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The role of magnetic resonance diffusion weighted imaging in evaluating perioperative chemotherapy for breast cancer

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Abstract

Dynamic monitoring of chemotherapy efficacy during perioperative period of breast cancer has great clinical significance. Diffusion-weighted magnetic resonance imaging (DW-MRI) is sensitive to changes of microenvironment after tumor treatment. Therefore, we aim to explore the value of DW-MRI in breast cancer after chemotherapy. 62 breast cancer patients who received neoadjuvant chemotherapy were subjected to conventional MRI plain scan and DW examination one week before and after chemotherapy. The tumor response to chemotherapy was divided into pCR and non-pCR efficacy groups. The ADC values of apparent diffusion coefficients were measured on DWI images. No significant differences in ADC value before treatment with histological grade and molecular subtype were found (p> 0.05). The best predicted pCRΔADC% cutoff was 25%. When using DWI-MRI, the cutoff has a sensitivity of 83%, specificity 84%, PPV 77%, and NPV 89%. Compared with that before chemotherapy, ADC value was significantly increased after chemotherapy and the change of ADC before and after chemotherapy was positively correlated with the change of long diameter, short diameter and average diameter (P <0.05). ADC value in pCR group and non-pCR group before chemotherapy had a negative correlation with the rate of change in the length and diameter (P <0.05). In conclusion, ADC value can sensitively reflect the early changes after chemotherapy in breast cancer and is helpful for the early and dynamic monitoring of the treatment efficacy.

Keywords: ADC, breast cancer, perioperative period.

Introduction

Perioperative neoadjuvant chemotherapy (NCT) is currently applied in treating breast cancer. In clinical practice, if the patient is eligible for breast-conserving conditions, neoadjuvant flower chemotherapy is also used to achieve non-surgical reduction [1]. Early evaluation can improve the treatment efficacy and provide more personalized management of the disease. The evaluation of neoadjuvant chemotherapy efficacy is particularly critical for selecting subsequent treatment options. In the past, for patients with neoadjuvant chemotherapy, thick needles are usually applied. Biopsy is performed by puncture and the treatment efficacy is judged by histology. However, this method has obvious shortcomings. There is uncertainty about the location of the biopsy. For patients, invasive injuries will cause unnecessary damage [2]. MRI is used to assess the outcomes of perioperative neoadjuvant chemotherapy and achieve pathological remission. At present, advanced imaging techniques have become a most widely used approach to assess the response to treatment in patients with tumor [3, 4]. Diffusion-weighted imaging (DWI) is quantified through calculating apparent diffusion coefficients (ADCs) and used to evaluate the efficacy of tumor response to treatment. However, ADC expression is affected by both diffuse tissue and pseudo-random motion caused by microcapillary perfusion [5, 6]. In addition, ADC helps to assess the tumor response to NCT. This response is related to a decrease in the number of tumor cells and increased ADC value. DWI-MRI can evaluate tumors non-invasively and improves individualized treatment based on the response [7]. Assessing residual tumors after NCT is crucial to determine the prognosis of patients as well as the subsequent decision of clinical treatment in the next step.

Prior to this, DWI is widely used in clinical practice because of its ability to make early predictions of patients' response after NCT. There

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are also research reports that DWI is used as a detection method for the classification of breast cancer. The identification of type classifications has also been reported [8]. However, there is no direct comparison of the treatment stages between these studies, especially in the advanced treatment or locally advanced treatment stages. The factors are mainly the lack of standardized operating procedures and restrictions on related technical parameters. However, there are not sufficient cases for the related studies at present. These limitations also prevent the widespread application of DWI in breast cancer patients with NCT [9, 10]. Our study intends to assess the predictive efficacy of neoadjuvant chemotherapy during perioperative evaluation using DWI-MRI.

