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Original Article

Analysis of gastrointestinal function and prognostic value of tumor markers in patients with laparoscopic radical resection of colorectal cancer

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Abstract: Objective: To analyze the gastrointestinal function and prognostic value of tumor markers (TMs) in patients with laparoscopic radical resection of colorectal cancer (LRRCC). Methods: The research population of this retrospective study comprised 141 patients with CC who received treatment in the Zhongshan Hospital of Xiamen University between July 2017 and August 2018, including 74 cases (observation group, OG) treated with LRRCC and 67 cases (control group, CG) undergoing open surgery (OS). Postoperative gastrointestinal function and complications were recorded. Besides, alterations in serum TMs carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), and the 3-years survival of patients were observed. Receiver operating characteristic (ROC) curves were used to determine the prognostic value of TMs. Risk factors affecting the prognosis of LRRCC patients were analyzed by the Cox regression model. Results: Significantly higher levels of motilin (MOT) and gastrin (GT) were determined in OG compared with CG. The two groups showed no notable difference in the postoperative complication rate. Postoperative serum CEA and CA199 levels were obviously lower in OG as compared with CG. A higher 3-year survival rate was determined in OG. The areas under the receiver operating characteristic (ROC) curve (AUCs) of CEA and CA19-9 levels in predicting patients' 3-year survival were 0.826 and 0.867, respectively. According to the Cox regression analysis, tumor diameter, lymph node involvement, TNM staging, vascular invasion, CEA, and CA19-9 were independent risk factors for poor prognosis of LRRCC patients. Conclusions: LRRCC is well-tolerated by patients with CC and contributes to favorable outcomes. Besides, CEA and CA19-9, the two TMs, may be candidate prognostic markers for patients undergoing LRRCC.

Keywords: Laparoscopic radical resection, colorectal carcinoma, colorectal cancer, tumor markers, prognosis

Introduction

Nowadays, irregular and unhealthy eating habits contribute to gradually increased risk of gastrointestinal cancer [1], a kind of cancer that accounts for approximately 20% of all cancer diagnoses and 22.5% of global cancer deaths [2]. Colorectal cancer (CC), as a common malignant gastrointestinal cancer, is second only to gastric, esophageal and primary liver carcinomas in morbidity and mortality among gastrointestinal cancers [3]. CC is a malignancy occurring in the colon mucosa epithelium, with nonspecific early clinical presentations, resulting in most patients being diagnosed in the middle and late stages [4]. Current research has identified multiple pathogenic factors of the disease, including family inheritance, living habits and alterations of intestinal microflora [5].

At present, surgery, targeted therapy, radiotherapy and other treatments can all be used for the treatment of CC. However, many patients who develop to the middle and late stages have poor survival and prognosis as the specific pathogenesis of CC has not been completely clarified [6, 7]. Laparoscopic radical resection of colorectal cancer (LRRCC) is the most effec-

tive means at present and has been extensively applied in the treatment of CC due to its advantages of low invasiveness and high safety [8]. However, many patients have missed the best opportunity for surgery after diagnosis. For them, simple radical surgery is unable to achieve good therapeutic effects, and some will even experience postoperative recurrence after radical surgery [9, 10]. Currently, there are few clinical indicators for predicting patients' outcomes. Accordingly, by studying the clinical value of tumor markers (TMs) in patients undergoing LRRCC, this study aimed to provide the basis and direction for clinical practice.

Data and materials

Patient data

This retrospective study enrolled 141 patients with early/mid-stage CC consecutively treated in the Zhongshan Hospital of Xiamen University between July 2017 and August 2018, and grouped them according to different surgical modalities. The observation group (OG; n=74) was treated with LRRCC, comprising 43 males and 31 females, with a mean age of 57.5±10.4 years. The control group (CG) included 67 patients (male to female ratio 38:29, mean age: 58.5±9.5 years) and was given open surgery (OS). The study was in line with the Declaration of Helsinki and was conducted after obtaining the approval from the Medical Ethics Committee. All subjects signed the informed consent.

