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ORIGINAL RESEARCH

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Prediction of HER2 status in breast cancer patients based on DCE-MRI imaging features combined Ki-67 and VEGF expression

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Abstract

Background: We aimed to investigate the value of dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) features of breast cancer patients in predicting the expression of human epidermal growth factor receptor 2 (HER2) and analyze the association between HER2 with proliferating cell nuclear antigen (Ki-67), and vascular endothelial growth factor (VEGF). **Methods**: This study enrolled 111 patients with breast cancer diagnosed by pathological analysis in our hospital. The association between preoperative DCE-MRI and the expression of HER2, Ki-67, as well as VEGF were analyzed. **Results**: The clinical analysis revealed that HER2 status was correlated with maximum tumor diameter, high expression of Ki-67 and VEGF. We observed statistical significant differences in apparent diffusion coefficient (ADC) values, multifocality and margins were statistically significant in breast cancer patients with different HER2 statuses. Whereas other DCE-MRI imaging features, such as mass type, shape, enhanced classification and time signal intensity curve (TIC), were not statistically significant. **Conclusions**: The clinicopathological and DCE-MRI imaging features of breast cancer patients may be used to evaluate the HER2 expression status in breast cancer patients, providing a theoretical basis for targeted therapy and prognosis evaluation.

Keywords

DCE-MRI imaging; HER2; Prediction; Ki-67; VEGF

1. Introduction

Breast cancer is the most common tumor of the reproductive system in women and is the leading cause of cancer-related death in women [1]. Breast cancer is a highly heterogeneous tumor, with different molecular subtypes showing different morphology, treatment response and outcome [2]. It is of practical significance to explore the indicators related to the diagnosis and prognosis of breast cancer. Human epidermal growth factor receptor (HER2) positive breast cancer (accounting for about 20–25% of breast cancer cases) has a higher rate of invasion and metastasis and shows poor prognosis [3]. The proto-oncogene HER2, located on human chromosome 17q21, is rarely expressed in normal breasts, hence, it is one of the common molecular markers and crucial indicators for the selection of targeted therapy and independent assessment of the prognosis for patients with breast cancer [3, 4]. HER2-positive breast cancer patients treated with trastuzumab in combination with chemotherapy, such as paclitaxel, could prolong their disease-free survival and overall survival after surgery [5, 6]. Therefore, early detection of the HER2 status is of great significance for treatment selection and prognosis prediction in breast cancer patients, especially for HER2 positive breast cancer patients.

Early and effective treatment can reduce the mortality rate of breast cancer. Dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) is an important diagnostic tool of breast cancer due to its high soft tissue resolution [7]. DCE-MRI has a high sensitivity for the detection of various breast diseases, especially breast cancer [8]. Increasing studies indicated that DCE-MRI features have a correlation with HER2 prediction [9, 10]. The progression of breast cancer was closely associated with abnormal expression of HER2, Ki-67 and VEGF [3, 11–13], but the relationship between molecular biological predictors and DCE-MRI signs of breast cancer has yet not been fully explored.

This study aims to investigate the relationship between DCE-MRI features and HER2 status as well as the status of Ki-67 and VEGF and to provide additional value for clinicians without increasing the additional financial burden on breast cancer patients. This may provide the clinic with a non-invasive method for predicting HER2 expression and a guide for clinicians in the diagnosis and treatment of breast cancer patients.

2. Materials and methods

2.1 Patients' enrollment

The clinical and DCE-MRI imaging data of breast cancer patients (n = 111) diagnosed at The Third Hospital of Nanchang from January 2019 to December 2022 were retrospectively collected. The inclusion criteria: (1) Patients with surgically and pathologically confirmed breast cancer as the primary lesion; (2) Complete clinical and imaging data available; (3) Patients without other malignant tumors; (4) DCE-MRI examination was performed within two weeks before surgery. Exclusion criteria: (1) The patients underwent surgery or neoadjuvant chemotherapy before DCE-MRI; (2) Patients with distant metastasis or other malignant tumors.

