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ORIGINAL ARTICLE

Diagnostic value of combined detection of multiple tumor markers and blood lipid indexes in colorectal cancer and its prediction on adverse reactions of chemotherapy

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Summary

Purpose: *The purpose of this study was to explore the clinical diagnostic value of combined detection of multiple tumor markers (CEA, CA242, CA19.9 and CA125) and blood lipid indexes in colorectal cancer, and to analyze their predictive effect on adverse reactions after chemotherapy.*

Methods: *The clinical data of 35 patients with colorectal adenoma, 64 patients with colorectal cancer I-II and 29 patients with colorectal cancer III-IV were retrospectively analyzed. All the patients were admitted to our hospital from April 2017 to December 2019. The antigen level of tumor markers and the plasma level in patients were detected before surgery to compare the expression difference of different tumor types. The Youden index, sensitivity and specificity of the four tumor markers were compared when used alone or in combination.*

Results: *After one year of follow-up, the levels of tumor markers in patients with tumor metastasis were significantly higher than those in patients without tumor metastasis, with a statistically significant difference ($p<0.001$). The combination of four markers was better than single tumor marker in the evaluation indexes of diagnostic effect. The combined detection of multiple tumor markers and blood lipid indexes was correlated with the occurrence of five adverse reactions of chemotherapy ($p<0.05$).*

Conclusion: *The detection of multiple tumor markers and blood lipid indexes can effectively improve the diagnosis of colorectal cancer and enhance the predictive effect on adverse reactions of chemotherapy. HDL, LDL and ApoAI indexes can be used to diagnose the benign and malignant properties of tumors, and determine the clinical stages.*

Key words: *blood lipid indexes, chemotherapy, colorectal cancer, diagnostic value, tumor markers*

Introduction

Colorectal cancer (CRC) is a common malignant tumor of the gastrointestinal tract, with insidious early symptoms. Like other malignant tumors, the etiology of CRC remains unclear [1-3]. The disease mainly occurs in people aged 40-70 years old, mostly in males. Although China is a country with low incidence of CRC, the incidence of many regions in China has shown an increasing trend in recent years. As malignant tumors of the digestive system with high incidence and high mortality, CRC can spread to other tissues and organs through blood circulation and lymph or spread directly. Therefore, early detection, timely diagnosis and radical surgery have become the key to the treatment of CRC, and the expected effect depends on early diagnosis and postoperative treatment [4-6]. Clinical researches have found that the occurrence of CRC is closely related to dyslipidemia and tumor markers are sensitive to colorectal cancer in detection, so the detection of single tumor or multiple tumor markers is of great significance for

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the diagnosis and prognosis of CRC [7]. CRC patients after surgery and chemotherapy are prone to adverse reactions such as hand-foot syndrome, thrombocytopenia, anemia, neutropenia and myelosuppression, which seriously affects the chemotherapy effect of patients. Therefore, the prediction of adverse reactions after chemotherapy is the key to improve the prognosis and recovery of CRC patients. Based on this, this study mainly explored the clinical diagnostic value of the combined detection of multiple tumor markers and blood lipid indexes in CRC, and analyzed the predictive effect of this method on adverse reactions of patients after chemotherapy

Methods

General information

From April 2017 to December 2019, 128 patients underwent CRC surgery in our hospital, including 35 patients with colorectal adenoma, 64 patients with CRC I-II and 29 patients with CRC III-IV. There were 45 females and 83 males, aged 40-75 years old (mean 52.2±9.8). All patients with primary dyslipidemia were excluded and were pathologically examined after surgery to determine benign and malignant lesions. Postoperative imaging examination showed 23 patients with tumor metastasis and 105 patients without tumor metastasis.

Inclusion criteria

(1) meeting the clinical diagnostic criteria of CRC; (2) The clinical medical records of the patients were complete; (3) The study was approved by the hospital ethics committee (no.20170325), and the patients and their families knew the purpose and process of this experimental study, accepted the treatment plan, and signed the informed consent.

Exclusion criteria

(1) The patients were complicated with other organ and tissue lesions such as brain, heart, kidney and liver; (2) The patients were allergic to the drugs used; (3) The patients had mental and other cognitive disorders or refused to cooperate with the experiment; (4) The clinical data of the patients were incomplete.

