Association between dynamic contrast enhanced MRI imaging features and WHO histopathological grade in patients with invasive ductal breast cancer

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Abstract. The present study aimed to investigate the dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and World Health Organization (WHO) histopathological grade in patients with invasive ductal breast cancer. A retrospective analysis on the results of DCE-MRI of 92 patients, who were diagnosed with invasive ductal breast cancer following surgery or biopsy, and these results were correlated with WHO histopathological grade. The statistical analysis demonstrated that the tumor size, shape and characteristics of early enhancement were associated with the WHO histopathological grade: The larger the lesion's long diameter, the higher the WHO histopathological grade; the WHO histopathological grades of round and oval masses were relatively lower, while those of lobulated and irregular masses were higher; and tumors with heterogeneous and ring-like enhancement exhibited higher WHO histopathological grades, while those of homogeneous enhancement were lower. The lesion's margin shape was not associated with the WHO histopathological grade. The present study demonstrates that features of DCE-MRI and WHO histopathological grade in patients with invasive ductal breast cancer are correlated, and these MRI features could be used to evaluate the biological behavior and prognosis of lesions.

Introduction

Breast cancer is the most common cancer detected in Chinese women in the past 20 years; the incidence rate is rising, and therefore the early detection, diagnosis and treatment are important for the survival and life quality of these patients (1-6). When assessing the tumorigenic process of breast cancer, the World Health Organization (WHO) histopathological grade is an important indicator that can be used to evaluate the malignant behavior and prognosis of breast cancer. However, histopathological grade can often only be obtained following surgery, thus limiting its roles in selecting the treatment options for breast cancer (7-10). Magnetic resonance imaging (MRI) allows high soft tissue contrast, multi-directions, multi-parameters and multi-functional imaging, thus it may be used to estimate the lesion size, number, boundary and internal structure more accurately than mammography and ultrasound. Dynamic contrast enhanced MRI (DCE-MRI) is particularly sensitive in revealing the morphological and hemodynamic features of tumors, thus it has increasingly demonstrated its superiority in the diagnosis of breast diseases (11-19). The present study retrospectively analyzed the clinical data from DCE-MRI of 92 patients, who were diagnosed with invasive breast cancer using surgical resection or biopsy, with respect to the WHO histopathological grade. The present study ultimately aimed to realize a mechanism of the *in vivo* evaluation of biological behavior and prognosis of breast cancer, thus facilitating the development of treatment programs.

Materials and methods

Subjects. A total of 142 patients, who were diagnosed using unilateral breast cancer by surgery or biopsy and who recieved DCE-MRI in West China Hospital, Sichuan University, (Sichuan, China) from June 2012 to December 2013, were collected, among which were 127 cases of invasive ductal cancer, 92 cases of tumor-like enhancement lesion, all females, aged 21 to 72 years old, with a mean age of 47.15 years old. The patients did not receive any clinical intervention prior to DCE-MRI examination, including neoadjuvant chemotherapy, hormonal therapy or acupuncture. The study was conducted in accordance with the Declaration of Helsinki (20). This study was conducted with approval from the Ethics Committee of Sichuan University. Written informed consent was obtained from all participants.

MRI examination technique and parameters. The Philips 3.0T MRI (Achieva, Phillips Medical Systems, Netherlands) scanner was used, which was equipped with a breast surface-dedicated phased array coil. The patient was placed in the prone position against the dedicated phased array coil, the breasts naturally hung in the cavity of coil, and remained still during the scanning. The scanning sequence was as follows:

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i) Fat-suppression T2WI sequence of fast inversion recovery fat suppression sequence (SPAIR): TR 1900 ms, TE 120 ms, TI 150 ms; ii) T1WI sequence of fast spin-echo imaging (TSE): TR 111 ms, TE 9 ms, slice thickness 8 mm, with 20 layers; iii) dynamic contrast enhanced scanning, used the fat suppression T1WI sequence of fast spoiled gradient echo 3D imaging sequence (FLASH-3D): TR 4.2 ms, TE 2.1 ms, flip angle (FA) 100˚, slice thickness 1.25 mm, 140 layers, field of vision (FOV) 320x320 mm, matrix 336x336 pixels, each scanning time 50.4 sec, and repeated 10 times; the high-pressure syringe was used to inject Gd-DTPA 0.1 mmol/kg through the hand-dorsal vein, with the flow rate as 2.5 ml/s; iv) post-DCE high-resolution scanning, following DCE, the bilateral breasts were examined with cross-sectional scanning using high-resolution enhanced fat suppression T1WI sequences, TR 4.6 ms, TE 1.73 ms, slice thickness 0.8 mm, FA 100, and the scanning time was 340 sec.

