JBUON 2019; 24(1): 33-39
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

The diagnostic value of MRI multi-parameter combination for breast lesions with ring enhancement

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Summary

Purpose: *To investigate the diagnostic value of MRI multi-parameter combination for breast lesions with ring enhancement (internal enhancement pattern) on dynamic contrast-enhanced (DCE)-MRI.*

Methods: *149 patients with histologically confirmed breast lesions underwent DCE-MRI and diffusion-weighted imaging (DWI) examinations were analyzed. Sixty-seven lesions were found and were allocated into the benign group and the malignant group. The pathological results were used as dependent variables, indexes with statistical differences were used as independent variables, and logistic regression model was performed to construct the newly combined parameters and to evaluate the diagnostic efficacy of the stepwise combined parameters.*

Results: *There were significant differences in the number of cases with different wall shapes concerning"enhanced ring" and the number of cases with wall nodules between the benign and the malignant group. Significant differences were found in the number of cases with different distribution locations of limited diffusion on DWI between the benign and the malignant group. There were significant differences in the semi-quantitative parameters including early enhancement ratio (EER) and maximum enhancement time (Tmax) between the benign group and the malignant group. There were significant differences in apparent diffusion coefficient* $(ADC)_{ring\ inner}$ *and* $ADC_{ring\ wall}$ *between the benign and the malignant group. The maximum Youden index of a newly-constructed parameter combination: morphological indexes of "enhanced ring" + distribution locations of limited diffusion on DWI + Tmax +* $ADC_{ring\ inner}$ *was 0.732 for combined diagnosis, the area under the ROC curve (Az) was 0.887, and the diagnostic sensitivity and specificity were 85.78 and 87.37%, respectively.*

Conclusions: *MRI multi-parameter combination can improve the diagnostic efficacy of breast lesions with ring enhancement.*

Key words: *ADC, breast lesions, diagnosis,DWI, MRI*

Introduction

Currently, it is been considered that ring enhancement (internal enhancement pattern) [1-3] of breast lesions on dynamic contrast-enhanced MRI (DCE-MRI) indicates with high accuracy malignant lesions, and the ring enhancement is associated with pathological grading. Kuhl et al. [4] pointed out that nearly two-thirds of the malignant lesions showed ring enhancement and clinical work found that some benign lesions also showed ring enhancement on DCE-MRI, resulting in a high rate of misdiagnosis concerning lesions with ring enhancement due to lack of experience in the differential diagnosis of benign and malignant lesions. DCE-MRI has been routinely used in the diagnosis of breast lesions, and can show the morphological and hemodynamic characteristics of the lesions.

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Received: 30/06/2018; Accepted: 27/07/2018

Diffusion-weighted imaging (DWI) reflected the diffusion function of water molecules in tissue cells and can quantify the diffusion-limited degree of water molecules in tissues by apparent diffusion coefficient (ADC) values. The above methods had their own limitations in terms of lesion morphology and MRI semi-quantitative or quantitative parameters. In this study, the optimal combination of MRI sequences resulted to the acquisition of multi-parameter information to evaluate the diagnostic value of MRI multi-parameter combination for breast lesions with ring enhancement.

Methods

Patient data

From January 2012 to October 2015, patients with clinical and imaging data meeting the following criteria were enrolled in this study. Inclusion criteria: (1) patients with breast lesions with ring enhancement (internal enhancement pattern) on DCE-MRI and complete MRI scanning sequences, including conventional MRI, dynamic contrast-enhanced T1-weighted imaging (DCE-T1WI) and DWI; (2) patients without any treatment before MRI; (3) patients with complete surgical or pathological puncture results. Finally, 67 patients were included in the study, their median age being 41.1 years (range 27-69). There were 49 malignant lesions (38 infiltrating ductal carcinoma, 7 infiltrating lobular carcinoma, 3 intraductal carcinoma and 1 mucinous adenocarcinoma) and 18 benign lesions (9 plasma cell mastitis, 7 obvious ductal ectasia associated with local chronic inflammation, 4 internal abscess formation, 4 intraductal papilloma, 3 idiopathic granulomatous mastitis and 2 cyst combined with infection).

