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Original Article

Diagnostic value of dynamic contrast-enhanced magnetic resonance imaging and ultrasonography for differentiating between breast benign and malignant lesions: a comparative study

Likun Wang[1], Xueliang Wu[2], Haifeng Zhou[3], Yicheng Wang[1], Guoqing Cui[4], Ruimin Yang[1]

Departments of [1]Ultrasound, [2]Vascular Gland Surgery, [3]Breast Surgery, [4]Nuclear Medicine, The First Affiliated Hospital of Hebei North University, Zhangjiakou 075000, Hebei Province, P. R. China

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Abstract: This study aims to evaluate the diagnostic value of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and ultrasonography (US) for differentiating breast benign and malignant lesions. The study included a total of 105 patients with breast lesions who received DCE-MRI and US examinations in the First Affiliated Hospital of Hebei North University from September 2013 to December 2015. More than two experienced radiologists who were double-blinded before surgery assessed the images from DCE-MRI and US jointly. In accordance with the Breast Imaging Reporting and Data System (BI-RADS), lesions were evaluated in order to differentiate between breast benign and malignant lesions. A Receiver operating characteristic (ROC) curve was used to assess the diagnostic value of DCE-MRI, US and DCE-MRI + US in differentiating between breast benign and malignant lesions. A total of 125 breast lesions were detected in 105 patients. The pathological diagnosis results criteria showed that there were 52 (41.6%) benign lesions and 73 (58.4%) malignant lesions. According to the ROC results, there were misdiagnoses by US; category 4 in BI-RADS scoring was considered as the optimal threshold to differentiate between benign lesions from malignant lesions. The area under the curve (AUC) of US, DCE-MRI and the combination of DCE-MRI and US (DCE-MRI + US) was 0.849 (95% CI = 0.781~0.918; $P < 0.001$), 0.915 (95% CI = 0.862~0.968; $P < 0.001$) and 0.938 (95% CI = 0.893~0.983; $P < 0.001$), respectively; the accuracy rate of DCE-MRI for diagnosing malignant lesions was higher than that of US (94.4% vs. 76.7%, $P = 0.043$); and sensitivity was highest in DCE-MRI + US, followed by DCE-MRI and US individually (97.3%, 90.4%, and 76.7%). Our study suggests that a combination of DCE-MRI and US is more efficient for the diagnosis and differentiation of breast lesions than DCE-MRI or US individually.

Keywords: Breast lesions, dynamic contrast-enhanced magnetic resonance imaging, ultrasonography, receiver operating characteristic curve, benign lesions, malignant lesions

Introduction

Breast cancer, the leading type of cancer among women of all ages worldwide, causes approximately 1.68 million cases and 522,000 deaths in 2012 [1]. Patients suffering from breast cancer in developed countries have a higher survival rate, with 80-90% of the patients in England and United States surviving for at least 5 years; whilst the survival rates are poorer in developing countries [2, 3]. Surgery is the main course of treatment for early-stage breast cancers, and the goal being to completely excise the tumor and achieve adequate safe margins [4-6]. Multiple methods have been suggested to optimize the margin clearance, including preoperative imaging and intraoperative surgical techniques [7]. Early detection of breast cancer is trivial for improved outcomes and will popularize the application of breast cancer screening, referring to testing healthy women in an attempt to achieve an earlier diagnosis for breast cancer [8-10]. Various screening tests including clinical exams, breast self-exams, mammography, genetic screening, ultrasonography (US), and magnetic resonance imaging (MRI) have been employed to achieve earlier diagnosis of breast cancer [11, 12].

However, clinical and breast self-exams are not always effective as lumps have to be large enough to be detected which further takes several years [10].

