

The value of multimodal magnetic resonance imaging in breast cancer and its correlation with pathological features and prognosis

Q. LUO¹, L. YANG², X. ZHOU³

¹Department of Medical Imaging, 3201 Hospital of Xi'an Jiaotong University Health Science Center, Hanzhong City, Shaanxi Province, China

²Department of Radiology, Xinhua Hospital Affiliated to Dalian University, Dalian City, Liaoning Province, China

³Department of Radiology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi City, China

Qi Luo and Liu Yang are co-first authors and they contributed equally to this study

Abstract. – OBJECTIVE: This study aimed to explore the diagnostic value of multimodal magnetic resonance imaging (MRI) in breast cancer (BC) and its correlation with pathological features of the disease.

PATIENTS AND METHODS: Clinical data of 85 BC patients (malignant group) and 85 patients with benign breast diseases (benign group), admitted to 3201 Hospital of Xi'an Jiaotong University Health Science Center from May 2020 to May 2022, were retrospectively collected. Both groups underwent multimodal MRI examinations. We compared the differences in multimodal MRI examination parameters between the groups, as well as between patients with different pathological characteristics and prognoses in the malignant group. The correlation between multimodal MRI examination parameters and pathological features of BC was analyzed.

RESULTS: The apparent diffusion coefficient (ADC) of the malignant group was lower than that of the benign group, while the extravascular extracellular volume fraction (V_e), reaction rate constant (K_{ep}), and volume transfer constant (K^{trans}) of the malignant group were higher compared to the benign group ($p<0.05$). In the malignant group, patients with stage III+IV disease, lymph node metastases, and low differentiation had lower ADC values, and higher V_e , K^{trans} , and K_{ep} compared to patients with stage I+II disease, no lymph node metastasis, and medium to high differentiation ($p<0.05$). ADC value negatively correlated with the stage of the disease, lymph node metastases but positively correlated with the degree of differentiation ($p<0.05$). V_e , K^{trans} , and K_{ep} positively correlated with the stage of the disease and lymph node metastasis, and negatively correlated with the degree of differentiation ($p<0.05$). ADC value of patients with poor prognosis was lower, while V_e , K^{trans} , and K_{ep} were

higher compared to patients with good prognosis ($p<0.05$). The Receiver operating characteristic (ROC) analysis showed that ADC, V_e , K^{trans} , and K_{ep} have certain predictive values for the poor prognosis of BC patients ($p<0.05$).

CONCLUSIONS: Multimodal MRI examination detected obvious differences in the examination parameters of BC patients, and the increase or decrease in these parameters is closely correlated with the pathological characteristics and prognosis of the disease. Multimodal MRI examination can be used for pathological evaluation and prognosis prediction in BC patients.

Key Words:

Breast cancer, Multimodal, Magnetic resonance imaging, Pathological characteristics.

Introduction

Breast cancer (BC) has the highest incidence rate among malignancies in women, and greatly impacts the quality of life and physical and mental health of patients^{1,2}. In recent years, the incidence rate of BC is rising, and the disease affects younger populations¹⁻³. BC is highly invasive⁴ and is often accompanied by axillary and peripheral tissue lymph node metastases, which makes treatment and prognosis difficult⁵. Early and accurate diagnosis and assessment of BC are, therefore, of great significance to ensure that patients receive timely targeted therapy³⁻⁵.

Multimodal MRI is an important imaging examination technique in clinical practice. It includes diffusion-weighted imaging (DWI) and dynamic contrast-enhanced dynamic contrast-enhanced

magnetic resonance imaging (DCE-MRI)^{6,7}. DWI can provide a reference for the diagnosis and evaluation of the disease by measuring the movement status of cellular water molecules in the body⁸, while DCE-MRI can clarify the microenvironment, hemodynamics, and morphological changes of the lesion⁷⁻⁹. MRI has a high false-positive rate (it identifies lesions as tumors which are not) and cannot reveal the presence of microcalcifications. To overcome these limitations in specificity, several functional MRI parameters should be investigated⁸⁻¹⁰.

