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Prognostic Impact of Primary Tumor Site on Resectable Colorectal Liver Metastases

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Abstract

Purpose: Currently, right colon cancer (RCC), left colon cancer (LCC), and rectal cancer (REC) are typically considered as different tumor entities. This study investigates the curative effect and differential prognoses of patients with colorectal liver metastases (CRLM) who underwent simultaneous radical surgery, based on the site of the primary tumor. **Methods:** This study analyzed 215 patients with CRLM at the First Affiliated Hospital of Sun Yat-sen University who were treated with radical surgery from 2008 to 2021. All data were analyzed by SPSS. **Results:** The proportion of right colon liver metastasis (RCLM) patients with a primary tumor longitudinal diameter ≥5cm was higher than that of left colon liver metastasis (LCLM) and rectal cancer liver metastasis (ReCLM) patients (61.0% vs. 34.3% vs. 33.3%, p = 0.001). Similarly, the proportion of patients with full circumferential involvement of the intestinal wall was higher in the RCLM group (74.6% vs. 57.8% vs. 50.0%, p = 0.021). The three-year overall survival (OS) of the RCLM group was significantly lower than that of the LCLM and ReCLM groups (37.5% vs. 64.7% vs. 62.5%, p = 0.016). Univariate and multivariate analysis showed that circumferential intestinal wall involvement, lymph node metastasis, and CA199 were independent risk factors for OS in RCLM, while circumferential involvement and CA199 were independent risk factors for DFS in CRLM. **Conclusion:** The primary tumor site should be considered when analyzing the outcomes of CRLM.

Keywords Colorectal Liver Metastases (CRLM); Surgery; Prognosis; Tumor site; Colorectal cancer (CRC)

1 Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and is ranked second in terms of cancer-related mortality[1]. It is estimated that the number of colorectal cancer cases worldwide will increase to 3.2 million new cases and 1.6 million deaths by 2040[2]. The liver is the most common site of

metastasis for patients with CRC, and 15–25% of patients are diagnosed with liver metastases at the time of diagnosis[3]. Based on the location of the primary tumor, CRC generally falls into three types: right colon cancer (RCC), left colon cancer (LCC), and rectal cancer (REC). Embryologically, the right half of our colon derives from the embryonic midgut and is bounded by the splenic flexure, while the left half and rectum derive from the hindgut[4-6]. Due to the differences in origin and microenvironment, there are different clinical manifestations, pathological patterns, molecular markers, prognoses, modes of tumor metastasis, and treatments between RCC, LCC and REC. Consequently, many studies in recent years have shown that prognoses differed owing to different locations of the primary tumor[7-10]. However, there is no definitive conclusion on whether the prognosis is different for patients with colorectal liver metastases (CRLM) who underwent simultaneous radical surgery as a result of different primary tumor sites[11-13]. This study compared the curative effect of radical operations in patients with CRLM, based on the primary tumor location.

2 Materials and methods

2.1 Patients

The institutional review board approved this study, which abided by the revised Declaration of Helsinki and the requirements of good clinical practice.

We retrospectively analyzed data from 215 patients with CRLM treated with simultaneous radical surgery from 2008 to 2021. Inclusion criteria for hepatectomy for CRLM were: oligo-hepatic metastasis, resectable metastases as determined by preoperative assessment, an expected compensatory residual liver volume, and eligibility for primary surgical resection of liver metastases without preoperative contraindications. The diagnosis of CRLM was based on colonoscopy with a pathology report, abdominal and pelvic CT, PET-CT, and elevated digestive tract tumor markers. The treatment plan was determined by a multidisciplinary team (MDT) consisting of professionals from departments including gastrointestinal surgery, oncology, hepatobiliary surgery, radiology, interventional radiology, nutrition, and rehabilitation. Simultaneous radical surgery was defined as total resection of the primary lesion along with the surrounding lymph node metastases, and resection of the liver metastases with normal liver tissue within 1 cm of the resection margin and no hilar lymph node enlargement.

