Original Article
Application value of MRI apparent diffusion coefficient (ADC) before and after radical mastectomy for patients with breast cancer

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Abstract: Objective: To explore the correlation between Apparent Diffusion Coefficient (ADC) of preoperative Magnetic Resonance Imaging (MRI) and the risk factors for prognosis among patients who have received radical mastectomy, and to study the role of ADC values measured in regions of interest (ROI) in the diagnosis of preoperative axillary lymph node metastasis and postoperative recurrence. Methods: Imaging data of diffusion weighted imaging (DWI) of 150 patients before and after radical mastectomy were reviewed. Multivariate linear regression was used to analyze the correlation between preoperative ADC parameters of lesions and prognostic factors such as lymph node metastasis, human mammaglobin (hMAM) and low expression of Ki67. Receiver operating characteristic (ROC) curve was used to evaluate the value of ADC parameters obtained from the ROI in the diagnosis of preoperative axillary lymph node metastasis and postoperative recurrence. Results: Comparisons of ADC values for the respective preoperative prognostic factor showed that there was a statistically significant difference between ADC values for patients with lymph node metastasis, Ki67 overexpression, human mammaglobin positivity (hMAM+), estrogen receptor negativity (ER-), progesterone receptor negativity (PR-), human epidermal growth factor receptor 2 positivity (HER2+) and the ADC values for patients without these symptoms (all $P<0.05$). Further, multivariate linear regression showed that there was a significant correlation between the preoperative ADC value of tumors and lymph node metastasis, Ki67 overexpression, hMAM (+), ER (-), PR (-) and HER2 (+) (all $P<0.05$). Pathological diagnosis of the 150 patients before surgery showed ipsilateral lymph node metastasis in 45 patients (30.00%). ROC curve analysis showed AUC=0.925 and IC 95% (0.791, 0.972). Youden index was 0.889, and the corresponding optimal threshold value was 1.07. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 88.89%, 92.38%, 83.38%, 95.10% and 91.33% respectively. Surgical pathology confirmed that there were 33 cancer recurrences (22.00%) in the 150 patients 2 years after operation. The ROI ADC value for patients with recurrent cancer was 1.32±0.19, which was significantly higher than that for patients without recurrent cancer (0.92±0.22), and the difference was statistically significant (t=10.302, $P<0.001$). ROC curve analysis showed AUC=0.963 and IC 95% (0.839, 0.989). Youden index was 0.896, and the corresponding optimal threshold value was 1.05. The sensitivity, specificity, positive predictive rate, negative predictive rate and diagnostic accuracy were 90.91%, 96.58%, 88.24%, 97.41% and 95.33%, respectively. Conclusion: There was a significant correlation between the preoperative ADC values measured using DWI and lymph node metastasis, Ki67 overexpression, hMAM+, ER-, PR- and HER+ for patients who have received radical mastectomy. And ADC values played an important role in the diagnosis of preoperative axillary lymph node metastasis and evaluation of postoperative recurrence. It is worth popularizing and applying in clinic.

Keywords: Breast cancer, radical mastectomy, magnetic resonance imaging, apparent diffusion coefficient

Introduction

Breast cancer is a major public health problem facing the world. According to a report issued by the IARC (International Agency for Research on Cancer), with a mortality rate of 6.4%, breast cancer accounts for 11.9% of all cancers and its incidence rate is on an upward trend [1, 2].

With the continuous development in medical technology, many different treatment options for breast cancer are now available [3-5]. Radical mastectomy is the optimal treatment of breast cancer as it can effectively remove the tumor, the surrounding cancer tissues, and the metastatic axillary lymph nodes. Research by Edward F et al. showed that the 5-year recurrence rate after radical mastectomy was 21.78% and the local/regional recurrence rate was 10.4%, despite its effectiveness in treating breast cancer [6]. At present, the clinical diagnosis of pre-operative axillary lymph node metastasis and post-operative recurrence of breast cancer mainly relies on invasive surgical biopsy, and assessment of prognosis mainly depends on the detection of tumor markers in the biopsy sample, which increases the patients' pain [7, 8]. Therefore, non-invasive procedures to assess preoperative lymph node metastasis and postoperative prognosis (including recurrence) have been researched extensively.