Image evaluation. The images were interpreted by two radiologists who were blind to the results of surgical pathology. The MRI features were described according to the American College of Radiology, Breast Image-Reporting and Data System (ACR BI-RADS) (1). The number, location, size (expressed as long diameter), shape, border and signal of the lesions were recorded,in addition to the enhancement characteristics of early lesions in DCE. Disagreement in features between the pathologists were discussed in order to reach a consensus. MRI features included: i) Tumor size. The delay-phase image was set as the standard, the single lesion was expressed by its maximal diameter, and the multiple lesions were expressed by the maximal diameter of the largest lesion. Primary tumors (T) were divided by their sizes according to the TNM staging of Union for International Cancer Control (UICC) (21): ≤2 cm, 2~5 cm, ≥5 cm (4). ii) Gross shape: Round, oval, lobulated and irregular. iii) Margin: Smooth, irregular and spiculated. iv) Characteristics of internal enhancement: Homogeneous enhancement, heterogeneous enhancement and ring-like enhancement. v) Other signs: Accompanied with or without skin thickening, nipple retraction, lymph node metastasis and clear retromamary space.

WHO histopathological grade. All specimens were examined histologically with hematoxylin-eosin (HE) staining, then evaluated for tumor ductal shape, nuclear atypia and nuclear splitting number according to the WHO histopathological grading method of invasive breast cancer (9), which is divided into 3 grades: Grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated.

Statistical analysis. SPSS statistical software, version 19.0 (IBM SPSS, Armonk, NJ, USA) was used to perform statistical analysis. The statistical method used was the χ^2 test, with the significance level set as α=0.05.

Results

Characteristics of lesion distribution. Among the 92 patients, the lesion presented in the right breast of 42 patients (45.65%), and 50 cases presented in the left breast (53.35%), and 9 cases exhibited multiple lesions (9.78%), while 83 cases exhibited a single lesion (90.22%).

DCE-MRI signs of lesions. Among the 92 patients, 29 cases presented with a tumor diameter of ≤2.0 cm (31.52%), 53 cases were between 2~5 cm (57.61%), and 10 cases were ≥5.0 cm (10.87%); 3 lesions were round (3.26%), 7 cases were oval (7.61%), 33 cases were lobulated (35.87%), and 49 cases were irregular (53.26%). 11 cases exhibited the smooth margin (11.96%), 47 cases were irregular (51.09%), and 34 cases were spiculated (36.96%). A total of 15 cases exhibited homogeneous enhancement of early lesions (16.30%), 40 cases exhibited heterogeneous enhancement (43.48%), and 37 cases exhibited ring-like enhancement (40.22%).

WHO histopathological grade. A total of 5 cases were classified as grade 1 (1.09%), 30 cases were classified as grade 2 (32.61%), and 57 cases were classified as grade 3 (61.96%).

DCE-MRI features correlate with WHO histopathological grade (Table I). As presented in Table I, the tumor size, shape and enhancement characteristics of early lesions were associated with the WHO histopathological grade (P=0.012, P=0.004, P=0.000, respectively), namely the larger the tumor diameter, the higher the WHO histopathological grade. Round (Fig. 1) and oval (Fig. 2) masses were a relatively lower WHO histopathological grade, while the lobulated and irregular masses were higher WHO histopathological grades (Figs. 3 and 4). The heterogeneous enhancement (Fig. 5) and ring-like enhancement (Fig. 6) presented as higher WHO histopathological grade, while those with homogeneous enhancement (Fig. 2) presented with lower WHO histopathological grade. The status of the lesion margin, whether smooth (Fig. 1), irregular (Fig. 6) or Spiculated (Fig. 5), was not associated with the WHO histopathological grade (P>0.05).

Discussion

The features revealed from the DCE-MRI scans were diverse and complex and were informed by histopathological features of tumors such as different growth patterns, growth rates and malignant degrees. Theoretically, the relationships between the lesions' imaging features and histopathological features may be used to performed the non-invasive prediction of tumor invasion, thus guiding the treatment selection and improving the prognosis for patients (22-26).

