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Retrospective Study

Predictive value of serum alpha-fetoprotein for tumor regression after preoperative chemotherapy for rectal cancer

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Abstract

BACKGROUND

Preoperative therapy is widely used in locally advanced rectal cancer. It can improve local control of rectal cancer. However, there are few indicators that can predict the effect of preoperative chemotherapy accurately.

AIM

To investigate whether the increase in serum α -fetoprotein (AFP) can predict better efficacy of preoperative chemotherapy.

METHODS

This was a retrospective study. We analyzed 125 patients admitted between 2017 and 2019 with locally advanced rectal cancer. All patients received six cycles of preoperative chemotherapy (mFOLFOX6 every 2 wk). Serum AFP of 26 patients rose slightly after three or four cycles of chemotherapy, and fell to normal again within 2 mo. The other 99 patients had a normal level of serum AFP during chemotherapy. Patients were divided into two groups (AFP risen and AFP normal). According to postoperative pathology, we compared tumor regression and complete response rate between the two groups. The primary outcome measure was the tumor regression grade (TRG) after chemotherapy. The difference in pathological complete response between the two groups was also investigated.

RESULTS

There were no tumor progression and distant metastasis in both groups during preoperative chemotherapy. Patients in the AFP risen group achieved better TRG 0/1 than those in the AFP normal group (61.5% vs 39.4%). The increase in AFP was a significant predictor for better tumor regression [$\chi^2 = 4.144$, odds ratio (OR)

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= 2.666, $P = 0.04$]. In the AFP risen group, the complete response rate was 30.8%, which was higher than in the AFP normal group (30.8% vs 12.1%, $\chi^2 = 4.542$, OR = 3.251, $P = 0.03$).

CONCLUSION

Patients with a slight increase in serum AFP can achieve better tumor regression during preoperative chemotherapy, and are more likely to achieve pathological complete response.

Key Words: Rectal cancer; Preoperative chemotherapy; Alpha-fetoprotein; Predictive value; Tumor

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Core Tip: We analyzed 125 patients with locally advanced rectal cancer retrospectively. The patients received 6 cycles of preoperative chemotherapy (mFOLFOX6 every 2 wk). Serum α -fetoprotein (AFP) of 26 patients rose slightly and returned to normal in two months. These patients achieved better tumor regression grade (TRG0-1) than those with normal AFP (61.5% vs 39.4%). Patients with a slight increase of serum AFP showed better tumor regression during preoperative chemotherapy, and were more likely to achieve pathological complete response (30.8% vs 12.1%).

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INTRODUCTION

According to guidelines, patients with locally advanced rectal cancer are recommended to receive preoperative chemoradiotherapy; especially those with a high risk of recurrence (positive circumferential resection margin, lymphovascular invasion and extensive lymph nodal involvement)[1]. Preoperative chemoradiotherapy can reduce the rate of local recurrence significantly[2]. However, the survival of these patients is not improved after radiotherapy[3]. Some patients who cannot achieve tumor regression experience radiation toxicity and delayed surgery. The potentially increased surgical complications and decreased quality of life associated with radiotherapy also cause pain in patients with low rectal cancer. Some researchers believe that preoperative chemotherapy without radiotherapy is another choice that can also achieve tumor downstaging. Several clinical trials have been carried out to prove chemotherapy alone is an effective choice for locally advanced rectal cancer[4]. Although the rate of complete response decreases significantly, it is suggested that there is no difference in patients' prognosis whether or not they receive radiotherapy before surgery[5]. Different protocols for preoperative chemotherapy alone that consist of oxaliplatin and 5-fluorouracil are recommended in our hospital. Although tumor regression is not as good as with long-course chemoradiotherapy, with approximately 9% complete response rate, the advantages are lack of toxicity from radiotherapy, reduced surgical complications and reduced cost of hospitalization. There are no methods to predict which patients can achieve a better effect from chemotherapy. In this course of treatment, several patients show a slight increase in serum α -fetoprotein (AFP) during chemotherapy and then return to normal. Some of these patients seem to more easily achieve a pathological complete response.

The aim of this study was to evaluate the association between AFP and tumor regression grade (TRG) of rectal cancer after preoperative chemotherapy. We compared TRG and complete response rate in different groups, and explored whether increased serum AFP can predict the effect of preoperative chemotherapy.

