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Clinical and Pathological Differences of Left and Right Colorectal Cancer and Prognostic Survival Analysis

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Wu X, Shang Y, Wang W These authors are contributed equally to this work.

Abbreviations:

CRC: Colorectal Cancer; LCC: Left Colon Cancer; RCC: Right Colon Cancer; MMR: Mismatch Repair; hs-CRP: High Sensitive C Reaction Protein; WBC: White Blood Cell Count; RBC: Red Blood Cell Count; PLT: Platelet; HGB: Hemoglobin; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; Ki-67: MKI-67/ Antigen KI67; CEA: Carcinoembryonic Antigen; EGFR: Epidermal Growth Factor Receptor; CK: Creatine Kinase; Vim: Vimentin; EMA: Epithelial Membrane Antigen; MMRP: Mismatch Repair Protein (MLH1, PMS2, MSH2, MSH6); MSI: Microsatellite Instability; CerbB2: Receptor Tyrosine Kinase 2; OS: Overall Survival; HR: Hazard Ratio; TCM: Traditional Chinese Medicine.

1. Introduction

CRC is the second most common cancer reported in women and the third in men [1,2]. The Lancet report has confirmed CRC as the fourth deadliest cancer in the world, with nearly 900,000 deaths each year [1]. The latest statistics of The Lancet shows that the number of deaths due to CRC accounts for 10% of that in all cancer each year [1,3]. The onset age of LCC and RCC has been reduced greatly [1-3]. In addition to eating habits, adverse risk factors such as obesity, lack of physical exercise, and smoking also increase the risk of CRC [1,16]. As early in 1990, LCC and RCC were shown to be two distinct colon cancers [4]. However, the definition of LCC and RCC is still controversial, with no clear division.

They are different in epidemiology, pathology, cytogenetics, and should be treated differently and correctly [5,6]. The embryonic origin of the left and right colons is different. The right colon orig-

inates from the central gastrointestinal tract, while the left colon is from the posterior gastrointestinal tract [7,8]. Besides, their main blood supply is also different. The right hemicolon is mainly supplied by the superior mesenteric artery, and blood returns to the right hemilobal liver through the superior mesenteric vein [9,10]. The left hemicolon is mainly supplied by the inferior mesenteric artery, and blood flows back to the splenic vein through the inferior mesenteric vein and then to the left hepatic lobe via the left branch of the portal vein [9,10]. In addition, the dissection structure of the left and right colons is also different. The right half of the colon has a large intestinal cavity, and its thin intestinal wall is easy to expand, while the left half of the colon has a relatively narrow intestinal cavity [10,11]. In this study, we choose the classification standard to divide nearly two-thirds of the transverse colon, ascending colon, and cecum into the right colon [4-6]. The distal third of the transverse colon, the descending colon, sigmoid colon, and rectum are divided into the left colon [4-6]. The molecular carcinogenic pathways in LCC and RCC are also different. Colon tumors mainly originate from chromosomal instability pathways, and Microsatellite Instability (MSI) is mainly found in right colon tumors [5,12]. The incidence of KRAS and BRAF mutant genes is higher in RCC than that in LCC [13,14]. In addition to above, the onset age of LCC and RCC is obviously different, the prognostic survival time after treatment is also different [15,16].

Currently, treatment methods for CRC include endoscopic and surgical local resection, staging of preoperative radiotherapy and systemic treatment, local area surgery and extensive surgery for metastatic disease, local ablation treatment of metastases, palliative chemotherapy, targeted therapy and immunotherapy [4,9]. Although these treatments have achieved certain results, the pathogenesis and specific cancer metastasis mechanism are not yet clear. Understanding the pathophysiology of CRC will increase the range of treatment options for local and advanced diseases, helping to develop individual treatment plans [17]. Therefore, finding out the differentially expressed proteins in LCC and RCC will lay a solid theoretical foundation for further research.

This study was performed to investigate the statistically significant differences in patients with LCC and RCC based on the differences in epidemiology, clinical, histological, molecular characteristics and disease progression time. The study used regular telephone follow-ups to further understand the postoperative recovery and survival time of patients. In-depth study of the difference between LCC and RCC, will help people get a comprehensive understanding of CRC, and further improve its prevention and treatment capabilities as well as postoperative survival time.