2.2 DCE-MRI

DCE-MRI scan was scheduled for the second week of the menstrual cycle of the patients. The scanning equipment used was a SIEMENS 1.5 Avanto superconducting MRI (Magnetom Avanto 1.5 T, Siemens, Erlangen, BY, Germany) with a dedicated breast coil. The patient was scanned in the prone position with the breast draped over the coil.

The conventional scan parameters described here. For T1-weighted images (T1WI) transverse position, the repetition time (TR) was 8 ms, time to echo (TE) 4.8 ms, layer thickness 1.5 mm, layer spacing 0.3 mm, scan repetition once, and field of view (FOV): 340 mm × 340 mm. For T2WI axial position, the TR was 4840 ms, TE 54 ms, slice thickness 4.0 mm, slice spacing 1.0 mm, scan repetition, twice, and FOV: 320 mm × 320 mm. For bilateral sagittal T2WI, TR was 3600 ms; TE, 77 ms; slice thickness, 4.0 mm; slice spacing, 0.8 mm, scan repetition, twice, and FOV, 200 mm × 200 mm. The parameters for DCE transverse scanning were as follows: TR 4.6 ms, TE 1.7 ms, slice thickness 1.5 mm, slice spacing 0.3 mm, scan repetitions once, FOV: 320 mm × 320 mm. The contrast agent used was gadopentetate dimeglumine (Gd-DTPA) with a dosage of 0.1 mmol/kg, and the injection rate was 2.5 mL/s with a special MRI-compatible power injector (Medrad, Warrendale, PA, USA). After injecting the contrast agent, 20 mL of saline was injected at the same rate. Before contrast enhancement, the mask was scanned 5 times consecutively and immediately after injecting of the contrast agent. The time for a single scan was about 60 s, and the total time was approximately 6 min.

2.3 Imaging post-processing and analysis

The images of all cases were analyzed and diagnosed by two or more senior attending physicians with more than five years of experience in breast MRI diagnosis in a blind manner. The Mean Curve software (version VE31B, Siemens Healthcare, Erlangen, BY, Germany) was used to select the region of interest (ROI) for the lesions with obvious enhancement, and the area of ROI was 15–25 mm^2, avoiding necrosis, hemorrhage, cystic degeneration or calcification areas. Additionally, the apparent diffusion coefficient (ADC) values were measured. The time signal intensity curve (TIC) of the lesion was plotted, and it was classified as follows according to Kuhl's criteria [14]: Type I, inflow type (no peak in reinforcement and a continuous increase); Type II, plateau type, (change in signal intensity of less than 10% after reaching a peak); Type III, outflow type, (reinforcement reaches a peak and then decreases more than 10%).

2.4 Ultrasound examination methods

Ultrasonic examination was performed using GE LOGIQ E9 (GE Healthcare, Wauwatosa, WI, USA), HI VISION 900 (Hitachi, Tokyo, Japan), or EPIQ7 (Philips Healthcare, Best, Netherlands) color Doppler ultrasound diagnostic instruments. The probe frequency was 7–15 MHz. The patient was placed in the supine position with her head in her hands, and the breast was fully exposed. The location, boundary, internal echo and blood flow of the lesion was observed.

2.5 Immunohistochemical staining

Fresh tissue specimens were obtained after surgery, fixed in 10% formalin, dehydrated and embedded in paraffin. Specimen slices of 3 μm in thickness were stained with hematoxylin and eosin (HE), and then immunohistochemical (IHC) staining was performed according to the pathological results of HE staining. Estrogen (ER), progesterone (PR), HER2, Ki-67 and VEGF were detected by IHC.

