



Association between the apparent diffusion coefficient and the preoperative chemotherapy response of patients with locally advanced gastric cancer

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Background: The apparent diffusion coefficient is a parameter measured by magnetic resonance imaging (MRI). Studies in breast cancer and osteosarcoma have shown that the apparent diffusion coefficient has a good correlation with the efficacy of neoadjuvant chemotherapy. However, to date, no studies have evaluated the association between the apparent diffusion coefficient and the preoperative chemotherapy response of patients with locally advanced gastric cancer.

Methods: The data of 143 patients with locally advanced gastric cancer admitted to Zhejiang Medical and Health Group Quzhou Hospital (Zhejiang Quhua Hospital) from January 2018 to January 2019 were retrospectively collected. All the patients underwent preoperative chemotherapy and dynamic enhanced MRI to analyze the correlation between the apparent diffusion coefficient and preoperative chemotherapy response.

Results: Compared to the control group, the apparent diffusion coefficient of the objective remission group was significantly increased [$(1.16 \pm 0.26) \times 10^{-3}$ vs. $(0.95 \pm 0.26) \times 10^{-3}$ mm²/s, $P < 0.001$]; the rate of the apparent diffusion coefficient $> 1.095 \times 10^{-3}$ mm²/s was significantly increased (61.29% vs. 30.00%, $P < 0.001$). The apparent diffusion coefficient was valuable in predicting objective remission after preoperative chemotherapy in patients with locally advanced gastric cancer, the area under the curve (AUC) was 0.708 [95% confidence interval (CI): 0.621–0.796, $P < 0.001$], the best diagnostic cut-off value was 1.095×10^{-3} mm²/s, and the sensitivity and specificity were 0.613 and 0.700, respectively. The multivariate logistics regression analysis showed that the apparent diffusion coefficient of $> 1.095 \times 10^{-3}$ mm²/s was associated with the objective response of patients with locally advanced gastric cancer after preoperative chemotherapy [$P = 0.004$, relative risk = 3.135 (95% CI: 1.452–6.768)]. The apparent diffusion coefficient was valuable in predicting the non-recurrence of locally advanced gastric cancer patients, and the AUC was 0.647 (95% CI: 0.557–0.738, $P = 0.003$). The apparent diffusion coefficient was also valuable in predicting the postoperative survival of patients with locally advanced gastric cancer, and the AUC was 0.630 (95% CI: 0.537–0.723, $P = 0.007$).

Conclusions: The elevated apparent diffusion coefficient was associated with objective remission of the preoperative chemotherapy response and prognosis of patients with locally advanced gastric cancer.

Keywords: Apparent diffusion coefficient; gastric cancer; preoperative chemotherapy; prognosis

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Introduction

The incidence rate and mortality of gastric cancer are high. Due to the relatively low prevalence of gastroscopy in China, some gastric cancer patients are already locally advanced when diagnosis. Preoperative chemotherapy is a common treatment method for locally advanced gastric cancer that is used to reduce tumor volume, increase the rate of R0 resection, kill small lesions, reduce the probability of recurrence after surgery, and determine the sensitivity of tumor cells to chemotherapy drugs. However, as malignant tumor cells are heterogeneous, and the type and degree of malignancy of tumor cells in different patients are inconsistent (1-3), some patients have a poor response to preoperative chemotherapy.

Cancer antigen 125 (CA-125) has been used to evaluate the response of patients with gastric cancer to chemotherapy (4,5), but as its sensitivity and specificity are not high, new indicators that predict the chemotherapy response of patients with locally advanced gastric cancer urgently need to be identified. The apparent diffusion coefficient is an indicator of water molecule movement in diffusion-weighted imaging (DWI), which can reflect the density of the tumor cell arrangement, cell matrix, and cell membrane integrity, and is valuable in predicting the prognosis of malignant tumor patients (6). A study of gastric cancer patients has also shown that the apparent diffusion coefficient is valuable in predicting postoperative mortality and is related to the clinical stage of gastric cancer patients (7).