The T staging is based on the size of the tumor. A previous study demonstrated that survival rates for breast cancer patients was negatively correlated with their tumor sizes. As the T stage increases, the metastasis rate to the lymph nodes increases, and the degree of differentiation becomes worse, indicating the poor prognosis of tumors (17). In the present study, the lesions were categorized according to the size of primary tumors (T) in the UICC TNM staging, among which 29 cases exhibited a tumor diameter of ≤2.0 cm (31.52%), 53 cases exhibited a 2-5 cm diameter (57.61%), and 10 cases exhibited a diameter of ≥5.0 cm in (10.87%). Tumor size was associated with WHO histopathological grade (P<0.05); as the tumor diameter increased, the degree of differentiation increased.

The tumor shape may reflect the growth pattern and biological characteristics of the tumor to a certain extent. According to the standard of ACR BI-RADS-MRI (2013) (1),

Table I. Correlation between DCE-MRI imaging and WHO histopathological grade in patients with invasive ductal breast cancer.

		WHO histopathological grade				
MRI imaging finding	N	Grade 1	Grade 2	Grade 3	χ^2-value	P-value
Size of mass (cm)						
≤2	29	4	14	11	12.832	0.012
2-5	53	1	14	38		
≥5	10	0	2	8		
Shape of mass						
Round	3	2	1	0	19.331	0.004
Oval	7	2	4	1		
Lobulated	33	1	14	18		
Irregular	49	0	11	38		
Margin of mass						
Smooth	11	1	7	3	9.173	0.057
Irregular	47	3	10	34		
Spiculated	34	1	13	20		
Characteristic enhancement						
Homogeneous	15	4	4	7	20.538	0.000
Heterogeneous	40	1	9	30		
Ring-like	37	0	17	20		

DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; WHO, world health organization; N, number.

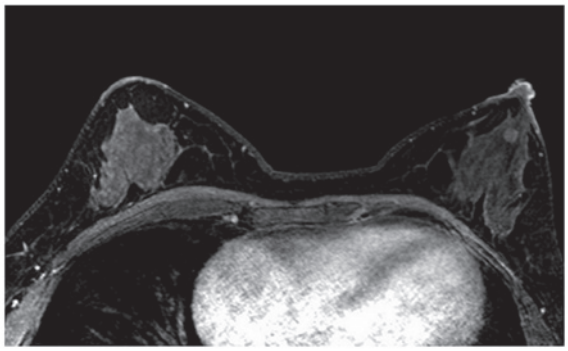

Figure 1. Female, 46 years old, grade 1, with round nodular shadow inside the central area of left breast, 0.8x0.8 cm, the margin was clear, and the enhanced scanning showed the homogeneous enhancement. Dynamic contrast enhanced-magnetic resonance image obtained at 40 sec.

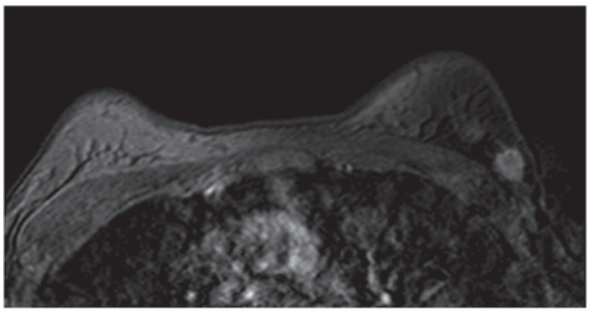

Figure 2. Female, 44 years old, grade 2, with oval nodular shadow in the lower outer quadrant of left breast, 2.3x2.1 cm, the margin was clear, and the enhanced scanning showed the homogeneous enhancement. Dynamic contrast enhanced-magnetic resonance image obtained at 40 sec.

tumor shapes may be divided into 4 types: i) Round, referring to the spherical growth of lesions; ii) oval, referring to the oval growth of lesions; iii) lobulated, referring to the edge of lump or nodule appeared the wave-like outline; iv) irregular, referring to the uneven outline of lesions (non-round, oval and lobulated). A lobulated shape results from unbalanced tumor growth rates in all directions and constraints by breast support structure; the tumor growth pattern is in a conglomerate type or expansive type. In the present study, among the 92 cases, the irregular pattern was the most commonly observed (49 cases, 53.26%), and the majority of tumors were WHO histopathologic grade 3 (57 cases, 61.96%). Tumors with a round pattern predominantly presented as WHO histopathological grade 1, while the lobulated and irregular lesions presented with a higher WHO histopathological grade.