US, an ultrasound-based diagnostic imaging technique used to reveal structural details of the arteries programmed to search for blood, is particularly beneficial in young women for detection of breast tumor [13]. MRI, an increasingly popular tool for the examination of breast cancer tissues, and moreover is highly sensitive because of the application of contrast enhancement material compared to US [14]. However, several studies have supported that MRI and US sensitivity is still inferior to dynamic contrast-enhanced MRI (DCE-MRI) [15-18]. DCE-MRI is an imaging method, dynamically acquiring T1-weighted MRI scans after the injection of MRI contrast agents [19]. DCE-MRI enables the analysis of blood vessels obtained from brain tumors, with the contrast agent being blocked by the regular blood-brain barrier but observable in blood vessels [19]. DCE-MRI has been applied as an accurate technique for detection and delineating some invasive and in situ cancers, such as breast cancer, cervical carcinoma, colorectal cancer, prostate cancer, nasopharyngeal carcinoma, etc. [20-24]. It is reported that US lacks the potential to replace conventional US for detection of breast cancer, although it may complement the diagnostic performance of breast lesions [25]. Another study has proposed that DCE-MRI has emerged as an important imaging tool instead of conventional X-ray mammography because of its high detection sensitivity, whilst the specificity is low in distinguishing breast malignant from benign lesions [26]. In regard to the clarifications above, the optimal way for the diagnosis of breast malignant and benign lesions is still unknown despite the achievements made by some studies on this aspect. Therefore, this study aims to evaluate the diagnostic value of DCE-MRI and US for differentiating between breast benign and malignant lesions.

Materials and methods

Ethics statement

The Ethics Committee of The First Affiliated Hospital of Hebei North University approved this study. All participants provided written informed consent before the experiments, and the study conformed to the Declaration of Helsinki [27].

Study subjects

A total of 105 patients with breast lesions (age, 24~74 years old; with a mean age of 57.6 ± 15.6 years) were collected from The First Affiliated Hospital of Hebei North University from September 2013 to December 2015. A total of 125 lesions were detected amongst the patients. All patients underwent DCE-MRI and US examinations for bilateral breasts, and none of the patients received any anti-tumor therapies, such as chemotherapy, radiotherapy, endocrine therapy, etc. before examinations. Eventually, all patients received surgical treatment and had confirmed pathological results.

DCE-MRI and US examinations

A SIEMENS Magnetom Avanto 1.5-T superconducting MRI scanner (Siemens Ltd, Erlangen, Germany) and a bilateral dedicated breast surface coil were applied for DCE-MRI scans. All subjects were in the prone position, with their bilateral breasts naturally drooping into the coil. T1 high resolution isotroPic volume excitation (THRIVE) sequence was used, and gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) was utilized as the contrast agent, which was injected into a forearm vein with the help of a high pressure injector at a rate and dosage of 2 ml/s and 0.1 mmol/kg (body weight) respectively, followed by a 0.9% sodium chloride solution (20 ml) injection at the same rate in order to irrigate the catheter. Prior to the contrast agent injections, subjects were scanned once, subsequently the contrast agent was injected at 40 s after scanning, and scanning was continuously repeated 8 times.

A Philips HD-11 ultrasonic color Doppler diagnostic apparatus (Philips, Andover, MA, USA) was used for breast US scanning, with a probe frequency of 7.5~10.0 MHz. The patients were in the supine position to fully expose the breasts. Radial inspection was conducted with the probe on the surface of the breasts to determine the conditions of the lesions, including the location, size, morphology, boundary, capsule, internal echo and posterior echo. Observations were made in order to check for the

Table 1. Basic characteristics of the 125 lesions in the 105 patients

Index	Lesion number (n = 125)	Percentage (%)
Age (years old)		
≤ 50	47	37.6
> 50	78	62.4
Clinical symptoms		
Mass	92	73.6
Non-mass	33	26.4
Benign lesion	52	41.6
Breast adenosis	32	25.6
Mammary gland fibroma	12	9.6
Lipoma	3	2.4
Mammary cysts	2	1.6
Plasma cell mastitis	5	4
Malignant lesion	73	58.4
Breast cancer	33	26.4
Infiltrating lobular carcinoma	6	4.8
Intraductal carcinoma	15	12
Other cancers	19	15.2
Tumor size		
≤ 2 cm	74	59.2
> 2 cm	51	40.8

presence of calcification within the mass and dilation of the catheter, whether it was solid or cystic, and whether swelling happened in axillary lymph nodes.