Materials and methods

Patients

Our study was approved by ethics committee of our unit and informed consent was acquired. 123 breast cancer patients aged 27 to 65 years (median 45 years) receiving NCT tests between January 2017 and July 2019 were enrolled. The inclusion criteria were: breast cancer confirmed by biopsy, ≥18 years old, no pregnancy, currently not breastfeeding, completed treatments, before and during treatment (after the first cycle). Multiparametric MRI examinations were performed after treatment. Exclusion criteria: Patients who had received MRI or therapy at other institution and had contraindications to MRI or MRI contrast were excluded.

69 patients (49%) were excluded due to multiple factors, because early MRI examinations were not performed in our hospital (n = 10), distant metastases were found at diagnosis (n = 4), and follow-up chemotherapy was received in the external hospital (n = 8). After learning about the study design, patients decided to give up (n = 5). The patients were excluded because their basic conditions did not meet the study conditions (n = 34). Finally, 62 (51%) patients were recruited (median age: 45.5 years, 26-72 years).

All patients' basic information were recorded in electronic files. Tumor proliferation (ki67) and lymph node status were assessed at the beginning of NCT. Patients received perioperative neoadjuvant chemotherapy followed by surgery. The perioperative neoadjuvant chemotherapy regimen was consisted of 4 cycles of anthracyclines and cyclophosphamide and subsequent 4 cycles of paclitaxel (AC-T) treatment (n = 37). In 16 patients with HER-2 overexpression, trastuzumab was added to the AC-T regimen. Other treatments included carboplatin to AC-T (n = 8) and pertuzumab to trastuzumab and docetaxel (n = 1).

MRI

Each patient received MRI test before perioperative neoadjuvant chemotherapy (MR1), after the first treatment cycle, before second treatment cycle (MR2), and after completion of NCT (MR3). Multi-parameter breast MRI used a 1.5 T MR imaging system (American General Electronics Co., Ltd. and Philips Biotechnology Co., Ltd.). The patient took a prone position and an 8-channel dedicated breast coil. The patient was given 20 ml of gadopentetate glucosamine injection (German Bayer Pharmaceutical Co., Ltd.) at 3 ml/s, and images were obtained by lying on the patient's back. DW images of bilateral breasts were obtained in cross section. Spin echoes, single-excitation echo planar imaging sequences. DW imaging included two b-values, 0s / mm2 and 750s / mm2. The latter recommended DWI in previous studies was applied to obtain five axial plane 3D t1-weighted gradient echo sequences and performed fat suppression.

Image analysis

Three radiologists in our department of radiology evaluated the MR images which were obtained from three examinations (MR1-3). MR1 and MR2 images were used for early response assessment. The primary tumor was identified by comparing t1-weighted images from pre-imaging. The solid tumor response assessment criteria (RECIST) guidelines defined the responders and non-responders. Areas with a signal greater than the normal parenchymal parenchyma were considered positive. After determining the low-density tumor area in the ADC map, a 2D ROI was drawn to avoid normal tissues.

Histopathological analysis

Patients were diagnosed by puncture biopsy, histological grade, estrogen receptor (ER), progesterone receptor (PR) status, and HER-2 expression. Histopathology from fine needle biopsy before chemotherapy was collected in the report. According to immunohistochemical results, tumors were classified into: intracavity A (ER+, Ki-67 <20%, HER-2-), intracavity B (ER+, ki-67 or HER-2-), HER-2 positive (ER- and HER-2+), triple negative (ER-, HER-2-, PR-). Histological manifestations of 62 lesions in neoadjuvant chemotherapy showed no special type of invasive carcinoma (53 cases), invasive lobular carcinoma (7 cases), and other types (2 cases). 30 (48.4%) tumors were ER+, 28 (45.2%) PR+, and 17 (27.4%) HER-2+. Among molecular subtypes, 35.5% (22/62) triple-, 16.1% (10/62) HER-2+, 37.1% (23/62) luminal B Ki-67, 11.3% (7/62) were a luminal B HER-

2 types. In order to facilitate analysis, the latter two groups were combined into cavity group B. A final pathological examination was performed after the last chemotherapy cycle after surgical resection. Pathological responses were assessed based on residual tumor burden protocol [11].