Magnetic resonance imaging (MRI) is an effective means to examine soft tissue lesions, which works by placing the examined body parts in a static magnetic field and applying specific radio frequency pulses to stimulate the resonance of hydrogen protons. When the RF pulse is turned off, it can receive MR signals emitted by protons in relaxation process and reconstruct images of soft tissue lesions [10].

As a non-invasive diagnostic method, DWI has been widely used in the clinical diagnosis of breast cancer. With high-resolution, high-sensitivity and high-specificity imaging, it can help examiners effectively assess the size of tumors and the severity of disease. Research by Thomas E et al. showed that ADC values derived from measuring the average diffusion coefficient in three orthogonal directions can effectively reflect the movement of water molecules in tissues; higher cell density of tumor tissues can lead to the decrease in water molecule movement, resulting in lower ADC values, which can be used for the diagnosis of benignity and malignancy of breast tumors [11]. However, there is no comprehensive report on the significance of ADC values in the diagnosis of preoperative axillary lymph node metastasis and postoperative recurrence, and the correlation between ADC values and prognostic factors is not clear.

Therefore, the purpose of this study was to evaluate the correlation between ADC values and the level of pathological biomarkers in tumor tissues related to prognosis, and to analyze the diagnostic value of preoperative axillary lymph node metastasis and postoperative recurrence in patients with breast cancer, so as to provide a reference for the selection of imaging examination among patients undergoing radical mastectomy. In order to ensure the reliability of the results, preoperative axillary lymph node metastasis and postoperative recurrence were confirmed by surgery.

Materials and methods

Patients

A total of 150 patients (all females) with breast cancer who underwent radical mastectomy in The People's Hospital of Shanting District from January 2014 to January 2017 were retrospectively studied. All patients were between 18 and 67 years old, with an average age of 45.1±7.5. Inclusion criteria: patients met the diagnostic criteria of breast cancer set forth in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Breast Cancer Screening and Diagnosis (Version 3.2013) [12]; DWI was performed in patients before and after operation, and the imaging was clear and imaging data was complete; patients had complete perioperative clinical data. Exclusion criteria: patients who had severe concurrent hematological disease, immune system disease or other malignant tumors; patients who did not receive the specified surgical treatment; patients with mental disorders who did not complete the follow-up.

This study was approved by the Ethics Committee of The People's Hospital of Shanting District. All patients in this study received radical mastectomy and signed informed consent.

MRI examination

Signa 1.5T Double pulsed-field gradient superconducting MRI scanner (GE Healthcare) was used for the MRI examination. T_1WI: TR 4-5 ms, TE 2-3 ms, flip angle 12°, FOV 320 mm×320 mm, slice thickness 1-2 mm, interslice gap 0-0.5 mm, matrix size 336×336; T_2WI: TR 3,000-3,500 ms, TE 120-130 ms, precise frequency inversion recovery sequence echo train length 11-27, flip angle 90°, matrix size 256× 256, FOV 260 mm×320 mm, slice thickness

3-4 mm, interslice gap 0-0.5 mm, matrix size 512×512. Chopper or mixed technique was used for chemical shift fat suppression with 2 excitations.

DWI: fast spin echo (FSE) plain scan, b=50 and 800 s/mm^2, TR 2,000-3,000 ms, TE100-120 ms, FOV 320 mm×320 mm, slice thickness 4-5 mm, interslice gap 0.5-1.0 mm, FOV 320 mm× 320 mm, 2-4 excitation. DCE-MRI: Contrast agent Gd-DTPA (0.2 mg/kg) was injected into forearm vein after the plain scan, and 20 mL saline was then injected rapidly. Before and immediately after injection, patients were scanned using 64, 128, 191, 255, 318 s fast gradient echo sequence. TR 4-5 ms, TE 2-3 ms, flip angle 12˚, FOV 320 mm×320 mm, slice thickness 1-2 mm, interslice gap 0-0.5 mm, matrix size 336×336, total scan time 7 min and 7 s.