Imaging analysis and diagnostic criteria of DCE-MRI and US examinations

More than two experienced radiologists who were double-blinded in The First Affiliated Hospital of Hebei North University before surgery assessed the images from DCE-MRI and US examinations jointly. The contents for lesions evaluation included the following: morphology, size, number, boundary, capsule, distribution, bloodstream, axillary lymph nodes, density/signal change and curve type, etc. Breast Imaging Reporting and Data System (BI-RADS) judged whether a lesion was benign or malignant comprehensively, together with the diagnostic outcomes and pathological results of DEC-MRI and US imaging. The classification of BI-RADS-US criteria was made according to the lesion morphology, aspect ratio, boundary, edge, posterior echo, changes in surrounding tissues, calcification, and the internal bloodstream as benign lesions (categories 0~3) and malignant lesions (categories 4~6) [28]. The BI-RADS-DCE-MRI assessments were made as follows: 1) regular lesion morphology (score, 0) or irregular lesion morphology or with burr (score, 1); 2) clear boundary (score, 0) or unclear boundary (score, 1); 3) homogeneous enhancement (score, 0), inhomogeneous enhancement (score, 1), or annular enhancement (score, 2); 4) the rate of early enhancement (REE) was the comparison between the image signal intensity (SI) at 1 min after the injection of contrast agent (S_{max1}) and the SI before radiography, and REE (%) = (S_{max1} - S_{pre})/S_{pre} × 100%, with score 0 for < 50%, 1 for 50%~100%, and 2 for > 100%; 5) time-intensity-curve (TIC) types of interest zone were classified into type I (score, 0; the curve showed a continuous increase, and the peak enhancement appeared after 6 min), type II (score, 1; the curve raised rapidly, the peak enhancement was appeared between 4~6 min, and the range of increase or decrease was within the 10% of peak intensity), and type III (score, 2; the peak enhancement was appeared between 2~4 min, followed by an obvious decrease, with a decrease range above the 10% of peak intensity) [30, 31]. According to BI-RADS-DCE-MRI, the scores were categorized as follows: category 1 (score, 0~1), category 2 (score, 2), category 3 (score, 3), category 4 (score, 4~5), and category 5 (score, 6~8); and the lesions were determined as benign lesions (category 0~3) or malignant lesions (category 4~5).

Statistical analysis

Statistical analysis was performed using the SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Enumeration data was presented as percentage or rate, and compared using the chi-square test between groups. Measurement data was presented as mean ± standard deviation. The Receiver operating characteristic (ROC) curve, based on the sensitivity and false positive rate of DCE-MRI and US, was used in order to compare the area under the curve (AUC) and determine the optimal diagnostic threshold value (the point value that was closest to the upper left corner). All *P* values were two-tailed, and $P < 0.05$ was considered as statistically significant.