Eligibility criteria

Inclusion criteria: patients with a diagnosis of CC via colonoscopy and pathological examination [11]; patients who met the surgical indications; patients and their families had given consent to surgical treatment; patient with complete follow-up data and clinical data.

Exclusion criteria: patients with an age <18 years; patients had received palliative surgery; patients with other malignant tumors or severe failure of heart, liver, kidney and other organs; patients with coagulation dysfunction; patients who declared a withdrawal from the study.

Treatment methods

CG was treated by OS, which was operated in the supine position after anesthesia. An incision was made at the rectus abdominis muscle of the costal arch, and the tumor lesions and the mesentery were carefully separated and excised after locating the lesions. The lymph nodes (LNs) were then dissected, followed by routine anastomosis. After that, the operative cavity was repeatedly irrigated, the drainage tube was routinely indwelled, and the incision was sutured [12].

Patients in OG received LRRCC, which was performed in the lithotomy position after anesthetization. A carbon dioxide pneumoperitoneum was established through the umbilicus, and a laparoscope was placed through the four-hole method. After locating the lesions using laparoscopy, the tumor lesion and mesentery were carefully separated and resected, and LN tissue was dissected. Then, a 5 cm auxiliary incision was made on the lateral side of the lesions, and the tumor was excised in vitro after specimen collection. After routine anastomosis, the abdominal cavity was irrigated and sutured [13].

Detection methods

Five milliliters of fasting peripheral venous blood were collected one day before surgery and seven days after surgery into coagulant tubes, which were then subjected to centrifugation (3000xg at 4°C for 10 min) to collect serum. Measurement of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels was conducted using Roche Automatic Chemiluminescence Analyzer (ECL 1010).

Follow-up

Three-year follow-up, which was conducted every 3 months in the first year and every 6 months thereafter, was performed among all the enrolled patients via telephone and return visit examination to record their conditions. No one was lost to follow-up in this study.

Outcome measures

Postoperative gastrointestinal functions of the two groups were observed. The incidence of postoperative adverse reactions, as well as the levels of CEA and CA19-9 before and after surgery, were counted. The 3-year survival of patients was visualized and compared using

Table 1. Clinical baseline data

	Observation group (n=74)	Control group (n=67)	t/χ^2	P
Age	57.5±10.4	58.5±9.5	0.594	0.554
Gender			0.028	0.867
Male	43 (58.11)	38 (56.72)		
Female	31 (41.89)	29 (43.28)		
Tumor diameter			0.608	0.435
<5 cm	51 (68.92)	42 (62.69)		
≥5 cm	23 (31.08)	25 (37.31)		
Differentiation degree			0.081	0.776
High differentiation	47 (63.51)	41 (61.19)		
Middle differentiation	27 (36.49)	26 (38.81)		
Lymph node involvement			0.151	0.698
With	14 (18.92)	11 (16.42)		
Without	60 (81.08)	56 (83.58)		
TNM staging			5.129	0.077
I	13 (17.57)	15 (22.39)		
II	38 (51.35)	42 (62.69)		
III	23 (31.08)	10 (14.93)		
ASA classification			0.568	0.753
I	20 (27.03)	16 (23.88)		
II	38 (51.35)	33 (49.25)		
III	16 (21.62)	18 (26.87)		
Vascular invasion			1.140	0.286
With	20 (27.03)	13 (19.40)		
Without	54 (72.97)	54 (80.60)		

Note: TNM, tumor node metastasis; ASA, American Society of Anesthesiologists.

the Kaplan-Meier (K-M) survival curve, and the patients in CG were sub-grouped (high and low expression groups) by the median values of CEA and CA19-9 to compare the 3-year survival between high and low expression groups. Receiver operating characteristic (ROC) curve analysis was carried out to determine the value of CEA and CA19-9 in predicting the 3-year survival of patients in OG [14].