Highlight box

Key findings

- The apparent diffusion coefficient was valuable in predicting preoperative chemotherapy response and prognosis of locally advanced gastric cancer patients and might be a potential therapeutic target.

What is known and what is new?

- The apparent diffusion coefficient is a parameter measured by magnetic resonance imaging technology. It has been used in the diagnosis and treatment of a variety of solid tumors and is valuable in judging the clinicopathological characteristics of tumors;
- The apparent diffusion coefficient may be a potential biological indicator of the efficacy of neoadjuvant chemotherapy.

What is the implication, and what should change now?

- The molecular mechanism by which the apparent diffusion coefficient affects the efficacy of chemotherapy and prognosis requires further study.

Studies in breast cancer and osteosarcoma showed that the apparent diffusion coefficient has a good correlation with the efficacy of neoadjuvant chemotherapy, elevated apparent diffusion coefficient was associated with better efficacy (8-12). However, to date, no such studies have been conducted in patients with gastric cancer. We present the following article in accordance with the STARD reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-30/rc>).

Methods

General information

The data of 143 patients with locally advanced gastric cancer admitted to Zhejiang Medical and Health Group Quzhou Hospital (Zhejiang Quhua Hospital) from January 2018 to January 2019 were retrospectively and continuously collected, all of whom underwent preoperative chemotherapy and dynamic enhanced magnetic resonance imaging (MRI). Inclusion criteria: (I) have gastric cancer confirmed by gastroscopy and pathological examination, and measurable lesions with a maximum diameter ≥ 2 cm (*Figure 1*); (II) be aged 18–80 years; (III) have diagnosis of locally advanced gastric cancer [clinical tumor, node, and metastasis (cTNM) stage III] according to the results of the imaging examination and gastroscopy; (IV) have received preoperative chemotherapy; (V) have received surgical treatment at our hospital after preoperative chemotherapy, and have postoperative pathological condition and follow-up data available. Exclusion criteria: (I) had gastric metastatic carcinoma; (II) had recurrent gastric cancer; (III) had other malignant tumors; (IV) were unable to cooperate with the treatment or were lost to follow-up, etc.; (V) had contraindications to chemotherapy; (VI) were receiving other special treatments, such as targeted drug therapy or radiotherapy at the same time; and/or (VII) had distant metastasis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective clinical study was approved by the ethics committee of Zhejiang Medical and Health Group Quzhou Hospital (Zhejiang Quhua Hospital) (No. c20220082), and the requirement for informed consent was waived.

Treatment method

After admission to the hospital, the patients completed

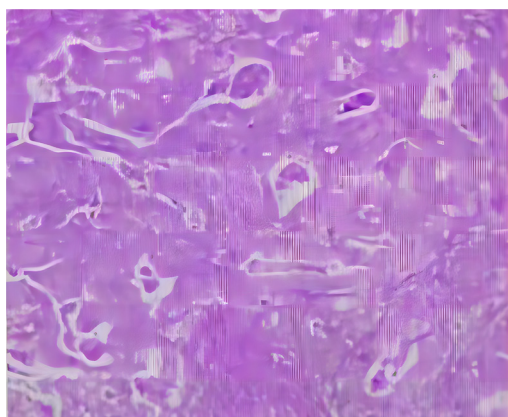


Figure 1 The diagnosis of gastric cancer was based on a pathological diagnosis (immunohistochemical staining, $\times 200$).

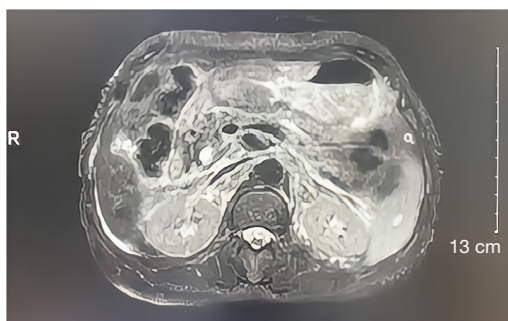


Figure 2 MRI scan of a gastric cancer patient before chemotherapy. MRI, magnetic resonance imaging; R, right.

the relevant tests and examinations before chemotherapy. Excluding those with contraindications to chemotherapy, all the patients received the XELOX chemotherapy regimen with 21 days for 1 cycle and a total of 3 cycles. The patients underwent laparoscopic radical gastric cancer resection about 30 days after the last chemotherapy cycle. After the operation, a decision was made as to whether each patient should receive follow-up adjuvant therapy according to the conventional pathological results.

