THE LEVEL OF SERUM TAP, CEA CAN BE USED TO EVALUATE THE CURATIVE EFFECT OF NEOADJUVANT CHEMOTHERAPY

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ABSTRACT

Objective: *To investigate the changes in serum tumour abnormal protein (TAP) and carcinoembryonic antigen (CEA) levels in patients with rectal cancer before and after neoadjuvant chemotherapy and its relationship with the curative effect of chemotherapy.*

Methods: *We retrospectively analysed 115 patients who had received neoadjuvant chemotherapy for rectal cancer. At the same time, 115 healthy people were selected. The serum CEA level was measured by radioimmunity and the serum TAP level was detected using a computerized TAP detection system. The relationship between TAP and CEA levels and chemotherapy efficacy was analysed using the receiver operator characteristic (ROC) curve.*

Results: *The serum TAP and CEA levels in the patients were 172.15±21.47 μm² and 37.82±6.61 ng/mL, respectively, which were significantly higher than that of the healthy subjects (82.63±10.32 μm² and 1.08±0.27 ng/mL, respectively, P<0.05]. After neoadjuvant chemotherapy, 18 cases (15.65%) had complete remission (CR), 76 cases (66.09%) had partial remission, 15 cases (13.04%) had stable disease (SD), and six cases (5.22%) had advanced (PD). The level and percentage of TAP and CEA in the CR and PR patients after chemotherapy were significantly lower than that before chemotherapy, and that in the PD patients were significantly higher after chemotherapy than before chemotherapy (P<0.05). The ROC curve analysis showed that the sensitivity, specificity, accuracy and ROC of neoadjuvant chemotherapy for rectal cancer were 92.6%, 72.6%, 92.0%, 0.724, 89.0%, 0.746, 96.4%, 70.4%, 88.0%, 0.746, 96.4%, 91.7%, 97.0% and 0.928, respectively. When the critical value of neoadjuvant chemotherapy was >21%, the critical values were 92.6%, 72.6%, 92.0% and 0.724, and the critical value of neoadjuvant chemotherapy was 92.6%, 72.6%, 92.0%, 0.724, 0.746, 96.4%, 91.7%, 97.0% and 0.928, respectively. The time of the two parameters combined was significantly higher than that of the two parameters alone (P<0.05).*

Conclusion: *Patients with rectal cancer have higher serum TAP and CEA levels, and the detection thereof can be used as an important index for evaluating the curative effect of neoadjuvant chemotherapy, and combined detection has better evaluation efficiency.*

Keywords: *Rectal cancer, neoadjuvant chemotherapy, tumour abnormal protein, carcinoembryonic antigen.*

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Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women in the Western world. In 2019, there were approximately 44,180 newly diagnosed cases of rectal cancer in the United States[1]. CRC accounts for one-third of the world's undefined tumours by incidence, with about 1.3 million new cases diagnosed each year[2]. Although many screening efforts are underway for early diagnosis, at least 50% of patients will develop local or distant disease recurrence or advanced disease[3-4].

The 5-year survival rate of patients with early CRC is 90.3%, and once metastasis occurs, the survival rate decreases to 50–70.4%[5]. Conventional therapies, including surgery, radiotherapy, chemotherapy or combination therapy, moderately improve the prognosis of patients[6-7], in which rectal cancer accounts for about one-third of all CRC[8]. Carcinoembryonic antigen (CEA) is one of the most common and convenient preoperative detection indexes in patients with CRC[9]. A glycoprotein, CEA has been recommended by the American Society for Clinical Oncology (ASCO) and the European Group on Tumor Markers (EGTM) as a prognostic bio-

marker that can be used to determine the prognosis and staging of CRC[10-11]. Tumour aberrant protein (TAP) is an abnormal glycoprotein and calmodulin complex expressed after mutations in intracellular oncogenes and tumour suppressor genes[12]. Abnormal glycoproteins are closely related to the occurrence, development, invasion, metastasis and prognosis of cancer[13]. Therefore, the detection of TAP in the serum can provide an important reference for clinical tumour diagnosis. However, there are few applications for evaluating the efficacy of neoadjuvant chemotherapy for rectal cancer. Here, we retrospectively selected 115 patients who had been treated with neoadjuvant chemotherapy for rectal cancer at xx hospital from January 2015 to January 2019. At the same time, 115 healthy personnel were selected. By testing the patients' TAP and CEA levels, we explored the changes therein before and after neoadjuvant chemotherapy for rectal cancer and their relationship with chemotherapy efficacy.

