ORIGINAL RESEARCH

Correlation of changes in serum CEA and CA19-9 levels with clinical efficacy and overall survival in advanced colorectal cancer patients

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Abstract

Background

Colorectal cancer (CRC) is a common malignant tumor in the gastrointestinal tract. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are commonly used tumor markers for gastrointestinal tumors, and they have specific reference values for postoperative recurrence and metastasis. This study aimed to analyze the changes in CEA and CA19-9 levels in CRC patients and their relationship with survival rate and clinical outcomes.

Methods

This was a retrospectively study. The clinical data of 101 patients with advanced CRC who visited Jiangsu Cancer Hospital from August 2013 to October 2020 were selected. They were divided into 61 cases in A-D group (increasing first and then decreasing) and 40 cases in D-A group (decreasing first and then increasing) based on the changes in CEA and CA19-9 levels before and after chemotherapy. The clinical characteristics of the two groups were compared, and the correlation between the levels of CEA and CA19-9 and the overall survival rate and clinical efficacy of the patients were analyzed.

Results

Compared with the D-A group, the survival rate and progression-free survival rate (PFS) of patients in the A-D group were higher. The partial response rate (PR) of the A-D group was 60.7%, and the objective response rate (ORR) was 60.7%, both significantly higher than 32.5% and 32.5% of the D-A group; the disease progression rate (PD) of the A-D group was 11.5%, significantly lower than 35% of the D-A group, and the difference was statistically significant. There was no significant difference in the disease stability (SD) rate between the two groups.

Conclusions

The changes in CEA and CA19-9 levels before and after chemotherapy in advanced CRC patients are related to the prognosis and clinical efficacy of these patients, and can be used as key indicators for evaluating the prognosis of advanced CRC patients.

Keyword: colorectal cancer, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), overall survival

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors worldwide, ranking third among all malignant tumors and fourth in terms of mortality rate[1]. With the change of people's dietary habits and lifestyles, the incidence rate and mortality rate of CRC in China are gradually increasing. The age of onset is gradually advancing, which seriously threatens the health of Chinese residents[2]. CRC is characterized by a long course, no obvious symptoms in the early stage, and good treatment outcomes, making early screening more difficult[3]. Up to date, the diagnosis of CRC mainly relies on endoscopy, imaging, and pathological histological examinations[4]. In recent years, tumor markers (TMs) have been widely used as non-invasive candidates for the diagnosis and prognosis assessment of CRC, with advantages such as low cost, convenient sampling, and minimal damage[5].

TMs are substances produced by tumor cells or the interaction between tumors and the body, and they play an important role in the detection and development of cancer[6]. Currently, the common TMs used in clinical examinations for CRC include carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen125 (CA125)[7]. However, the value of these markers varies in CRC. CEA has a lower economic cost and higher sensitivity, and CEA is more accurate in diagnosing metastasis and recurrence of CRC than CA19-9 and CA125[8]. CEA was extracted as a tumor-related antigen by Gold et al. in 1965 from CRC and embryonic tissues[9]. CEA is a broad-spectrum TM that can be expressed in different ways in non-endodermal tumors (such as breast and lung cancer) besides CRC[10,11]. The level of CEA in patients with CRC is more commonly elevated, and it is more common in smokers and patients with inflammatory diseases. It cannot be used as an independent basis for diagnosing CRC[12]. Therefore, when the serum CEA level significantly increases (regardless of whether there are symptoms), clinicians should combine clinical manifestations and other auxiliary examination results to reduce the occurrence of misdiagnosis and missed diagnosis. In 1979, CA19-9 was obtained by immunizing mice with colon cancer tissues and hybridizing them with bone marrow[13]. Currently, it is mainly used for preoperative diagnosis of gastrointestinal

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tumors, observation of tumor treatment effects, and even has a certain role in determining prognosis[14]. CA19-9 is usually expressed in pancreatic bile duct cells[15], gastric and colonic epithelial cells[16,17] and is considered a broad-spectrum tumor marker. CA19-9 has positive expression in various degrees in malignant and benign diseases such as pancreatitis[18] and jaundice[19], and often shows a transient increase, so it needs to be distinguished. However, the correlation between abnormal levels of CEA and CA19-9 and treatment effects and prognosis of colorectal cancer remains unclear.