MRI protocol

Patients were examined using a 3.0 T Trio TIM MRI superconducting scanner (Siemens, Germany) and a dedicated 16-channel phased-array breast coil. Initially, patients were examined in prone position with the head entered at first, with bilateral breasts naturally hanging inside double holes of the coil. Scanning sequences and parameters were: (1) cross-section turbo inversion recovery magnitude (TIRM) sequences: repetition time (TR)/echo time (TE), 4,000 ms/70 ms; thickness, 4 mm; field of view (FOV), 340 mm×340 mm; excitation frequency, twice; (2) cross-section single-shot echo-planar imaging-DWI (EPI-DWI) sequences: TR/TE, 8200 ms/80 ms; thickness, 4 mm; FOV, 360 mm×140 mm; excitation frequency, 3 times; diffusion sensitivity coefficient (b-value), 0~850 s/mm^2; (3) cross-section three-dimensional fast spoiled gradient echo (3D-FSPGR) sequences for breast DCE-MRI:TR/TE, 4.5 ms/1.6 ms; thickness, 1 mm; FOV, 340 mm×340 mm; angle of twist, 10 degrees; excitation frequency, once; the first-phase scanning was performed before contrast injection, followed by bolus injection of contrast agent (GD-DTPA, 15 mL) with the high pressure syringe at a speed of 2.0 mL/s; (4) after injection, the syringe was washed with normal saline (equal in volume and speed); and (5) phase consecutive scanning was performed 20 s after contrast agent injection.

Table 1. Multi-parameter comparison of breast lesions with ring enhancement

	Group		x^2	*p*
	benign N=18	*malignant N=49*		
Shape			0.228	0.633
Round/orbicular-ovate	10	24		
Irregular	8	25		
Margin			0.071	0.79
Distinct	8	20		
Indistinct	10	29		
Wall shapes of “enhanced ring”			14.186	0.001
Thin-walled ring	13	11		
Thick-walled irregular ring	5	38		
Wall nodules			12.483	0.001
No	15	17		
Yes	3	32		
TIC curve typesDistribution location of limited diffusion on DWI			0.08819.595	0.9570.003
Gradually rising	5	13		
Platform	6	15		
Outflow	7	21		
Whole part	4	15		
Periphery	3	26		
Center	11	5		

Image analysis

All data was transferred to Siemens Syngo workstation for image post-processing. A region of interest (ROI) (area ≥20 mm^2) regarding solid lesion area was outlined by the Mean-Curve software, avoiding cystic/necrotic areas and vascular areas, to generate time-signal intensity curve (TIC) on DCE-MRI; 3D reconstruction was performed concerning the second-phase DCE-MRI and mask subtraction images with MIP software to display the maximum reconstructed image of lesions; ADC values at the inner part, the wall and the periphery (less than 1 cm) of the "enhanced ring" of the lesions were measured. The average ADC value was obtained from 3 times of measurement.

After scanning, the images were analyzed by two experienced radiologists in the radiology department (more than 5 years in breast imaging diagnosis). The following data of the lesions was measured, analyzed and recorded according to the newly revised content regarding Breast Imagine-Report and Date System Magnetic Resonance Imaging (BI-RADS-MRI) established by American College of Radiology (ACR) in 2013: 1. Overall morphological indexes of lesions on DCE-MRI: (1) Shape: A: round/orbicular-ovate; B. irregular shape; (2) Margin: A: clear boundary; B: unclear boundary (irregular). 2. Morphological indexes of lesions with "ring enhancement" on DCE-MRI: (1) Ring wall shape: A: thin-walled ring; B: thick-walled irregular ring; (2) Wall nodular: A :yes; B: no; 3. Dynamics indexes of lesions on DCE-MRI: (1) TIC: A: gradually rising type [signal intensity (SI) increased by>10%]; B: platform type (SI increased by 10-10%; C: outflow type (SI decreased by>10%); (2) semi-quantitative parameters: early enhancement ratio (EER) = $(SI_{post} - SI_{pre})/SI_{pre} \times 100\%$, and the SI_{pre} was the SI of the lesion pre-enhancement; B: maximum enhancement time (Tmax): the time corresponding to the signal peak of the TIC. 4. Distribution locations of limited diffusion of lesions on DWI: (1) central; (2) peripheral; and (3) overall. 5. Multi-point ADC value measurement of "enhanced ring": (1) inner; (2) wall; and (3) periphery.