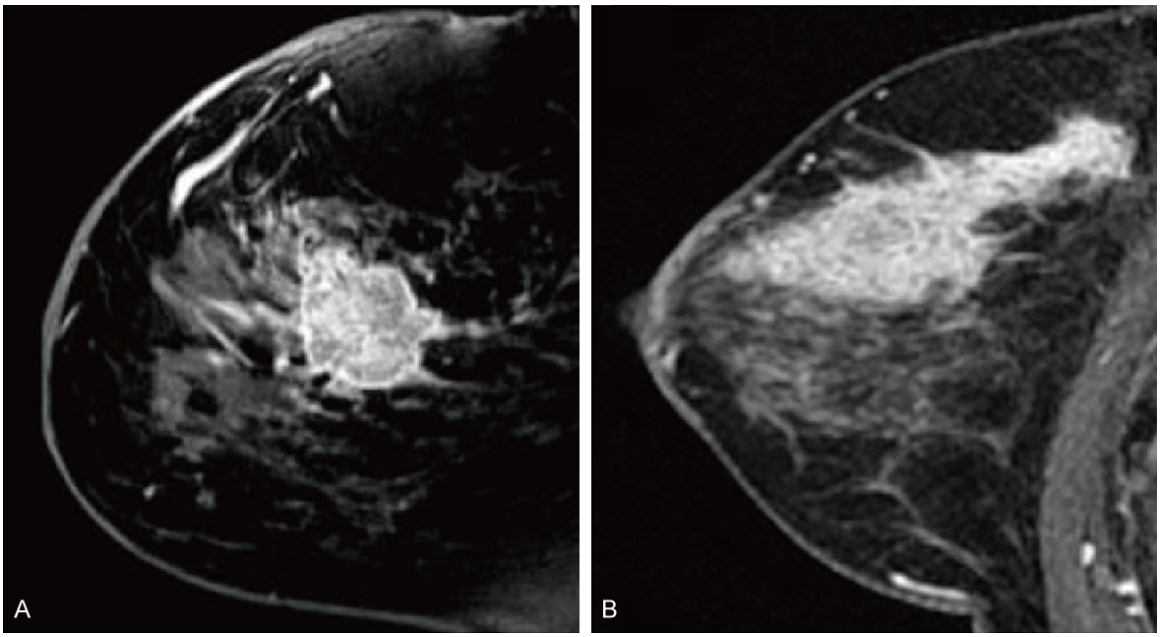

Figure 1. Diagnostic results of DCE-MRI for patients with breast lesions. A: DCE-MRI result of a patient's right breast showed lesions in the outer upper quadrant, which were mass-like after enhancement, and presented irregular morphology, unclear boundary and burr at the edge. B: DCE-MRI radiograph of a left breast lesion showed non-mass like (flake-shape) after enhancement, and presented irregular morphology, unclear boundary and surrounding burr, accompanied with obvious nipple retraction, surrounding mammary areola and thickened skin with obvious enhancement. DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging.

Results

Baseline characteristics and pathological results of patients with breast lesions

All 105 patients were female, aging from 24 to 74 years old, with a calculated mean age of 57.6 ± 15.6 years. A total of 125 lesions were detected; among them, 92 clinically presented mass lesions (73.6%), and 33 cases demonstrated non-mass lesions (26.4%). Postoperative pathological results revealed 52 cases of benign lesions (41.6%), which included 32 cases of breast adenosis (25.6%), 12 cases of mammary gland fibroma (9.6%), 3 cases of lipoma (2.4%), 2 cases of mammary cysts (1.6%), and 5 cases of plasma cell mastitis (4.0%), and 73 cases of malignant lesions (58.4%), among which, there were 33 cases of breast cancer, 6 cases of infiltrating lobular carcinoma (ILC), 15 cases of intraductal carcinoma and 19 cases of other cancers (**Table 1**).

Diagnostic results of DCE-MRI and US of patients with breast lesions

Among the 73 cases of pathologically confirmed malignant breast lesions, DCE-MRI diagnosed 42 lesions with malignant mass-like enhancement (**Figure 1A**), and 31 lesions with non-mass like enhancement (**Figure 1B**), with distributed in flake-, irregular-, nodular- or section shape. Among the 52 cases of pathologically confirmed benign breast lesions, DCE-MRI revealed 38 regularly shaped nodules or masses, and 14 irregularly-and flake-shaped enhancements; 35 lesions showing clear boundary while 17 lesions presenting unclear boundaries.

In the diagnostic results of US in 73 malignant breast lesions, 3 infiltrating ductal carcinomas were misdiagnosed as benign lesions (category 3) due to regular morphology and clear boundary (**Figure 2A**); 3 breast adenocarcinomas were misdiagnosed as benign lesions (category 2) because of combined cystic hyperplasia, and the US scan merely detected cysts instead of malignant lesions (**Figure 2B**); 4 intraductal carcinomas accompanied with early infiltration did not show any lesions. In the diagnostic results of US in 52 benign breast lesions, 2 fibroadenomas and 1 cystic hyperplasia were misdiagnosed as malignant lesions (category 4) because of irregular morphology and the aspect ratio < 1; 2 intraductal