Therefore, the objective of this study was to analyze the changes in the levels of CEA and CA19-9 in CRC patients and their correlations with the survival status and clinical outcomes of the patients.

Methods

Study design

This was a retrospectively study. The clinical data of 101 patients with advanced CRC who visited Jiangsu Cancer Hospital from August 2013 to October 2020 were selected (including 63 males and 38 females, with ages ranging from 26 to 82 years old). This study was approved by the Ethics Committee of Nanjing Medical University, and the approval number was NJ13_0005L. Before the start of the study, all patients signed written informed consent forms.

Inclusion criteria

1. The pathological type of advanced CRC was adenocarcinoma;

2. The patient initially received the chemotherapy regimen of capecitabine combined with oxaliplatin (CapeOX protocol; oxaliplatin 130 mg/m2, capecitabine 10000 mg/m2) and bevacizumab;

3. The patient had complete clinicopathological data.

Exclusion criteria

1. Patients requiring emergency surgery;

2. Patients with malignant tumors in other organs;

3. Patients with intestinal obstruction;

4. Patients who received neoadjuvant radiotherapy before chemotherapy;

5. Patients with systemic immune diseases;

6. Patients with liver and kidney multi-organ dysfunction indicated by blood biochemical indicators and imaging manifestations;

7. Patients with thrombotic disorders;

8. Patients who had taken drugs affecting coagulation function within the past month.

Collection of clinical data

The collected clinical case information included: gender (male, female), age (≥65 years old, <65 years old), plasma CEA, plasma CA19-9, primary tumor site (rectum, left hemicolectomy, right hemicolectomy), and metastatic sites (liver metastasis, lung metastasis, peritoneal metastasis, multiple metastases). During the first four months of treatment, CEA and CA19-9 were monitored every three weeks.

Evaluation of serological parameters

Before and after chemotherapy, fasting elbow venous blood was collected from all patients and centrifuged at 3,000 rpm for 20 min at 4°C. The supernatant was stored at -80°C for measurement. The levels of CEA and CA19-9 were measured in our hospital's laboratory department using the electrochemiluminescence method (Roche Cobas 6000).

Follow-up investigation

In this study, the survival information of the patients was collected through a quarterly telephone follow-up. The overall survival period was defined as the time from the diagnosis of colorectal cancer to death or the end of the follow-up.

Statistical analysis

SPSS 20.0 software was used to analyze the data statistically. We first conducted a normality test using the Shapiro-Wilk test. When the measured values did not follow a normal distribution, the median plus or minus the interquartile range (M ± Q) was used to represent their concentration and dispersion trend, and the Mann-Whitney U test was employed for comparison; for the measured values that followed a normal distribution, they were expressed in the form of mean plus or minus standard deviation ($x \pm s$), and the independent sample t-test was used for comparison. Categorical variables were expressed as (n, %) and were subjected to the chi-square test. In addition, the Kaplan-Meier method was applied to estimate the overall survival rate and progression-free survival rate of the two groups. The log-rank test was then used to compare the survival curves between the two groups. Regarding the calculation of hazard ratios (HRs), a Cox proportional-hazards model was employed. The HRs were calculated by exponentiating the estimated coefficients from the Cox regression model. A HR greater than 1 indicates an increased risk of the event in the group of interest compared to the reference group, while a HR less than 1 suggests a decreased risk. A 95% confidence interval (CI) was also calculated for each HR. If the 95% CI of the HR does not include 1, it is considered statistically significant. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological information of advanced CRC patients

According to the fluctuation patterns in the levels of CEA and CA19-9 during the treatment course, we divided 101 advanced CRC patients into two groups, namely A-D group and D-A group.

The assignment of patients to each group was based on the following precise criteria: For the A-D group, which comprised 61 patients, we closely monitored the serial measurements of CEA and CA19-9 levels at multiple time - points during the treatment. These patients were classified into this group when their CEA and CA19-9 levels showed an initial upward trend. Specifically, we defined an upward trend as a continuous increase in the levels of both CEA and CA19-9 over at least two consecutive measurement time-points compared to the baseline levels (the levels measured at the start of the treatment). After this initial rise, these patients' CEA and CA19-9 levels subsequently demonstrated a downward trend, which was characterized by a continuous decrease in the levels of both markers over at least two consecutive measurement time-points following the peak levels.