Statistics

Statistical analyses were performed using SPSS 17 software package (IBM, Armonk, NY, USA). According to the pathological results, the lesions (n=67) were allocated into a benign and a malignant group, and the differences in the indexes of overall morphology on DCE-MRI, "enhanced ring" morphology, TIC types and distribution locations of limited diffusion on DWI between the benign and the malignant group were compared using x^2 test. Independent sample *t*-test was used to compare the differences in semi-quantitative parameters on DCE-MRI and multi-point ADC values of the "enhanced ring" between the benign and the malignant group. The pathological results were used as dependent variables, indexes with statistical differences were used as inde-

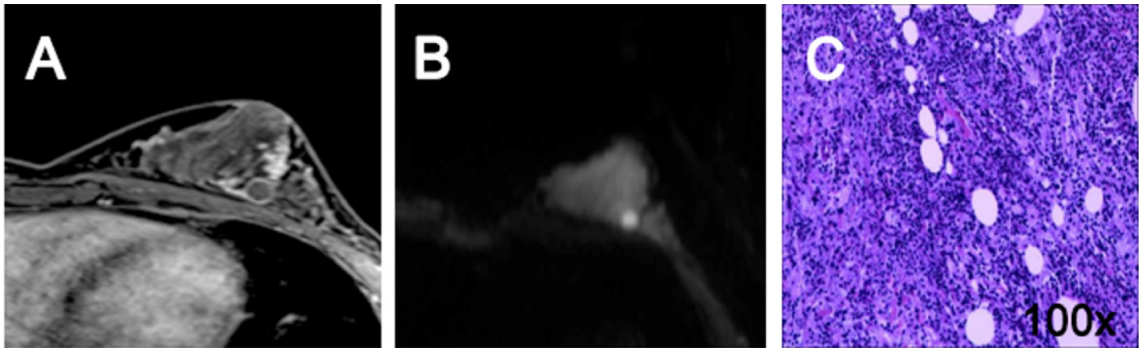

Figure 1. Female, 44 years old, plasma cell mastitis. **(A):** The "enhanced ring" on DCE-MRI showed thin ring wall and relatively uniform wall thickness. **(B):** The limited diffusion on DWI was mainly located in the center of the lesion. **(C):** The pathological result was plasma cell mastitis combined with duct ectasia and chronic abscess (Magnification: 100×).

