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Original Article

The relationship between DCE-MRI imaging manifestations, semi-quantitative parameters, and VEGF expression in breast cancer

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Abstract: Objective: To explore the relationship between dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and its semi-quantitative parameters and the expression of vascular endothelial growth factor (VEGF) in breast cancer. Methods: Clinical data of 138 patients with breast cancer who underwent surgery were retrospectively analyzed. The patients were divided into malignant lesion (n=82) and benign lesion (n=56) groups according to their postoperative pathological lesions. All patients underwent preoperative DCE-MRI. Images were analyzed, and early enhancement and peak parameters were calculated. Post-operative VEGF expression of the pathological specimens was also detected by immunohistochemical staining. We compared the first-pass enhancement rate (Efirst), first-pass enhancement velocity (Vfirst), early enhancement rate (Ee), early enhancement velocity (Ve), maximum enhancement rate (Emax), maximum enhancement velocity (Vmax), maximum relative enhancement slope (Eslop), time to peak (Tmax), VEGF score, and the expression level between the malignant lesion and benign lesion groups. Pearson correlation test was used to analyze the relationship between early enhancement parameters (Efirst, Vfirst, Ee, Ve) and peak parameters (Emax, Vmax, Eslop, Tmax) of breast cancer DCE-MRI imaging and the VEGF score. Results: Breast cancer DCE-MRI images showed lobulated, quasi-circular nodular or irregular morphologies, which were asymmetrical enhancement and were dominated by circular enhancement. Most of them could be seen with spicule signs. The time-signal intensity curves included plateau type or outflow type, and the monophasic type was not observed. No difference was found in the Efirst and Emax between the two groups (both $P>0.05$). The Vfirst, Ee, Ve, Vmax, and Eslop in the malignant lesion group were significantly greater than those in the benign lesion group (all $P<0.05$), and Tmax was significantly shorter than that in the control group ($P<0.05$). VEGF scores of the malignant lesion group were significantly higher than those in the benign lesion group ($P<0.05$), and the χ^2 test for dichotomous data showed that the overall VEGF expression level was significantly higher in the malignant lesion group than that in the benign lesion group ($P<0.05$). Pearson correlation analysis showed that breast cancer DCE-MRI imaging semi-quantitative parameters (Vfirst, Ee, Ve, Vmax, and Eslop) were positively correlated with the VEGF score, and the Tmax was negatively correlated with the VEGF score, with statistical significance (all $P<0.05$). Conclusion: Breast cancer shows characteristic DCE-MRI imaging, and some dynamic enhancement semi-quantitative parameters are correlated with the VEGF expression levels.

Keywords: Breast cancer, dynamic contrast-enhanced magnetic resonance imaging, vascular endothelial growth factor

Introduction

Breast cancer is one of the most common malignant tumors in women. With the increasing incidence, it is of great significance to strengthen effective assessment and early prediction of breast cancer metastasis and recurrence trends in order to optimize the treatment plan and improve the survival rate of patients [1]. Many studies have shown that breast cancer is vascular-dependent, and tumor angiogenesis is a unique pathological feature of the disease. Vascular endothelial growth factor (VEGF) expression is an important clinical marker for predicting the formation of tumor microvascular networks, and is closely related to the ability of

tumor angiogenesis [2, 3]. However, the tissues used for detecting VEGF are obtained from surgery or biopsy, which are more invasive and less reproducible than imaging; therefore, it is difficult to use routinely for early screening or dynamic evaluation of breast cancer. In recent years, non-invasive dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) techniques have been developed which can dynamically reflect the distribution of contrast agents in tumor-generating blood vessels. The sensitivity of DCE-MRI in the differential diagnosis of breast cancer is extremely high, and it can also provide information on the infiltration and perfusion of tumor-generated blood vessels to indirectly assess tumor angiogenesis conditions [4]. The latest studies have shown that VEGF expression is an important indicator reflecting the angiogenic activity of breast cancer tumors, and DCE-MRI images of breast cancer may be related to the expression level of VEGF. However, there are very few relevant reports [5]. Because the DCE-MRI images of breast cancer are difficult to quantify, the early enhancement parameters and peak parameters can better distinguish breast malignant lesions from benign lesions [6]. However, the relationship between these parameters and VEGF expression is still not clear, and it has become the current research hotspot and difficulty. The aim of the present study was to investigate the relationship between early enhancement parameters and peak parameters of breast cancer DCE-MRI images and VEGF scores, and to verify the diagnostic and prognostic value of DCE-MRI for tumor angiogenesis.