This study aims to retrospectively analyze clinical data of BC patients in our hospital and to assess the diagnostic value of multimodal MRI-related examination parameters and their correlation with pathological features.

Materials And Methods

General Information

We retrospectively selected clinical data of BC patients (n=85), (malignant group), and patients with benign breast diseases (n=85; benign group), admitted to 3201 Hospital of Xi'an Jiaotong University Health Science Center from May 2020 to May 2022. Written informed consent was obtained from the patient or legal guardian. The ethics committee of 3201 Hospital approved this study on June 9th, 2023, with the number 2023-008.

Inclusion criteria

- The benign and malignant group meets the diagnostic criteria for BC¹¹.
- BC diagnosis confirmed through pathological examination.
- No treatment such as radiotherapy or chemotherapy was administered before the inclusion in the study.
- Complete clinical data.
- Unilateral onset.
- More than one year of follow-up available.

Exclusion criteria

- Presence of other benign and malignant tumors;
- Communication disorder, cognitive barrier and mental system disease;
- Image blurring and presence of artifacts.

Examination Method

All patients underwent multimodal MRI-related examinations. The equipment used was GE Signa

HDxt 3.0T magnetic resonance instrument (Boston, USA). Firstly, routine MRI scans were performed, including T1 weighted image (T1WI) on the transverse axis: 17 ms for echo time (TE) and 500 ms for repetition time (TR). The transverse axial T2 weighted image (T2WI): TE is 92 ms, TR is 3,800 ms, and the Coronal plane T2WI: TE is 90 ms, TR is 3,200 ms. DWI adopted the spin-echo echoplanar imaging (SE-EPI) sequence, with relevant parameter settings: layer spacing of 1 mm; layer thickness 5 mm; reverse angle 15°; TE 100 ms; TR 5500 ms; B values 0 and 800 s/mm²; matrix 192 × 192; field of view 20 cm × 20 cm - 40 cm × 40 cm.

DCE-MRI scanning

Coronal plane scanning was performed by three position volume interpolation body examination sequence. Related scanning parameter settings: field of view 40 cm × 40 cm; layer thickness 4 mm; matrix 320 × 320; reverse angle 25°; TE 1.07 ms; TR 2.9 ms. After the completion of the first phase, 0.1 mmol/kg Gadopentetic acid (Gd-DTPA) was injected into the anterior cubital vein through a high-pressure syringe (at a rate of 4 ml/s). Physiological saline (20 ml) was injected at the same rate, and gap-free scanning, with a total of 50 scanning phases, was performed.

Image post-processing

Two physicians from the department with a working experience of ≥10 years were invited to review the film together. 1) For the apparent diffusion coefficient (ADC) value measurement, DWI raw images were transmitted to the post-processing workstation. According to conventional contrast-enhanced T1WI, the most significant area of tumor enhancement is delineated on the b-value 800 s/mm² image at the corresponding location. Care was taken to avoid areas of calcification, bleeding, and liquefaction necrosis as much as possible. The average value was calculated after measuring three times. 2) DCE-MRI measurement: DCE-MRI data were processed using Siemens Tissue 4D post-processing software (Munich, Germany). Two compartment pharmacokinetic Tofts model was selected. Adjacent arterial blood vessels of the tumor body were selected as the arterial input function. Pseudo-color images of three quantitative parameters, V_e , K_{ep} , and K^{trans} , were obtained. Region of interest (ROI) was drawn on DCE-MRI coronal images with reference to the enhanced solid portion of the tumor. Care was taken to avoid areas of cystic degeneration, bleeding, and liquefaction necrosis as much as possible. ROI was copied into the

corresponding three quantitative parameter maps to obtain V_e , K_{ep} , and K^{trans} . The average value was calculated after measuring three times.