Statistical methods

Statistical analysis was performed by SPSS *v*20.0 software (SPSS Co., Ltd., Chicago, USA). The measurement data conforming to normal distribution were expressed as mean ± standard deviation. Independent t-test was utilized for testing between the two groups, and paired t-test was used for comparison within the same group, with the results represented by t. The categorical variables were denoted by the number of cases or percentage, and Chi-square analysis was used for testing, with the results recorded as χ^2. The predictive value of CEA and CA19-9 for 3-year postoperative survival in OG was analyzed by ROC curve. The K-M curve of patients was drawn, based on which the difference in the 3-year survival was compared between groups and analyzed by the log-rank test. Cox regression was used to analyze the risk factors influencing the prognosis of LRRCC patients.

Results

Patient baseline data

By comparing patients' baseline data, we found no evident difference in age, gender, tumor diameter, tumor location, differentiation, LN involvement, tumor node metastasis (TNM) staging, American Society of Anesthesiologists (ASA) classification and vascular invasion between OG and CG (**Table 1**).

Postoperative gastrointestinal function of patients

By comparing the postoperative gastrointestinal function, it was found that there was no significant difference in intestinal exhaust time between OG and CG, while motilin (MOT) and gastrin (GT) levels were statistically higher in OG (**Figure 1**).

Postoperative adverse reactions

Both cohorts of patients developed intestinal obstruction, urinary incontinence, wound infection and anastomotic leakage, but the overall incidence of adverse reactions was significantly lower in OG (**Table 2**).

Alterations in TMs before and after surgery

The comparison of the alterations in TMs revealed no statistical difference in CEA and CA19-9 between the groups before treatment, while significantly lower postoperative CEA and CA19-9 levels were witnessed in OG compared with CG (**Figure 2**).

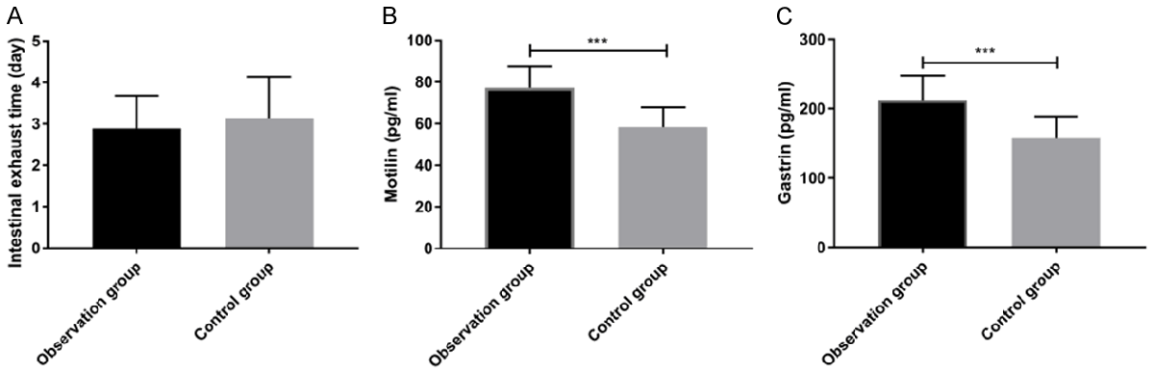

Figure 1. Postoperative gastrointestinal function of patients. A. There was no significant difference in anal exhaust time between the two groups (P>0.05). B. The level of motilin in the observation group was significantly higher than that in the control group (P<0.05). C. The level of gastrin in the observation group was significantly higher than that in the control group (P<0.05). Note: ***indicates P<0.001.

Table 2. Postoperative adverse reactions

	Observation group (n=74)	Control group (n=67)	χ^2	P
Intestinal obstruction	3 (4.05)	4 (5.97)	4.910	0.027
Urinary incontinence	2 (2.70)	5 (7.46)		
Wound infection	2 (2.70)	6 (8.96)		
Anastomotic fistula	2 (2.70)	3 (4.48)		
Total adverse reactions	9 (12.16)	18 (26.87)		