Right colon cancer (RCC) included ascending colon cancer and cancer of the hepatic flexure of the colon. Left colon cancer (LCC) included cancer of the splenic flexure of the colon, descending colon, and sigmoid colon. Rectal cancer was considered a separate category. In addition, “well differentiated” refers to high, medium-high, and medium-low differentiation, and “poorly differentiated” refers to medium-low, low, and undifferentiated tumors. This study was approved by the Medical Ethics Committee of the Seventh Affiliated Hospital of Sun Yat-sen University (No. KY-2023-053-01). Individual consent for this retrospective analysis was waived.

2.2 Follow-up

The information collected included patient characteristics, characteristics of the primary tumor, operative indications, tumor markers, postoperative pathological staging, postoperative complications, postoperative gastrointestinal function recovery, and features of liver metastases. Overall survival (OS) was defined as the time from radical surgery to death or last follow-up; relapse-free survival (RFS) was recorded from the time of radical surgery to death, new metastasis, or recurrence. The follow-up data were retrieved from clinical data, phone interviews, and readmission records, if available. The patients were monitored with abdominal CT every 1 to 2 months after surgery and with periodic reviews afterwards.

2.3 Statistical analysis

Patients were divided into three groups based on the site of the primary tumor. The RCLM group included patients with cancer of the cecum, ascending colon, and hepatic flexure of the transverse colon. The LCLM group consisted of patients with cancer of the splenic flexure of the transverse colon, descending colon, and sigmoid colon. Finally, the ReCLM group was made up of rectal cancer patients. To evaluate the differences in clinicopathological characteristics and short- and long-term clinical outcomes among the three groups, the ANOVA test was used. Values of $p < 0.05$ were regarded as statistically significant. Long-term outcomes and survival curves were analyzed using the Kaplan-Meier method. Logistic regression analysis was used to analyze the risk factors. Values of $p < 0.1$ were regarded as statistically significant. All analyses were performed using IBM SPSS Statistics 25.0 software (Chicago, IL, USA).

3 Result

3.1 Study cohort characteristics

In total, 215 patients were included in this study (Fig. 1), including 59 (27.4%) RCLM patients, 102 (47.5%) LCLM patients, and 54 (25.1%) ReCLM patients. Table 1 summarizes the clinicopathological characteristics of the study cohort by group. There were no statistically significant differences in sex ($p = 0.572$), age ($p = 0.937$), Body Mass Index (BMI) ($p = 0.425$), number of liver metastases ($p = 0.792$), differentiation ($p = 0.624$), pT stage ($p = 0.805$), pN stage ($p = 0.714$), lymph node metastasis ($p = 0.834$), neoadjuvant chemotherapy ($p = 0.971$), CEA > 5 ng/ml ($p = 0.253$), CEA > 200 ng/ml ($p = 0.307$), CA-125 > 40 ng/ml ($p = 0.194$), and complications ($p = 0.410$). The proportion of patients with a primary tumor longitudinal diameter ≥ 5 cm was higher in the RCLM group than in the LCLM and ReCLM groups (RCLM group: 61.0% vs. LCLM group: 34.3% vs. ReCLM group: 33.3%; $p = 0.001$). Moreover, the proportion of patients with the percentage of intestinal wall circumference involved $= 1$ in the RCLM group was also higher than that of the LCLM and ReCLM groups (RCLM group: 74.6% vs. LCLM group: 57.8% vs. ReCLM group: 50.0%, $p = 0.021$). The incidence of CA-199 > 40 ng/ml was greater in the LCLM group than in the other groups (RCLM group: 8.4% vs. LCLM group: 20.5% vs. ReCLM group: 6.0%; $p = 0.042$). Further inter-group analysis of the percentage of intestinal wall circumference involved showed that the RCLM group was higher than the LCLM group (74.6% vs. 57.8%, $p = 0.036$) and the ReCLM group (74.6% vs. 50.0%, $p = 0.008$), while there was no distinction between the LCLM and ReCLM groups (57.8% vs. 50.0%, $p = 0.336$). The incidence of complications is illustrated in Fig. 3a (Percentage of total complications). The most common was intra-abdominal infection (36%), followed by stomal fistula (18%), pulmonary infection (15%), incision infection (8%), bile fistula (8%), and intestinal obstruction (5%).