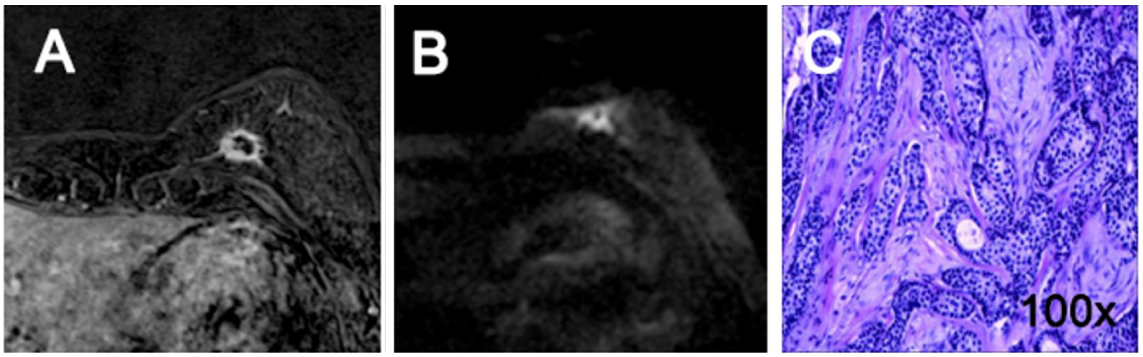

Figure 2. Female, 44 years old, infiltrating ductal carcinoma class III. **(A):** The "enhanced ring" on DCE-MRI showed thick-walled irregular ring and wall nodules. **(B):** The limited diffusion on DWI was mainly located at the margin of the lesion. **(C):** The pathological result was infiltrating ductal carcinoma class III (Magnification: 100×).

Table 2. Semi-quantitative parameters and multi-point ADC values of breast lesions with ring enhancement

	Group		*t*	*p*
	benign N=18	*malignant N=49*		
Semi-quantitative parameters				
EER	84.2±55.1	113.3±53.9	2.353	0.022
Emax	115.7±32.3	135.7±31.7	0.926	0.358
Tmax	128.5±69.4	86.5±20.6	4.655	0.007
ADC values				
Inner	1.086±0.319	1.891±0.365	1.352	0.001
Wall	1.195±0.279	0.941±0.465	2.882	0.005
Periphery	1.376±0.327	1.075±0.234	1.045	0.3

Table 3. Diagnostic efficacy of stepwise combined parameters

Combined parameters	*Sensitivity %*	*Specificity %*	*Youden index*	*Az*
Morphology + DWI	90.47	86.80	0.773	0.951
Morphology + EER + Tmax	92.86	89.47	0.823	0.964
Morphology + Tmax	90.47	89.47	0.799	0.961
Morphology + ADC	88.09	78.95	0.67	0.898
Morphology + DWI+EER	83.33	86.84	0.701	0.926
Morphology + DWI + Tmax	88.09	86.84	0.749	0.939
Morphology + DWI + ADC	92.86	89.47	0.823	0.964
Morphology + DWI + EER + ADC	92.86	92.11	0.849	0.963
Morphology + DWI + EER + Tmax + ADC	92.86	89.47	0.823	0.964

Table 4. Diagnostic efficacy of newly combined parameters

Statistical indexes	*Diagnostic indexes*
Az	0.887
p value	<0.0001
95%CI	0.834~0.927
Best cut-off score	1.81
Sensitivity	87.37%
Specificity	85.78%
Youden index	0.73

pendent variables, and the logistic regression model was performed to construct the newly combined parameters and to evaluate the diagnostic efficacy of the stepwise combined parameter. P value <0.05 indicated statistical significance.

Results

Measurement results of the MRI parameters of the benign and malignant breast lesions with ring enhancement

There were significant differences in the ring wall shape, wall nodule and distribution location of limited diffusion on DWI of the "enhanced ring" between the benign group and the malignant group (Table 1). The thin-walled ring was frequently observed in the benign group (13/18), the "enhanced ring" on DCE-MRI showed thin ring wall and relatively uniform wall thickness (Figure 1A-1C), and 3 cases (3/18) presented wall nodules. Thick-walled irregular ring was frequently observed in the malignant group (38/49), and the "enhanced ring" showed uneven thickness regarding the ring wall and rough margins (Figure 2A-2C), and 32 cases (32/49) had visible wall nodules. The limited diffusion on DWI was mainly located in the center of the lesion in the benign group (11/18) and at the margin of the lesion in the malignant group (29/49). There were no significant differences in the overall shape and margin of the lesion on DCE-MRI or the TIC types between the benign group and the malignant group (all p>0.05). However, there were significant differences in EER, Tmax, $ADC_{ring\ inner}$ and $ADC_{ring\ wall}$ between the benign group and the malignant group (all p<0.05) (Table 2), except $ADC_{ring\ periphery}$.