2. Materials and Methods

2.1. Research Participants

This study combines retrospective analysis and prospective analysis. A total of 277 patients from January 1, 2010 to December 31, 2018, in the Gastrointestinal Surgery Department of Shanghai Tenth People's Hospital were enrolled. These inpatients were operated on and pathologically confirmed to be CRC. The inclusion criteria were as follows: (1) Complete clinical data (2) No anti-tumor treatments such as chemotherapy, radiotherapy, or biological therapy received before the surgery. (3) No infectious diseases or hematological diseases affecting the peripheral blood were found. (4) No previous history of other malignant tumors.

2.2. Data Collection

The general clinical data of patients, such as age, gender and symptoms were collected. The whole blood analysis of patients was conducted, and the serum biochemical test report was issued by the laboratory within 24 hours after admission. Also, the test report of the gastrointestinal tumor marker was issued by the Department of Nuclear Medicine. All patients' surgical specimens were sent to the Department of Pathology for pathological tissue biopsy. The report of pathological tissue biopsy included the pathological tissue type and stage of the primary lesion. All research participants were followed-up telephonically after discharge. The follow-up results included the patient's survival time, medical treatment and physical recovery after surgery. The deadline for follow-up is May 15, 2020. The follow-up time was 5 to 110 months, and the median follow-up time was 38 months. Those who could not be followed up due to loss of contact and who had passed away were excluded.

2.3. Statistical Analysis

Data were analyzed using SPSS22.0 statistical software. The $\chi 2$ test or Fisher exact probability method was used for analyzing the samples. The Overall Survival time (OS) was selected, and the log-rank test was used to compare the survival time. Further, the Cox regression equation was used for multifactorial analysis. Part of the data analysis used GraphPad Prism 6.0 software for data statistics and plotting of survival curves. The data were expressed as mean ± standard deviation. P value <0.05 indicated a statistically significant difference.

3. Results

3.1. Data Analysis

118 patients had RCC, included 55 (46.6%) men and 63 (53.3%) women, aged 36–92, average age 69.84 ± 11.03 years. Further, 159 patients had LCC, including 109 (68.6%) men and 50 (31.4%) women, aged 25–87 years, with an average of 62.97 ± 11.26 years. A significant difference was found in the age of onset of LCC and RCC ($P < 0.0001$).

3.2. Differences in Clinical and Pathological Characteristics

The 277 patients with RCC included in this study had carcinoma of the cecum (32.5%), carcinoma of the ascending colon (61.0%), Carcinoma of hepatic flexure of colon (4%), and nearly two thirds of the transverse colon cancer (2.5%). Patients with LCC had cancer of one-third of the transverse colon or carcinoma of the splen-

ic flexure of the colon (2%), carcinoma of the descending colon (5%), carcinoma of the sigmoid (33.3%), and carcinoma of the rectum (59.7%) (Figure1A and B).

The most common clinical manifestations of all patients with CRC included in the study were changes in bowel habits (61.43%), blood in the stool (59.64%), changes in bowel traits (57.50%), and abdominal pain (49.29%). Moreover, 40.71% were positive for the digital rectal examination, and 88.04% were positive for the occult blood. Also, 38.71% had anemia, 36.74% had an increase in the level of Carcinoembryonic Antigen (CEA), and 26.34% had an increase in the level of high-sensitivity C-Reactive Protein (hs-CRP).

The single-factor statistical analysis of RCC and LCC revealed statistical differences in gender, age, tumor type, degree of differentiation, depth of tumor invasion, number of lymph node metastases, and survival time ($P < 0.05$) (Figure 1C-G). No statistically significant difference was observed in the presence of distant metastasis, number of lymph nodes removed by surgery, and presence or absence of vascular infiltration or nerve infiltration ($P > 0.05$) (Table1).

The blood test, hemagglutination test, and biochemical test results were collected for patients with LCC and RCC. The most common and basic indicators were collected for statistical analysis, including CRP level, White Blood Cell count (WBC), Red Blood Cell count (RBC), Platelet (PLT) count, Hemoglobin (HGB) level, alanine Aminotransferase (ALT) level, and aspartate Aminotransferase (AST) level, which showed no statistically significant difference ($P > 0.05$) (Table 2 and Fig.2A-G).