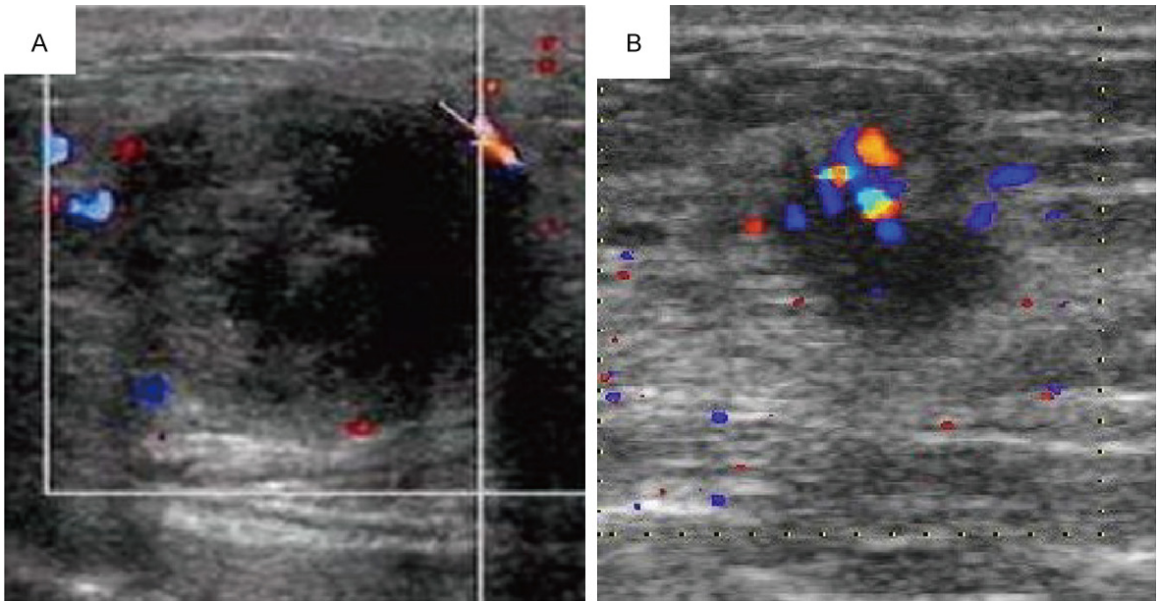

Figure 2. Diagnostic results of US for patients with breast lesions. A: US imaging of a patient's right breast showed regular morphology and clear boundary, which was misdiagnosed as category 3 according to BI-RADS-US. B: US imaging of a patient's right breast showed irregular morphology and unclear boundary, which was misdiagnosed as category 2 according to BI-RADS-US. BI-RADS: Breast Imaging Reporting and Data System, US: ultrasonography.

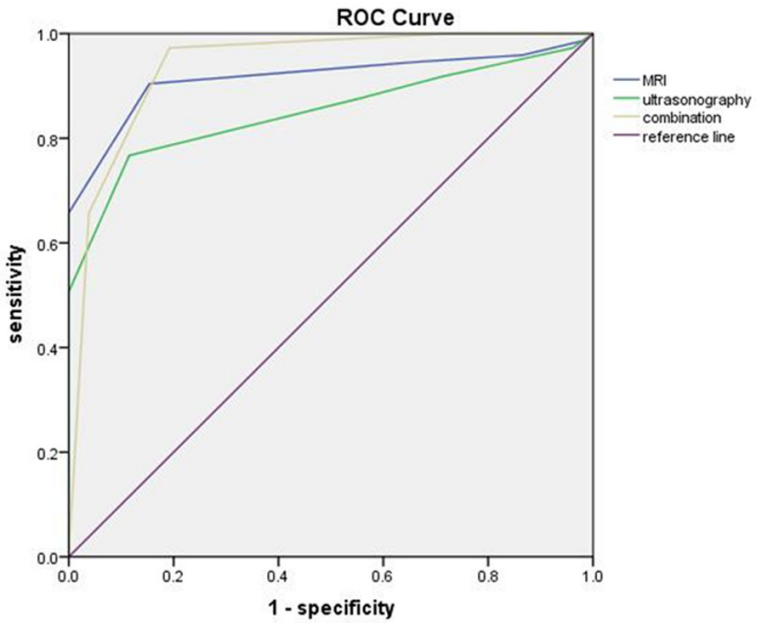

Figure 3. ROC curves of DCE-MRI, US and DCE-MRI + US in diagnosing benign breast lesions and malignant breast lesions. ROC: receiver operating characteristic; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; US, ultrasonography.

papillomas were misdiagnosed as malignant lesions (category 5) due to irregular morphology and abundant blood flow signal; and 2 cystic hyperplasia did not show any lesions.

ROC curves of DCE-MRI, US and DCE-MRI + US in differentially diagnosing benign lesions and malignant lesions

The ROC curves of DCE-MRI, US and DCE-MRI + US in differentially diagnosing benign breast lesions and malignant breast lesions are displayed in **Figure 3**. The AUC of DCE-MRI, US and the DCE-MRI + US were 0.915 (95% CI = 0.862~0.968, $P < 0.001$), 0.849 (95% CI = 0.781~0.918, $P < 0.001$), and 0.938 (95% CI = 0.893~0.983; $P < 0.001$), respectively. The results revealed that the diagnostic value of DCE-MRI was superior to US, and the diagnostic value of the DCE-MRI + US was superior to DCE-MRI individually or US individually (as seen in **Table 2**).

