class.

The sub-classification of breast cancer by the combination of DWI and CE-MRI has great significance for the clinical diagnosis. However, there are some shortcomings of this study. First, the sample number in this study was relatively small, so bias might exist in the selection of cases. Second, the 3 benign 4C lesions were all non-mass enhancement lesions, and the one malignant 4A class lesion was also a non-mass enhancement lesion. This suggests that more misdiagnosis can be caused by non-mass enhancement lesions. Thus, it is necessary to analyze and classify the mass enhancement and non-mass enhancement lesions. Third, because the malignant possibility of the 5th class lesions is high and all the 5th class lesions in this study were malignant, the application of DWI in the 5th class lesions was not discussed.

To sum up, reasonable sub-classification of BI-RADS-MRI 4 classes of lesions can be performed with the help of DWI. Combining the dynamic blood vessel imaging and the results of sub-classification, the rate of unnecessary puncture biopsy can be dramatically decreased, and the misdiagnosis of breast cancer can be effectively avoided to help design appropriate clinical treatment plan.

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Disclosure of conflict of interest

None.

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References

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