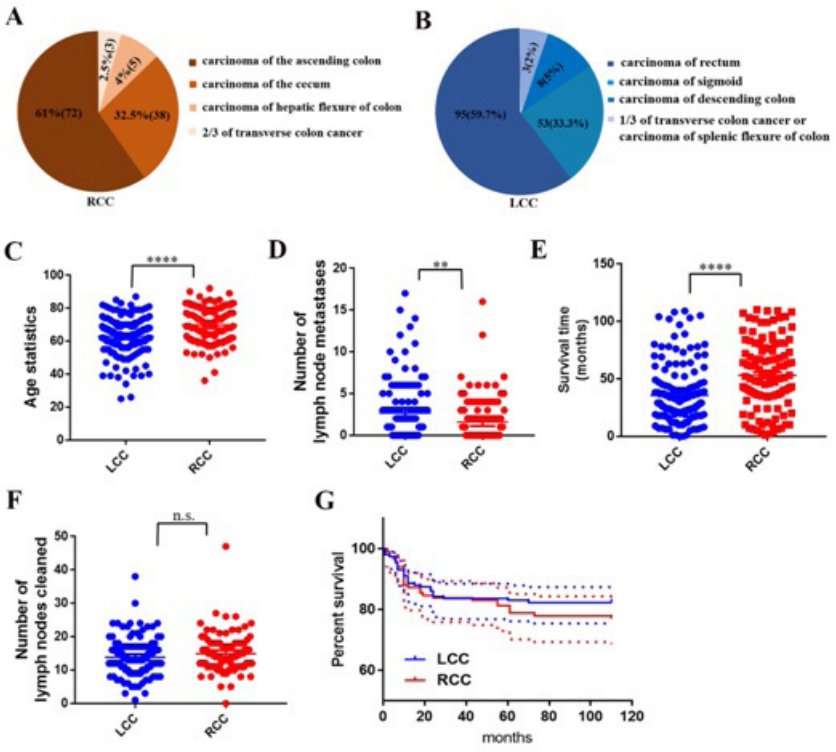

Figure 1: Distribution and percentage of patients with LCC and RCC. (A) Patients with RCC had carcinoma of the ascending colon (61.0%), carcinoma of the cecum (32.5%), Carcinoma of hepatic flexure of colon (4%), and nearly two-thirds of the transverse colon cancer (2.5%). (B) Patients with LCC had carcinoma of the rectum (59.7%), carcinoma of the sigmoid (33.3%), carcinoma of the descending colon (5%), and one-third of the transverse colon cancer or carcinoma of the splenic flexure of colon (2%). (C) Analysis of the difference in the age distribution of LCC and RCC. (D) Analysis of the difference in the number of lymph node metastases between LCC and RCC. (E) Analysis of the difference in survival time (months) between the LCC and RCC. (F) Analysis of the difference in the number of surgically cleared lymph in LCC and RCC. (G) Survival time curve in LCC and RCC. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

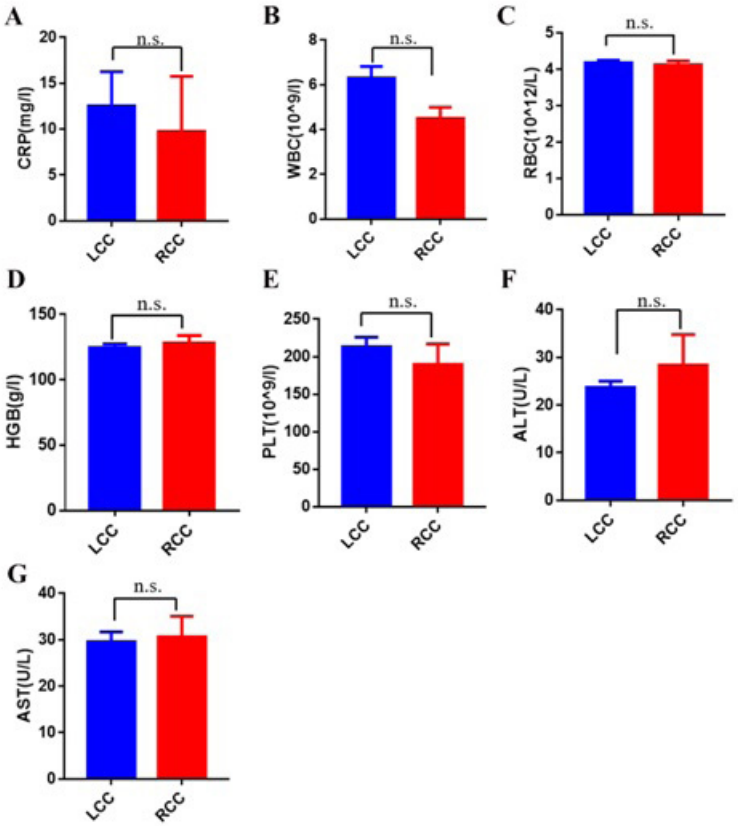

Figure 2 (A–G): Analysis of differences in C-reactive protein level, white blood cell count, red blood cell count, hemoglobin level, platelet count, alanine aminotransferase level, and aspartate aminotransferase level in LCC and RCC. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, n.s. $P > 0.05$.