Materials and methods

General information

There were 115 cases: 68 male and 47 female. The mean age was 54.66±11.42 years. Twenty-six patients had tumour-node-metastasis (TNM) stage II disease, while 55 and 34 patients had stage III and stage IV disease, respectively.

The inclusion criteria were:

• Rectal cancer confirmed by clinical symptoms, laboratory, imaging and other examinations;

• No history of mental illness;

• No other anti-tumour treatment 1 month prior;

• Patients or family members had granted informed consent.

The exclusion criteria were:

• Special population of pregnancy and lactation;

• People with physical allergies;

• Serious heart, liver and kidney diseases;

• Rejected or terminated by the researcher.

This study was approved by the hospital ethics committee. In the same period, 115 healthy people were selected, comprising 64 men and 51 women. The mean age was 53.72±13.40 years. There was no significant difference in sex and age between the two groups (P>0.05), suggesting comparability.

Methods

Adjuvant Chemotherapy Regimen

FOLFOX6 chemotherapy was administered with the patient's knowledge, namely 135 mg/m^2 oxaliplatin intravenous infusion for 3 h, 200 mg/m^2 calcium folovate (CF) intravenous infusion for 2 h and 400 mg/m2 5-fluorouracil (5-FU) intravenous infusion, and finally 2400–3600 mg/m2 5-FU was added to a Baxter pump for 48-h continuous intravenous infusion. We administered the preventive use of drugs for reducing the toxic and adverse effects of chemotherapy, such as central antiemetic drugs, liver protection drugs and drugs for enhancing immunity. Blood routine examination and liver function, renal function and other biochemical routine examination after chemotherapy showed no abnormalities, and there were no obvious adverse reactions to chemotherapy.

Detection Methods

Fasting venous blood (6 mL) from the upper arm was extracted from all patients before and after chemotherapy and from the health staff, and placed in sterile test tubes. The serum was separated (3000 rpm, 12 min, 8.5 cm centrifuge radius), and the supernatant was obtained, and serum CEA was detected by radioimmunoassay using a kit purchased from Shanghai Que Min Biotechnology Co., Ltd. At the same time, TAP was detected using a special computerized TAP detection system, using 25 μL fingertip blood from the patients before and after chemotherapy and from the health personnel (two smears were made, evenly spaced, and dried using the TAP detection reagent). The TAP polymer area was observed and detected using a biological microscope, camera image sensor and the computer TAP detection system. The TAP detector and its supporting coagulation aids, graphic system and software analysis system were purchased from Shanghai Xinyu Biotechnology Co, Ltd.

Indicator observation and criteria

TAP and CEA levels and chemotherapy were statistically analysed in all subjects.

The chemotherapy efficacy criteria refer to the World Health Organization evaluation criteria for solid tumours[14] as follows:

• Complete response (CR), tumour has completely disappeared and no new lesions for 1 month or more;

• Partial response (PR): the tumour diameter and maximum vertical diameter are smaller or greater and 50% for ≥1 month, and other lesions are without progression;

• Stable disease (SD), the product of the maximum diameter and maximum vertical diameter of the

tumour is decreased by >50% or increased by ≤25%;

• Progressive disease (PD): the product of maximum diameter and maximum vertical diameter of the tumour is increased by >25%, where CR and PR indicate that treatment is effective, but not PD and SD.

Statistical data processing

The data were analysed using SPSS 22.0 statistical software processing data, and are expressed in (%) for categorical data by chi-square test. The measurement data (mean ± standard deviation) were compared using the t-test, multiple data sets were compared using the F test, repeated measures variance analysis of the decreased TAP and CEA percentages were used to assess the efficacy of rectal cancer neoadjuvant chemotherapy using receiver operating characteristic (ROC) curve analysis.

The joint TAP and CEA percentage was used to assess the efficacy of rectal cancer neoadjuvant chemotherapy efficiency. For decreased TAP or CEA percentage where any diagnosis was confirmed, the Z test was used to compare the difference in area under the two sites. When P<0.05, the difference was statistically significant.

Results

Serum TAP and CEA levels

The serum TAP and CEA levels of the patients were significantly higher than that of the healthy subjects (P<0.05) (Table 1).

	n	TAP (μm²)	CEA (ng/mL)
Patients	115	172.15±21.47	37.82±6.61
Controls	115	82.63±10.32	1.08±0.27
T		40.30	59.56
P		<0.001	<0.001

Table 1: Comparison of serum TAP and CEA levels.