Materials and methods

General information

Clinical data of 138 female patients with breast cancer who were treated by surgery from January 2017 to January 2018 in The Fifth People's Hospital of Ji'nan were retrospectively analyzed. The age of included patients ranged from 19 to 72 years old, and the median age was 44 years old. The patients were divided into the malignant lesion (n=82, 34-72 years, median age of 51 years) and benign lesion (n=56, 19-72 years, median age of 39 years) groups according to their postoperative pathological lesions. The malignant lesions group included 61 cases with invasive ductal carcinoma, 9 with invasive lobular carcinoma, 6 with mucinous adenocarcinoma, 4 with intraductal papillary carcinoma, and 2 with medullary carcinoma. The benign lesions group included 19 cases of fibroadenoma, 11 with hyperplasia lesions, and 26 cases with other lesions.

Inclusion criteria: Patients who underwent DCE-MRI before surgery, and pathological biopsy and VEGF expression analysis after surgery; patients who were newly diagnosed breast tumors that were treated by surgery; patients who were not performed other anti-breast tumor therapy before surgical treatment; patients with complete clinical data.

Exclusion criteria: Patients with other malignant tumors, and vital organ dysfunctions; patients with recurrent breast tumors; patients who were pregnant or lactating.

This study was approved by the Ethics Committee of The Fifth People's Hospital of Ji'nan and all patients signed the informed consent.

Examination methods

All patients underwent preoperative DCE-MRI with a US GE fiber Optix MR 1.5T MRI scanner. The contrast agent used was gadopentetate dimeglumine injection. Before the examination, the patient was placed in a prone position with both breasts fully exposed and naturally suspended in the double-hole mammary gland phased array surface coil. For plain MRI scan, T1WI and T2WI fat suppression sequence scans were performed to determine the T1WI scan parameters; the TR and TE were 560 ms and 16 ms respectively. Fat suppression was performed by the pre-saturation method with an average of 6 times. The T2WI scan parameters were: TR and TE 2,000 ms and 100 ms respectively with echo chain length of 13. Reversal recovery sequence of fat suppression was performed with a reversal time of 170 ms and an average of 6 times. The field of view, layer thickness, spacing, matrix, and reversal angle were 300 mm*300 mm, 5 mm, 0.5 mm, 256*512, and 90° respectively. After detecting the lesions on plain MRI, a fast gradient backflow sequence DCE-MRI was performed. Then the contrast agent was injected through the elbow vein at 0.1 mmol/kg and 10 s later, 20 mL saline was injected. After one plain scan, 10 scans were performed each time during and after injection of contrast agent. Each scan lasted for 10 s, the inter-scan interval for the first 10 scans was 10 s, and that for the last 10

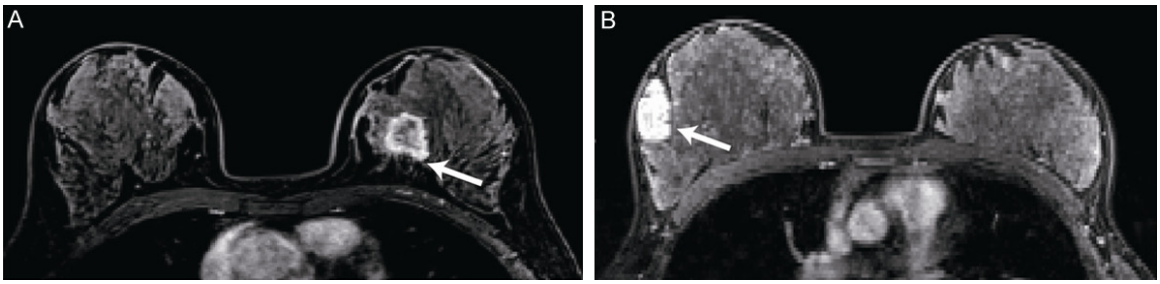

Figure 1. DCE-MRI images of breast tumors. A: Infiltrating ductal carcinoma of the left breast, with quasi-circular nodules and circular enhancement; B: Fibrotic adenoma of the right breast, with oval-shaped, smooth edges. The arrow points to a breast tumor.

scans was 30 s. Each scan acquired 5 frames of images with a total of 600 s. The TR and TE were 75 ms and 4.6 ms respectively with an average of one time, and the field of view, layer thickness, spacing, matrix and reversal angle were 300 mm*300 mm, 5 mm, 0.5 mm, 192*256, and 80° respectively.