3.2 Long-term outcomes

The survival analysis is shown in Table 2. The median follow-up periods were as follows: RCLM group, 46 months; LCLM group, 47 months; and ReCLM group, 60 months. The three-year OS was significantly different among the three groups (RCLM group: 37.5% vs. LCLM group: 64.7% vs. ReCLM group 62.5%; $p = 0.016$), and the median survival times for the RCLM, LCLM, and ReCLM groups were 24 months, 36 months, and 35 months, respectively, as represented by the survival curve in Fig. 2. Moreover, the results of the intra-group analysis were as follows: RCLM group vs. LCLM group (37.5% vs. 64.7%, $p = 0.006$); RCLM group vs. ReCLM group (37.5% vs. 62.5%, $p = 0.032$); and LCLM group vs. ReCLM group (64.7% vs. 62.5%, $p = 0.883$). However, the three-year RFS and five-year OS and RFS were not significantly different among the three groups (three-year RFS: RCLM group: 35.0% vs. LCLM group:

39.7% vs. ReCLM group 37.5%; $p = 0.889$; five-year OS: RCLM group: 27.3% vs. LCLM group: 43.6% vs. ReCLM group 38.1%; $p = 0.461$; five-year RFS: RCLM group: 27.3% vs. LCLM group: 20.5% vs. ReCLM group 33.3%; $p = 0.553$). The incidence of relapse or metastasis is illustrated in Fig. 3b (Percentage of total recurrence or metastasis). The most common was liver metastasis (53%), followed by pulmonary metastasis (18%), local relapse (7%), and liver and lung metastasis (7%).

3.3 Risk factors of OS and DFS

Table 3 shows the results of univariate and multivariate analyses of factors affecting OS in patients with LCLM. The results of the univariate analysis showed that the percentage of intestinal wall circumference involved ($p = 0.048$) was a risk factor for overall survival in patients with LCLM.

Table 4 shows the results of univariate and multivariate analyses of factors affecting OS in patients with RCLM. Percentage of intestinal wall circumference involved ($p < 0.001$), lymph node metastasis ($p = 0.049$) and CA199 ($p = 0.003$) were independent risk factors for OS in patients with RCLM.

Table 5 shows the results of univariate and multivariate analyses of factors affecting OS in patients with ReCLM. None of the factors were proven to be related to OS in patients with ReCLM.

Table 6 shows the results of univariate and multivariate analyses of factors affecting RFS in patients with CRLM. The percentage of intestinal wall circumference involved ($p < 0.001$) and CA199 ($p = 0.084$) were independent risk factors for RFS in patients with CRLM.

4 Discussion

CRC is one of the most common tumors in the world, and once liver metastases are confirmed, the disease is defined as advanced. Previously, metastatic colorectal cancer (mCRC) was considered a contraindication for surgery, but in recent years, resection of liver metastases has been widely accepted with a prognostic benefit.

This study analyzed short- and long-term outcomes of CRLM to investigate the prognostic impact of primary tumor sites by classifying tumors into three groups: RCLM, LCLM, and ReCLM. The results showed that the three-year OS in the LCLM and ReCLM groups outstripped that of the RCLM group (RCLM: 37.5% vs. LCLM: 64.7% vs. ReCLM: 62.5%, $p = 0.016$). These results were partly consistent with some studies, which reported that the survival of RCLM patients was significantly lower than that of the LCLM and ReCLM patients[11-12, 14-17]. However, due to the small sample size, there was no significant difference in five-year OS (RCLM: 37.5% vs. LCLM: 64.7% vs. ReCLM: 62.5%, $p = 0.461$). To sum up, different tumor locations of CRLM have different prognostic implications for survival after curative resection, which suggests that the primary tumor location might serve as a prognostic indicator in CRLM. This study proposes that RCLM, LCLM, and ReCLM should be considered different solid tumors and elaborates on the implications of this distinction for clinical practice.