The D-A group included 40 patients. These patients were assigned to this group when their CEA and CA19-9 levels first showed a downward trend.

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Table 1. Basic information of all enrolled CRC patients

Parameter	A-D group (n = 61)	D-A group (n = 40)	P value	X² value
Gender			0.389	0.740
Male	36 (59%)	27 (67.5%)		
Female	25 (41%)	13 (32.5%)		
Age			0.968	0.001
<65	44 (72.1%)	29 (72.5%)		
≥65	17 (27.9%)	11 (27.5%)		
ECOG scores			0.524	1.292
0	26 (42.6%)	15 (37.5%)		
1	29 (47.5%)	18 (45.0%)		
2	6 (9.8%)	7 (17.5%)		
Primary site			0.597	1.030
Left hemicolon	22 (36.1%)	11 (27.5%)		
Right hemicolon	22 (36.1%)	18 (45.0%)		
Rectum	17 (27.9%)	11 (27.5%)		
Metastatic site			0.084	6.643
Hepatic metastasis	21 (34.3%)	12 (30.0%)		
Pulmonary metastasis	13 (21.3%)	2 (5.0%)		
Peritoneum metastasis	13 (21.3%)	11 (27.5%)		
Multiple metastasis	14 (23.0%)	15 (37.5%)		

Table 2. Evaluation of therapeutic efficiency between two groups

Parameter	A-D group (n = 61)	D-A group (n = 40)	P value	X² value
PR	37 (60.7%)	13 (32.5%)	0.0056	7.661
SD	17 (27.9%)	13 (32.5%)	0.6184	0.248
PD	7 (11.5%)	14 (35.0%)	0.0044	8.117
ORR	37 (60.7%)	13 (32.5%)	0.0056	7.661

the lowest levels.

After collecting demographic and clinical parameters of A-D and D-A groups, we analyzed the data. As shown in Table 1, there were no significant differences in gender, age, Eastern Cooperative Oncology Group (ECOG) scores, primary site, and metastatic site between the two groups.

Treatment efficacy was evaluated between two groups

Partial response (PR) refers to the situation of partial response, where the total maximum diameter of the target lesions has decreased by at least 30% over a period of 4 weeks. Progressive disease (PD) refers to the progression of the disease, where the maximum diameter of the target lesions has increased by at least 20%, or new lesions have appeared. Objective response rate (ORR) refers to the objective response rate, which indicates the proportion of patients whose tumors have shrunk to a certain extent and have maintained that state for a certain period of time, including complete response (CR; all target lesions disappear, no new lesions appear, and tumor markers remain normal for at least 4 weeks) + PR cases.

As shown in Table 2, the PR and ORR of the D-A group were higher than those of the D-A group. However, there was no significant difference in the rate of stable disease (SD).

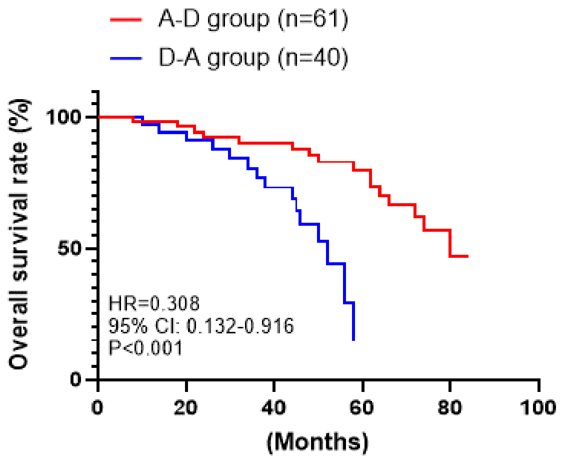

Figure 1: Overall survival rate in two groups according to the fluctuation of CEA and CA199.A-D group refers to the "ascending and then descending group". D-A refers to the "descending and then ascending group"