The tumor margins may be divided into 3 types: i) Smooth, referring to the clear margin; ii) irregular, uneven margin, round or uneven (non-smooth, non-spiculated); iii) speculated, characterized by radial lines, and with a 'starry-like' or 'crab foot-like' appearance. Clear margins indicated that the tumor exhibited the extrapolated growth pattern; irregular margins indicated that the tumor exhibited invasive growth patterns; and spiculated margins are widely considered as the typical signs of malignant tumor, indicating that the tumor cells spread in all directions around or stimulated the proliferation of breast condulets and the surrounding fibrous tissues; there may also be the invasion of cancer cells, resulting in pure ductal hyperplasia and fibroplasia (6,7,10). Tozaki *et al* (11) analyzed

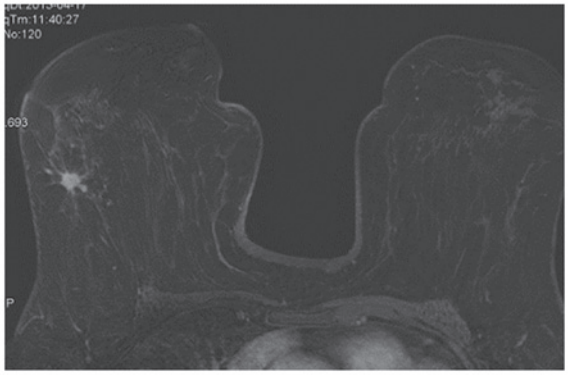

Figure 3. Female, 37 years old, grade 2, with mild lobulated nodular shadow in the lower inner quadrant of right breast, 0.8x0.8 cm, the margin was spiculated, and the enhanced scanning showed the homogeneous enhancement. Dynamic contrast enhanced-magnetic resonance image obtained at 40 sec.

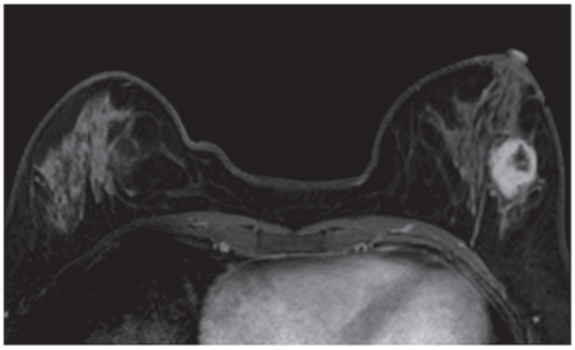

Figure 5. Female, 43 years old, grade 3, with mild lobulated mass in the upper outer quadrant of left breast, 3.8x3.6 cm, the margin was clear, ring enhancement. Dynamic contrast enhanced-magnetic resonance image obtained at 60 sec.

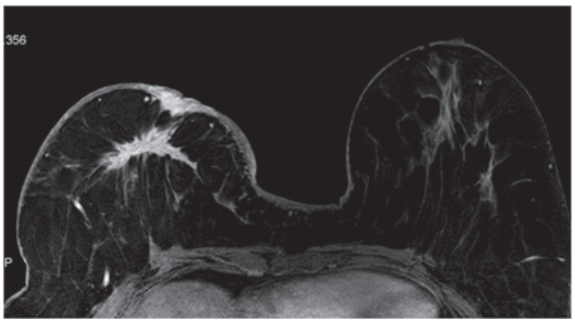

Figure 4. Female, 39 years old, grade 3, with irregular soft-tissue shadow in the posterior area of right breast, 3.5x2.8 cm, the margin was spiculated, the nipple was retracted, heterogeneous enhancement. Dynamic contrast enhanced-magnetic resonance image obtained at 60 sec.