ER and PR were considered positive when the number of nuclear staining positive cells was $\geq$1%, otherwise they were considered negative. The Ki-67 expression was defined as high expression when the number of nuclear staining positive cells was $\geq$14% and as low expression when it was $<$14% [15]. In the IHC analysis of the HER2 status, no staining or less than 10% of tumor cells with brownish-yellow granular staining of the cell membrane was graded as (−), weak or incomplete staining of the cell membrane in $>$10% of tumor cells was graded as (+), and weak to moderate complete staining of the cell membrane in $>$10% of tumor cells was graded as (++). Cases with (++) grade were additionally tested using fluorescence in situ hybridization (FISH) to determine is the presence of gene amplification. Cases with strong and complete membrane staining in more than 10% of tumor cells were graded as (+++). Positive cases were defined as (++) with definition gene amplification and cases with (+++) were considered HER2-positive. Vascular endothelial growth factor (VEGF) expression was considered positive if $\geq$5% of the tumor cell were stained and negative if no cells or less than 5% of cells were stained.

2.6 Statistical analysis

SPSS 26.0 software (IBM, Armonk, NY, USA) was used for statistical analysis and data were expressed as mean $\pm$ standard deviation (SD). The χ^2 test was used to analyze the count data. Independent sample *t*-test was used to analyze the measurement data. A *p*-value under 0.05 was considered statistically significant.

3. Results

3.1 Representative DCE-MRI and ultrasound images of diagnosis of breast cancer patients

The breast cancer patients include 43 luminal A patients, 18 luminal B patients, 33 HER2 positive patients, and 17 triple negative breast cancer (TNBC) patients. Figs. 1,2 are the representative images of a breast cancer patient (48 years old). DCE-MRI study showed ring enhancement and spiculated edge (Fig. 1A–F). Ultrasound showed the malignant features, including irregular shape, indistinct margins, lack of posterior echo attention, and Grade II-III blood flow signals (Fig. 2A,B). TIC curve was Type II TIC (Fig. 2C). The lesion was pathologically proven to be left invasive ductal carcinoma, Grade III, with ductal carcinoma in situ (high grade with necrosis), and no metastatic carcinoma in sentinel lymph nodes (HER2+++, ER− and PR−) (Fig. 2D–G).

3.2 Correlation of HER2 with clinical features, Ki-67 and VEGF expression in breast cancer patients

The ages of cases in negative (50.52 ± 9.11 years) and positive HER2 groups (49.18 ± 10.42) had no statistical difference. The T stage ($p = 0.161$) and N stage ($p = 0.079$) between the two groups had no significant difference. The max diameters in the positive HER2 group (28.29 ± 17.49 mm) were higher than that in the HER2 negative group (21.12 ± 14.37 mm) ($p = 0.022$). A greater tumor diameter was significantly positively correlated with HER2 expression. T1 stage and N stage did not correlate with HER2 expression ($p > 0.05$). Moreover, the data revealed that positive HER2 expression was correlated with high Ki-67 ($p < 0.001$) and positive VEGF expression ($p = 0.002$). The detailed results are shown in Table 1.

3.3 Relationship between HER2 and DCE-MRI features of breast cancer patients

The DCE-MRI features mainly included ADC values, multifocality, mass type breast cancer, shape, margin, type of enhancement, and TIC curve (Table 2). We observed that the high ADC values ($p = 0.033$), blurry margins ($p = 0.025$), and multifocality ($p = 0.046$) were significantly correlated with HER2 positivity ($p < 0.05$). The ADC values were higher in HER2-positive patients (971.65 ± 251.40) than in HER2-negative patients (870.70 ± 241.31). Most patients have single lesion (n = 102), while those with multiple lesions (n = 9) showed a significant correlation with positive HER2 expression ($p = 0.046$). However, other DCE-MRI imaging features, such as mass type, shape, enhanced classification, and TIC curve were not significantly correlated with HER2 expression ($p > 0.05$).

4. Discussion

Early detection and treatment of breast cancer have drawn more attention to enhancing patients' prognoses as the incidence of breast cancer has markedly increased [16]. Non-invasive DCE-MRI is a non-invasive diagnostic method of breast cancer as well as DCE-MRI features may have a significant correlation with HER2 status. Moreover, the study of tumor molecular expression in breast cancer manifesting different outcomes has also received attention [17]. In the study, tumor max diameters, Ki-67 and VEGF expression were correlated with HER2 status, while no significant difference was observed in patients' age, T stage and N stage. The DCE-MRI imaging features as ADC values, multifocality and margins that were significantly correlated with HER2 status.