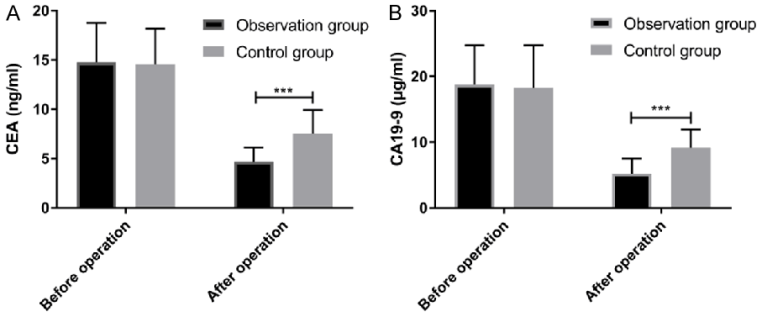

Figure 2. Changes in tumor markers in patients. A. There was no significant difference in CEA between the two groups before surgery (P>0.05), but the CEA level in the observation group was significantly lower than that in the control group after surgery (P<0.05). B. There was no significant difference in CA19-9 between the two groups before surgery (P>0.05), but the CA19-9 level in the observation group was significantly lower than that in the control group after surgery (P<0.05). Note: ***indicates P<0.001. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Correlation of TMs with patient survival

We followed up all the patients for 3 years. Among the pati-ents in OG, 51 cases survived, and 23 cases died, with a survival rate of 68.92%. While 34 cases survived and 33 cases died in CG, with a 3-year survival rate of 50.75%. By drawing the K-M curve, it was found that the 3-year survival rate was significantly higher in OG than in CG. Based on the median values of postoperative CEA and CA19-9, we sub-grouped the patients in OG into high and low level groups, and found an obviously lower 3-year survival in patients with high CEA and high CA19-9 levels compared with those with low levels (**Figure 3**).

Prognostic significance of TMs

Patients in OG were subdivided into survival group and death group according to their survival data after 3-year survival. The value of CEA level and CA19-9 level in predicting patients' survival in 3 years was analyzed by the ROC curve, showing the areas under the curve (AUCs) of 0.826 and 0.867 for CEA and CA19-9, respectively (**Figure 4**).

Analysis of influencing factors of poor prognosis of LRRCC patients

Age, gender, tumor diameter, tumor location, differentiation degree, LN involvement, TNM staging, ASA classification, vascular invasion, CEA, and CA19-9 were included in the analysis

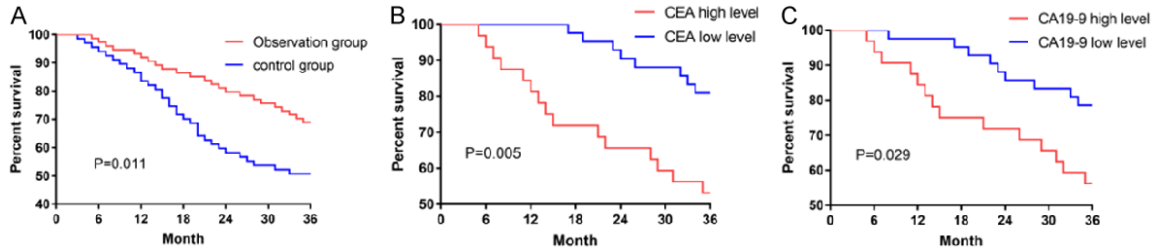

Figure 3. Relationship between tumor markers and patients' survival. A. The 3-year survival rate of patients in the observation group was significantly higher than that in the control group (P=0.011). B. The 3-year survival rate of patients with low CEA expression was significantly higher than that of patients with high CEA expression (P=0.005). C. The 3-year survival rate of patients with low CA19-9 expression was significantly higher than that of patients with high CA19-9 expression (P=0.029). Note: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