Statistical method

SPSS 20.0 software was adopted for analysis. Pathological evaluation was used as the gold standard to detect ADC changes in MR1-2. A ROC curve determines the threshold for ADC changes. P < 0.05 suggests a difference.

Results

The relationship between histopathological characteristics and ADC values

As shown in Table 1, after neoadjuvant chemotherapy, pCR appeared in 24 tumors (38.7%) including triple-negative tumors (58%), HER-2 tumors (25%), and luminal B tumors (16.7%). No difference was found in the pretreated ADC values between the three negative groups (0.917 x 10^3 mm^2/s), the HER-2 overexpression group (0.834x10-3mm^2 / s), and the lumen B group (0.795 x 10^3 mm^2/s, p> 0.05) with a difference of ADC value between intracavity B and triple-negative tumors (p <0.05). ADC values before treatment were not different to histological grades and molecular subtypes. However, in MR1, PR and ER expression contributed to the reduction of ADC (p <0.05). No difference was found in the mean value of the pre-CRCR ADC value (0.832 ± 0.198 x 10^3 mm^2/s) and the mean value of the non-pCR pre-treatment ADC value (0.853 ± 0.171 x 10^3 mm^2/s) (p> 0.05).

Relationship between treatment outcome assessment and ADC value

As seen in Table 2, the average ADC value at MR2 in pCR group was significantly elevated compared to MR1 (p <0.001). Table 2 revealed the relationship between the increase in ΔADC% and the decrease in Δ tumor size. Figure 1 showed the change in the ADC value and the dimensional change between MR1 and MR2. ADC values for triple negative cases also increased significantly between MR1 and MR3. The ADC value of HER-2 subtype was not statistically different in all examinations, and the intraluminal B type had significant changes only between MR1 and MR2.

DCE-MRI evaluation

Tumor size changes before and after MRI treatment ranged from 15-92 mm (median 38 mm) without difference between MR1 and MR2 (p> 0.05) as well as no difference between MR1 and MR2 tumor size and absolute RCB value (p> 0.05) (Figures 1A and 1B). DCE-MRI did not find a decrease in tumor size after the treatment of first cycle, thereby predicting pCR (Mann-Whitney test, p> 0.05). When using ADC value, the cutoff value has a sensitivity of 83%, specificity 84%, PPV 77%, and NPV 89% (Figure 2).

Changes of each line and ADC value before and after treatment

The change rate of ADC value before and after therapy for breast cancer was positively correlated with the tumor length. The correlation between the rates of change was relatively highest (Table 3); ADC value prior to chemotherapy in pCR group was negatively correlated with the rate of change in tumor length before and after chemotherapy (r = -0.812, P <0.05), and ADC value before chemotherapy in non-pCR group revealed a negative association with the tumor diameter change rate (r = -0.739, P <0.05). No significant correlation between the ADC value before chemotherapy and the tumor diameter change rate and the mean diameter change rate was observed in pCR group and non-pCR group (Table 4).

Discussion

Our study found that in tumors responsive to treatment, the functional parameter ADC, which provides information about the structure of the intratumoral cells, varies more between MR1 and MR2. In addition, the early predictive sensitivity of DWI-MRI for pCR after neoadjuvant therapy was 83% and specificity was 84%.

Obtaining feasible parameters has great significance for perioperative neoadjuvant chemotherapy monitoring of breast cancer patients. Genetic variation of tumors and genetic changes in patients after drug resistance remain the main challenges for ADC standardization to assess tumor response [12]. However, our results indicate that DWI-MRI is a promising approach, and individualized treatment can be achieved earlier, which may lead to higher pathological remissions after treatment. Studies on assessing ADC values of DWI-MRI after one cycle of perioperative neoadjuvant chemotherapy have found that changes in ADCs in the first two tests are a good predictor of breast cancer's early response to perioperative neoadjuvant chemotherapy [13]. However, some are not statistically significant, which may be due to limited number of patients enrolled [14]. Iwasa et al., reported that increased ADC precedes the reduced tumor size in perioperative neoadjuvant chemotherapy, and also reported that ADC value was significantly increased

after the first treatment cycle [15]. In subsequent studies, MR imaging parameter results found that changes in DCE and ADC preceded tumor size as assessed by physical examination. However, only ADCs have significant results [16].