We observed that HER2 status was correlated with max diameters, which suggests that HER2 was related to rate of tumor growth. However, no significant correlation was observed between patients' HER2 status and age, T stage or N tumor staging. Moreover, previous study based on 100 cases indicated that HER2 status was related to the patient's age and tumor size but not to the lymph node status [18]. Inconsistent results were observed in a study of 66 patients with primary breast cancer, where HER2 showed no significant correlation with age, menopausal status, positive nodes or tumor size, but strongly correlated with nodal status [19]. A similar number of studies exhibited similar results, which suggested that the number of cases might affect the statistical analysis. Thus, the clinical correlation with HER2 status should be verified in a large cohort in the future. In breast cancer, Ki-67 is one of the most widely used molecular markers to evaluate the activity of cancer cells [11]. VEGF can stimulate tumor angiogenesis, which is over-expressed in different types of cancers, such as breast cancer [20, 21]. In this study, we observed that the HER2-positive patients had high Ki-67 and VEGF expression, as assessed by IHC staining, which suggests that HER2 positive cases may have a higher proliferation ability and angiogenesis.

Furthermore, HER2 status correlated with some DCE-MRI features, including ADC values, multiplicity and margins. Previous literature demonstrated that HER2-enriched breast tumors have high ADC values [22]. These data revealed that high ADC values may predict the HER2 positive status. However, TIC curve was not correlated with HER2 expression. A previous study indicated TIC curve was significantly related to HER2 subtype but not related to ER and PR subtypes [23]. These data suggest that the value of DCE-MRI features to predict HER2 expression remain need to be verified. From the prognosis perspective, positive HER2 levels have a worse prognosis than negative HER2 levels. Although there are only 9 patients who have multiple lesions, most of the patients (7/9) showed positive HER2 status, which revealed that multifocality of breast cancer may have dissatisfactory survival outcomes. The margin of the breast cancer mass in the HER2-positive group was not circumscribed, whereas the HER2-negative group had circumscribed margins. The appearance of the blurry margins is associated with the invasive growth of the tumor and interaction with fibroblasts and adipocytes [24]. The fibrotic focus of tumors is related to VEGF and increases the risk of blood and lymphatic metastasis [25]. Here, we observed that both blurry margin, ADC value and positive VEGF expression were related to HER2 positive status, which indicated that the DCE-MRI margin features may predict the HER2 status.

This study has some limitations. There was no follow-up data on the patients or follow-up survival analysis. The sample