Outcome measures

Baseline data of patients; multimodal MRI-related examination parameters (ADC, V_e , K_{ep} , K^{trans}); prognosis (setting patients who died or relapsed during the follow-up period as having poor prognosis) were collected.

Statistical Analysis

The statistical software used was SPSS 22.0 (IBM Corp., Armonk, NY, USA). The measurement data all met the normal distribution and were expressed as ($\bar{x} \pm s$), and the comparison between the two groups adopted an independent sample *t*-test. Spearman correlation was used to test the correlation between variables. The prognostic value of multimodal MRI parameters was analyzed by Receiver operating characteristic (ROC). According to the test level, $p < 0.05$ indicated that the difference was statistically significant.

Results

The age of the patients in the malignant group was 46-77 years old, with an average of (61.74 ± 8.37) years old. The body mass index was 17.48-26.97 kg/m², with an average of (22.35 ± 2.5) kg/m². In terms of disease staging, 41 patients were in stage I+II, and 44 were in stage III+IV. In terms of lymph node metastases, 37 patients had metastases, and 48 patients were metastasis-free. Of 85 BC patients, 31 were poorly differentiated, and 54 were moderately well differentiated. The age of the benign group was 44-79 years old, with an average of (59.95 ± 9.22) years old. The body mass index was 17.40-27.61 kg/m², with an average of (22.48 ± 2.49) kg/m². There was no significant

difference in general data, such as age and body mass index, between the two groups ($p > 0.05$).

The ADC values of the malignant group were lower, while V_e , K_{ep} , and K^{trans} were higher than those of the benign group ($p < 0.05$) (Table I).

The ADC values of patients with BC stage III+IV, lymph node metastases, and low differentiation were significantly lower than those of patients with stage I+II, no lymph node metastasis, and medium to high differentiation. At the same time, V_e , K_{ep} , and K^{trans} were all higher in patients with BC stage III+IV, lymph node metastases, and low differentiation compared to patients with stage I+II, no lymph node metastasis, and medium to high differentiation ($p < 0.05$) (Table II).

There was a negative correlation between ADC value and BC disease stage, occurrence of lymph node metastases, and a positive correlation with the degree of differentiation ($p < 0.05$). V_e , K_{ep} , and K^{trans} all positively correlated with the stage of BC and lymph node metastases, and negatively correlated with the degree of differentiation ($p < 0.05$) (Table III).

Among 85 BC patients in the malignant group, 23 had a poor prognosis, and 62 had a good prognosis. Patients with poor prognoses have lower ADC values than those with good prognoses. V_e , K_{ep} , and K^{trans} were higher in the poor prognosis patients compared to patients with good prognosis ($p < 0.05$) (Table IV).

The Receiver operating characteristic analysis showed that the area under the curve (AUC) of ADC was 0.818, the sensitivity was 91.3%, and the specificity was 58.1%. The AUC of V_e was 0.653, with a sensitivity of 56.5% and a specificity of 74.2%. K_{ep} had an AUC of 0.750, a sensitivity of 95.7%, and a specificity of 51.6%. The AUC of K^{trans} was 0.703, with a sensitivity of 78.3% and a specificity of 56.5%. These results indicate that all analyzed parameters have certain predictive values for poor prognosis of BC patients ($p < 0.05$) (Figure 1) (Table V).

Table I. Comparison of multimodal MRI-related examination parameters between malignant group and benign group.

Group	n	ADC ($\times 10^3 \text{ mm}^2/\text{s}$)	V_e	$K_{ep} (\text{min}^{-1})$	$K^{trans} (\text{min}^{-1})$
Malignant group	85	0.91 ± 0.24	0.70 ± 0.20	1.52 ± 0.51	3.19 ± 1.11
Benign group	85	1.39 ± 0.27	0.32 ± 0.07	0.69 ± 0.25	1.48 ± 0.47
<i>t</i>		-12.216	16.849	13.322	13.085
<i>p</i>		<0.001	<0.001	<0.001	<0.001

ADC: apparent diffusion coefficient; V_e : extravascular extracellular volume fraction; K_{ep} : reaction rate constant; K^{trans} : volume transfer constant

Table II. Comparison of multimodal MRI parameters in patients with different pathological characteristics.

