Predictive value of apparent diffusion coefficient for neoadjuvant chemotherapy in locally advanced colorectal cancer patients

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Background: The efficacy of neoadjuvant chemotherapy is closely related to the long-term prognosis of colorectal cancer (CRC) patients. Apparent diffusion coefficient (ADC) is an index in dynamic enhanced magnetic resonance imaging (MRI), reflecting the density of tumor cells. ADC has been shown to be related to the efficacy of neoadjuvant chemotherapy in other malignant tumors, but there is still a lack of relevant research in CRC patients.

Methods: A total of 128 patients with CRC treated with neoadjuvant chemotherapy in The First Affiliated Hospital of Xiamen University from January 2016 to January 2017 were retrospectively collected. According to the response after neoadjuvant chemotherapy, the patients were divided into an objective response group (n=80) and a control group (n=48). The clinical characteristics and ADC levels of the two groups were compared, and the predictive value of ADC on the efficacy of neoadjuvant chemotherapy was analyzed. The patients were followed up for 5 years to observe the difference of survival rate between the two groups, and further analyzed the correlation between ADC and survival rate.

Results: Compared with the control group, the tumor size in the objective response group was significantly reduced (3.32±1.60 *vs.* 5.07±2.19 cm, P=0.000); ADC significantly increased (1.23±0.18 *vs.* 0.98±0.18 ×10^{-3} mm^2/s, P=0.000); albumin significantly increased (39.32±4.14 *vs.* 37.46±4.18 g/L, P=0.016); the proportion of patients with poorly differentiated or undifferentiated tumor cells was significantly lower (51.25% *vs.* 72.92%, P=0.016); and the 5-year mortality decreased significantly (40.00% *vs.* 58.33%, P=0.044). ADC had the highest predictive value of objective response for locally advanced CRC patients after neoadjuvant chemotherapy, and the area under the curve (AUC) was 0.834 [95% confidence interval (CI): 0.765–0.903, P=0.000]; ADC had certain predictive value for the 5-year survival of locally advanced CRC patients, and the AUC was 0.778 (95% CI: 0.696–0.861, P=0.000). ADC >1.055×10^{-3} mm^2/s, tumor size <4.1 cm, and moderately or well differentiated tumors were favorable factors for patients with locally advanced CRC to obtain objective response after neoadjuvant chemotherapy (P<0.05).

Conclusions: ADC could be used as a predictor of the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients.

Keywords: Apparent diffusion coefficient (ADC); colorectal cancer (CRC); neoadjuvant chemotherapy; objective response

Introduction

The incidence rate and mortality of colorectal cancer (CRC) rank third among malignant tumors, and the number of its patients accounts for about 8% of malignant tumor cases (1). Since early CRC can have no obvious symptoms, more than 20% of patients with CRC are at a locally advanced stage at the first diagnosis. Neoadjuvant chemotherapy is an important method for the treatment of locally advanced CRC. Its purpose is to reduce the stage of CRC before surgery, at the same time promote the sensitivity of tumor cells to chemotherapy drugs, and finally achieve the goal of improving the prognosis of patients (2-4). Neoadjuvant chemotherapy can significantly improve the prognosis of CRC patients (5), but 30–50% of patients are not sensitive to neoadjuvant chemotherapy. Such patients are prone to progress and even lose the opportunity to receive surgical treatment (6,7). Therefore, the key to further improve the prognosis of CRC is to accurately identify patients who are not sensitive to neoadjuvant chemotherapy at an early stage. Previous studies have confirmed that many clinical indicators of patients with malignant tumors can be affected by chemotherapeutic drugs (8,9), and these indicators can also be used to predict the efficacy of neoadjuvant chemotherapy. Carcinoembryonic antigen (CEA) is a common biological indicator for CRC patients (10,11), but a study showed that CEA level at baseline was not significantly related to the progression-free survival (PFS) rate of CRC patients with liver metastasis