MATERIALS AND METHODS

Patients

A retrospective consecutive study of 125 patients (77 male and 48 female) with locally advanced rectal cancer was performed. Eastern Cooperative Oncology Group (ECOG) status was 0 or 1. Liver and lung metastases were excluded by computed tomography. All patients received preoperative chemotherapy and surgery at the China-Japan Friendship Hospital between 2017 and 2019. These patients were treated with preoperative chemotherapy alone. Radiotherapy was not performed before surgery. All these patients underwent radical resection 1 mo after chemotherapy. Some serum markers, including AFP, carcinoembryonic antigen (CEA) and other markers, were detected when patients received chemotherapy. Serum AFP rose slightly in 26 patients after three or four cycles of chemotherapy, and fell to normal again within 2 mo. Among them, the median increase in serum AFP was 33.41 (range 15.62–85.73) ng/mL. The other 99 patients had a normal level of serum AFP during chemotherapy. All patients underwent total mesorectal excision (TME).

Chemotherapy and AFP testing

A standard chemotherapy regimen for rectal cancer was applied. Patients received mFOLFOX6 (oxaliplatin 85 mg/m² and leucovorin 400 mg/m² as a 2 h infusion, followed by 5-fluorouracil 400 mg/m² as a bolus and 2400 mg/m² as a 46 h infusion) every 2 wk. Surgery was performed after six cycles of chemotherapy. During chemotherapy, serum markers (including AFP) were detected every month. Every 6 wk, pelvic magnetic resonance imaging and digital rectal examination were used to evaluate local tumor regression.

Surgery

After 1 mo off chemotherapy, all 125 patients underwent laparoscopic rectal surgery at the China-Japan Friendship Hospital. TME was the standard approach for surgical treatment of rectal cancer. There were no cases of distal and circumferential margin involvement. Low anterior resection (LAR) was performed in 112 patients. Abdominoperineal resection (APR) was performed in 13 patients. Intraoperative colonoscopy was applied to mark the masses and scars in patients with clinical complete response and small tumors after chemotherapy.

Tumor regression and complete response

All patients underwent radical resection. Regional rectal tumor and lymph nodal involvement was evaluated. Tumor regression was based on the residual tumor cells and tumor fibrosis. TRG classification used the American Joint Committee on Cancer (AJCC) standard. Pathological complete response was defined as TRG 0 and was confirmed by two different pathologists.

Statistical analysis

The association between patients' characteristics and increased serum AFP was analyzed using two-sided χ^2 or Fisher's exact test. Complete response was also discussed. The clinical variables included general information about the patients and tumor characteristics, as well other serum markers such as CEA. Logistic regression was performed to investigate the independent factors associated with tumor regression and complete response. $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics and groups

We analyzed 125 patients with locally advanced rectal cancer who received preoperative chemotherapy. All patients received six cycles of mFOLFOX6 followed by TME after 1 mo. One hundred and twelve patients underwent LAR, and 13 APR. In twenty patients (16.0%), we could not find tumor cells in the resected rectum after chemotherapy. Forty-nine (39.2%) patients had a high level of serum CEA. CEA was the most relevant marker. Before chemotherapy, serum AFP was normal in all patients.

Serum AFP of some patients rose slightly during chemotherapy. Among them, the highest level of serum AFP was 85.73 ng/mL. Compared with serum AFP in hepatocellular carcinoma, the increase was small. The median value was 33.41 (range 15.62–85.73) ng/mL. The patients were divided into two groups according to the change in serum AFP during preoperative chemotherapy. AFP risen group: 26 patients whose AFP rose slightly and returned to normal before surgery. AFP normal group: 99 patients who had a normal level of serum AFP during chemotherapy. Other serum tumor markers such as CEA and carbohydrate antigen (CA) 19-9 were analyzed. Some laboratory indicators related to liver function were also detected, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and albumin. The analysis of clinical and pathological characteristics was summarized in [Table 1](#).

Association between TRG and AFP

All 125 patients underwent R0 radical resection. The effect of preoperative chemotherapy was evaluated by the number of residual tumor cells in the resected rectum. TRG was analyzed by pathologists, using the AJCC standard. TRG0 (20 patients): Complete response and no residual tumor cells. TRG1 (35 patients): Moderate response and single or few residual tumor cells. TRG2 (46 patients): Mild response and several residual tumor cells. TRG3 (24 patients): Nearly no response.

More patients in the AFP risen group had fewer residual tumor cells [8 patients (30.8%) with TRG0 and 8 patients (30.8%) with TRG1]. In the AFP normal group, we found 12 patients (12.1%) with complete response and 27 (27.3%) with TRG1. Patients in the AFP risen group achieved better TRG (TRG0-1) than those in the AFP normal group (61.5% *vs* 39.4%). The difference was significant [$\chi^2 = 4.144$, odds ratio (OR) = 2.666, 95% confidence interval (CI) = 1.037–6.855, $P = 0.04$] ([Table 2](#)).