Evaluation criteria

Each patient's responsiveness to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST1.1), which adopts the following definitions: complete response: the complete disappearance of lesions for a duration >4 weeks; partial response: the sum of the maximum diameter of the target lesion was reduced

by $>30\%$ from the baseline level, and the maintenance time was >4 weeks, and no new lesions appeared; stable disease: disease between progressive disease and partial response; progressive disease: the sum of the maximum diameter of the target lesion increases by $>20\%$ or a new lesion appears. The objective response rate (ORR) was calculated using the following formula: $\text{ORR} = \text{complete response rate} + \text{partial response rate}$.

Adverse reactions

The adverse reactions included hypertension, proteinuria, hand-foot syndrome, nausea and vomiting, leukopenia, fatigue, and neurotoxicity.

Dynamic enhanced MRI examination

The MRI examination was performed before the chemotherapy by Siemens 3.0T MRI, and gadolinium spray glucosamine (0.2 mmol/kg, 2.5 mL/s) was administered through the forearm intravenously. Images were acquired 6 consecutive times before and after enhancement, and MRI with DWI was obtained with the apparent diffusion coefficient (Figure 2).

Follow-up

The patients were rechecked every 6 months after surgery and were followed-up for 3 years. The recurrence-free rate and survival rate were observed. Follow-up was conducted through outpatient clinics and telephone calls.

Study groups

All the patients received preoperative chemotherapy. Gastroscopy and abdominal MRI were performed before and after chemotherapy. According to the changes of lesions before and after chemotherapy, the efficacy of the preoperative chemotherapy was evaluated. The patients were divided into the objective response group ($n=93$) and control group ($n=50$) according to the chemotherapy effect. There were 0 cases of complete response, 93 cases of partial response, 45 cases of stable disease, and 5 cases of progressive disease.

Statistical analysis

SPSS 26.0 was used to complete the data analysis of this

study. A two-tailed P value <0.05 was considered statistically significant. The measurement data that conformed to a normal distribution are presented as the mean \pm standard deviation, and the differences between the 2 groups were analyzed using an independent sample *t*-test. The counting data are expressed as the number (percentage), and the chi-square test was used to analyze the differences between the 2 groups. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of the apparent diffusion coefficient on the ORR, recurrence and metastasis within 3 years of surgery. At the same time, a Binary Logistics regression analysis was used to explore the factors related to achieving an objective response after preoperative chemotherapy. Variables with potential statistical differences between the two groups ($P < 0.100$) were included in the regression analysis.

Results

Comparison of the clinicopathological features between the 2 groups

Compared to the control group, the apparent diffusion coefficient of the objective remission group was significantly increased [$(1.16 \pm 0.26) \times 10^{-3}$ vs. $(0.95 \pm 0.26) \times 10^{-3}$ mm²/s, $P < 0.001$]; the rate of the apparent diffusion coefficient $> 1.095 \times 10^{-3}$ mm²/s was significantly increased (61.29% vs. 30.00%, $P < 0.001$); the proportion of patients with the pathological type of signet-ring cell carcinoma was lower (6.45% vs. 18.00%, $P = 0.032$); and the proportion of patients with moderate or low differentiation was significantly reduced (40.86% vs. 60.00%, $P = 0.029$). The recurrence-free rate was significantly increased at 3 years after surgery (50.54% vs. 34.00%, $P = 0.033$) (Table 1).