Comparison of diagnostic value among DCE-MRI, US and DCE-MRI + US

Examination results of 73 cases of malignant lesions showed there were 66 cases of ma-

Table 2. Comparison in ROC curves of DCE-MRI, US and DCE-MRI + US in differentially diagnosing benign breast lesion and malignant breast lesion

Examination methods	AUC	SE	*P*	95% CI
DCE-MRI	0.915	0.027	< 0.001	0.862~0.968
US	0.849	0.035	< 0.001	0.781~0.918
DCE-MRI + US	0.938	0.023	< 0.001	0.893~0.983

Notes: ROC, receiver operating characteristic; AUC, area under the curve; SE, standard error; 95% CI, 95% confidence interval; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; US, ultrasonography.

Table 3. Comparison of diagnostic value of DCE-MRI, US and DCE-MRI + US

Index	Pathology	Category						Sensitivity (%)
		0	1	2	3	4	5	
DCE-MRI	Malignant	1	6	11	25	8	1	90.4
	Benign	1	4	1	3	16	48	
US	Malignant	2	13	8	23	6	0	76.7
	Benign	2	4	0	8	22	37	
DCE-MRI + US	Malignant	0	3	11	28	8	2	97.3
	Benign	0	0	0	2	23	48	

Notes: DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; US, ultrasonography.

lignant lesions and 7 cases of misdiagnosed benign lesions, and the accuracy rate of DCE-MRI for diagnosing malignant lesions was 94.4% (66/73) based on DCE-MRI; there were 56 cases of malignant lesions and 17 cases of misdiagnosed benign lesions, and the accuracy rate of US for diagnosing malignant lesions was 76.7% (56/73) based on US; there was significant difference in the accuracy rate of DCE-MRI and US for diagnosing malignant lesions (P = 0.043). Examination results of 52 cases of benign lesions showed there were 43 cases of benign lesions and 9 cases of misdiagnosed malignant lesions, and the accuracy rate of DCE-MRI for diagnosing benign lesions was 82.7% (43/52) based on DCE-MRI; there were 46 cases of benign lesions and 6 cases of misdiagnosed malignant lesions, and the accuracy rate of US for diagnosing benign lesions was 88.5% (46/52) based on US; no significant difference in the accuracy rate of DCE-MRI and US for diagnosing benign lesions (P = 0.578).

According to the ROC curves, Category 4 in BI-RADS scoring was the optimal threshold to differentiate benign lesions from malignant lesions. Therefore, the detection results of DCE-MRI, US and DCE-MRI + US with category 4 or above were deemed positive, and results with categories below 4 as negative. The results of DCE-MRI, US and the DCE-MRI + US seen in **Table 3**, show that the sensitivity was highest in DCE-MRI + US, followed by that of DCE-MRI and US (97.3%, 90.4%, and 76.7%).

Discussion

In the present study, we retrospectively analyzed the imaging data of 105 patients with 125 breast lesions who underwent both DCE-MRI and US examinations to determine the diagnostic value of DCE-MRI and US for differentiating between breast benign and malignant lesions. Our study suggests that DCE-MRI with higher sensitivity was more valuable for the diagnosis and differentiation of breast lesions in comparison to US; and the combination of DCE-MRI and US showed greater efficacy than DCE-MRI or US individually.

US imaging is a cheap, real-time and non-invasive imaging technique with a high soft tissue contrast without radiation risks, extensively applicable in broad fields [31]. US imaging contributes to visualizing anatomical features of breast tissues to help distinguish malignant from benign tissues, however, tissue architecture usually does not provide enough information about the tumor, including the tendency to grow or metastasize [32]. With US technique, some breast cancers are missed or falsely detected [33, 34]. For US imaging, determining whether the lesion is benign or malignant is judged on the behalf of the morphology of the lesions, however, sometimes the provided information may be inadequate to make the right judgment [35]. In the present study, 3 infiltrating ductal carcinomas, 2 fibroadenomas, 1 cystic hyperplasia and 2 intraductal papillomas were misdiagnosed as malignant lesions because of their irregular morphology. Referring to the misdiagnoses in our study, it shows that observations based on anatomic features are inadequate for the detection of early breast cancers. During breast cancer progression, certain functional alterations occur before mor-

phologic changes are visible on US scans [36, 37].