Table 1: Single factor analysis based on RCC and LCC

Pathological features		**RCC (n=118)**	**LCC (n=159)**	χ^2	**P**
Gender	man	55	109	13.503	≤0.01
	woman	63	50		
Age	≥65	63	67	10.544	0.001
	＜65	45	92		
General classification	Infiltrating type	75	126	8.531	0.014
	DISCOID type	10	6		
	Protuberance type	33	27		
Differentiation	Low differentiation	12	2	12.588[a]	0.002
	Intermediate differentiation	103	155		
	High differentiation	3	2		
T	T1	7	4	15.639[a]	0.001
	T2	7	16		
	T3	52	100		
	T4	52	39		
N	N0	67	80	1.153	0.562
	N1	33	52		
	N2	18	27		
M	M0	107	147	1.791	0.181
	M1	11	8		
Number of lymph nodes cleaned	≥13	73	74	2.302	0.316
	＜13	45	85		
Lymph node metastasis	>3	26	48	6.386	0.012
	3-Jan	23	28		
	0	69	83		
Vascular infiltration	Negative	114	151	0.44[a]	0.507
	Positive	4	8		
Nerve infiltration	Negative	112	150	0.044	0.834
	Positive	6	9		
"a" means that it does not meet the χ2 test requirement, Fisher's exact probability method is used					

Table 2: Statistical analysis of basic blood tests

Abbreviation	Unit	RCC	LCC	P
CRP(mean±SD)	mg/L	9.76 ± 5.986	12.56 ± 3.705	0.791
WBC(mean±SD)	10^9/L	4.504 ± 0.4962	6.319 ± 0.5014	0.172
RBC(mean±SD)	10^12/L	4.118 ± 0.1107	4.175 ± 0.07822	0.785
HGB(mean±SD)	g/L	127.9 ± 5.962	124.7 ± 2.67	0.669
PLT(mean±SD)	10^9/L	189.9 ± 27.04	213.2 ± 12.6	0.507
ALT(mean±SD)	U/L	28.41 ± 6.374	23.63 ± 1.424	0.364
AST(mean±SD)	U/L	30.68 ± 4.372	29.55 ± 2.147	0.882

3.3. Analysis of Differences in Immunohistochemical Indexes

The pathological tissues of the 277 patients enrolled were collected for immunohistochemical analysis. The 2010–2015 immunohistochemical indicators were different from those of 2015–2018, but the main indicators were included in the statistical scope. Analysis of differential protein results showed that the expression of Ki67, EGFR, CAM5.2, CerbB2, and P53 had statistically significant differences in LCC and RCC ($P < 0.05$). However, no statistically significant difference was found among the expression of CA199, CEA, AE1/AE3, Villin, CK, CK-P, CK7, CK8/18, CK20, VIM, EMA, MLH1, MSH2, MSH6, and PMS2 ($P > 0.05$). This study had a large amount of data, which were difficult to organize. The goal of the study was to discover molecular proteins specifically expressed in LCC and RCC (Table 3).

Table 3: Analysis of expression differences between LCC and RCC immunohistochemical proteins

Protein molecule	HR	P
KI67	0.527	≤0.01
CA199	0.926	0.227
CEA	2.411	0.312
EGFR	0.371	0.011
CerbB2	2.763	0.011
Villin	0.675	0.544
CK-P	8.7	0.308
CK7	2.119	0.135
CK8/18	3	0.13
CK20	0.362	0.145
VIM	0.75	0.1
P53	0.519	0
EMA	4.134	0.388
CAM5.2	0.742	0.014
MLH1	0.431	0.343
MSH2	0.296	0.214
MSH6	6.384	0.284
PMS2	0.807	0.734

Next, survival time was used as the dependent variable in the analysis, aiming to find immunohistochemical protein molecules related to prognosis. Cox proportional-hazards model analysis was conducted, revealing CA199 and MSH2 as risk factors affecting the prognostic survival time of colorectal cancer ($P < 0.05$) (Table 4). CA199 and MSH2 are independent risk factors that affect the prognostic survival time.