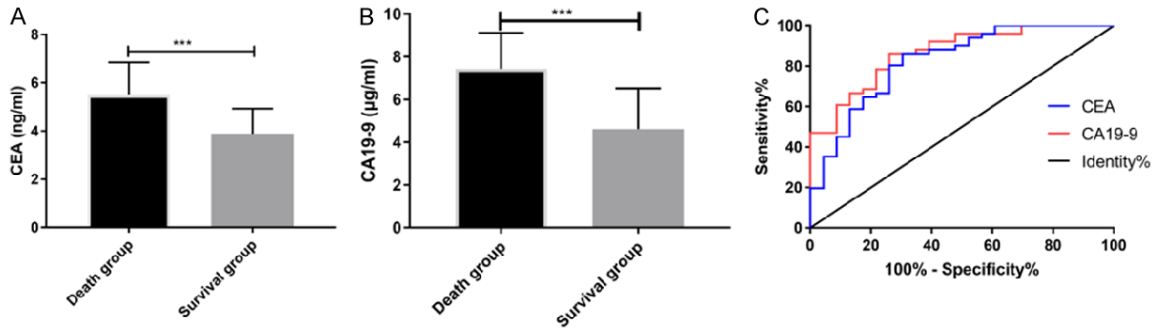

Figure 4. Prognostic value of tumor markers. A. The CEA level in the survival group was significantly lower than that in the death group (P<0.05). B. The level of CA19-9 in the survival group was significantly lower than that in the death group (P<0.05). C. The ROC curve of CEA for predicting 3-year mortality was 0.826, and the specificity and sensitivity were 69.57% and 86.27%, respectively. The ROC curve of CA19-9 for predicting 3-year mortality was 0.867, and the specificity and sensitivity were 73.91% and 86.27%, respectively. Note: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ROC, receiver operating characteristic curves.

and assigned as independent variables, while the prognosis of LRRCC patients was used as the dependent variable. Multivariate analysis using the Cox regression model identified that tumor diameter (P<0.001), LN involvement (P=0.026), TNM staging (P=0.001), vascular invasion (P=0.025), CEA (P=0.003) and CA19-9 (P=0.038) were independent predictors for poor prognosis in LRRCC patients (**Tables 3** and **4**).

Discussion

CC is one of the most commonly seen neoplastic diseases in the world at present, affecting many people in both economically developed countries and developing countries [15]. The death rate for CC is on the decline, thanks to advances in imaging, diagnosis and treatment [16]. With the development of laparoscopic technology, laparoscopic radical surgery has gradually become the main surgical modality for CC patients [17]. It is repeatedly demonstrated that laparoscopic radical surgery contributes to shorter postoperative recovery time and fewer postoperative complications than conventional open surgery [18]. However, not all patients are suitable for surgical treatment, for whom, adjuvant chemotherapy is shown to be effective in shrinking tumors and prolonging the overall survival time after systemic chemotherapy. Moreover, many studies have shown a certain probability of recurrence and metastasis after radical resection. For example, Young et al. [19] reported a recurrence rate of 30-50% in patients with CC who underwent therapeutic resection. Here, we compared the postoperative gastrointestinal function of patients. The results revealed no evident difference in postoperative intestinal exhaust time between groups, but higher postoperative GT and MOT levels in OG, indicating that LRRCC was well tol-

Table 3. Evaluation of factors affecting the poor prognosis of LRRCC patients

Factors	Variables	Assignments
Age	X1	Continuous variable
Gender	X2	Male =0, female =1
Tumor diameter	X3	<5 cm =0, ≥5 cm =1
Differentiation degree	X4	Well differentiated =0, moderately differentiated =1, poorly differentiated =2
Lymph node involvement	X5	Yes =0, no =1
TNM staging	X6	I=0, II=1, III=2
ASA classification	X7	I=0, II=1, III=2
Vascular invasion	X8	Yes =0, no =1
CEA	X9	Continuous variable
CA19-9	X10	Continuous variable

Note: TNM, tumor node metastasis; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA19-9, Carbohydrate antigen 19-9.