Calculation of ADC value

DWI images corresponding to different b values were transmitted to the computer aided diagnosis platform FireVoxel (Center for Advanced Imaging Innovation and Research (CAI2R), New York University School of Medicine, New York, USA). The ADC values of ROI images were measured and calculated by two staff members. Three points were measured and the average was taken as the final ADC values. The two staff members alternated between calculation and data checking.

Immunohistochemistry

Tumor tissues were resected during the surgery, which were immediately fixed with formaldehyde and embedded in paraffin. Histological observation of the tissue section was then performed. MaxVisionTM rapid immunohistochemical kit (AMRESCO, Inc., USA) was used to detect the expressions of hMAM and Ki-67. Ki-67 staining ≤14% was low expression, otherwise it was high expression. ER and PR expression <10% was negative, otherwise it was positive. The expression of HER2 -/1+ was negative, otherwise it was positive.

Other examination

The tubular structure, pleomorphism and mitotic counts of the tumor cells were examined and WHO histological grading system was used as the reference index [13]. The axillary lymph node metastasis was confirmed by surgical pathology. The lymph node status was evaluated

by HE staining, and the results of biopsy were the gold standard.

Statistical analysis

The SPSS 24.0 statistical software was used. Enumeration data was expressed as n (%) and compared with χ^2 test. The significance level was set at α=0.05 (bilateral). Measurement data was expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent t test was used for comparison between groups. The significance level was also set at α=0.05 (bilateral). ADC value was the independent variable, while lymph node metastasis, histological grade, low expression of Ki67, hMAM positivity, ER negativity, PR negativity and HER2 positivity were dependent variables. Multiple linear regression was used to analyze the correlation between ADC parameters and prognostic factors. B stood for regression coefficient. SE stood for standard error. SC stood for standardization coefficient. ROC curve analysis was used to evaluate the significance of ADC values in the diagnosis of preoperative axillary lymph node metastasis and postoperative recurrence. Area under the curve (AUC) >0.5 meant the result was better than random guess, and there was a predictive value. The greater the AUC value, the greater the predictive value. P<0.05 meant the difference was statistically significant.

Results

Correlation between preoperative tumor ADC values and prognostic factors

Comparison of ADC values for preoperative prognostic factors showed that there was a statistically significant difference between the ADC values for patients with lymph node metastasis, Ki67 overexpression, hMAM (+), ER (-), PR (-) and HER2 (+) and those for patients without these symptoms (**Table 1**, all P<0.05). Further Multivariate linear regression showed that there was a significant correlation between the preoperative ADC value of tumors and lymph node metastasis, Ki67 overexpression, hMAM (+), ER (-), PR (-) and HER2 (+) (**Table 2**, all P<0.05).

Two cases of ADC value applied in lymphatic metastasis diagnosis

Preoperative MRI findings (Patient A, 37 years old): Solid nodules in bilateral breasts and multiple echogenic lymph nodes were noted in the

Table 1. Comparison of preoperative prognostic factors related to grouping ADC values

Relevant factors	Cases (n, %)	ADC value	t	P
Lymph node metastasis				
Y	45 (30.00)	1.25±0.12	16.058	<0.001
N	105 (70.00)	0.93±0.09		
Histological grading				
G1-2	81 (54.00)	1.14±0.25	0.261	0.795
G3	69 (46.00)	1.15±0.22		
High expression of Ki67				
Y	107 (71.33)	1.11±0.26	2.280	0.025
N	43 (28.67)	1.22±0.27		
hMAM				
+	88 (58.67)	1.19±0.22	2.080	0.040
-	62 (41.33)	1.11±0.24		
ER				
+	95 (63.33)	1.13±0.21	2.390	0.018
-	55 (36.67)	1.21±0.19		
PR				
+	79 (52.67)	1.11±0.19	2.307	0.023
-	71 (47.33)	1.19±0.23		
HER2				
+	36 (24.00)	1.22±0.25	2.234	0.029
-	114 (76.00)	1.11±0.28		

Note: ADC, apparent diffusion coefficient; hMAM, human mammaglobin; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2. Multiple linear regression analysis of factors related to preoperative tumor ADC value and patient prognosis