Image processing and parameter calculation

The DCE-MRI images of breast cancer were transferred to the post-processing workstations for analysis. The most obvious enhancement parenchymal areas were considered regions of interest (ROIs), and areas that were discernible to the naked eye i.e. areas with calcification, liquefaction, and necrosis were avoided as much as possible. The area of each ROI was estimated to be 10 mm^2, and four areas with obvious enhancement were selected. The time signal intensity curve was plotted, and the early enhancement parameters and peak parameters were calculated. The early enhancement parameters included first-pass enhancement rate (Efirst), first-pass enhancement velocity (Vfirst), early enhancement rate (Ee) and early enhancement velocity (Ve); the peak parameters included maximum enhancement rate (Emax), maximum enhancement velocity (Vmax), maximum relative enhancement slope (Eslop) and peak time (Tmax).

Immuno-histochemical (IHC) staining

IHC was performed to measure the expression of VEGF in pathological specimens after surgery, using ZLI-9032 concentrated DAB kit, universal Ultrasensitive SP kit, and mouse anti-human VEGF monoclonal antibody (all purchased from Beijing Zhongshan Jinqiao Biotechnology. Co., Ltd.). Appearance of brown granules in the cytoplasm of the stained cells was considered a positive region. After viewing the entire slide under a 100× microscopes, areas with a dense distribution of positive cells were selected and observed under a 200× microscope. The total number of cells and the number of positive cells were counted in 3 fields, and the proportion of positive cells was calculated. The samples were scored as 0, 1, 2, and 3 when the proportion of positive cells were <10%, 10-25%, 26-50%, and >50% respectively. Based on negative (-), weakly positive (±), positive (+), and strongly positive (++) intensity of staining, the samples were scored as 0, 1, 2 and 3 respectively. The sum of the two scores was the VEGF score. Samples were considered negative expression, weakly positive expression, positive expression and strongly positive expression for VEGF when the respective scores were 0, 1-2, 3-4, and 5-6. Finally, the tissue specimens that were positive and strongly positive were stratified as high expression and the negative and weak positive specimens as low expression [7, 8].

Data processing

SPSS18.0 software was used for statistical analysis. All measurement data had normal distribution and homogeneity of variance, and are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Early enhancement parameters and peak parameters between the two groups were compared by independent sample t-test. Dichotomous data between the two groups were expressed as a percentage, and compared by χ^2 test. Pearson correlation was used to analyze the relationship between early enhancement parameters (Efirst, Vfirst, Ee, Ve) and peak parameters (Emax, Vmax, Eslop, Tmax) of breast cancer DCE-MRI images and VEGF scores. $P<0.05$ (bilateral) is considered statistically significant.

Table 1. Comparison of early enhancement parameters between the two groups

Group	Efirst (%)	Vfirst (SI/I)	Ee (%)	Ve (SI/I)
Malignant lesion (n=82)	1.658±0.715	1.792±0.836	3.014±0.814	1.601±0.325
Benign lesion (n=56)	1.534±0.817	1.023±0.451	2.361±0.647	1.204±0.126
t	0.861	4.012	3.692	3.458
P	0.134	0.042	0.046	0.048

Note: Efirst, first-pass enhancement rate; Vfirst, first-pass enhancement velocity; Ee, early enhancement rate; Ve, early enhancement velocity.

Table 2. Comparison of peak parameters between the two groups

Group	Emax (%)	Vmax (SI/I)	Eslop (%/S)	Tmax (s)
Malignant lesion (n=82)	3.314±0.792	1.458±0.427	0.019±0.008	241.25±85.46
Benign lesion (n=56)	3.154±0.903	0.592±0.237	0.006±0.003	536.14±158.24
t	0.924	5.624	5.314	29.124
P	0.076	0.031	0.036	<0.001

Note: Emax, maximum enhancement rate; Vmax, maximum enhancement velocity; Eslop, maximum relative enhancement slope; Tmax, time to peak.