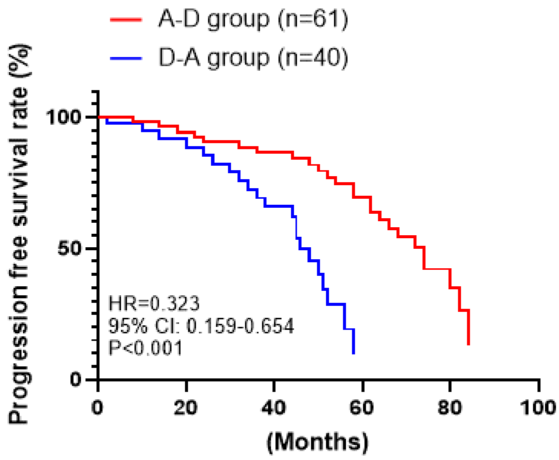

Figure 2: Progression free survival rate in two groups according to the fluctuation of CEA and CA199.A-D group refers to the "ascending and then descending group". D-A refers to the "descending and then ascending group".

A downward trend was defined as a continuous decrease in the levels of both CEA and CA19-9 over at least two consecutive measurement time-points compared to the baseline levels. Subsequently, their CEA and CA19-9 levels exhibited an upward trend, which was characterized by a continuous increase in the levels of both markers over at least two consecutive measurement time-points following

Collectively, we could conclude that the therapeutic efficiency of the A-D group was better than that of the D-A group.

Overall survival and progression free rate between two groups

Based on the follow-up results, we found that the medium overall survival time of the A-D group was 80 months, and that of the D-A group was 52 months. Compared with

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the D-A group, the A-D group had better overall survival rate (HR=0.308, 95% CI: 0.132-0.916, P<0.001, Figure 1). Meanwhile, the medium progression free survival time of the A-D group was 74 months, and that of the D-A group was 46 months. Compared with the D-A group, the A-D group had better progression free survival rate (HR=0.323, 95% CI: 0.159-0.654, P<0.001, Figure 2).

Discussion

Currently, the diagnosis of CRC mainly relies on methods such as c colonoscopy, computed tomography (CT), magnetic resonance imaging (MRI) and tissue biopsy[20]. These methods are complex, expensive, and invasive, resulting in poor patient compliance. In recent years, with the in-depth study of the pathogenesis of CRC and the rapid development of molecular biology, TMs have been widely used in the diagnosis of CRC[21].

CEA is a high-molecular acidic glycoprotein that is mainly present on the surface of digestive tumor cells derived from the endodermal, and is often used for the diagnosis of CRC and the determination of tumor recurrence[22]. When normal cells undergo cancer transformation, the secreted CEA enters the blood, causing an increase in the CEA level in the blood[23]. When CRC cells invade veins and lymphatic vessels, the serum CEA concentration will increase. In addition, the higher the tumor stage, the greater the increase in serum CEA concentration[23]. Therefore, the elevated preoperative CEA expression level is now considered a poor prognostic indicator for colorectal cancer in clinical practice and is mainly used for postoperative follow-up, having important clinical value for recurrence and metastasis.

Currently, the serum CA19-9 level is mainly used as one of the indicators for monitoring postoperative recurrence and metastasis in patients with CRC. However, the debate about the role of CA19-9 in predicting the overall survival of CRC patients has not stopped. An analysis was conducted on 101 CRC patients who underwent radical resection. According to the study by Morita et al., there is no clinical evidence to support CA19-9 as a predictive indicator for CRC recurrence[24]. However, Kouri et al. found in a study analyzing 85 CRC patients who underwent radical surgery that, in addition to CEA, CA19-9 is also an important predictive indicator for the prognosis of CRC, especially for advanced CRC, where it is one of the best prognostic indicators[25]. The higher the preoperative serum CEA and CA19-9 expression levels, the more accurate the diagnosis of CRC, and the CEA and CA19-9 levels are related to the severity of the patient's condition[26].