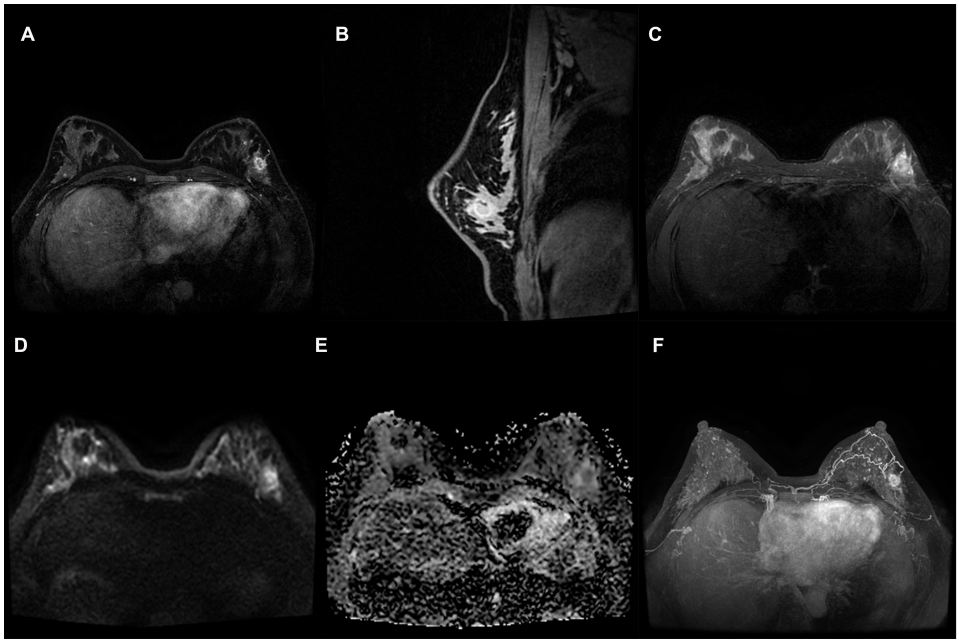

FIGURE 1. Representative images of invasive ductal carcinoma of the left breast on dynamic contrast enhanced-magnetic resonance imageing. (A) T1WI + C transverse position image. (B) T1WI + C sagittal position image. (C) T2WI image. (D) Diffusion weighted imaging (DWI) with restricted diffusion. (E) ADC image. (F) Three-dimensional maximal intensity projection of DCE-MRI breast image. WI: weighted imaging. DWI: diffusion-weighted imaging; ADC: apparent diffusion coefficient.

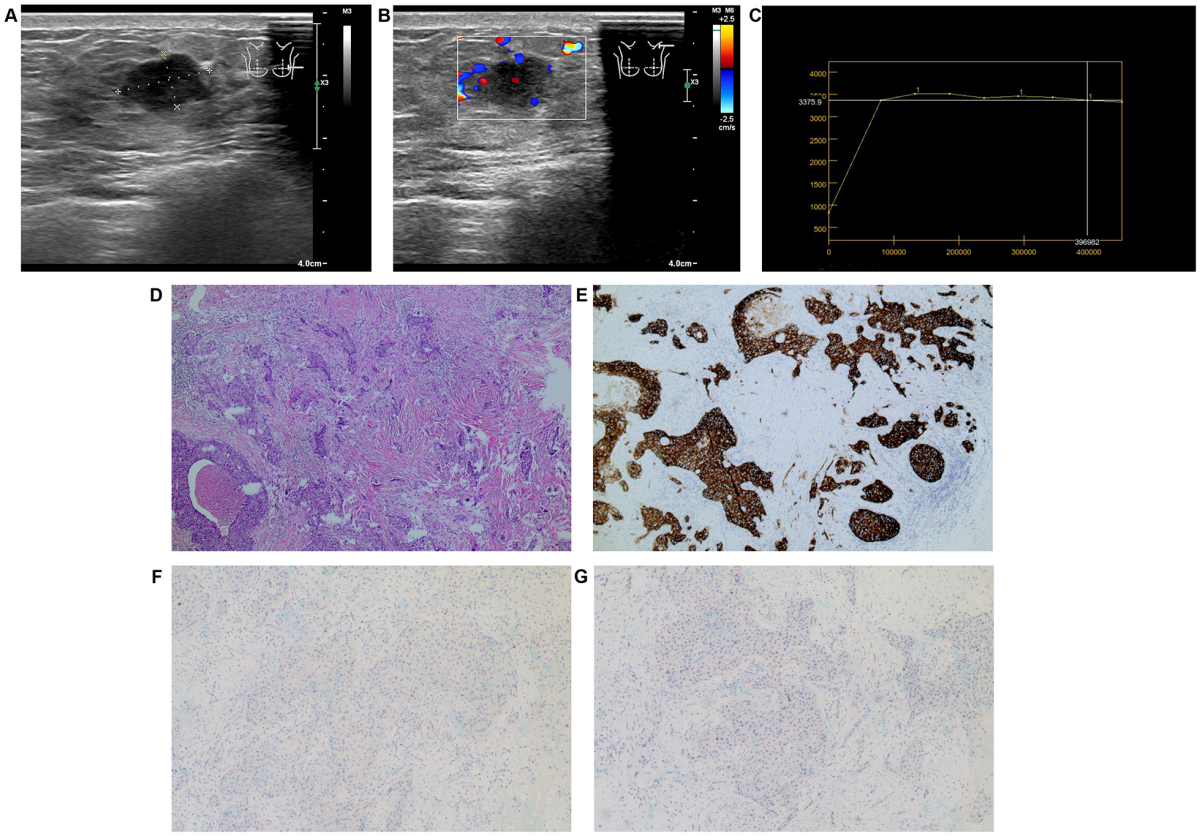

FIGURE 2. Post-processing results of breast cancer patients. (A) The tumor was irregular in shape with ill-defined margins and no significant posterior echo attention. (B) Grade II-III blood flow signals. (C) TIC curve. (D) HE stains (×100) showed invasive ductal carcinoma Grade III. (E) Immunohistochemical (IHC) staining (×100) indicated HER2 was (+++). (F) ER-negative (×100). (G) PR negative (×100).