Relevant Factors	B	SE	SC	P
Intercept	1.597	0.192		0.000
Lymph node metastasis	-0.132	0.045	-0.238	0.001
Histological grading (G3)	-0.018	0.038	-0.149	0.512
High expression of Ki67	0.142	0.047	0.245	0.003
hMAM (+)	0.133	0.046	0.233	0.042
ER (+)	0.135	0.067	0.235	0.041
PR (+)	-0.044	0.068	-0.074	0.048
HER2 (+)	-0.089	0.037	-0.182	0.024
Adjusted R^2	0.343			

Note: ADC, apparent diffusion coefficient; hMAM, human mammaglobin; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

left axillary area. The larger one was about 1.7 cm*1.1 cm (**Figure 1A**), with an average ADC value of 1.32±0.17. No obvious enlarged echogenic lymph nodes were found in the right axillary area. The average ADC value was 0.91±0.10. The average ADC value of lymph nodes with tumor infiltration was significantly higher than that of lymph nodes free of tumor infiltration (t=2.028, P<0.001).

Preoperative MRI findings (Patient B, 74 years old): Solid nodules in the right breast and multiple lymph nodes in the right axillary area. The lager one was about 1.3 cmx0.9 cm (**Figure 1B**), with an average ADC value of 1.29±0.14. There were no obvious enlarged lymph nodes in the left axillary area, and the average ADC value was 0.94±0.12. The average ADC value of lymph nodes with tumor infiltration was significantly higher than that of lymph nodes free of tumor infiltration (t=3.132, P< 0.001).

ROC curve analysis of preoperative ROI ADC for diagnosis of preoperative axillary lymph node metastasis

Pathological diagnosis of the 150 patients before operation showed ipsilateral lymph node metastasis in 45 patients (30.00%). ROC curve analysis showed AUC= 0.925 (**Figure 2**) and IC 95% (0.791, 0.972). Youden index was 0.889, and the corresponding optimal threshold value was 1.07. **Table 3** showed preoperative ROI ADC value for the diagnosis of preoperative axillary lymph node metastasis. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 88.89%, 92.38%, 83.38%, 95.10% and 91.33% respectively.

ROC curve analysis of postoperative ROI ADC value for diagnosis of postoperative recurrence

Surgical pathology confirmed that there were 33 cancer recurrences (22.00%) in the 150 patients 2 years after operation. The ROI ADC value for patients with recurrent cancer was 1.32±0.19, which was significantly higher than that for patients without recurrent cancer (0.92±0.22), and the difference was statisti-
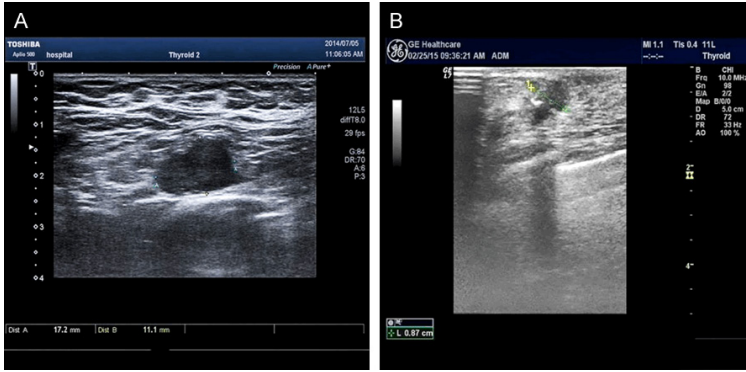
Figure 1. MRI examination image data of preoperative lymphatic metastasis in 2 patients. A. The largest lymph node in the left axilla of patient A; B. The largest lymph node in the right axilla of patient B. MRI, Magnetic Resonance Imaging.
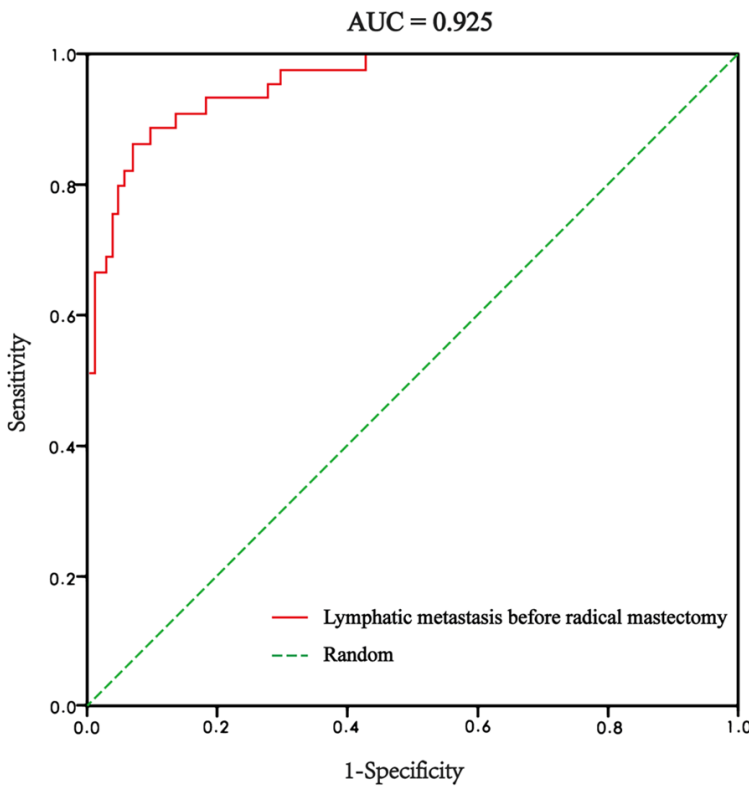