Association between complete response and AFP

Twenty patients achieved a pathological complete response. No tumor cells were found in these patients. Twelve patients (12.1%) reached complete response in the AFP normal group. In the AFP risen group, the complete response rate was 30.8% (8 patients). Complete response was more easily reached if AFP rose during chemotherapy ($\chi^2 = 4.542$, OR = 3.251, 95% CI = 1.099–9.616, $P = 0.03$) ([Table 3](#)).

DISCUSSION

Neoadjuvant radiotherapy has become an important method to reduce local recurrence of locally advanced rectal cancer. An increasing number of patients have been recommended to receive radiotherapy before surgery. However, it does not improve patients' prognosis. The increase in postoperative complications has been a major concern. Especially for some patients with low rectal cancer, radiotherapy is always associated with worse quality of life and destroyed anal function[6-8]. In recent years, preoperative chemotherapy has become a choice of patients with locally advanced rectal cancer. Researchers have tried to use chemotherapy to achieve tumor regression and downstaging for some selected patients. Compared with radiotherapy, there are no differences in survival and radical resection rate. The FOWARC study showed similar outcomes. Patients receiving preoperative radiotherapy and chemotherapy can achieve similar prognosis[9].

We found that some patients achieved tumor downstaging and even complete response after chemotherapy, but others had no tumor regression and worse prognosis. Several studies have investigated which indicators can predict the sensitivity[10,11]. The conclusions are not in agreement and no reliable markers have been found. In the present study, some patients with locally advanced rectal cancer who received preoperative chemotherapy showed a transient increase in AFP during chemotherapy and a gradual decrease to normal before surgery. Compared with other patients, these patients had a higher rate of complete pathological remission (30.8% *vs* 12.1%), and they were more sensitive to preoperative chemotherapy.

In previous studies, serum CEA was the most associated tumor marker with rectal cancer. Approximate 40%–70% of patients had an increased CEA and always had worse prognosis. In our study, the proportion of patients with abnormal CEA was 39.2%. AFP is a serum tumor marker closely related to hepatocellular carcinoma. It had no obvious correlation with rectal cancer in previous studies. Even in the presence of liver metastases, AFP hardly increases in patients with rectal cancer.

Table 1 Clinical and pathological characteristics of patients (*n* = 125), *n* (%)

Characteristics	<i>n</i> = 125
Age, median (yr, range)	63 (29-86)
Sex	
Male	77 (61.6)
Female	48 (38.4)
Location (distance from anal verge, cm)	
< 5	85 (68)
≥ 5	40 (32)
Clinical T stage	
T2	6 (4.8)
T3-4	119 (95.2)
CEA	
High	49 (39.2)
Normal	76 (60.8)
CA19-9	
High	17 (13.6)
Normal	108 (86.4)
ALT	
High	11 (8.8)
Normal	114 (91.2)
AST	
High	4 (3.2)
Normal	121 (96.8)
Bilirubin	
High	23 (18.4)
Normal	102 (81.6)
Albumin	
High	3 (2.4)
Normal	122 (97.6)

AFP: α -fetoprotein; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

In our study, patients with transient increase in AFP during chemotherapy did not have liver metastasis or abnormal liver function. For these patients, other serum tumor markers (CEA, CA19-9 and CA153) were detected simultaneously, and no similar changes were found. We found that the concentration of serum AFP in these patients was < 50 ng/mL, which is different from hepatocellular carcinoma. We followed up all these patients. Serum AFP did not increase after surgery. We did not find any previous studies which had reported similar changes in AFP during chemotherapy. It is difficult to explain why these patients were sensitive to chemotherapy.

In some cases of acute hepatitis and cirrhosis, hepatocyte injury may cause a mild increase in AFP (often < 400 ng/mL). AFP may be secreted by regenerated immature hepatocytes and fall to normal after patients recover from hepatitis. All patients in this study underwent chemotherapy (oxaliplatin combined with fluorouracil), and chemotherapeutic toxicity caused hepatocyte injury. We were not sure whether it was associated with increased AFP. Reviewing the treatment of these patients, we found that aminotransferases and bilirubin did not increase during chemotherapy, nor did

Table 2 Logistic regression analysis of tumor regression grade

Characteristics	TRG 0-1/2-3		
	χ^2	OR (95%CI)	P value
Age	0.356	1.265 (0.585–2.735)	0.55
Sex	0.003	1.022 (0.464–2.252)	0.96
Distance from anal verge	5.226	2.679 (1.1519–6.236)	0.02 ^a
Clinical T stage	0.050	1.231 (0.200–7.562)	0.82
CEA	4.666	2.410 (1.085–5.348)	0.03 ^a
AFP	4.144	2.666 (1.037–6.855)	0.04 ^a