TABLE 1. The relationship between HER2 and clinical parameters of breast cancer patients.

Features	Cases	HER2 expression		*p*-value
	n = 111	Negative (n = 60)	Positive (n = 51)	
Age (yr)	111	50.52 ± 9.11	49.18 ± 10.42	0.471
Max diameter (mm)	111	21.12 ± 14.37	28.29 ± 17.49	0.022
T stage				
T1	60	33	27	0.161
T2	45	26	19	
T3	6	1	5	
N stage				
N0	73	36	37	0.079
N1	33	23	10	
N2	3	1	2	
N3	2	0	2	
Ki-67 (%)				
≤14	18	17	1	<0.001
>14	93	43	50	
VEGF				
Negative	90	55	35	0.002
Positive	21	5	16	

HER2: human epidermal growth factor receptor 2. VEGF: vascular endothelial growth factor.

TABLE 2. The relationship between HER2 and image features of breast cancer patients.

Sign	Cases	HER2 status		*p*-value
		Negative (n = 60)	Positive (n = 51)	
ADC value (10^{-6} mm^2/s)	111	870.70 ± 241.31	971.65 ± 251.40	0.033
Multifocality				
Single	102	58	44	0.046
Multiple	9	2	7	
Mass type				
Mass type	86	49	37	0.252
Non-mass type	25	11	14	
Shape				
Regular	66	37	29	0.607
Irregular	45	23	22	
Margin				
Circumscribed	81	49	32	0.025
Not circumscribed (irregular, spiculated)	30	11	19	
Type of enhancement				
Homogeneous	7	4	3	0.826
Heterogeneous	91	50	41	
Ring	13	6	7	
TIC curve				
I	2	1	1	0.984
II	69	37	32	
III	40	22	18	

HER2: human epidermal growth factor receptor 2. ADC: apparent diffusion coefficient. TIC: time signal intensity curve.

size was insufficient, and the statistical significance of the data may not be sufficient and have statistical bias, thus, more data in a bigger population will be useful and necessary to verify these results.

5. Conclusions

DCE-MRI features, including ADC values, multifocality and irregular/spiculated margins, have potential value for the evaluation of HER2 status. The clinicopathological features and DCE-MRI features of breast cancer patients may be used to predict the HER2 expression status in breast cancer patients, which may provide a theoretical basis for targeted therapy and prognosis evaluation. This may provide decision support for clinicians in the diagnosis and treatment of HER2 positive breast cancer.

ABBREVIATIONS

DCE-MRI: dynamic contrast enhanced-magnetic resonance imaging; HER2: human epidermal growth factor receptor 2; Ki-67: proliferating cell nuclear antigen; VEGF: vascular endothelial growth factor; ADC: apparent diffusion coefficient; TIC: time signal intensity curve; T1WI: T1-weighted images; TR: repetition time; TE: time to echo; FOV: field of view; Gd-DTPA: gadopentetate dimeglumine; ROI: region of interest; HE: hematoxylin and eosin; IHC: immunohistochemical; ER: Estrogen; PR: progesterone; FISH: fluorescence in situ hybridization; SD: standard deviation; TNBC: triple negative breast cancer; DWI: Diffusion weighted imaging.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

ZLH—designed the research study; TTQ—performed the research; ZLH and TTQ—analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by The Ethics Committee of the Third Hospital of Nanchang (No. 20181109) and followed the principles outlined in the Declaration of Helsinki. In addition, informed consent has been obtained from the participants involved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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