Results

Analysis of breast cancer DCE-MRI images

Breast cancer DCE-MRI images showed lobulated, quasi-circular nodular or irregular morphologies with asymmetrical enhancement and were dominated by circular enhancement. Most were associated with spicule signs. The time-signal intensity curves were the plateau or outflow type, and the monophasic type was not observed. In contrast, benign breast tumor DCE-MRI images showed more regular morphologies, and uniform light and moderate enhancement. The majority of the edges were smooth with less spicule signs. Time-signal intensity curves of benign lesions were of the single-phase or plateau type, and no outflow type was seen. See **Figure 1**.

Comparison of early enhancement parameters and peak parameters between the two groups

The Efirst and Emax of the malignant and benign lesions were not significantly different (both P>0.05). The Vfirst, Ee, Ve, Vmax, and Eslop were significantly higher, and Tmax was significantly shorter in the malignant lesion group compared with the benign lesion group (all P<0.05) as shown in **Tables 1**, **2**.

Comparison of VEGF scores between the two groups

VEGF staining of malignant and benign breast tumors is shown in **Figure 2**. The VEGF scores of the malignant lesions were significantly higher than those of the benign lesions (1.714±0.592 vs. 0.682±0.531, P<0.05) as shown in **Table 3**.

Comparison of VEGF expression levels between the two groups

The proportion of low VEGF expression rate was 29.27% and that of high expression VEGF rate was 70.73% in the malignant lesion group, and those in the control group were 89.29% and 10.71% respectively. The χ^2 test showed that high VEGF expression rate was significantly higher in the malignant lesion group compared to that in the benign lesion group (P<0.05) as shown in **Table 4**.

Correlation analysis between semi-quantitative DCE-MRI image parameters and VEGF scores in breast cancer

Pearson correlation analysis showed that the breast cancer DCE-MRI image semi-quantitative parameters (Vfirst, Ee, Ve, Vmax, and Eslop) were all positively correlated, while Tmax was negatively correlated with VEGF scores, with statistical significance (both P<0.05) as shown in **Table 5**.

Discussion

Breast cancer is dependent on the vasculature. With the continuous growth and development of tumors, it is accompanied by angiogenesis and increased microvessel density, which was used as the basis for DCE-MRI application

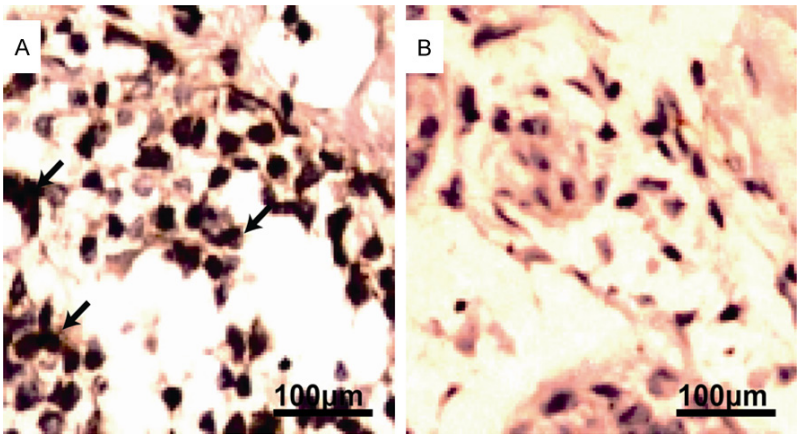

Figure 2. VEGF expression in breast tumor specimens by immuno-histochemical staining. A: VEGF expression in breast infiltrating ductal carcinoma cells with arrows pointing to the brown/sepia cytoplasm indicating strong positive expression; B: Negative VEGF expression in breast fibroadenomas cells. VEGF, vascular endothelial growth factor.

Table 3. Comparison of VEGF scores between the two groups

Group	VEGF score
Malignant lesion (n=82)	1.714±0.592
Benign lesion (n=56)	0.682±0.531
t	6.017
P	0.026

Note: VEGF, vascular endothelial growth factor.