who received neoadjuvant treatment (12). Therefore, it is of great significance to find new biological indicators to predict the efficacy of neoadjuvant chemotherapy in CRC patients. Apparent diffusion coefficient (ADC) reflects the density of tumor cells. The lower its level, the greater the density of tumor cells, and the higher the degree of malignancy will be, so the tumors become more likely to metastasize (13). Studies in patients with breast cancer and osteosarcoma have confirmed that the ADC was related to the clinicopathological characteristics of patients, and had a good value in predicting the efficacy of neoadjuvant chemotherapy (14-16). In addition, exploring prognostic indicators of malignant tumors is also one of the purposes of clinical research (17). A study in patients with liver metastasis of CRC showed that ADC had good value in predicting the prognosis of patients with CRC (18). Therefore, we speculated that the ADC was related to the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients, but there is no relevant research at present. The purpose of this study was to explore the predictive value of ADC for neoadjuvant chemotherapy in locally advanced CRC patients. We present the following article in accordance with the STARD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-124/rc).

Methods

General information

A total of 128 patients with CRC treated with neoadjuvant chemotherapy in The First Affiliated Hospital of Xiamen University from January 2016 to January 2017 were retrospectively collected. According to the response after neoadjuvant chemotherapy, the patients were divided into an objective response group (n=80) and a control group (n=48). The inclusion criteria were as follows: (I) patients with locally advanced CRC (pathological diagnosis obtained through colonoscopy before operation); (II) age ≥18 years old; (III) receiving neoadjuvant chemotherapy; (IV) the presence of measurable lesions. The exclusion criteria were as follows: (I) recurrent CRC; (II) combination with other malignant tumors; (III) liver and kidney insufficiency (any liver or kidney disease); (IV) immune insufficiency; (V) lost to follow-up; (VI) neuroendocrine tumors, stromal tumors, and other special types of malignant tumors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen

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Highlight box

Key findings
• The ADC could be used as a predictor of the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients.

What is known and what is new?
• The ADC reflects the density of tumor cells. In other malignant tumors, it has been shown to be related to the efficacy of neoadjuvant chemotherapy, but in patients with CRC, there is still a lack of relevant research.
• This study confirmed that the ADC is related to the efficacy of neoadjuvant chemotherapy in patients with CRC.

What is the implication, and what should change now?
• The ADC could be used as a predictor for the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients. Combined with the ADC, clinicians can better evaluate the efficacy of neoadjuvant chemotherapy, providing a theoretical basis for clinicians to choose appropriate treatment plans.
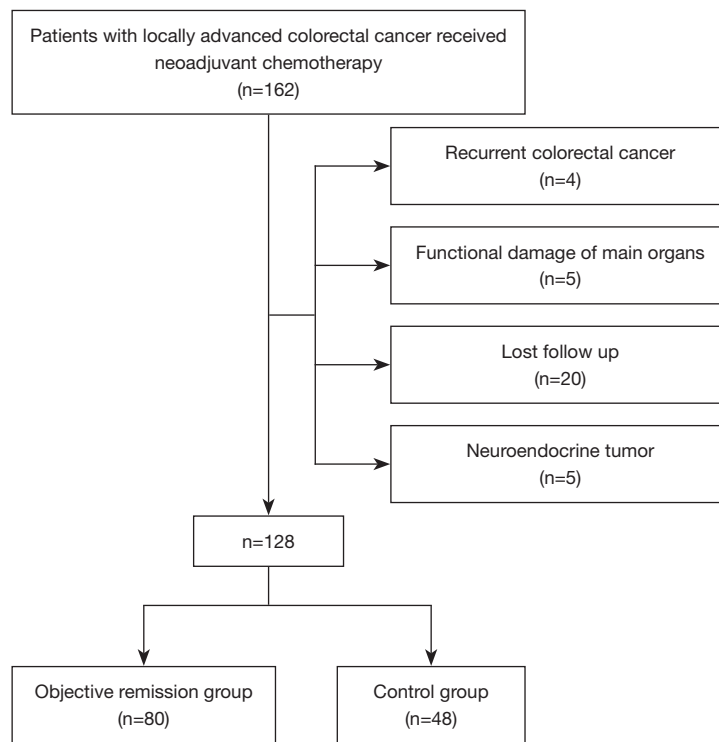

Figure 1 Inclusion flow chart of locally advanced CRC patients. CRC, colorectal cancer.