Diagnostic efficacy of optimized combinations of MRI parameters

Stepwise combination of the indexes with statistical differences was performed (Table 3). The maximum Youden index, a newly-constructed parameter combination of morphological indexes of "enhanced ring" + distribution locations of limited

diffusion on DWI + Tmax + $ADC_{ring\ inner}$ were 0.732 for the combined diagnosis of breast lesions with ring enhancement. The area under the ROC curve (Az) was 0.887 (95%CI: 0.834-0.927). The diagnostic sensitivity and specificity were 87.37% and 85.78%, respectively (Table 4).

Discussion

Comparative analysis of MRI parameters in benign and malignant breast lesions with ring enhancement

In some studies [1-4], it was considered that breast lesions with ring enhancement on DCE-MRI (internal enhancement pattern) highly indicated malignancy, and the ring enhancement was related to pathological grading. Stomper and some other authors [5-7] suggested that the pathological basis of ring enhancement in malignant breast lesions included hypoperfusion in the tumor center, differences in fibrosis degree between the center and the margin of the lesion, high expression of vascular endothelial growth factor (VEGF) in tumor margin, significantly increased microvessel density (MVD), etc. In clinical practice, partial breast benign lesions also show ring enhancement, and the differential diagnosis between malignant and benign lesions is difficult. The morphologic features of benign and malignant breast lesions on DCE-MRI were of great value in the differential diagnosis. Wedegartner et al. [8] and Schnall et al. [9] reported that the irregular shape of the lesion and unclear boundary of the margin and the surrounding tissue structure were reliable signs for the diagnosis of malignant breast lesions. Results of this study revealed that there was no significant difference in overall morphological characteristics between benign and malignant lesions with ring enhancement. However, overall morphological characteristics of the benign lesions showed malignant signs, characterized by higher proportions of irregular shape and unclear margin, and the possible reason may be that the benign lesions manifested as ring enhancement had relatively high proportion of inflammatory lesions, a large number of inflammatory cell infiltration in the surrounding tissues, as well as adjacent tissue edema, occurring during the inflammatory reaction, resulting in irregular shape and unclear boundaries with surrounding tissues. In addition, there were significant differences in the morphological features of the "enhanced ring" between benign and malignant lesions, thin-walled ring without wall nodules was frequently observed in benign lesions, and thick-walled irregular ring was frequently observed in malignant lesions with the majority accompanied with wall nodules. There were significant differences in the shape of the ring wall and the wall nodules between benign and malignant lesions, which may be explained as follows: the pathological basis of "enhanced ring" in the benign lesions mainly included abscess wall, inflammatory cyst wall, duct wall ectasia associated with inflammatory cell infiltration, mostly characterized by the enhancement of the ring wall, showing thin-walled ring uniform in thickness; the main pathological basis of "enhanced ring" in the malignant lesions was tumor cell with different proliferation and growth speed, so that the malignant lesions were mainly characterized by "enhanced ring" with rugged inner side of the ring wall, irregular outer side, uneven thickness and partially visible wall nodules on DCE-MRI.

Some studies [10,11] have suggested that DWI can reflect functional changes of water molecules of different tissue components under the pathological states through detecting microscopic motion of the water molecules, malignant tumor cells generally manifested as limited diffusion on DWI due to higher proliferation speed, greater nucleus-to-cytoplasm ratio and less extracellular space. The benign lesions in our study, except 2 cases of intraductal papilloma with no obvious limited diffusion, showed limited diffusion different in degrees. Previous studies [12-14] also proved that limited diffusion in mastitis lesions on DWI might result from the dual roles of increased macromolecular protein contents and inflammatory cell infiltration. Our further analysis on the locations of limited diffusion in the benign and malignant lesions on DWI showed that the benign group mainly manifested as limited diffusion at the lesion center, and in the malignant group at the lesion periphery, the results were statistically different. The reason why limited diffusion was mainly located in the center of the benign lesions may be that the central part of the benign lesions had abscess pus, ductal ectasia or inflammatory cells and viscous secretions accumulated in inflammatory cyst. Moreover, the possible explanation for marginal limited diffusion in the malignant lesions may be that necrosis and liquefaction of tumor tissues frequently occurred in the central part of the malignant lesions, while tumor cell proliferation was active in lesion margins with greater cell density, thus limiting the water molecule activity, resulting in limited diffusion at the margins of the malignant lesions. Quantitative results were obtained by measuring multi-point ADC values, and showed significant difference in the $ADC_{inner\ ring}$ value between the benign and malignant lesions.