Figure 2. ROC curve analysis of preoperative ROI ADC value for diagnosis of preoperative axillary lymph node metastasis. ROC, receiver operating characteristic; ADC, apparent diffusion coefficient; ROI, regions of interest.

cally significant (t=10.302, P<0.001). ROC curve analysis showed AUC=0.963 (**Figure 3**) and IC 95% (0.839, 0.989). Youden index was 0.896, and the corresponding optimal threshold value was 1.05. **Table 4** showed preoperative ROI ADC value for the diagnosis of postoperative recurrence. The sensitivity, specificity, positive predictive rate, negative predicti-

ve rate and diagnostic accuracy were 90.91%, 96.58%, 88.24%, 97.41% and 95.33% respectively.

Discussion

Theoretical basis for clinical diagnosis with ADC values

DWI can reflect the diffusion of water molecules in tissues by ADC values, and evaluate the structure and internal changes of lesions. The ADC value is positively correlated with diffusion speed of water molecules; the lower the ADC value, the slower the speed of water molecule diffusion within tissues [3, 14, 15]. Due to the loss of inhibition of tumor cell proliferation, the number of tumor cells is larger than the number of cells in normal tissues, resulting in high cell density. And there is a negative correlation between cell density and water molecule movement. Therefore, the ADC value of tumors is theoretically lower than that of normal tissues, which is also the theoretical basis for studying the application of ADC value in the diagnosis of the benignity and malignancy of breast masses [16-19]. Shingo et al. have shown that ADC is a useful parameter for differentiating benign and malignant breast tumors [20]. At present, the science behind the application of ADC value in the discrimination of benign and malignant lesions has been recognized in clinical practice, but there is an urgent need to explore the role of ADC value in other fields before and after radical mastectomy for breast cancer.

Application of ADC values in the diagnosis of preoperative lymphatic metastasis

Lymphatic metastasis of breast cancer is one of the main factors affecting its prognosis.

Table 3. Preoperative ROI ADC value for diagnosis of preoperative axillary lymph node metastasis (n)

| | Surgical pathology | | Total |
	+	-	
ADC value			
+	40	8	48
-	5	97	102
Total	45	105	

Note: ADC, apparent diffusion coefficient; ROI, regions of interest; + stands for ipsilateral lymph node metastasis before operation; - stands for no ipsilateral lymph node metastasis before operation.