University (No. c202200174) and individual informed consent was waived in this retrospective study. The patient inclusion flow chart is shown in *Figure 1*.

Treatment strategy

After admission, all patients completed the baseline assessment and were treated with 3 cycles of XELOX (capecitanine and oxaliplatin) regimen neoadjuvant chemotherapy after excluding the contraindications of chemotherapy. A total of 21 days constituted 1 cycle. After neoadjuvant chemotherapy, radical resection of CRC was performed within a definite time (6–8 weeks after the last neoadjuvant chemotherapy).

Efficacy evaluation

According to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), the magnetic resonance imaging (MRI) examination result and pathological findings after neoadjuvant chemotherapy, the patients' response to neoadjuvant chemotherapy was evaluated. Complete response (CR) meant complete disappearance of lesions

for a duration of more than 4 weeks; partial response (PR) meant that the sum of the maximum diameters of the target lesions had decreased by more than 30% compared with the baseline level, for a duration of more than 4 weeks, and no new lesions had appeared; stable disease (SD) was between progressive disease (PD) and PR; PD meant that the sum of the maximum diameters of the target lesions had increased by more than 20% or new had lesions appeared. Objective response rate (ORR) = CR rate + PR rate.

Study variables

Age at diagnosis, gender, body mass index (BMI), diabetes, tumor size, lymph node metastasis, number of lymph node dissection, CEA level, ADC level, leukocyte number, neutrophil number, lymphocyte number, albumin level, primary site, degree of differentiation, pathological type, vascular tumor thrombus, invasion of adjacent tissue, and 5-year mortality.

Detection methods

Examination instrument: Siemens 3.0T MRI (Siemens,

Germany), contrast agent: gadolinium gluconate, dose: 0.2 mmol/kg, forearm intravenous injection, flow rate: 2.5 mL/s. The images were collected for 6 consecutive times before and after enhancement to evaluate the ADC (total tumor volume analysis, b values were set to 50, 400, and 800 s/mm^2).

Statistical analysis

The software SPSS 26.0 (IBM Corp., Armonk, NY, USA) was used to complete the data analysis of this study. A two-tailed P<0.05 indicated that the difference was statistically significant. The measurement data of the two groups of patients were expressed by mean ± standard deviation, and the differences between the two groups were analyzed by independent sample t-test; the counting data of the two groups were expressed by n (%), and the difference between the two groups was analyzed by chi-square test; the predictive value of different biological indicators on the efficacy of neoadjuvant chemotherapy and 5-year survival rate after neoadjuvant chemotherapy was analyzed using the receiver operating characteristic (ROC) curve, and the value of the point closest to the upper left of the ROC curve was the best diagnostic threshold; multivariate logistic regression analysis was used to explore the influencing factors of objective response after neoadjuvant chemotherapy.

Results

Comparison of clinical characteristics of the two groups

Compared with the control group, in the objective response group the tumor size was significantly lower (3.32±1.60 *vs.* 5.07±2.19 cm, P=0.000); the ADC was significantly higher (1.23±0.18 *vs.* 0.98±0.18 ×10^{-3} mm^2/s, P=0.000); albumin was significantly higher (39.32±4.14 *vs.* 37.46±4.18 g/L, P=0.016); the proportion of patients with poorly differentiated or undifferentiated tumor cells was significantly lower (51.25% *vs.* 72.92%, P=0.016); and the 5-year mortality was significantly lower (40.00% *vs.* 58.33%, P=0.044) (*Table 1*).