Predictive value of the apparent diffusion coefficient in evaluating the objective response of locally advanced gastric cancer patients after preoperative chemotherapy

The apparent diffusion coefficient was valuable in predicting the objective remission of patients with locally advanced gastric cancer after preoperative chemotherapy, the area under the curve (AUC) was 0.708 [95% confidence interval (CI): 0.621–0.796, $P < 0.001$], the best diagnostic cut-off value was 1.095×10^{-3} mm²/s, and the sensitivity and specificity were 0.613 and 0.700, respectively (Figure 3).

Factors related to the objective response of patients with locally advanced gastric cancer after preoperative chemotherapy

The results of the multivariate logistics regression analysis showed that the apparent diffusion coefficient of $> 1.095 \times 10^{-3}$ mm²/s was associated with the objective response of patients with locally advanced gastric cancer after preoperative chemotherapy [$P = 0.004$, relative risk = 3.135 (95% CI: 1.452–6.768)] (Figure 4).

Predictive value of the apparent diffusion coefficient in evaluating the postoperative non-recurrence of locally advanced gastric cancer

The apparent diffusion coefficient was valuable in predicting the non-recurrence of gastric cancer patients in the locally advanced stage, and the AUC was 0.647 (95% CI: 0.557–0.738, $P = 0.003$) (Figure 5).

Predictive value of the apparent diffusion coefficient on the postoperative survival of patients with locally advanced gastric cancer

The apparent diffusion coefficient was valuable in predicting the postoperative survival of patients with locally advanced gastric cancer, and the AUC was 0.630 (95% CI: 0.537–0.723, $P = 0.007$) (Figure 6).

Discussion

Preoperative chemotherapy is a commonly used treatment method for locally advanced gastric cancer. Its purpose is to improve the R0 resection rate, kill the micro metastasis, and ultimately reduce the postoperative recurrence and mortality rates (13–15). Thus, it is of great significance to accurately identify the responsiveness of gastric cancer patients to preoperative chemotherapy. We designed this study to explore the value of the apparent diffusion coefficient in predicting the preoperative chemotherapy response of locally advanced gastric cancer patients. The results showed that the apparent diffusion coefficient of patients who achieved an objective response was significantly higher than that of other patients, and had certain value in predicting the objective response, non-recurrence, and survival after preoperative chemotherapy. The multivariate logistics

Table 1 Comparison of the clinicopathological features between the 2 groups

Category	Objective response group (n=93)	Control group (n=50)	χ^2 value	P value
Age (years)			0.458	0.499
≥ 65	52 (55.91)	25 (50.00)		
<65	41 (44.09)	25 (50.00)		
Gender			1.273	0.259
Male	61 (65.59)	28 (56.00)		
Female	32 (34.41)	22 (44.00)		
Body mass index (kg/m ²)			0.077	0.782
≥ 24.0	58 (62.37)	30 (60.00)		
<24.0	35 (37.63)	20 (40.00)		
CA-125 (U/mL)	455.67 \pm 236.59	529.88 \pm 215.65	1.844	0.067
Apparent diffusion coefficient ($\times 10^{-3}$ mm ² /s)	1.16 \pm 0.26	0.95 \pm 0.26	4.605	<0.001
Apparent diffusion coefficient ($\times 10^{-3}$ mm ² /s)			12.736	<0.001
>1.095	57 (61.29)	15 (30.00)		
≤ 1.095	36 (38.71)	35 (70.00)		
Pathology type			4.619	0.032
Adenocarcinoma	87 (93.55)	41 (82.00)		
Signet-ring cell carcinoma	6 (6.45)	9 (18.00)		
Differentiation			4.776	0.029
Moderate and poor differentiation	38 (40.86)	30 (60.00)		
Well differentiation	55 (59.14)	20 (40.00)		
Tumor site			0.036	0.849
Cardiac cancer	32 (34.41)	18 (36.00)		
Non cardiac cancer	61 (65.59)	32 (64.00)		
Tumor size (cm)			0.128	0.721
≥ 5	21 (22.58)	10 (20.00)		
<5	72 (77.42)	40 (80.00)		
cTNM stage			0.677	0.713
IIIA	62 (66.67)	35 (70.00)		
IIIB	18 (19.35)	7 (14.00)		
IIIC	13 (13.98)	8 (16.00)		
Adverse reaction				
Hypertension	1 (1.08)	2 (4.00)	1.354	0.245
Proteinuria	0 (0.00)	1 (2.00)	1.873	0.171
Hand-foot syndrome	0 (0.00)	1 (2.00)	1.873	0.171
Nausea and vomiting	12 (12.90)	8 (16.00)	0.259	0.611
Leukopenia	21 (22.58)	15 (30.00)	0.950	0.330
Fatigue	16 (17.20)	13 (26.00)	1.556	0.212
Neurotoxicity	4 (4.30)	3 (6.00)	0.202	0.653
Recurrence rate 3 years after operation	47 (50.54)	17 (34.00)	4.534	0.033
Survival rate 3 years after operation	51 (54.84)	20 (40.00)	2.864	0.091