Serum TAP and CEA levels in patients with different rectal cancer treatment efficacy

After neoadjuvant chemotherapy, 18 patients had CR (15.65%), 76 patients had PR (66.09%), 15 patients had SD (13.04%) and six patients had PD (5.22%). CR and PR patients had significantly decreased TAP and CEA levels and percentages after chemotherapy compared with before chemotherapy, while PD patients had significantly increased TAP and CEA levels and percentages after chemotherapy compared with before chemotherapy (P<0.05). SD patients had decreased TAP and CEA levels and percentages after chemotherapy compared with before chemotherapy (P>0.05) (Table 2 and 3).

Group	n	Before chemotherapy	After chemotherapy	Percentage decrease (%)
CR	18	172.16±21.37	130.94±13.61	33.18±5.11
PR	76	177.26±23.19	141.05±18.92	25.18±3.64
SD	15	175.81±25.33	164.73±20.81	6.22±1.14
PD	6	172.64±25.87	205.46±28.16	-34.64±6.27
F		0.28	29.97	157.2
P		0.841	<0.001	<0.001

Table 2: Comparison of serum TAP levels in patients with different therapeutic effects after neoadjuvant chemotherapy for rectal cancer ($\bar{x}\pm s$).

Group	n	Before chemotherapy	After chemotherapy	Percentage decrease (%)
CR	18	37.44±8.16	10.06±3.07	55.28±4.14
PR	76	38.91±7.28	15.42±4.11	30.07±4.72
SD	15	37.64±7.63	30.54±6.29	6.26±1.64
PD	6	36.43±7.91	45.28±7.62	-8.14±1.38
F		0.41	137.87	137.87
P		0.75	<0.001	<0.001

Table 3: Comparison of serum CEA levels in patients with different therapeutic effects after neoadjuvant chemotherapy for rectal cancer ($\bar{x}\pm s$).

Analysis of efficacy of neoadjuvant chemotherapy for rectal cancer

The ROC curve analysis showed that, with TAP > 21% as the critical value, the sensitivity, specificity, accuracy and ROC for evaluating the effectiveness of neoadjuvant chemotherapy for rectal cancer was 92.6%, 72.6%, 92.0% and 0.724, respectively; that for CEA >25% as the critical value was 89.0%, 70.4%, 88.0% and 0.746, respectively, and that for the combination of the two was 96.4%, 91.7%, 97.0% and 0.928, respectively. When combined, the sensitivity, specificity, accuracy and ROC of TAP and CEA for evaluating neoadjuvant chemotherapy effectiveness in rectal cancer was significantly higher than that of TAP and CEA alone (P<0.05). When the two were compared separately, the difference was not statistically significant (P>0.05) (Figure 1, Table 4).

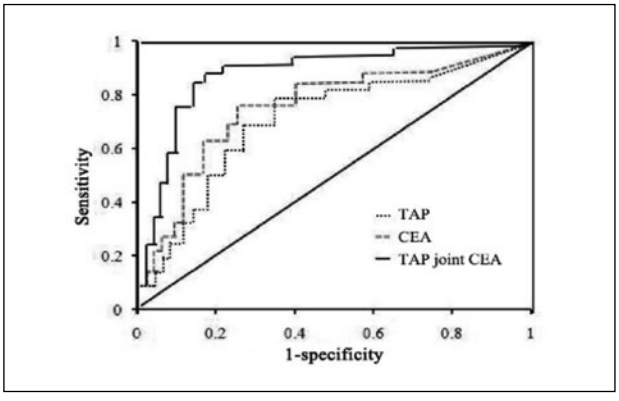

Figure 1: ROC curve analysis of different methods for evaluating the effectiveness of neoadjuvant chemotherapy for rectal cancer.

Group	Sensitivity, %	Specificity, %	Accuracy, %	Area under the curve
TAP	92.0	72.6	92.0	0.724
CEA	89.0	70.4	88.0	0.746
Combined	96.4	91.7	97.0	0.928
c^2	6.03	5.49	5.84	15.74
P	<0.001	<0.001	<0.001	<0.001

Table 4: Efficacy comparison of different methods for evaluating the effectiveness of neoadjuvant chemotherapy for rectal cancer (n = 115).