Pathological Characteristics	n	ADC ($\times 10^3 \text{ mm}^2/\text{s}$)	V_e	$K_{ep} (\text{min}^{-1})$	$K^{trans} (\text{min}^{-1})$
Disease Staging					
I+II	41	1.03 \pm 0.20	0.65 \pm 0.20	1.35 \pm 0.50	2.86 \pm 1.16
III+IV	44	0.79 \pm 0.22	0.75 \pm 0.19	1.67 \pm 0.48	3.50 \pm 0.98
<i>t</i>		5.237	-2.547	-2.942	-2.763
<i>p</i>		<0.001	0.013	0.004	0.007
Lymph node metastasis					
Transfer	37	0.76 \pm 0.21	0.77 \pm 0.17	1.71 \pm 0.49	3.59 \pm 1.09
No transfer	48	1.02 \pm 0.21	0.65 \pm 0.21	1.37 \pm 0.49	2.88 \pm 1.04
<i>t</i>		-5.710	2.744	3.123	3.043
<i>p</i>		<0.001	0.007	0.002	0.003
Degree of differentiation					
Poorly differentiated	31	0.76 \pm 0.23	0.79 \pm 0.20	1.75 \pm 0.54	3.63 \pm 1.03
Medium to high differentiation	54	0.99 \pm 0.21	0.65 \pm 0.18	1.39 \pm 0.46	2.94 \pm 1.08
<i>t</i>		-4.707	3.297	3.280	2.896
<i>p</i>		<0.001	0.001	0.002	0.005

ADC: apparent diffusion coefficient; V_e : extravascular extracellular volume fraction; K_{ep} : reaction rate constant; K^{trans} : volume transfer constant

Table III. Correlation analysis.

Pathological Characteristics	ADC		V_e		K_{ep}		K^{trans}	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Pathological characteristics	-0.483	<0.001	0.252	0.020	0.297	0.006	0.310	0.004
Lymph node metastasis	-0.550	<0.001	0.284	0.008	0.292	0.007	0.302	0.005
Degree of differentiation	0.416	<0.001	-0.338	0.002	-0.321	0.003	-0.317	0.003

ADC: apparent diffusion coefficient; V_e : extravascular extracellular volume fraction; K_{ep} : reaction rate constant; K^{trans} : volume transfer constant

Table IV. Comparison of multimodal MRI parameters among patients with different prognosis.

Group	n	ADC ($\times 10^3 \text{ mm}^2/\text{s}$)	V_e	$K_{ep} (\text{min}^{-1})$	$K^{trans} (\text{min}^{-1})$
Poor prognosis	23	0.71 \pm 0.22	0.79 \pm 0.20	1.81 \pm 0.37	3.73 \pm 0.98
Good prognosis	62	0.98 \pm 0.21	0.67 \pm 0.19	1.41 \pm 0.52	2.99 \pm 1.10
<i>t</i>		-5.326	2.626	3.439	2.841
<i>p</i>		<0.001	0.010	0.001	0.006

ADC: apparent diffusion coefficient; V_e : extravascular extracellular volume fraction; K_{ep} : reaction rate constant; K^{trans} : volume transfer constant

Table V. Predictive value of multimodal MRI parameters for prognosis.