CA199 is a mucin-type glycoprotein. It is a glycolipid on the cell membrane and a gastrointestinal tumor-associated antigen present in the blood circulation [18, 19]. MSH2 is one of the four Mismatch Repair (MMR) genes closely related to the occurrence of Lynch syndrome [12]. MMR gene mutations disrupt the function of the proteins, resulting in Microsatellite Instability (MSI) in the patient's DNA [20-22]. Most Lynch syndrome families (85%–90%) have MLH1 and MSH2 mutations [25]. The remaining 10%–15% of the families have MSH6 mutations, and a few have PMS2 mutations [23, 24]. Normal people take 8–10 years to develop from adenoma to adenocarcinoma, while patients with Lynch syndrome need only about 2–3 years [25, 26].

3.4. Survival Analysis

A statistically significant difference was noted in Overall Survival (OS) between patients with LCC and RCC ($\chi 2 = 156.02$, $P = 0.014$). The 1-year survival rate of LCC and RCC was 90.68% and 88.7%, the 2-year survival rate was 83.9% and 84.3%, the 3-year survival rate was 83.05% and 83.6%, the 4-year survival rate was 82.20% and 83.6%, the 5-year survival rate was 81.36% and 83%, and the 10-year survival rate was 77.12% and 82.4%, respectively.

The Cox analysis showed that gender, number of lymph node metastases, CA199, and MSH2 were the influencing factors for the OS of CRC ($P < 0.05$). The results of the immunohistochemical analysis indicated that the expression of CEA, KI67, P53, CK20, CK8/18, CK7, EGFR, Vim, as well as age, general tumor typing, and use of Traditional Chinese medicine (TCM) after the surgery, were not influencing factors for the OS of CRC ($P > 0.05$) (Table 4).

Table 4: Cox analysis of survival time

Factors	HR	P	95% Cl
Gender	0.461	0.008	0.259-0.819
Age	0.826	0.496	
Chinese treatment	0.244	0.16	
General shape	1.356	0.129	
Number of lymph node metastases	0.716	0.039	0.521-0.983
KI67	0.776	0.212	
CA199	0.359	0.042	0.133-0.969
CEA	2.248	0.381	
EGFR	1.283	0.55	
CerbB2	0.829	0.684	
Villion	0.463	0.146	
CK7	1.862	0.188	
CK-P	20.757	0.734	
CK8/18	1	1	
CK20	0.733	0.634	
Vim	2.971	0.296	
P53	1.219	0.28	
EMA	22.673	0.604	
MLH1	0.32	0.113	
MSH2	0.236	0.047	0.057-0.980
MSH6	20.883	0.621	
PMS2	0.373	0.053	

4. Discussion

This study showed that LCC was more prevalent in men than women and occurred at a younger age. The overall age of patients with RCC was relatively high. Both types had infiltrative growth [27,28]. Compared with RCC, the survival rate of patients with LCC was higher, and the number of lymph node metastases and the degree of invasion were lower. And After a large number of telephone follow-ups, it was found that patients with LCC and RCC were still troubled by gastrointestinal symptoms after discharge, such as diarrhea, constipation, and indigestion [29-35]. Clinically, CRC should be actively prevented and treated, and a reasonable treatment plan should be selected according to the specificity of LCC and RCC to improve the sequelae of the digestive tract after discharge.

The proposal of individualized treatment and precision medicine provides directions for overcoming CRC. Its significance lies in finding the differences between LCC and RCC, formulating individualized treatment plans according to different types of characteristics, improving the treatment effect and the quality of postoperative survival time [36-38].

In addition, during the telephone follow-up, about 19.5% of the patients chose to take TCM for maintenance treatment after they were discharged from the hospital. However, due to the small number of participants in the statistics, after statistical analysis, the use of traditional TCM has no significant effect on the prognosis of survival time. The impact and significance of TCM on cancer patients needs further exploration.

A large number of studies have shown that the prognosis of RCC is worse than that of LCC, and the OS of patients with RCC is significantly shorter than that of LCC [39,40]. The study started with the collection of clinical data and involved a combination of retrospective and prospective analyses. However, this study had certain limitations. The number of patients was relatively small. Future studies will conduct telephonic return visits for existing patients and continue to collect new clinical cases, continuously providing important clues and treatment basis for clinical treatment.

5. Declarations

5.1. Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81572061), and the Outstanding academic leaders plan of Shanghai (Grant No. 2018BR07).

5.2. Ethics statements

Since our research is a retrospective research, it only analyzes the test data and results of patients, and does not involve patient samples. We guarantee the privacy of patients and confirm that the data has been anonymized.

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