Discussion

Rectal cancer is one of the most common malignant tumours of the digestive system in China. Its pathogenesis is complicated. The early clinical stage has no obvious symptoms. In the intermediate and late stages, it can be manifested as blood, and pus and blood, respectively. It destroys the normal tissues and organs easily. The case fatality rate is high, rendering it the third most fatal malignant tumour. With the change in life rhythms and the influence of environmental factors in recent years, the incidence rate has increased markedly, and it tends to occur in the young. Therefore, timely diagnosis and treatment of rectal cancer has important clinical significance[15-16]. As a more effective means of chemotherapy, neoadjuvant chemotherapy has been widely used for treating various cancers, and is an important assistant to treatment in the perioperative period, which can inhibit the reduction of tumour volume and decrease the clinical stage effectively, which is consistent with our report[17]. However, due to the abnormal proliferation and rapid metastasis of the cancer cells, and the unsuitable physical constitution of some patients for chemotherapy, the curative effect is unsatisfactory, and the condition of the patient deteriorates further. With continuous treatment of the tumour and strengthening of the comprehensive treatment concept in recent years, most studies have indicated tumour markers, as a characteristic of malignant tumour cells, and tumour marker levels in the body, are related to the occurrence and development of malignant tumour, and are beneficial for assessing the disease outcome after treatment[18-19].

CEA is an acidic glycoprotein of the specific determinant human embryonic antigen, and can reflect the existence of various malignant tumours; it is a better marker of the therapeutic effect on the tumour and of disease development[20]. At the same time, when the normal cells of the rectum begin to deteriorate into cancer cells, the glycan structure of the cell membrane surface becomes abnormal, leading to increased N-chain glycan branches, causing a large amount of TAP to be released into the body fluids, and is clinically used as an important tumour marker for diagnosing rectal cancer; its detection requires a special detection system[21]. Thus, both TAP and CEA can be used as tumour markers such as rectal cancer.

In the present study, the relationship between serum TAP and CEA levels in patients with rectal cancer and the effect of chemotherapy was analysed. The results showed that the TAP and CEA levels in the patients were significantly higher than that of healthy individuals, indicating that the serum TAP and CEA are closely related to the pathological development of rectal cancer[22]. The serum TAP and CEA levels can be used as a reference for the pathological development of rectal cancer. At the same time, after neoadjuvant chemotherapy, in patients with rectal cancer, there were 18 patients had CR (15.65%), 76 patients had PR (66.09%), 15 patients had SD (13.04%) and six patients had PD (5.22%). The possible mechanism may be that the patients in whom chemotherapy is effective are more sensitive to neoadjuvant chemotherapy, so the chemotherapy can kill or inhibit the rectal cancer cells effectively, reduce the tumour tissue, promote normal cell self-regulation and improve the glycosylation modification enzymes and carbohydrate structures in the body, thereby reducing patients' TAP and CEA levels[23]. In the patients in whom chemotherapy is ineffective, the tumour cells are continuously stimulated to generate TAP and CEA, which are then continuously released into the plasma, so that the serum TAP and CEA levels are high. In addition, the ROC curve analysis showed that for TAP, the specificity, accuracy and area under the curve are 92.6%, 72.6%, 92.0%, 0.724, respectively, and that for CEA are 89.0%, 70.4% and 88.0%, respectively, for assessing the sensitivity, specificity, accuracy and area under the curve of neoadjuvant chemotherapy effectiveness in rectal cancer. The CEA joint assessment has a better evaluation performance. It is possible that TAP and CEA are independently evaluated and are susceptible to a variety of factors, and it is difficult to assess the tumour function or activity accurately and effectively. Therefore, combined testing after chemotherapy is preferred for more effective assessment of the outcome of the patient's undefined condition. If the levels of both do not decrease after chemotherapy, other effective treatment methods

should be sought to prevent deterioration of the condition. The present study has some limitations, such as the complexity of rectal cancer pathogenesis, and the occurrence of TAP and CEA might have been affected by other unknown factors. If other tumour markers can be increased or if the effect of chemotherapy can be suggested earlier, the sample size of the study cannot represent the actual condition of all cases. However, the serum TAP and CEA levels in the patients with rectal cancer had abnormal changes before and after chemotherapy, and the change in levels can be used as an important index for evaluating the efficacy of the neoadjuvant chemotherapy, as can their combination.

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