Data are presented as mean \pm standard deviation or n (%). CA-125, cancer antigen 125; cTNM, clinical tumor, node, and metastasis.

regression analysis showed that the apparent diffusion coefficient of $>1.095 \times 10^{-3} \text{ mm}^2/\text{s}$ was associated with the objective response of patients with locally advanced gastric cancer after preoperative chemotherapy [P=0.004, relative risk =3.135 (95% CI: 1.452–6.768)].

The apparent diffusion coefficient is an index that reflects the movement of water molecules in DWI, which can show the density of tumor cells, and the integrity of the cell matrix and cell membrane. When the density of tumor cells is high, the movement of water molecules is limited, and the apparent diffusion coefficient decreases. Thus, when the apparent diffusion coefficient is low, the density of malignant tumor cells is high. This provides the theoretical basis for the apparent diffusion coefficient to be used to diagnose and predict the prognosis of patients

with solid tumors (16). At present, few studies have been conducted on the application of the apparent diffusion coefficient in gastric cancer patients. A previous study showed that the apparent diffusion coefficient was related to the T stage of gastric cancer patients, and the level of the apparent diffusion coefficient was lower in patients with T4 stage tumors than that of other patients (17). Another study showed that a decrease in the apparent diffusion coefficient was related to an increase in the invasiveness of gastric cancer cells (18). Giganti *et al.* conjectured that the decrease of the apparent diffusion coefficient was related to local progress, lymph node metastasis, and TNM staging, and suggested that the apparent diffusion coefficient could serve as a prognostic marker for gastric cancer patients (7). Similar results were obtained in several other studies (19–21).

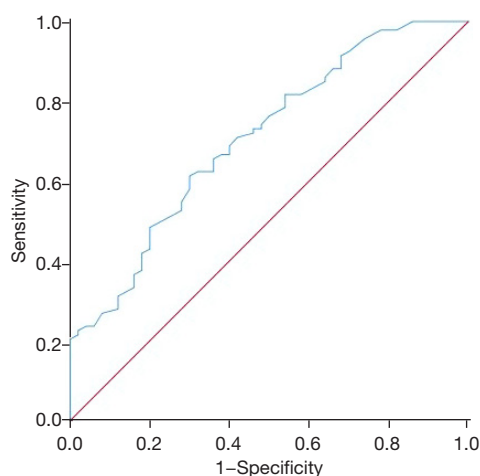


Figure 3 Predictive value of the apparent diffusion coefficient in evaluating the objective response of locally advanced gastric cancer patients after preoperative chemotherapy.

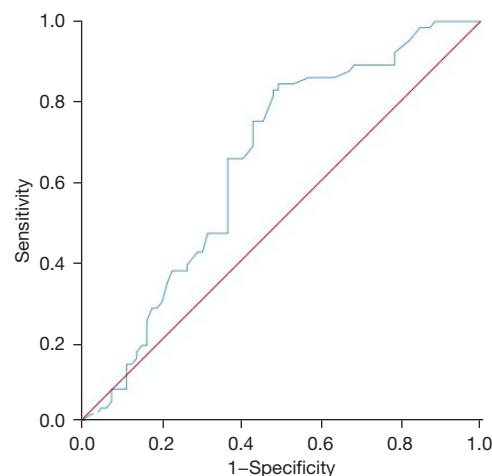


Figure 5 Predictive value of the apparent diffusion coefficient in evaluating the postoperative non-recurrence of locally advanced gastric cancer.