The theory of embryonic origin may explain why the location of the primary tumor may be a predictor of survival. The right-sided colon is derived from the embryonic mid-gut while the left-sided colon and rectum are derived from the embryonic hind-gut, which leads to differences in genetic background, tumor microenvironment, clinical manifestations, histological types, molecular characteristics, and blood supply[4-5]. Therefore, right colon, left colon, and rectal tumors should be considered as three distinct solid tumors with different prognoses.

For most RCC, it is usually at an advanced stage when discovered because of the late onset of its clinical symptoms. On the contrary, the clinical symptoms of LCC and REC can be detected very early and can therefore be treated early as well, as long as the patient seeks medical attention. The factors reported in this article are consistent with previous reports[18-20], including the proportion of primary

tumors with a longitudinal diameter ≥ 5 cm ($p = 0.001$) and the proportion with a percentage of intestinal wall circumference involved $= 1$ ($p = 0.021$), which are all greater in the RCLM group than the LCLM and ReCLM groups.

Univariate analysis showed that the percentage of intestinal wall circumference involved was the risk factor for OS of LCLM; the longitudinal diameter of the primary tumor ≥ 5 cm, the percentage of intestinal wall circumference involved, and CA199 were the risk factors for OS of RCLM; and no risk factors were found for OS of ReCLM. Multivariate analysis showed that the percentage of intestinal wall circumference involved and CA199 were independent risk factors for OS of RCLM, and no independent risk factors were discovered for OS of LCLM and ReCLM. In addition, univariate and multivariate analysis showed that the percentage of intestinal wall circumference involved and CA199 were not only risk factors for RFS of CRLM but also independent risk factors for RFS of CRLM. Several studies had reported similar results as well[21–25]. This may be because the larger the tumor, the greater the strain it puts on the body, and so more micro-invasions and micro-metastases will go undetected. The tumor infiltrates and grows around the bowel, which can lead to micro-invasion and tumor residual, resulting in a worse prognosis. Regarding the influence of tumor markers on prognosis, some studies have also found similar results[26–35]. Carcinoembryonic antigen (CEA) is the most routinely used tumor marker for CRC, and it has been widely recommended for prognosis, detection of treatment response, and detection of metastatic disease and recurrence. On the other hand, carbohydrate antigen 125 (CA125) is a sensitive tumor marker of peritoneal dissemination (PD), which has been linked in many studies to colorectal cancer. Carbohydrate antigen 199 (CA199) is a mucin-type carbohydrate protein tumor marker, and many studies have linked it to colorectal cancer[36–39]. Thus, the longitudinal diameter of the primary tumor, the percentage of intestinal wall circumference involved, and CA199 levels may be factors that we should prioritize since they help us develop individualized and systematic treatment for patients with CRLM.

Furthermore, according to the consensus reached in 2005, resectable was defined as: no incurable extrahepatic lesions, suitable for surgery, and 30% of normal liver parenchyma can be retained after surgery, or the affected range is no more than 6 hepatic segments[40]. Chemotherapy further provides the possibility of radical resection for patients with colorectal cancer liver metastases[41]. Similar to our center, before surgical resection, most surgeons will require imaging proof of the absence of hepatic artery, major bile duct, portal vein trunk, or abdominal/para-aortic lymph node involvement, and an adequate prediction of functional residual liver volume[42]. Therefore, the removal of liver tissue does not accelerate the death of patients with colorectal cancer liver metastases.

Postoperative complications are one of the most important factors affecting the results of liver metastasis surgery for colorectal cancer[43–46]. Complications can affect the recovery of patients or even delay the treatment of the primary disease. In our study, the major complications included intra-abdominal infection, followed by stomal fistula, pulmonary infection, incision infection, bile fistula, and intestinal obstruction.