Table 4. Comparison of VEGF expression levels between the two groups (n, %)

Group	Low expressing	High expressing
Malignant lesion (n=82)	24 (29.27)	58 (70.73)
Benign lesion (n=56)	50 (89.29)	6 (10.71)
χ^2	10.429	
P	0.002	

in our study. Analyzing the characteristics of breast cancer DCE-MRI imaging provides important basis for the differential diagnosis of benign and malignant breast lesions. In our study, breast cancer DCE-MRI images were analyzed for lesion morphology, enhancement characteristics, and time-signal intensity curves. This study revealed that breast cancer DCE-MRI images showed lobulated, quasi-circular nodular or irregular morphologies, while most of DCE-MRI images of breast benign tumors showed regular morphologies. Due to the rapid formation of tumors in breast cancer, it is difficult for new blood vessels to supply oxygen, leading to necrosis within the tumor, and even with hemorrhage, resulting in mixed DCE-MRI signals. Therefore, contrast agents are unevenly distributed and show a centripetal enhancement compared with benign breast tumors, which are mainly light, moderately enhanced, and uniform. However, this does not rule out the rapid growth of individual breast benign tumors that can also cause mixed internal signals [9, 10]. From this study, it could be seen that the DCE-MRI enhancement features of breast cancer were uneven and remarkable enhancement, mainly circular enhancement, and mostly spicule signs were visible. We hypothesize that the main reason for circular enhancement and spicule is the infiltration of cancer cells into the surrounding tissues that causes para-carcinoma tissue hyperplasia leading to unclear edges. The benign breast tumors are mostly mild, moderately enhanced and evenly reinforced, and most of the edges are smooth with less spicule signs. Consistent with study of Li et al., the DCE-MRI enhancement characteristics of benign and malignant tumors were significantly different [11].

In addition, the time-signal intensity curve of DCE-MRI images can objectively reflect the blood perfusion of breast lesions. Because the blood perfusion levels of benign and malignant breast tumors are significantly different, the time-signal intensity curves of the DCE-MRI images of the two groups can also be helpful in their differential diagnosis [12]. In the present study, the time-signal intensity curve of breast cancer DCE-MRI images were classified as plateau or outflow type, and no single-phase type was found. However, the benign breast tumors were either monophasic or plateau type and no outflow type was observed. Therefore, we infer that malignant breast cancer manifests as irregular morphology, non-uniform obvious enhancement, dominated by circular enhancement, visible spicule signs, and outflow type time-signal intensity curve. On the other hand, if the time-signal intensity curve type is the

Table 5. Correlation analysis between semi-quantitative DCE-MRI image parameters and VEGF scores in breast cancer

Parameter	Vfirst	Ee	Ve	Vmax	Eslop	Tmax
r	0.612	0.586	0.541	0.601	0.592	-0.691
P	0.001	0.001	0.005	0.002	0.003	<0.001

Note: Vfirst, first-pass enhancement velocity; Ee, early enhancement rate; Ve, early enhancement velocity; Vmax, maximum enhancement velocity; Eslop, maximum relative enhancement slope; Tmax, time to peak.

monophasic type, the diagnosis is likely that of benign breast tumors. For patients with the plateau type time-signal intensity curve, it is necessary to combine the DCE-MRI semi-quantitative parameters for differential diagnosis.