Index	AUC	95% CI	<i>p</i>	Sensitivity (%)	Specificity (%)	Cut-off value
ADC	0.818	0.725-0.911	0.000	91.3	58.1	0.94
V_e	0.653	0.520-0.786	0.031	56.5	74.2	0.85
K_{ep}	0.750	0.643-0.856	0.000	95.7	51.6	1.4
K^{trans}	0.703	0.584-0.823	0.004	78.3	56.5	3.3

ADC: apparent diffusion coefficient; V_e : extravascular extracellular volume fraction; K_{ep} : reaction rate constant; K^{trans} : volume transfer constant; AUC: area under the curve

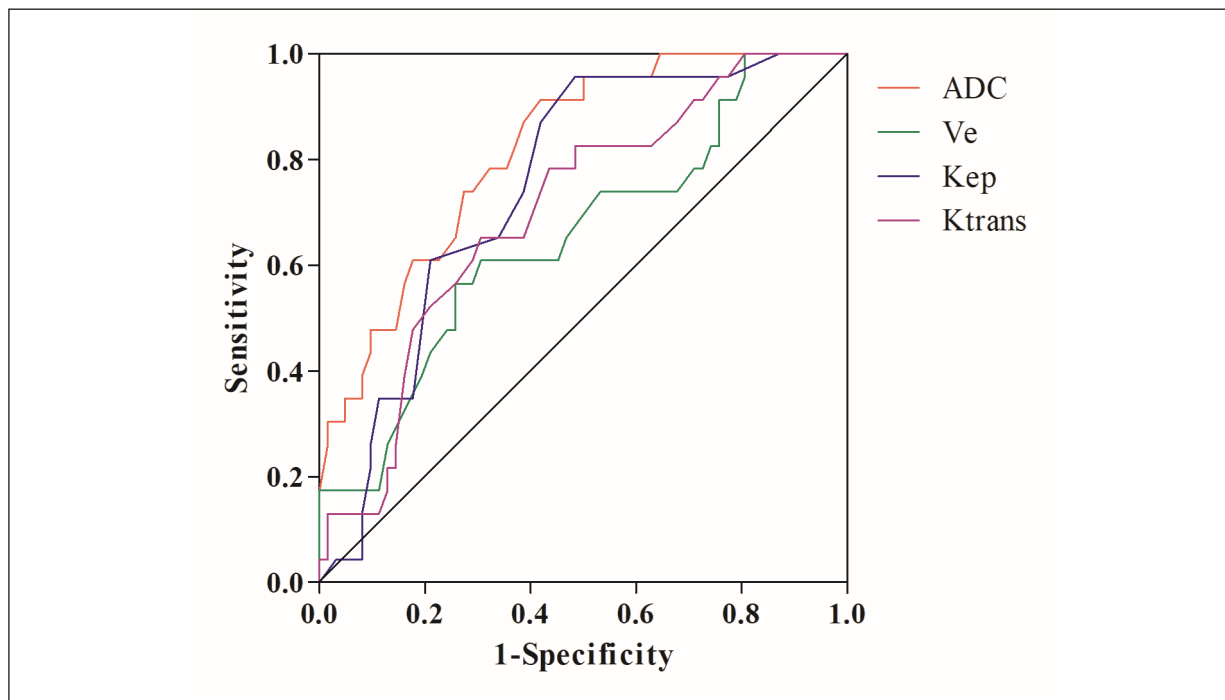


Figure 1. Receiver operating characteristic of multimodal MRI parameters predicting poor prognosis.

Discussion

The results of our study show that BC is associated with lower ADC value and higher V_e , K_{ep} , K_{trans} parameters of the multimodal MRI, indicating that these quantitative indicators can differentiate between the benign and malignant nature of breast diseases.

This differentiating ability may be based on the fact that DWI is able to measure thermally-driven movement of water molecules in the tissue^{6,7,12}. ADC that is quantified on DWI can reflect the combined effect of water molecular diffusion and microcirculation perfusion¹¹. Since there are differences in cell density and perfusion status in the benign and malignant breast lesions, these differences allow to recognize the nature of breast tumors¹². V_e , K_{ep} , and K_{trans} mainly reflect the microvascular permeability status of the lesion tissue and are closely related to the microvascular density and vascular permeability^{9,13}. Compared to benign breast lesions, BC lesions typically exhibit more vigorous metabolism and proliferation, abundant neovascularization, and lower wall maturity, resulting in a lower exchange rate between the inside and outside of the vessels. Therefore, V_e , K_{ep} , and K_{trans} levels in malignant tissue are significantly increased compared to the benign ones^{14,15}. McDonald et al¹⁶ pointed out that