Methods

5ml of fasting venous blood was collected from all the patients, and centrifuged at 3000r/min for 10 min [8,9]. Enzymic method was used to measure the plasma low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglyceride (TG) of the patients. Immunoturbidimetry was used to measure the levels of apolipoprotein AI (ApoAI) and apolipoprotein B (ApoB). An electrochemiluminescence immunoassay system and matching reagents were used to determine the expression levels of tumor markers which were carcinoembryonic antigens and carbohydrate antigens (CEA, CA242, CA19.9 and CA125) [10-13].

Determination of antibody indexes

The critical values of CEA, CA19.9, CA242 and CA125 were 5 U/ml, 35 U/ml, 20 U/ml and 35 U/ml, respectively.

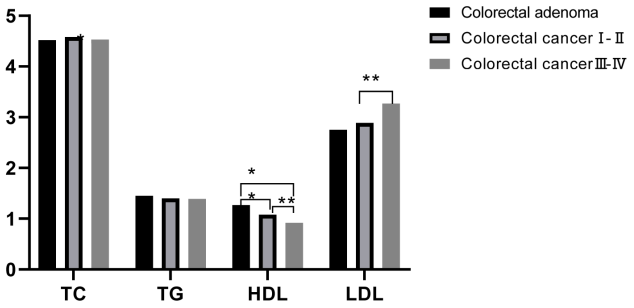

Figure 1. Comparison of TC, TG, HDL and LDL indexes in patients with different types of colorectal tumors (mmol/L). Note: The abscissa represents the blood lipid indexes (TC, TG, HDL and LDL), and the ordinate represents the blood lipid level (mmol/L). The TC, TG, HDL and LDL levels of colorectal adenoma were (4.52±0.71) mmol/L, (1.45±0.22) mmol/L, (1.27±0.28) mmol/L and (2.75±0.64) mmol/L respectively; The TC, TG, HDL and LDL levels of CRC I-II were 4.58±0.69 mmol/L, 1.40±0.29 mmol/L, 1.08±0.29 mmol/L and 2.89±0.51 mmol/L, respectively. The TC, TG, HDL and LDL levels of CRC III-IV were 4.53±0.71 mmol/L, 1.39±0.31 mmol/L, 0.92±0.23 mmol/L and 3.27±0.61 mmol/L, respectively.
*from bottom to top indicated that the HDL level of colorectal adenoma was significantly different from that of CRC I-II and CRC III-IV (t =3.1542, 5.3895; p=0.0021, 0.000). **from left to right indicated that there were significant differences in HDL and LDL levels between the CRC I-II and CRC III-IV (t=2.6187, 3.1278; p=0.0103, 0.0024).

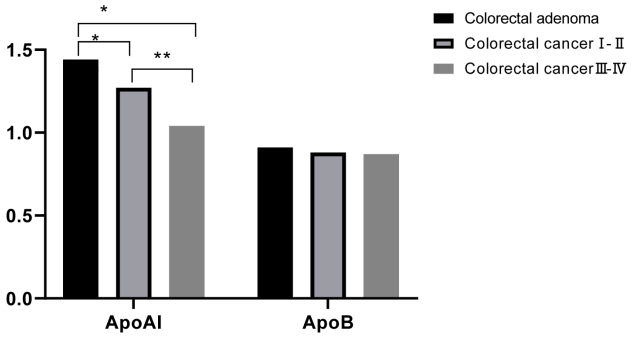

Figure 2. Comparison of ApoAI and ApoB indexes in patients with different types of colorectal tumors (g/L). Note: The abscissa represents ApoAI and ApoB, and the ordinate represents the detection level (g/L). The ApoAI and ApoB levels of colorectal adenoma were 1.44±0.25 g/L and 0.91±0.14 g/L, respectively. The ApoAI and ApoB levels of CRC I-II were 1.27±0.24 g/L and 0.88±0.16 g/L, respectively. The ApoAI and ApoB levels of CRC III-IV were 1.04±0.25 g/L and 0.87±0.22 g/L, respectively.
*from bottom to top indicated that the ApoAI level of colorectal adenoma was significantly different from that of CRC I-II and CRC III-IV (t=3.3202, 6.3718; p=0.0013, 0.000). **from left to right indicated that there was a significant difference in the ApoAI level between the CRC I-II and CRC III-IV (t=4.2262, p=0.0001).

Statistics

In this study, the data processing software was SPSS20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to draw pictures of the data. The data included in the study were count data and measurement data, tested by x^2 test, t-test and normality test. The difference was statistically significant when $p<0.05$.