Preoperative diagnosis of lymphatic metastasis and complete dissection of metastatic lymph nodes during radical mastectomy are of great clinical significance. In the past, lymph node metastasis was mainly judged by the status of lymph nodes. Lymph node metastasis was confirmed by symptoms including enlargement and increase of lymph nodes on physical examination as well as signs including matted lymph nodes, disappearance of lymph node hilum and blurred margin on imaging examination [15, 21-23]. But this kind of diagnostic method is subjective and diagnostic errors may occur because of radiologists' experience in taking and reading films. For metastatic lymph nodes of breast cancer, their cell growth pattern is similar to that of primary tumor cells because of the invasion of cancer cells, resulting in the increase of cell density and the slowdown of water molecule diffusion [14]. Therefore, the theoretical basis for the application of ADC value in the clinical diagnosis of preoperative lymphatic metastasis of breast cancer is scientifically sound. In this study, 45 of the 150 patients were diagnosed with lymphatic metastasis before operation. The ROC curve analysis showed that ADC value was highly valuable for clinical diagnosis (AUC= 0.925, **Figure 2**). Statistical analysis showed that the optimal threshold value was 1.07, and a 91.33% diagnostic accuracy was obtained after diagnosis with the optimal threshold value was made. Xinghua et al. evaluated the diagnostic value of DWI in lymph node metastasis assessment, and studied whether ADC value could be used to differentiate metastatic and non-metastatic lymph nodes in breast cancer patients [24]. A total of 13 studies were reviewed, including 676 cases of metastatic lymph nodes and 811 cases of non-metastatic lymph nodes. It was clear that ADC value has a significant role to play in diagnosing lymphatic metastasis of breast cancer. The results of this study are consistent with the above findings.
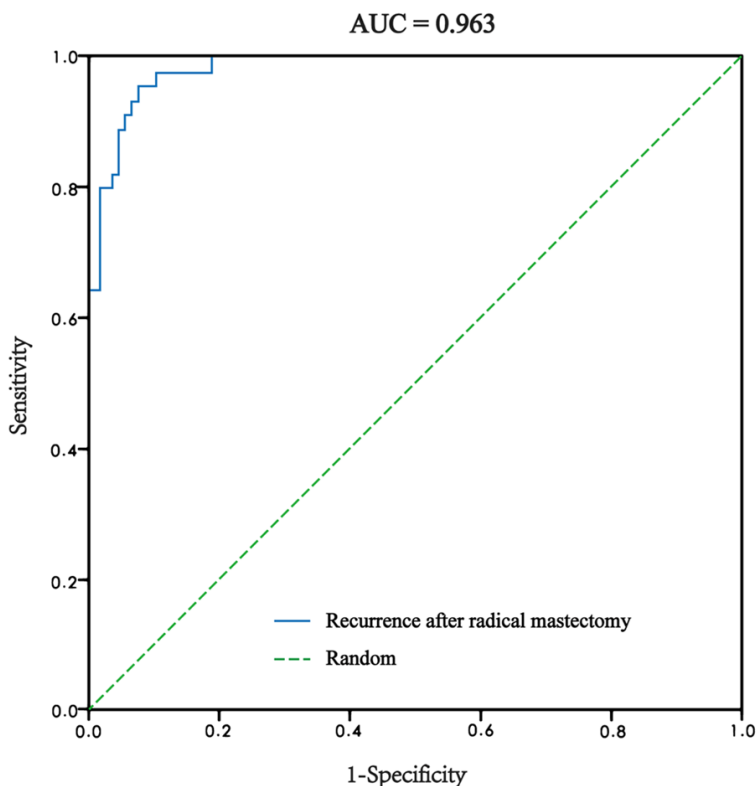
Application of ADC values in postoperative prognosis evaluation

DWI can not only diagnose the change of cell density, but also effectively evaluate the structure of cancer tissues. Tumor cell structure is a good index for assessing the invasiveness of cancer cells, which is closely related to the prognosis of patients. At present, the assessment of malignancy, benignity and prognosis of tumors is mainly based on pathological examination, which comprehensively evaluate tumors by the study of cell morphology and the detection of histopathological biomarkers [25].