DCE-MRI [15-17] can be applied in the differential diagnosis of benign and malignant breast tumors by evaluating tumor angiogenesis through

TIC, EER, Tmax and other parameters. Previous studies [18,19] demonstrated that the number of blood vessels and vascular permeability were increased in malignant tumors, and the malignant breast lesions mostly presented type II and type III TIC. However, the results of the present study showed that there were 13 cases of benign lesions (n=18) with type II-III TIC. The possible causes for this contrast may be that the benign lesions in our study, such as plasma cell mastitis, non-specific granulomatous mastitis and abscess formation, had local granulation tissue hyperplasia, increased blood supply, and increased capillary permeability, thus resulting in higher proportions of type II-III TIC. Additionally, the subjectivity of radiologists in the interpretation of TIC may also contribute to this discrepancy. The results of this study revealed that there were significant differences in the semi-quantitative parameters including EER and Tmax between the benign and malignant lesions. EER and Tmax mainly reflected the situation regarding seepage velocity, MVD and vasopermeability of the lesion area after injection of the contrast agent [20]. Although granulation tissue hyperplasia in the benign group produced a large number of new vessels with increased vascular permeability and accelerated perfusion speed, thus manifesting as type II-III TIC, the semi-quantitative parameters including EER and Tmax can show the differences between the benign and malignant lesions, when compared with abnormal proliferation of tumor vessels and the presence of large numbers of arteriovenous fistulae in the malignant group.

Diagnostic efficacy of multi-parameter optimized combination

Multiple-sequence obtained parameters on breast MRI showed diversity, since differential diagnosis of benign and malignant breast lesions with ring enhancement was difficult, but reasonable use and integration of multi-parameters of the lesions were necessary to make a diagnosis in order to avoid the limitation of single index. Logistic regression analysis [21] is obtained by the maximum likelihood method, the maximal specificity can be obtained under a certain sensitivity, the maximum sensitivity can be obtained under a certain specificity, so as to obtain the maximum area under the ROC curve (AUC). A meta-analysis based on the morphology and dynamics of breast tumors has been reported by Peters et al. [22], suggesting that the sensitivity and specificity of DCE-MRI in the diagnosis of breast lesions were 90% and 72%, respectively. In addition, a meta-analysis conducted by Medeiros et al. [23] indicated that the diagnostic sensitivity and specificity of DCE-MRI to distinguish benign and malignant breast lesions were 88-92% and 70-79%, respectively. There were crossing and overlapping in the morphology and dynamics of benign and malignant breast lesions with ring enhancement, and misdiagnosis occurred frequently. Results of the study showed that the maximum Youden index of a newly-constructed parameter combination: morphological indexes of "enhanced ring" + distribution locations of limited diffusion on DWI + Tmax + $ADC_{ring\ inner}$ was 0.732, the diagnostic sensitivity and specificity were 85.78% and 87.37%, respectively, showing a relatively high diagnostic efficiency.

Limitations

Some limitations in the present study should be underlined. First, our results were limited by a relatively small sample size concerning the enrolled lesions with ring enhancement, and the diagnostic value of MRI multi-parameters in breast lesions with ring enhancement needed to be further evaluated with large sample size. Second, the volume transfer constant (K_{trans}), rate constant (k_{ep}), extravascular extracellular volume fraction (V_e) and other quantitative parameters can be introduced as important directions for future studies.

Conclusions

In conclusion, MRI multi-parameter combination can improve the diagnostic efficacy for breast lesions with ring enhancement.

Conflict of interests

The authors declare no conflict of interests.

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