Currently, semi-quantitative parameters of breast cancer DCE-MRI imaging dynamic enhancement are commonly used to evaluate angiogenesis of tumors, and VEGF is used as a specific marker to quantify the angiogenic capacity of tumors. This study analyzed the relationship between early enhancement parameters and peak parameters of breast cancer DCE-MRI images and the VEGF expression levels, with the aim of improving the value of DCE-MRI in the diagnosis and treatment of breast cancer. The main mechanism of VEGF in promoting tumor angiogenesis is mainly to stimulate the growth of vascular endothelial cells and increase vascular permeability. A study has shown that VEGF could induce tumor angiogenesis in breast cancer and become one of the specific factors regulating tumor angiogenesis [13]. Its high expression levels in malignant gastric, liver, and lung tumors were positively correlated with angiogenesis levels [14-16]. Comparing the VEGF levels in normal breast tissue and breast cancer tissue, studies have shown that normal breast tissue does not express VEGF, whereas breast cancer tissue does at high levels, and the expression level was associated with pathological features such as tissue differentiation, lymph node metastasis, and microvessel density [17]. From the results of **Tables 3** and **4** in this study, the VEGF scores in the malignant lesions group were significantly higher compared to the benign lesions group ($P<0.05$). The χ^2 test of the dichotomous data showed that the high VEGF expression rate was also significantly higher in the malignant lesion group than that in the benign lesion group ($P<0.05$). It has been demonstrated that the level of VEGF expression is significantly different between breast cancer and benign breast tumors. In this study, we aimed to objectively reflect the hemodynamic characteristics of tumors, by calculating the early enhancement parameters and peak parameters of breast cancer DCE-MRI imaging manifestations, and using the Pearson correlation analysis to analyze the relationship between the semi-quantitative parameters of breast cancer DCE-MRI images and the VEGF expression levels. While Efirst and Emax were not significantly different between the two lesion groups (both $P>0.05$), the Vfirst, Ee, Ve, Vmax, and Eslop were significantly greater, and Tmax was significantly shorter, in the malignant lesion group compared to those in the benign lesion group (all $P<0.05$; **Table 1**). Consistent with the findings of Su et al., Vfirst, Ee, Ve, Vmax, and Eslop are clinically significant parameters to evaluate tumor angiogenesis [18].

Using all the Vfirst, Ee, Ve, Vmax, Eslop, and Tmax as enhancement model parameters after injecting contrast agents into breast cancer tissues can achieve dynamic enhancement semi-quantitative analysis of the lesions. Among them, Vfirst, Ee, and Ve can comprehensively reflect the change of contrast agent concentration, tumor vascular volume, and permeability in the tumors before balance, along with the permeability and perfusion level of tumor blood vessels [19]. The Vmax, Eslop, and Tmax also depend on the degree of vascularization of the tumors. The higher the level of VEGF expression is, the higher the Vmax and Eslop will be, and the shorter the duration of the enhancement signal is to reach the peak [20]. From this study, we learned that the expression level of VEGF in breast cancer tissue was significantly increased, indicating that there were relatively abundant new-born capillaries in breast cancer tissues. It is beneficial for absorption and leakage of the contrast agent after injection into the breast cancer due to capillary network and its high permeability, which is easier to reach the saturation point than the benign breast tumors, resulting in a significant increase in Vfirst, Ee, Ve, Vmax, Eslop, and significant shorter of Tmax. From **Table 5**, we found that breast cancer DCE-MRI image semi-quantitative parameters (Vfirst, Ee, Ve, Vmax, Eslop) are positively correlated with the VEGF score by Pearson correlation analysis. The Tmax was negatively

associated with the VEGF score, the differences were statistically significant (all $P<0.05$). These data indicated that the VEGF increased the uptake rate of contrast agent by increasing the permeability of blood vessels in tumor tissues, thereby affecting the early perfusion process, fully demonstrating the correlation between part of the dynamic enhancement semi-quantitative parameters of breast cancer DCE-MRI images and the VEGF expression levels. This study has initially shown that some of the semi-quantitatively enhancement parameters have significant potential in aspects such as reflecting the hemodynamics, speculating microvascular density and angiogenic capacity of breast cancer lesions, which can objectively reflect the morphological characteristics of breast cancer and the pathological characteristics of blood supply. However, our study is still at the preliminary stage and needs to be further validated. In addition, since the sample size of this study was small, the changes in DCE-MRI manifestations between benign and malignant breast lesions cannot be completely explained by vascular theory. It is essential to analyze the relationship between DCE-MRI images and the VEGF expression levels in breast cancer tissues of different molecular subtypes.

In conclusion, breast cancer shows characteristic DCE-MRI imaging manifestations, and some of the dynamic enhancement semi-quantitative parameters are closely related to VEGF expression levels. The technique can objectively judge the tumor angiogenesis, and, to a certain extent, can be used for preoperative differential diagnosis, assessment of severity and prognosis, which is worthy of further research and application.

Disclosure of conflict of interest

None.

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