DCE-MRI has been reported to be a valuable tool for acquiring functional tissue information clinically and preclinically, mainly providing an automated kinetic evaluation by the means of color-coding the changes in intensity per voxel during the enhancement of the tumor tissue [38]. DCE-MRI is an upcoming alternative for the diagnosis of breast cancer, which reflects the pathological changes, including fiber response, new blood vessels, as well as intraductal component organization to a certain extent, according to the morphological characteristics and enhanced scanning performance of the breast lesions [39, 40]. Generally, DCE-MRI has shown a high sensitivity for the detection of breast cancer, ranging from 89% to 100% [19]. Our findings reveal evident differences in the morphology and enhanced form demonstrated by the results as: 1) the malignant breast lesions were typically distributed in flake-, irregular-, nodular-or section shapes whilst benign lesions mostly showed regularly-shaped nodules or masses, frequently with clear boundaries; and 2) out of the 73 malignant lesions, 42 lesions showed mass-like enhancements and 31 non-mass like enhancements, and on the contrary, only 14 benign lesions showed enhancements. Malignant lesions usually represent burrs, lobulated margins, or blurred boundaries, and do not show clear boundaries with surrounding tissues when diagnosed by DCE-MRI; meanwhile, malignant lesions mostly show irregular enhancement. The results are consistent with the findings related to DCE-MRI, which evidenced demonstrates the significant role of DCE-MRI in differentiating between benign and malignant lesions. DCE-MRI supplies structural and physiologic data on the tumor vasculature. In a typical DCE-MRI study, a small molecule contrast agent (CA) is administered to the patient by a single bolus dose or short infusion, and subsequent changes in the concentration of CA within tissues are inferred from signal intensities measurements, to accurately interpret the observed kinetics of CA in tissues [20]. Therefore, estimates of CA transfer rates and distribution spaces within tissues can be obtained according to DCE-MRI scans and applied as an indicator prior to treatment [20]. Due to this advantage, DCE-MRI has been used in numerous oncologic tasks, such as early diagnosis, tumor staging, treatment planning, and treatment response evaluations [41].

Furthermore, ROC curve results in our study confirm that the diagnostic value and sensitivity of DCE-MRI was superior to US, implying that DCE-MRI may serve as a more accurate technique for the detection and delineating breast cancer compared to US, which further provides theoretical basis for the treatment of breast cancer. In line with the results of our present study, Agner et al. demonstrated that DCE-MRI combined with textural kinetic attributes, resulted in a probabilistic boosting tree classifier, yielding an accuracy of 89%, a sensitivity of 99%, and an AUC of 0.91 [26]. US is regularly used for the assessment of tissue vascularization and vessel occlusion using Doppler, however, it is insufficient for poorly vascularized tumors with small vessels or slow blood flow, while DCE-MRI is a well-known imaging modality aimed at visualizing tumor vasculature [33]. Previous studies have been conducted to evaluate the efficacy of DCE-MRI in comparison with power Doppler US (PDUS), and the results reveal that DCE-MRI was significantly more sensitive than transrectal PDUS in peripheral zones [42]. Additionally, the ROC curve and sensitivity analysis results also showed that a combination of DCE-MRI and US may further improve the diagnostic efficiency in breast lesions. US scans can accurately differentiate between cystic lesions (as small as 1 mm), and solid lesions (as small as 3 mm) [43]. And US scans act as a cheap and non-invasive technique, compensating for the disabilities of DCE-MRI. Therefore, it is suggested that a combination of two detection methods is more efficient that applying only one imaging scan for differentiating between benign and malignant lesions.

In conclusion, a more sensitive DCE-MRI scan was more valuable in the diagnosis and differentiation of breast lesions in comparison to US; and the combination of DCE-MRI and US showed better efficiency than DCE-MRI or US individually, providing theoretical basis for the prevention and diagnosis of breast lesions in clinical treatment in future. However, limitations of our study lie in the retrospective design and small sample size of the subjects. Therefore, further studies based on a larger sample size are required to increase the power

of the statistical tests and to detect statistical differences between benign and malignant lesions.

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Disclosure of conflict of interest

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Address correspondence to: Dr. Ruimin Yang, Department of Ultrasound, The First Affiliated Hospital of Hebei North University, 12 Changqing Road, Qiaoxi District, Zhangjiakou 075000, Hebei Province, P. R. China. Tel: +86-313-8043582; E-mail: yangruiminrm@163.com

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