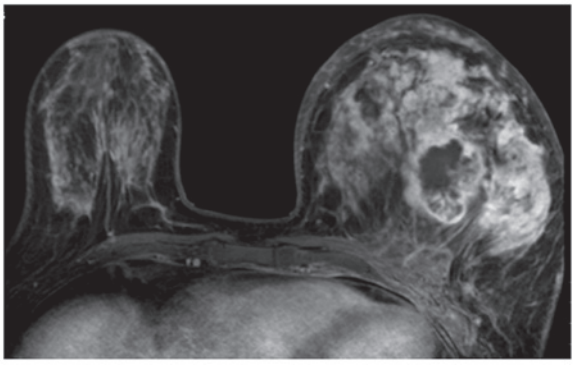

Figure 6. Female, 49 years old, grade 3, with irregular mass shadow in the lower outer quadrant of right breast, 9.5x11.5 cm, the margin was irregular, with obvious liquefactive necrosis in the central area, the peripheral essence swelled, involved in the post-breast fat gap, and the skin was thickened. Dynamic contrast enhanced-magnetic resonance image obtained at 120 sec.

171 lesions of breast masses, and determined that the malignant feature that had the highest positive predictive value was the presence of a speculated margin (100%). The speculated margin may appear in a large proportion of tumors, particularly peripheral lung cancer; however, there remains a controversy about whether there is a correlation between the presence of a speculated margin in breast cancer tumors and the malignant degree. Lamb *et al* (10) performed ultrasound and mammography X-ray studies, and demonstrated that a speculated margin appeared more commonly in lesions with lower histopathological grade, which represents lower levels of tumor invasion: The authors considered that the speculated margin was the result of reactive hyperplasia of tumor interstitial fibrous connective tissues, which may limit the spread of tumor cells, and it may also be an early protective mechanism against cancer. Lee *et al* (6) also hypothesized that the speculated margin was more prone to appear in well-differentiated tumors, indicating an improved prognosis in patients. Paradiso *et al* (18) also reported that tumors with speculated margins exhibited lower aggression, and that endocrine therapy exhibited better results in these tumors. The results of the present study indicated that the tumor margin was not associated to the WHO histopathological grade. Whether the speculated margin is a protective mechanism requires further study.

In the present study, the breast lesions presented with 3 enhancement patterns: i) Homogeneous enhancement, referring to the even consistent enhancement in the entire lesions; ii) heterogeneous enhancement, meaning an absence of characteristic mottle-like diffused enhancement; iii) ring-like enhancement, where the tumor's margin enhancement was much more apparent. When the tumor grew to a certain size, particularly in highly malignant breast cancer cases, the internal blood supply may be deficient, liquefactive necrosis and signs of minor bleeding may occur inside the parenchyma, which may lead to mixed signals in MRI conventional scanning. In enhanced scanning, because the tumor's internal structures are uneven, concentric enhancement which penetrated from the margin to the center would appear, which is an important diagnostic feature of breast cancer, with the diagnostic sensitivity as 100%. It is widely accepted that ring enhancement is an important morphological sign to distinguish between benign and malignant tumors. Buadu *et al* (23) performed histopathological analysis investigating the ring enhancement of breast lesions, and the results demonstrated that the accumulation of microvessels around the tumor margin was the main cause of DCE-MRI margin enhancement. Kuhl *et al* (25) demonstrated that nearly two-thirds of breast cancer cases would present with ring enhancement, the tumor's margin ring enhancement was associated with its histopathological characteristics: Partial areas around the tumor had dense angiogenesis, thus

the permeability would be increased, the proliferation of tumor cells was active and the interstitial substances would be rich, so that the contrast agent could enter early; while the center of the tumor may have hemorrhage, necrosis, cystic changes and central fibrosis, the densities of tumor blood vessels would be low, and the contrast agent distribution would be lower; the adjacent tissues were predominantly the normal breast glandular tissues, although they may be associated with such changes as atypical hyperplasia, adenosis and cysts. The densities of microvessels were significantly lower than those in the tumor center and tumor-adjacent tissues (25). A previous study demonstrated that the enhancement features of the breast cancer tissue were associated with its tissue differentiation, the proliferation abilities of breast cells increased from low to high in homogeneous enhancement, ring enhancement and heterogeneous enhancement, respectively (17). Lee *et al* (6) demonstrated that the presence of ring enhancement alone may indicate the high-differentiation of tumors and relatively larger lesions. However, Mussurakis *et al* (27) reported that ring enhancement was not related with the histopathological prognostic factors. The results of the present study indicated that the DCE-MRI enhancement patterns of tumors were related to the histopathological grades, and that ring enhancement and heterogeneous enhancement often occurred in the high-level breast cancer.

In conclusion, DCE-MRI signs exhibited certain associations with the WHO histopathological grades, and MRI features could be used to evaluate the biological behaviors and prognosis of lesions, thus providing guidance for the clinical treatment.

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