Tumor recurrence and metastasis are among the most important factors affecting the long-term survival of patients with colorectal cancer liver metastasis[31,47–50]. The liver is the most common site of metastasis from colorectal cancer, not only before but also after surgery. Our study showed that postoperative recurrence or metastasis was most common in the liver, followed by pulmonary metastasis, local relapse, liver and lung metastasis, brain metastasis, bone metastasis, and adrenal metastasis.

The study has some limitations. First, the small number of CRLM cases available in this study is irrefutable. Second, we are lacking in powerful and definitive RCT results. Third, data were obtained from a single center. Fourth, the surgeries were performed by different treatment groups that may have different surgical techniques. Fifth, the surgical learning curve was not considered. Sixth, the MDT diagnosis and treatment model has been implemented more for recent cases than for past ones. Seventh, due to the small number of neoadjuvant chemotherapy cases, neoadjuvant chemotherapy factors cannot be measured. Eighth, the study range is 2008–2021, and much has changed during this period. Finally,

molecular detection and targeted immunotherapy data are required to complete this study.

5 Conclusion

In this single-center retrospective study, the proportions of patients with a primary tumor longitudinal diameter ≥ 5 cm and percentage of intestinal wall circumference involved were higher in the RCLM group than in the LCLM and ReCLM groups. The top three complications were intra-abdominal infection, stomal fistula, and pulmonary infection, while the top three sites for recurrence or metastasis were liver, lung, and local relapse. The prognosis for the RCLM group was found to be worse than for the LCLM and ReCLM groups. We should consider the site of the primary tumor as a stratification factor when studying the prognosis of CRLM.

Conflict of Interest The authors declare no conflict of interest.
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Table 1: Clinicopathological characteristics of patients with CRLM

Variable	All	RCLM (%)	LCLM (%)	ReCLM (%)	p value
n	215	59 (27.4%)	102 (47.5%)	54 (25.1%)	
Sex					0.572
Male	151 (70.2%)	40 (18.6%)	70 (32.6%)	41 (19.1%)	
Female	64 (29.8%)	19 (8.8%)	32 (14.9%)	13 (6.0%)	
Age (years) $\geq$ 60	110 (51.2%)	29 (13.5%)	53 (24.7%)	28 (13.0%)	0.937
BMI (normal)	145 (67.4%)	40 (67.8%)	65 (63.7%)	40 (74.1%)	0.425
Longitudinal diameter of primary tumor ($\geq$ 5 cm)	89 (41.4%)	36 (61.0%)	35 (34.3%)	18 (33.3%)	0.001
Percentage circumference of intestinal wall involved (=1)	130 (60.5%)	44 (74.6%)	59 (57.8%)	27 (50.0%)	0.021
Pairwise: R vs. L		44 (74.6%)	59 (57.8%)		0.036
Pairwise: R vs. Re		44 (74.6%)		27 (50.0%)	0.008
Pairwise: L vs. Re			59 (57.8%)	27 (50.0%)	0.336
Number of liver metastases (> 1)	80 (37.2%)	23 (40.0%)	39 (38.2%)	18 (33.3%)	0.792
Differentiation (well)					
Well	204 (94.9%)	57 (96.6%)	97 (95.1%)	50 (92.6%)	0.624
Poorly	11 (5.1%)	2 (3.4%)	5 (4.9%)	4 (7.4%)	
pT stage (pT0–pT3)	87 (40.5%)	26 (44.1%)	40 (39.2%)	21 (38.9%)	0.805
pT0	2 (0.9%)	0 (0%)	1 (0.5%)	1 (0.5%)	
pT1	8 (3.6%)	3 (1.4%)	1 (0.5%)	4 (1.9%)	
pT2	8 (3.7%)	4 (1.9%)	0	4 (1.9%)	
pT3	69 (32.1%)	23 (10.7%)	34 (15.8%)	12 (5.6%)	
pT4	128 (59.5%)	33 (15.3%)	62 (28.8%)	33 (15.3%)	
pN stage					0.714
pN0	70 (32.6%)	21 (9.8%)	30 (14.0%)	19 (8.8%)	
pN1	90 (41.9%)	25 (11.6%)	46 (21.4%)	19 (8.8%)	
pN2	55 (25.6%)	13 (6.0%)	26 (12.1%)	16 (7.5%)	
Lymph node metastasis					0.834
Yes	146 (67.9%)	39 (18.1%)	72 (33.5%)	35 (16.3%)	
No	69 (32.1%)	20 (9.3%)	30 (14.0%)	19 (8.8%)	
Neoadjuvant chemotherapy					0.971
Yes	50 (23.3%)	13 (6.0%)	24 (11.2%)	13 (6.0%)	
No	165 (76.7%)	46 (21.4%)	78 (36.3%)	41 (19.0%)	
CEA					
> 5 ng/ml	136 (63.3%)	36 (16.7%)	70 (32.6%)	30 (14.0%)	0.253
$\leq$ 5 ng/ml	79 (36.7%)	23 (10.7%)	32 (14.9%)	24 (11.2%)	
> 200 ng/ml	12 (5.6%)	5 (2.3%)	6 (2.8%)	1 (0.5%)	0.307
$\leq$ 200 ng/ml	203 (94.4%)	54 (25.1%)	96 (44.7%)	53 (24.7%)	
CA125					
> 40 ng/ml	20 (9.3%)	8 (3.7%)	10 (4.7%)	2 (0.9%)	0.194
$\leq$ 40 ng/ml	195 (90.7%)	51 (23.7%)	92 (42.8%)	52 (24.2%)	
CA199					
> 40 ng/ml	75 (34.9%)	18 (8.4%)	44 (20.5%)	13 (6.0%)	0.042
$\leq$ 40 ng/ml	140 (65.1%)	41 (19.1%)	58 (27.0%)	41 (19.1%)	
Complications					0.410
Yes	36 (16.7%)	9 (4.2%)	15 (7.3%)	12 (5.6%)	
No	179 (83.3%)	50 (23.3%)	87 (40.5%)	44 (20.5%)	