Results

There were significant differences in the HDL levels among colorectal adenoma, CRC I-II and CRC III-IV, and there was also significant difference in the LDL levels between CRC I-II and CRC III-IV, as shown in Figure 1. There were statistically significant differences in the ApoAI levels among colorectal adenoma, CRC I-II and CRC III-IV, as shown in Figure 2.

As for different types of colorectal tumors, there were statistical differences in the levels of four tumor markers, as shown in Figure 3.

All patients were followed up for 1 year. After follow-up, the levels of tumor markers in patients with tumor metastasis were significantly higher than those in patients without tumor metastasis. The percentages of tumor markers CEA, CA125, CA242 and CA19.9 higher than the critical values in patients with tumor metastasis were 30.43%, 65.22%, 65.22% and 60.87%, respectively, while those in patients without tumor metastasis were 2.86%, 18.20%, 19.05% and 17.14%, with statistically significant differences between the two groups of patients ($p<0.001$), as shown in Table 1.

The combination of four markers was better than single tumor marker in the evaluation indexes of diagnostic effect, as shown in Table 2.

There was no significant correlation between the single tumor marker and adverse reactions of chemotherapy such as hand-foot syndrome, thrombocytopenia, anemia, neutropenia and myelosuppression ($p>0.05$). The combined detection of multiple tumor markers and blood lipid indexes was correlated with the occurrence of five adverse reactions of chemotherapy ($p<0.05$), as shown in Table 3.

Discussion

Lipid is the main component of the cell membrane and an important signal molecule on the cell membrane. Since the growth of tumors requires energy, tumor patients often have a high blood lipid level [14-17]. Therefore, the blood lipid level of tumor patients is of great significance for the diagnosis and

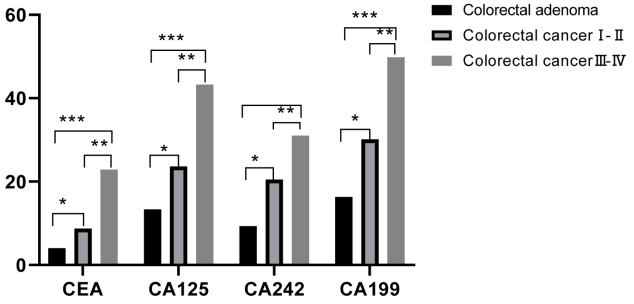

Figure 3. Comparison of tumor marker levels in different colorectal tumor types (U/mL). Note: The abscissa represents four different tumor markers (CAE, CA125, CA242 and CA19.9), and the ordinate represents the expression level (U/mL). The CAE, CA125, CA242 and CA19.9 expression levels of colorectal adenoma were 4.01±1.35 U/mL, 13.31±6.42 U/mL, 9.35±2.16 U/mL and 16.31±9.24 U/mL, respectively. The CAE, CA125, CA242 and CA19.9 expression levels of CRC I-II were 8.73±2.42 U/mL, 23.61±10.38 U/mL, 20.47±7.69 U/mL and 30.12±11.58 U/mL, respectively. The CAE, CA125, CA242 and CA19.9 expression levels of CRC III-IV were 22.89±14.02 U/mL, 43.28±17.68 U/mL, 31.02±20.34 U/mL and 49.82±21.79 U/mL, respectively.
*from left to right indicated that there were significant differences in the CAE, CA125, CA242 and CA19.9 levels between colorectal adenoma and CRC I-II (t=10.6521, 5.3322, 8.3334, 6.0725; $p<0.001$). **from left to right indicated that there were significant differences in the CAE, CA125, CA242 and CA19.9 levels between CRC I-II and CRC III-IV (t=7.8743, 6.7243, 3.6336, 5.6935; $p<0.05$). ***from left to right indicated that there were significant differences in the CAE, CA125, CA242 and CA19.9 levels between colorectal adenoma and CRC III-IV (t=7.9357, 9.3264, 6.2643, 8.2564; $p<0.001$).