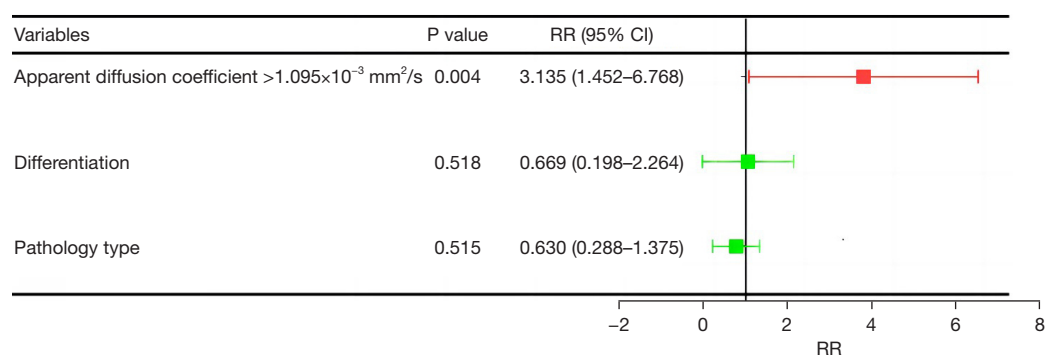


Figure 4 Factors related to the objective response of patients with locally advanced gastric cancer after preoperative chemotherapy. RR, relative risk; CI, confidence interval.

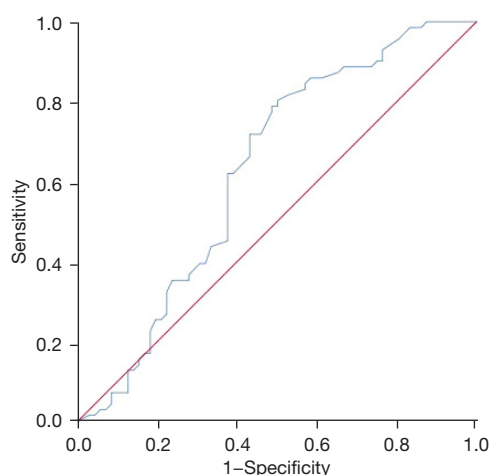


Figure 6 Predictive value of the apparent diffusion coefficient in evaluating the postoperative survival of patients with locally advanced gastric cancer.

However, no study had explored the correlation between the apparent diffusion coefficient and the preoperative chemotherapy response of gastric cancer patients.

The present study showed that an increase in the apparent diffusion coefficient was related to the objective response of patients after chemotherapy. Given that CA-125 was shown to have no significant correlation with the chemotherapy response, the apparent diffusion coefficient could be used to replace CA-125 as a marker for predicting chemotherapy response. Studies of other malignant tumors, including colorectal cancer with liver metastasis, and breast cancer, have also confirmed that a reduction in the apparent diffusion coefficient is related to poor chemotherapy efficacy, which reflects the findings of this study (8,22-25).

Limitations

This study had a number of limitations. Notably, it was a retrospective clinical study that did not explore the molecular mechanism by which the apparent diffusion coefficient affects the efficacy and prognosis of chemotherapy.

Conclusions

In conclusion, the elevated apparent diffusion coefficient was associated with objective remission of the preoperative chemotherapy response and prognosis of patients with locally advanced gastric cancer.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-30/rc>

Data Sharing Statement: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-30/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-30/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). This retrospective clinical study was approved by the ethics committee of Zhejiang Medical and Health Group Quzhou Hospital (Zhejiang Quhua Hospital) (No. c20220082), and the requirement for informed consent was waived.

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