Table 2: Long-term survival analysis of CRLM

	All	RCLM	LCLM	RECLM	P value
Three-year survival analysis (n)	140	40	68	32	
OS rate	56.4%	37.5%	64.7%	62.5%	0.016
RCLM vs. LCLM		37.5%	64.7%		0.006
RCLM vs. RECLM		37.5%		62.5%	0.032
LCLM vs. RECLM			64.7%	62.5%	0.883
Median survival time (months)		24	36	35	
DFS rate	37.9%	35.0%	39.7%	37.5%	0.889
Five-year survival analysis (n)	82	22	39	21	
OS rate	37.8%	27.3%	43.6%	38.1%	0.461
DFS rate	25.6%	27.3%	20.5%	33.3%	0.553

Table 3: Univariate and multivariate analyses of factors affecting overall survival in patients with LCLM

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (Male)	0.952 (0.340–2.667)	0.926		
Age (≥60)	0.705 (0.260–1.914)	0.493		
BMI (normal)	0.481 (0.160–1.450)	0.194		
Longitudinal diameter of primary tumor (≥5cm)	0.587 (0.208–1.658)	0.315		
Percentage circumference of intestinal wall involved (=1)	0.289 (0.084–0.989)	**0.048**		
Number of liver metastases (>1)	1.018 (0.341–3.038)	0.974		
Differentiation (Well)		0.999		
pT0–pT3 stage	0.506 (0.159–1.632)	0.256		
Lymph node metastasis (yes)	1.192 (0.410–3.468)	0.747		
CEA (ng/ml)				
>5 ng/ml	0.628 (0.193–2.040)	0.439		
>200 ng/ml	1.683 (0.165–17.126)	0.660		
CA125 (>40 ng/ml)	0.238 (0.040–1.410)	0.114		
CA199 (>40 ng/ml)	0.913 (0.338–2.470)	0.858		
Complications (yes)	1.176 (0.314–4.409)	0.809		