Table 1. Baseline characteristics and tumor marker detection of patients after chemotherapy

Detection indexes	*Patients with tumor metastasis (n=23)*	*Patients without tumor metastasis (n=105)*	x^2/t	*p*
CAE	28.19±24.06	1.68±1.13	11.3943	0.000
CA125	175.48±149.51	16.69±13.08	10.8458	0.000
CA242	176.08±150.09	16.73±12.67	10.8551	0.000
CA19.9	175.39±149.82	17.01±12.54	10.8114	0.000
CAE>5U/ml	7 (30.43%)	3 (2.86%)	19.9232	0.000
CA125>35U/ml	15 (65.22%)	19 (18.20%)	21.4769	0.000
CA242>20U/ml	15 (65.22%)	20 (19.05%)	20.2438	0.000
CA19.9>35U/ml	14 (60.87%)	18 (17.14%)	19.2398	0.000

Table 2. Diagnostic results of tumor markers in patients (n=128)

Indexes	*CAE*	*CA125*	*CA242*	*CA199*	*CA242+CA199*	*Combination of four markers*
Positive (number of cases)	53	58	67	79	88	114
Positive rate	41.41	45.31	52.34	61.71	68.75	89.06
Sensitivity	47.94	53.64	60.03	65.34	75.89	88.15
Specificity	89.05	89.10	91.58	85.06	80.64	92.02
Positive predictive value	87.94	82.11	93.86	89.91	82.96	92.39
Negative predictive value	50.13	67.21	48.21	52.35	72.66	80.07
Youden index	36.29	42.56	50.91	49.73	58.74	73.42

Table 3. Correlation analysis of tumor markers combined with lipid indexes and adverse reactions of chemotherapy

	Hand-foot syndrome		*Thrombocytopenia*		*Anemia*		*Neutropenia*		*Myelosuppression*	
	P	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*
CEA	0.545	0.061	0.841	0.022	0.155	0.148	0.526	0.066	0.724	0.032
CA125	0.836	0.310	0.246	0.191	0.943	0.011	0.135	0.246	0.184	0.216
CA242	0.732	0.295	0.167	0.214	0.859	0.215	0.425	0.148	0.566	0.045
CA19.9	0.108	0.160	0.123	0.161	0.280	0.113	0.886	0.013	0.312	0.101
Combined detection of multiple tumor markers and blood lipid indexes	0.002	6.315	0.016	6.742	0.006	8.896	0.009	8.473	0.036	4.782

prognosis of diseases. Tumor markers are substances related to tumor development and growth, which are suitable for early diagnosis of tumors. Studies have shown that a single tumor marker has low specificity and sensitivity [18-21]. The results of this study showed that there were significant differences in the HDL levels among colorectal adenoma, CRC I-II and CRC III-IV. There was also significant difference in the LDL levels between CRC I-II and CRC III-IV. There were statistically significant differences in the ApoAI levels among colorectal adenoma, CRC I-II and CRC III-IV. As for different types of colorectal tumors, there were significant differences in the levels of four tumor markers. After one year of follow-up, the levels of tumor markers in patients with tumor metastasis were significantly higher than those in patients without tumor metastasis, with a statistically significant difference ($p<0.001$). The combination of four markers was better than single tumor marker in the evaluation indexes of diagnostic effect. In addition, there was no significant correlation between the single tumor marker and adverse reactions of chemotherapy such as hand-foot syndrome, thrombocytopenia, anemia, neutropenia and myelosuppression ($p>0.05$). The combined detection of multiple tumor markers and blood lipid indexes was correlated with the occurrence of five adverse reactions of chemotherapy ($p<0.05$). As an apolipoprotein, ApoA1 is also a structural protein of HDL and LDL, so its level can directly affect the transport rates of HDL and LDL in the body. Therefore, the changes in transport rates and lipoprotein occur simultaneously [22-26]. The results of this study are consistent with the results of Chen et al [27] who stated in their study that the combination of tumor markers before surgery could determine the specific parameters of patients between the positive reference value and the normal standard value, which could effectively improve the clinical diagnosis of CRC and had high clinical application value for the detection of postoperative recurrence in patients. This fully proves the clinical diagnostic value and predictive effect of the combined detection of multiple tumor markers and blood lipid indexes on the adverse reactions of CRC.

In conclusion, the detection of multiple tumor markers and blood lipid indexes can effectively improve the diagnosis of colorectal cancer. HDL, LDL and ApoAI indexes can be used to diagnose the benign and malignant properties of tumors, and determine the clinical stages. The combined use of multiple tumor markers is able to make up for the deficiencies of single markers. In addition, this method has a good predictive effect on the occurrence of adverse reactions after chemotherapy such as hand-foot syndrome, thrombocytopenia, anemia, neutropenia and myelosuppression.

Conflict of interests

The authors declare no conflict of interests.

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