Our study found that in advanced CRC patients, those whose CEA and CA19-9 expression levels first increase and then decrease had better prognosis and treatment outcomes than those whose CEA and CA19-9 levels first decrease and then increase. A possible biological explanation for this phenomenon lies in the dynamic interaction between the tumor and the host's immune and therapeutic responses. When the CEA and CA19-9 levels first ascend, it may indicate an initial active phase of the tumor. During this phase, the tumor cells are rapidly proliferating, which leads to an increased release of these biomarkers into the bloodstream. This could be due to enhanced cellular activity, such as increased synthesis and secretion of CEA and CA19-9 by the tumor cells. Subsequently, when the levels start to descend, it may suggest that the treatment has started to take effect. The immune system of the patient, along with the chemotherapy, begins to target and destroy the tumor cells. As the tumor cells are damaged and undergo apoptosis or necrosis, the release of CEA and CA19-9 into the bloodstream decreases. This indicates a reduction in the tumor burden and a more favorable response to the treatment. In contrast, patients whose CEA and CA19-9 levels first decrease and then increase may have a different biological scenario. The initial decrease in biomarker levels could potentially be due to a temporary suppression of the tumor by the immune system or an early response to treatment. However, the subsequent increase may imply that the tumor has developed resistance to the treatment or has undergone genetic or phenotypic changes that allow it to evade the immune attack and resume growth. This resurgence of the tumor leads to a renewed release of CEA and CA19-9 into the bloodstream, indicating a worsening prognosis. Consistently, it has been reported that persistent postoperative elevation of CEA/CA19-9 is associated with a poor prognosis of stage II colon cancer patients[27]. Yu et al. proposed that CEA changes mirror the tumor response to first-line chemotherapy and are associated with prognosis. CEA monitoring may be a substitute for computed tomography during the CEA stable period of treatment[28].

In terms of clinical applicability, monitoring the fluctuations of CEA and CA19-9 levels holds great promise in guiding treatment decisions and follow-up strategies for CRC patients. For patients undergoing treatment, regular measurement of these markers can serve as an early indicator of treatment response. If the levels start to decline after the initiation of therapy, it may suggest that the treatment is effective, and the current treatment regimen can be continued. On the contrary, if the levels continue to rise or remain stable, it may indicate treatment resistance, and the healthcare provider can consider adjusting the treatment plan, such as changing the chemotherapy drugs, adding targeted therapy, or exploring other treatment options. During the follow-up period, close monitoring of these biomarkers can help in the early detection of tumor recurrence. A sudden increase in CEA or CA19-9 levels may prompt further investigations, such as imaging studies or endoscopic examinations, to confirm the presence of recurrent disease. This early detection allows for timely intervention, which can potentially improve the patient's prognosis and quality of life. Moreover, by stratifying patients based on the patterns of biomarker fluctuations, clinicians can personalize the follow-up frequency and intensity. Patients with a more favorable biomarker pattern may require less frequent follow-up compared to those with an unfavorable pattern, optimizing the allocation of medical resources.

However, it is essential to acknowledge several limitations that may impact the generalizability and robustness of our findings. One major limitation is the relatively small sample size of our study. This may restrict the statistical power, making it difficult to detect small but clinically relevant differences. It also limits the ability to conduct subgroup analyses, which could provide more detailed insights into the relationship between biomarker changes and prognosis in different patient subgroups. Another limitation is the single-center nature of the study. The patient population may not be representative of the general advanced CRC patient group, as it is influenced by local factors such as referral patterns, treatment practices, and patient demographics. This could affect the external validity of our results. In addition, we did not account for stage distribution in our analysis. Since

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different stages of advanced CRC have distinct prognoses, this omission may affect the accuracy of our conclusions regarding the prognostic value of biomarker changes. Comorbidities, which are common in these patients and can impact both prognosis and biomarker levels, were also not considered in a multivariate framework. Additionally, genetic differences, known to influence CRC prognosis and treatment response, were not included in the analysis. Further research with larger, multi-center cohorts, and incorporation of multivariate analysis of these confounding factors is warranted to validate and refine our results.

Conclusion

The changes in CEA and CA19-9 levels before and after chemotherapy in advanced CRC patients are related to the prognosis and clinical efficacy of these patients, and can be used as key indicators for evaluating the prognosis of advanced CRC patients.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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