Studies have shown that in a meta-analysis, 15 studies found that the use of MRI to assess 4 cycles of tumors before and after neoadjuvant chemotherapy was superior to DCE regarding the assessment of CR [17]. In addition, some studies found that after the second cycle of perioperative NCT, ADC and tumor size values in the pCR group were different. In this study, significant changes of ADC value were found from the acquired DCE images, but no significant changes in tumor size were found [18]. These results confirm that the functional variability of the tumor precedes the morphological change. A previous study has shown that lower ADC value tumors respond better to perioperative NCT [18]. Similarly, triple-negative tumors in the non-responding group showed a significant increase of ADC values [19]. In this study, ADC values could not predict pathological responses before treatment, which is consistent with other studies. In addition, when measuring other prognostic factors, ADC values are not significant in predicting tumor biology, and they do not affect the NCT treatment choices or prognosis. These findings are also consistent with other studies [20]. This study has some limitations. First, due to the heterogeneity of the chemotherapy received by our subjects, we cannot evaluate the specific biological effects of each drug based on ADC values; Second, for evaluating the pathological response of perioperative neoadjuvant chemotherapy, pCR may exist in ductal carcinoma in situ, so there may be differences between imaging and pathology. We will further analyze the images caused by these factors in subsequent studies to further confirm the findings in our study.

Conclusion

Increased ADC value after the first cycle after NCT is closely related to pCR. Magnetic resonance diffusion-weighted imaging shows a reduction in tumor volume, indicating that it might be used as an indicator for assessing the treatment response in patients with tumors.

Disclosure of conflict of interest

None.

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Tables and Figure legends

Table 1. **Relationship between histopathological characteristics and ADC values.**

	ADC MRI Average ($\times10^{-3}mm^2/s$)				
	ADC	**p**	**pCR**	**Non-pCR**	**p**
Histology type		＞0.05			
Invasive ductal carcinoma in situ	0.823±0.278		0.872±0.276	0.856±0.328	＞0.05
Invasive lobular carcinoma	0.784±0.212		0.698±0.278	0.895±0.368	＞0.05
Other	1.029±0.217			1.027±0.451	
Histology level		＞0.05			
Ⅱ	0.882±1.128		0.923±0.372	0.917±0.431	＞0.05
Ⅲ	0.892±1.198		0.872±0.325	0.837±0.286	＞0.05
ER status		＜0.05			
+	0.765±0.547		0.728±0.271	0.813±0.298	＞0.05
-	0.894±0.364		0.826±0.296	0.837±0.128	＞0.05
PR status		＜0.05			
+	0.742±0.522		0.623±0.317	0.729±0.265	＞0.05
-	0.949±0.473		0.872±0.429	0.928±0.271	＞0.05
HER-2 status		＞0.05			
+	0.832±0.534		0.827±0.319	0.912±0.282	＞0.05
-	0.847±0.476		0.793±0.297	0.824±0.391	＞0.05
Tumor phenotype		＞0.05			
Luminal B	0.722±0.512		0.813±0.329	0.838±0.421	＞0.05
Triple negative	0.763±0.398		0.839±0.311	0.914±0.384	＞0.05
HER-2	0.824±0.451		0.832±0.372	0.876±0.411	＞0.05

Table 2. **Mean ADC values of MR1 and MR2 after treatment.**

Pathological response	ADC MR1（x10^{-3}）	ADC MR2（x10^{-3}）	ΔADC（%）	Δ tumor change
pCR	0.823±0.329	1.328±0.348	42.87±8.2	4.7±2.9
Non-pCR	0.897±0.248	0.838±0.632	8.72±3.4	3.2±3.1
p	＞0.05	<0.001	<0.001	＞0.05