The predictive value of different biological indicators on the efficacy of neoadjuvant chemotherapy in patients with locally advanced CRC

ADC had the highest predictive value of objective response for locally advanced CRC patients after neoadjuvant chemotherapy, with an area under the curve (AUC) of 0.834 [95% confidence interval (CI): 0.765–0.903, P=0.000]; the best diagnostic threshold was 1.055×10^{-3} mm^2/s, and the specificity and sensitivity were 0.687 and 0.788, respectively (*Table 2, Figure 2*).

Factors influencing the objective response of locally advanced CRC patients after neoadjuvant chemotherapy

ADC >1.055×10^{-3} mm^2/s, tumor size <4.1 cm, and moderately or well differentiated tumors were favorable factors for patients with locally advanced CRC to obtain objective response after neoadjuvant chemotherapy (P<0.05) (*Table 3*).

The predictive value of ADC for 5-year survival of locally advanced CRC patients

ADC had certain predictive value for the 5-year survival of locally advanced CRC patients, with an AUC of 0.778 (95% CI: 0.696–0.861, P=0.000). The best diagnostic threshold was 1.165×10^{-3} mm^2/s, and the sensitivity and specificity were 0.691 and 0.783, respectively (*Figure 3*).

Discussion

The incidence rate and mortality of CRC is high, and it is one of the major diseases threatening the lives of middle-aged and elderly people. This study explored the predictive value of ADC on the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients. The results showed that ADC had good predictive value on the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients. ADC >1.055×10^{-3} mm^2/s was a favorable factor for locally advanced CRC patients to achieve objective response after neoadjuvant chemotherapy (P<0.05). Moreover, the ADC had certain predictive value for the 5-year survival rate.

The ADC is currently widely used in the diagnosis and treatment of malignant tumors. Its theoretical basis is that the ADC can reflect the diffusion speed of water molecules in the tissue. When the cell density is low, the water molecules move fast, so the ADC is relatively high. When the cell density is high, the diffusion speed of water molecules decreases, so the ADC level decreases. In addition, the ADC also reflects the integrity of cell matrix and cell membrane in tissues. Due to the high cell density in solid malignant tumor tissue, the ADC in malignant tumor

Table 1 Comparison of clinical characteristics of the two groups

Variables	Objective response group (n=80)	Control group (n=48)	t/χ^2 value	P value
Age at diagnosis (years)	57.86±11.34	60.31±12.33	1.145	0.254
BMI (kg/m^2)	24.69±3.64	23.60±3.81	1.624	0.107
Tumor size (cm)	3.32±1.60	5.07±2.19	5.230	0.000
Lymph node metastasis			0.333	0.563
Yes	67 (83.75)	42 (87.50)		
No	13 (16.25)	6 (12.50)		
Lymph node dissection number	13.56±5.27	15.33±6.42	1.694	0.093
CEA (U/mL)	255.79±147.70	210.75±121.68	1.780	0.077
ADC (×10^{-3} mm^2/s)	1.23±0.18	0.98±0.18	7.810	0.000
Leukocyte number (×10^9/L)	5.36±2.34	6.14±1.83	1.969	0.051
Neutrophil number (%)	0.64±0.11	0.63±0.12	0.490	0.625
Lymphocyte number (%)	0.23±0.10	0.26±0.10	1.465	0.145
Ratio of neutrophil number to lymphocyte number	3.79±2.69	3.33±2.61	0.933	0.353
Albumin level (g/L)	39.32±4.14	37.46±4.18	2.453	0.016
Gender			0.460	0.498
Male	61 (76.25)	34 (70.83)		
Female	19 (23.75)	14 (29.17)		
Diabetes			2.743	0.098
Yes	7 (8.75)	9 (18.75)		
No	73 (91.25)	39 (81.25)		
Primary site			0.212	0.645
Colon	23 (28.75)	12 (25.00)		
Rectum	57 (71.25)	36 (75.00)		
Degree of differentiation			5.839	0.016
Low differentiated and undifferentiated	41 (51.25)	35 (72.92)		
Moderately and well differentiated	39 (48.75)	13 (27.08)		
Pathological type			0.723	0.395
Adenocarcinoma	75 (93.75)	43 (89.58)		
Non-adenocarcinoma	5 (6.25)	5 (10.42)		
Vascular tumor thrombus			0.035	0.853
Yes	32 (40.00)	20 (41.67)		
No	48 (60.00)	28 (58.33)		
Invasion of adjacent tissue			0.332	0.564
Yes	26 (32.50)	18 (37.50)		
No	54 (67.50)	30 (62.50)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Objective response group (n=80)	Control group (n=48)	t/χ^2 value	P value
5-year mortality			4.049	0.044
Yes	32 (40.00)	28 (58.33)		
No	48 (60.00)	20 (41.67)		