Ki-67 is closely related to mitosis and recurrence of tumor cells. Increased mitosis can lead to an increase in cell density. As discussed above, cell density has an impact on the results of DWI imaging. HMAM was first found in tumor cells derived from patients with endometrial cancer and salivary gland cancer. Follow-up studies found the abnormal expression of hMAM in epithelial cells of tumor tissues. It has become one of the markers for the clinical evaluation of cell invasiveness and proliferation activity. Steroid hormone receptor proteins ER and PR are good markers for prognosis.

Some studies have shown that ER (a confounding factor affecting PR) can affect the structure of tumor tissues by inhibiting vascular access and inducing tissue perfusion reduction, and the expression of ER and PR is related [26-28]. The expression of HER2 is mainly related to the growth and metastasis of tumor cells. It can increase angiogenesis of tumor tissues by inducing the expression of vascular endothelial growth factor (VEGF), improve the blood supply of tumor cells and promote cell metastasis. Studies have also shown a positive correlation between the ADC value provided by DWI and the blood supply and extracellular fluid volume of tumors, which serves as a proof of the theoretical basis for the reflection of prognostic factors by ADC values [29, 30].

In this study, statistical analysis of the ADC values of lymph node metastasis, histological

Figure 3. ROC curve analysis of postoperative ROI ADC value for diagnosis of postoperative recurrence. ROC, receiver operating characteristic; ADC, apparent diffusion coefficient; ROI, regions of interest.

Table 4. Preoperative ROI ADC value for diagnosis of postoperative recurrence (n)

	Surgical pathology		Total
	Recurrence	No recurrence	
ADC value			
Recurrence	30	4	34
No recurrence	3	113	116
Total	33	117	

Note: ADC, apparent diffusion coefficient; ROI, regions of interest.

grade, Ki67 overexpression, hMAM positivity, ER negativity, PR negativity and HER2 positivity were performed, followed by multiple linear regression analysis. The results showed a significant correlation between preoperative ADC values of tumors and lymph node metastasis, Ki67 overexpression, hMAM (+), ER (-), PR (-) and HER2 (+), but no correlation with histological grade. This result was different from the results predicted. After literature review, we believe this discrepancy can be explained by the subjectivity involved in the histological grading of tumors.

Application of ADC value in the diagnosis of postoperative recurrence

The basis for ADC value being used in diagnosing the recurrence of breast cancer after radical mastectomy is similar to the rationale behind the diagnosis of benign and malignant tumors and lymphatic metastasis as mentioned above. The ADC values were recorded after DWI examination of ROI was performed in follow-up visits. The average ADC values of ROI for patients with confirmed recurrence of tu= mors were significantly higher. The results of ROC curve analysis showed that ADC value was of great significance in clinical diagnosis (AUC=0.963, **Figure 3**). The statistical analysis showed that the optimal threshold value was 1.05. A 95.33% diagnostic accuracy was obtained after diagnosis with the optimal threshold value was made. The difference between the results and the gold standard (results of biopsy) was small, which indicated that ADC value could be used for clinical diagnosis of recurrence of breast cancer after radical mastectomy.

Limitation of this study

There are still some limitations in this study. First, subjects in this study are not representative and the selection process may be biased as all patients were from a single medical institution. Second, given the knowledge of results from previous imaging examinations, the possibility of researchers' impact on the results of this study during the follow-up period cannot be ruled out. Besides, the follow-up period of this study was 2 years, which only reflected the role of ADC value in diagnosis of recurrence shortly after surgery. Third, ADC values were not calculated with different b values when DWI was performed, so there may be some bias in perfusion or diffusion effects. Finally, the level of pathological tissue biomarkers used as a reference standard was obtained only th-

rough a review of pathological reports; there could be changes in pathological measurements during the preservation and preparation of each tissue specimen.

Research conclusion

In conclusion, MRI is a valuable tool in the diagnosis of preoperative axillary lymph node metastasis and the evaluation of postoperative recurrence. There is a significant correlation between the preoperative ADC values measured using DWI for patients who have received radical mastectomy and lymph node metastasis, Ki67 overexpression, hMAM positivity and HER2 positivity, which proves the role of ADC values in the assessment of prognosis for patients.

Disclosure of conflict of interest

None.

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