Table 3. **Correlation analysis of the change rate of ADC value before and after neoadjuvant chemotherapy.**

ADC changes（10^{-3}mm^2/s）	Diameter change ratio（%）		r	p
14.38±15.38	Long diameter	16.89±12.54	0.617	＜0.05
	Short diameter	13.24±15.23	0.679	＜0.05
	Mean diameter	15.46±13.75	0.534	＜0.05

Table 4. **Correlation analysis between the change rate of ADC value and the change rate of each trajectory in the curative effect group before neoadjuvant chemotherapy.**

Before treatment ADCs（10^{-3}mm^2/s）		Diameter change ratio (%)		r	p
Non-pCR	1.387±0.276	Long diameter	34.87±17.29	-0.739	＜0.05
		Short diameter	23.28±12.43	-0.234	＞0.05
		Mean diameter	36.89±13.42	-0.539	＞0.05
pCR	1.272±0.352	Long diameter	3.49±12.78	-0.628	＜0.05
		Short diameter	4.39±8.92	-0.498	＞0.05
		Mean diameter	4.87±9.12	-0.528	＞0.05

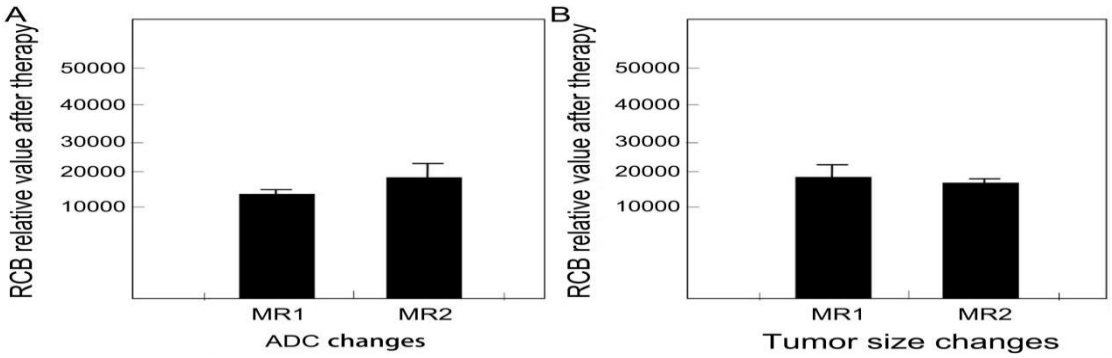

Figure 1. **ADC changes and tumor size changes for MR1 and MR2. A shows changes in ADC after neoadjuvant chemotherapy; B shows changes in tumor size after MR1 and MR2 neoadjuvant chemotherapy. (There was no statistical difference between the two groups, p> 0.05).**

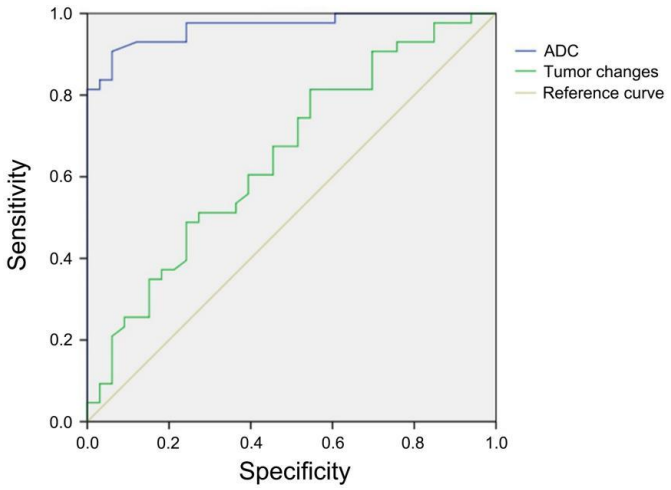

Figure 2. **ROC curve changes after neoadjuvant chemotherapy.**