Data are presented as mean ± standard deviation or n (%). BMI, body mass index; CEA, carcinoembryonic antigen; ADC, apparent diffusion coefficient.

Table 2 The predictive value of ADC, albumin level and tumor size in the objective response of locally advanced CRC patients after neoadjuvant chemotherapy

Variables	Areas under the curve	Standard error	P value	95% CI	Diagnostic threshold	Sensitivity	Specificity
ADC	0.834	0.035	0.000	0.765–0.903	1.055×10^{-3} mm^2/s	0.788	0.687
Albumin	0.648	0.049	0.005	0.552–0.744	37.9 g/L	0.663	0.542
Tumor size	0.761	0.045	0.000	0.674–0.848	4.1 cm	0.646	0.787

ADC, apparent diffusion coefficient; CRC, colorectal cancer; CI, confidence interval.
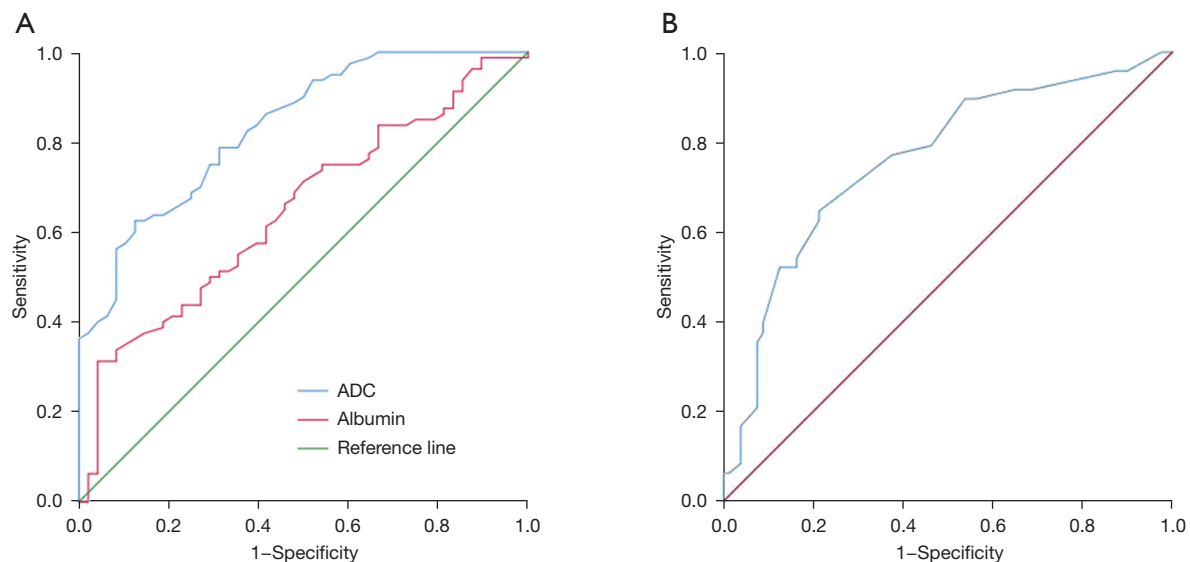

Figure 2 The predictive value of different biological indicators on the efficacy of neoadjuvant chemotherapy in patients with locally advanced CRC. (A) The predictive value of ADC and albumin level in the objective response of locally advanced CRC patients after neoadjuvant chemotherapy. (B) The predictive value of tumor size on the objective response of patients with advanced CRC after neoadjuvant chemotherapy. ADC, apparent diffusion coefficient; CRC, colorectal cancer.