in MRI multimodal imaging, a conventional plain scan can clearly present and diagnose hamartoma, lipoma, cyst, etc. DCE-MRI uses the injection of contrast agents and can perform multiphase scans in a relatively short period of time. Due to the differences in enhancement patterns and characteristics between benign and malignant tumor tissues and normal breast tissue, the diagnosis and differentiation are based on the enhancement characteristics^{15,16}. Goto et al¹⁷ showed that there are certain differences in ADC values between patients with BC and benign lesions, which can be used for the differential diagnosis of the benign and malignant nature of diseases. Additionally, compared to a regular MRI, the combination of DWI and DCE-MRI is associated with improved accuracy of differential diagnosis and can clarify the morphological and texture features of the lesion, and provide an objective reference basis for the diagnosis and evaluation of diseases. Zhang et al¹⁸ showed that there are significant differences in multimodal MRI-related examination parameters, such as ADC values, in patients with various breast tumors, which can be used for the diagnosis and differentiation of diseases. Their results also showed that malignant tumors contain tightly-arranged dense cells with poor differentiation ability and strong proliferative ability. As a result, water molecular diffusion in

tumor tissue is limited, resulting in decreased ADC^{17,18}. These observations are consistent with the conclusions of our study.

Our results also showed significant differences in the parameters of multimodal MRI examination in BC patients with different pathological characteristics of BC. There was a close correlation between ADC values, V_e , K_{ep} , and K^{trans} and different disease stages, lymph node metastasis, and degree of differentiation. Li et al¹⁹ also confirmed that there are significant differences in ADC values in BC patients with different breast parenchymal grading, tumor size, axillary lymph nodes involvement, etc. Consistent with the results of this study, we further confirmed that multimodal MRI examination can also be used for evaluating the pathological features of BC and may guide the clinical development of more targeted intervention plans. Patients with different disease stages, lymph node metastases, and differentiation levels have tight cell arrangement and varying density, resulting in differences in water molecule movement, that would manifest in various ADC values²⁰. Similarly, different pathological characteristics of BC tissues with different metabolic and proliferative states, and different neovascularization conditions would lead to changes in V_e , K_{ep} , and K^{trans} ²¹. Our study also showed that poor prognosis in BC patients was associated with higher values of ADC, and lower V_e , K_{ep} , and K^{trans} . ROC analysis showed that each MRI parameter had a certain value in predicting the poor prognosis of patients. Our results are consistent with those of Tahmassebi et al²² confirming the high value of multimodal MRI examination in the prognosis evaluation of BC patients.

Limitations

It is a single-center retrospective study with a relatively small total number of patients, and therefore, a risk of statistical bias cannot be excluded. Therefore, the conclusion of this study is preliminary only and further research is needed to confirm it and add radiomics analysis. In the future, we need to provide details regarding follow-up examinations. What could be implemented is the assessment of the cut-off value for ADC for distinguishing malignant from benign breast tumors.

Conclusions

BC patients showed obvious abnormalities on multimodal MRI examination and the increase

or decrease in the related parameters is closely related to the pathological characteristics and prognosis of the disease. Multimodal MRI examination can be used for pathological evaluation and prognosis prediction in breast cancer patients.

Authors' Contributions

QL and LY conceived and designed the study, QL and LY collected data and performed data analysis. QL and LY wrote the draft of this manuscript. XZ edited the manuscript.

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No funding was received for this study.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Approval

The ethics committee of 3201 Hospital approved this study on June 9th, 2023, with the number 2023-008.

Informed Consent

Written informed consent was obtained from the patient or legal guardian.

Availability of Data and Materials

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

ORCID ID

QL: 0009-0007-2854-4068

LY: 0009-0006-7959-3110

XZ: 0009-0000-8507-6140.

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