Table 4. Analysis of influencing factors of poor prognosis of LRRCC patients

Factors	P	OR	95% CI
Age	0.727	1.006	0.974-1.038
Gender	0.740	1.105	0.614-1.988
Tumor diameter	<0.001	3.632	2.058-6.411
Differentiation degree	0.341	1.354	0.726-2.526
Lymph node involvement	0.026	5.051	1.217-20.966
TNM staging	0.001	2.195	1.358-3.546
ASA classification	0.777	0.938	0.601-1.463
Vascular invasion	0.025	3.905	1.191-12.802
CEA	0.003	1.173	1.055-1.304
CA19-9	0.038	1.094	1.005-1.191

Note: TNM, tumor node metastasis; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

erated by patients and could regulate GT and MOT secretion by improving patients' conditions. However, Sun et al. [20] reported that the intestinal exhaust time of patients after laparoscopic radical surgery was significantly shorter than that of patients undergoing open surgery, which is possibly related to information bias caused by the small sample size. Li et al. [21] pointed out in their study that the application of enhanced recovery after surgery on the basis of laparoscopic colorectal cancer surgery would help further promote the recovery of gastrointestinal function, which was mainly manifested by shorter first exhaust time, first defecation time and extubation time. We also compared the incidence of postoperative adverse reactions such as intestinal obstruction, urinary incontinence, wound infection and anastomotic leakage between the groups, and found a significantly lower overall incidence in OG, similar to the research results of Zhou et al. [22]. Open surgery is also known as a risk factor for serious complications in patients undergoing radical surgery for colon cancer [23]. This may be related to the clearer and magnified visual field during laparoscopic radical surgery, thus reducing the potential surgical stress response of patients and the risk of postoperative complications [24].

In order to effectively implement the treatment plan, it is crucial to predict patients' prognosis. At present, clinicopathological and imaging indicators are increasingly used to predict the prognosis of CC patients. The molecular diversity of CC is prominent and thus can provide markers with high predictive value. TMs are often used to diagnose and monitor malignant tumors. High serum levels of CA19-9 and CEA are risk factors for poor prognosis in multiple cancers. In the present research, we also found a notably higher 3-year survival rate in patients undergoing LRRCC compared with those undergoing OS (68.92% *vs.* 50.75%), indicating that LRRCC can provide a better prognosis for patients. In the study of Yan et al. [25], the overall survival rate and disease-free survival rate of 196 patients with stage III CC after LRRCC were significantly higher than those of traditional OS group, which was similar to our results. This may be attributed to the fact that LRRCC has less impact on the immune system of patients, which fully stimulates the potential of the

patient's body to exert anti-tumor immunity [26]. Furthermore, a higher 3-year survival rate was found in patients with low CEA and low CA19-9 compared with those with high levels. As a macromolecular glycoprotein, CA19-9 is synthesized by the epidermis of pancreas, colon, endometrium and salivary gland and is mainly stored in cells. But when cancer progresses in these sites, the concentration of CA19-9 in blood increases as the cellular structure is destroyed [27, 28]. This also suggests a certain correlation of CEA and CA19-9 with the prognosis of patients after LRRCC. Furthermore, CEA and CA19-9 had good predictive value for postoperative prognosis of patients undergoing LRRCC, as indicated by ROC curve analysis. Lakemeyer et al. [29] also pointed out that the 5-year survival rate of patients with high expression of CEA and CA19-9 was significantly lower, and CEA and CA19-9 could be used as independent prognostic indicators for the survival of patients with CC. Finally, our research also found that in addition to pathological parameters such as tumor diameter, LN involvement, TNM staging and vascular invasion, CEA and CA19-9 were also independent predictors of the poor prognosis of LRRCC patients, suggesting that suppressing CEA and CA19-9 levels might be beneficial to the prognosis of LRRCC patients.

However, this study still has some room for improvement. First of all, some special types of CC patients have not been discussed in depth. For example, CC patients are prone to liver or lung metastasis [30, 31], and the characteristics of TMs in these patients need to be further explored later. Besides, some newer imaging techniques are helpful to predict the prognosis of tumor patients, and the related imaging indicators can be combined to increase the prediction value of TMs in follow-up studies [19, 32]. Finally, it is hoped that more effective prediction and treatment methods for relapsed patients can be explored.

Collectively, LRRCC is well-tolerated by CC patients and contributes to favorable outcomes. In addition, tumor makers CEA and CA19-9 may be candidate prognostic indicators and independent predictors for the prognosis of patients undergoing LRRCC.

Disclosure of conflict of interest

None.

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