tissue is often in a reduced state. At present, the ADC is used to predict the prognosis of patients with malignant tumor (19-21), and has also been reported in patients with CRC (18). In the field of neoadjuvant chemotherapy, studies have also confirmed that the ADC is significantly related to the efficacy of neoadjuvant chemotherapy in patients with breast cancer and osteosarcoma (16,22,23). However, in patients with CRC, research is relatively insufficient. A study showed that the ADC had better recognition ability for patients with CRC complicated

Table 3 Factors influencing the objective response of locally advanced CRC patients after neoadjuvant chemotherapy

Category	B	Standard error	Wald	P value	Relative risk (95% CI)
ADC >1.055×10⁻³ mm²/s	2.203	0.500	19.402	0.000	9.050 (3.396–24.115)
Tumor size <4.1 cm	1.561	0.473	10.875	0.001	4.762 (1.884–12.042)
Moderately or well differentiated tumor	1.521	0.542	7.871	0.005	4.576 (1.581–13.241)
Albumin >37.9 g/L	0.562	0.485	1.341	0.247	1.754 (0.678–4.540)
Constant	−9.213	1.756	27.539	0.000	0.000

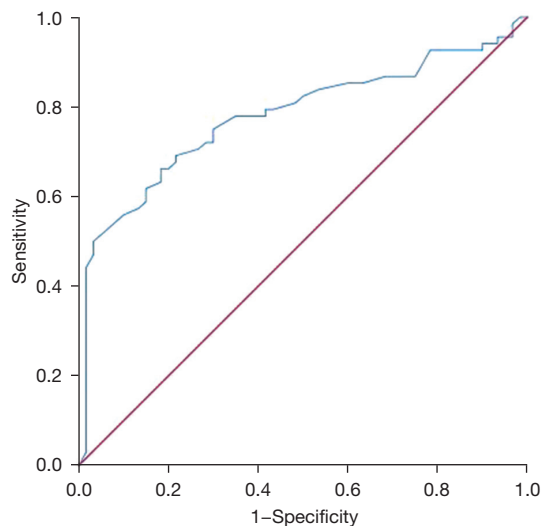CRC, colorectal cancer; CI, confidence interval; ADC, apparent diffusion coefficient.

Figure 3 The predictive value of ADC for 5-year survival of locally advanced CRC patients. ADC, apparent diffusion coefficient; CRC, colorectal cancer.

with distant metastasis after chemotherapy (24), and also showed that the ADC had certain predictive value for the curative effect after chemotherapy in patients with CRC with liver metastasis (13). These studies supported this study and suggested that the ADC could be used as a predictor of the efficacy of neoadjuvant chemotherapy for locally advanced CRC patients. However, the cases in this study were locally advanced CRC patients receiving neoadjuvant chemotherapy, which is different from the above studies. In addition, this study also showed that the ADC was significantly correlated with the long-term prognosis of patients, and the patients with higher ADC had better prognosis. A high ADC indicated that the tumor density was low, whereas a low ADC indicated that the tumor cell density was relatively high. Therefore, patients with low ADC are relatively prone to metastasis, leading to poor prognosis of patients. This had been confirmed in patients with CRC and other malignant tumors (18,25-27), supporting this study.

Limitations

This study was a retrospective clinical study with limited sample size. This study failed to explore the dynamic change of ADC during neoadjuvant chemotherapy.

Conclusions

The ADC could be used as a predictive index of the efficacy of neoadjuvant chemotherapy in locally advanced CRC patients. Combined with the ADC, clinicians can better evaluate the efficacy of neoadjuvant chemotherapy, providing a theoretical basis for clinicians to choose appropriate treatment plans.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups. com/article/view/10.21037/jgo-23-124/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (No. c202200174) and individual informed consent was waived in this retrospective study.

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