^a*P* < 0.05.TRG: Tumor regression grade; CEA: Carcinoembryonic antigen; AFP: α -fetoprotein.**Table 3 Logistic regression analysis of pathological complete response**

Characteristics	Pathological complete response		
	χ^2	OR (95%CI)	P value
Age	0.172	1.244 (0.444–3.486)	0.68
Sex	0.038	1.113 (0.380–3.259)	0.85
Distance from anal verge	2.535	2.953 (0.779–11.199)	0.11
Clinical T stage	1.226	2.945 (0.435–19.926)	0.27
CEA	0.088	1.170 (0.416–3.293)	0.77
AFP	4.542	3.251 (1.099–9.616)	0.03 ^a

^a*P* < 0.05.CEA: Carcinoembryonic antigen; AFP: α -fetoprotein.

serum albumin. There was no evidence of symptomatic hepatocyte injury. There were also no significant imaging changes in cirrhosis on computed tomography. There were more oral mucosal ulcers, gastrointestinal reactions, and hand-foot syndrome in these patients. We guessed that these patients might be more sensitive to chemotherapy, whether therapeutic or adverse effects. The increase in AFP was probably one of the indicators. We do not know whether it was related to immune factors such as function of T lymphocytes.

The increase in AFP was closely associated with better preoperative chemotherapy effect in our study. Although we have not established the reason, the increase in AFP might be used as a predictor of chemotherapeutic efficacy in patients with rectal cancer. Patients with transient increase in AFP during chemotherapy are more sensitive to chemotherapeutic drugs. These patients may have better tumor regression and a higher rate of complete response. Some researchers have suggested that patients whose tumors completely disappear after chemotherapy should not be treated with resection[12]. Less than 20% of these patients will suffer from local and distant tumor recurrence[13,14]. Frequent follow-up and “wait and watch” approach can find possible local recurrence in time and bring better quality of life[15,16]. We will pay more attention to these patients with rising serum AFP. The small sample size was a limitation of our study. Future research will include more patients to verify our conclusions. In subsequent follow-up, we want to know whether these patients can achieve better prognosis and whether the probability of recurrence is decreased. Our future studies will focus on whether serum AFP can predict complete response and become an indicator before “wait and watch” approach.

CONCLUSION

Patients with locally advanced rectal cancer who had a slight increase in serum AFP can achieve better tumor regression during preoperative chemotherapy, and these patients are more likely to achieve pathological complete response. These findings may guide our future treatment for such patients.

ARTICLE HIGHLIGHTS

Research background

Preoperative therapy can improve local control of rectal cancer. Some tumors regress after preoperative therapy. Few indicators can predict the effect accurately. In this study, we try to find how to predict which patients will be sensitive to preoperative therapy.

Research motivation

The motivation is to find the effective indicators to predict the effect of preoperative therapy. It may screen out sensitive patients to receive preoperative therapy, and the others to receive surgery directly.

Research objectives

The objective is investigating whether the increase in serum α -fetoprotein (AFP) can predict better efficacy of preoperative chemotherapy. It will guide the treatment of rectal cancer after further research.

Research methods

We retrospectively analyzed 125 patients admitted between 2017 and 2019 with locally advanced rectal cancer. All patients received preoperative chemotherapy (mFOLFOX6 every 2 wk). Patients were divided into two groups (AFP risen and AFP normal). Serum AFP of 26 patients rose slightly after three or four cycles of chemotherapy, and fell to normal again within 2 mo. Among them, the median increase in serum AFP was 33.41 (range 15.62–85.73) ng/mL. The other 99 patients had a normal level of serum AFP during chemotherapy. All patients underwent total mesorectal excision. Tumor regression grade (TRG) and complete response rate were both compared between the two groups.

Research results

Patients in the AFP risen group achieved better TRG (0/1) than those in the AFP normal group. The increase in AFP was a significant predictor for better tumor regression. In the AFP risen group, the complete response rate was 30.8%, which was also higher than in the AFP normal group. It provides an indicator to predict the efficacy of chemotherapy. However, the proportion of these patients is low. Other effective indicators are needed.

Research conclusions

Patients with an increase in serum AFP during preoperative chemotherapy can achieve better tumor regression. They are more likely to achieve pathological complete response. These patients should be recommended to receive preoperative chemotherapy.

Research perspectives

In this study, we could predict efficacy of chemotherapy by detecting changes in AFP. In future studies, we focus on finding more effective indicators. It is also needed to investigate whether they can be applied simultaneously to improve sensitivity.

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