Table 4: Univariate and multivariate analyses of factors affecting overall survival in patients with RCLM

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (Male)	1.062 (0.272–4.153)	0.931		
Age (≥60)	3.000 (0.786–11.445)	0.108		
BMI (normal)	2.161 (0.538–8.678)	0.277		
Longitudinal diameter of primary tumor (≥5cm)	0.941 (0.241–3.679)	0.931		
Percentage circumference of intestinal wall involved (=1)	0.099 (0.017–0.581)	**0.010**	**8.034 (6.826–9.456)**	**<0.001**
Number of liver metastases (>1)	0.646 (0.158–2.637)	0.543		
Differentiation (Well)		0.999		
pT0–pT3 stage	0.492 (0.134–1.810)	0.286		
Lymph node metastasis (yes)	0.259 (0.067–1.003)	0.050	**0.153 (0.024–0.995)**	**0.049**
CEA (ng/ml)				
>5 ng/ml	1.547 (0.379–6.310)	0.543		
>200 ng/ml	6.000 (0.563–63.984)	0.138		
CA125 (>40 ng/ml)	0.615 (0.104–3.658)	0.593		
CA199 (>40 ng/ml)	0.196 (0.036–1.056)	0.058		**0.003**
Complications (yes)	0.472 (0.081–2.752)	0.404		

Table 5: Univariate and multivariate analyses of factors affecting overall survival in patients with ReCLM

Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (Male)	0.750 (0.136–4.127)	0.741		
Age (≥60)	1.145 (0.270–4.867)	0.854		
BMI (normal)	0.169 (0.018–1.592)	0.120		
Longitudinal diameter of primary tumor (≥5cm)	0.538 (0.125–2.313)	0.405		
Intestinal canal seepage (=1)	1.167 (0.251–5.413)	0.844		
Number of liver metastases (>1)	0.857 (0.185–3.977)	0.844		
Differentiation (Well)		0.999		0.999
pT0–pT3 stage	1.000 (0.192–5.222)	1.000		
Lymph node metastasis (yes)	0.500 (0.103–2.436)	0.391		
CEA (ng/ml)				
>5 ng/ml	0.407 (0.084–1.970)	0.264		
>200 ng/ml		0.162		0.162
CA125 (>40 ng/ml)		0.999		0.999
CA199 (>40 ng/ml)	0.350 (0.072–1.711)	0.195		
Complications (yes)	0.500 (0.095–2.620)	0.412		

Table 6: Univariate and multivariate analyses of factors affecting disease-free survival in patients

Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Sex (Male)	1.080 (0.545–2.140)	0.825	—	—
Age (≥ 60)	1.077 (0.543–2.135)	0.832	—	—
BMI (normal)	0.980 (0.475–2.022)	0.956	—	—
Longitudinal diameter of primary tumor (≥ 5 cm)	0.703 (0.352–1.406)	0.319	—	—
Percentage circumference of intestinal wall involved (=1)	0.252 (0.117–0.542)	< 0.001	0.252 (0.116–0.547)	< 0.001
Number of liver metastases (> 1)	0.961 (0.458–2.018)	0.596	—	—
Differentiation (Well)	1.857 (0.188–18.329)	0.596	—	—
pT0–pT3 stage	0.665 (0.323–1.372)	0.270	—	—
Lymph node metastasis (Yes)	0.601 (0.294–1.226)	0.161	—	—
CEA (>5 ng/ml)	0.903 (0.432–1.886)	0.785	—	—
CEA (>200 ng/ml)	1.694 (0.405–7.079)	0.470	—	—
CA125 (>40 ng/ml)	0.375 (0.101–1.396)	0.114	—	—
CA199 (>40 ng/ml)	0.532 (0.258–1.096)	0.087	0.506 (0.233–1.097)	0.084
Complications (Yes)	0.492 (0.192–1.261)	0.140	—	—

HR, hazard ratio; CI, confidence interval. A dash (—) indicates the covariate was not retained in the multivariable model.

Figure legends

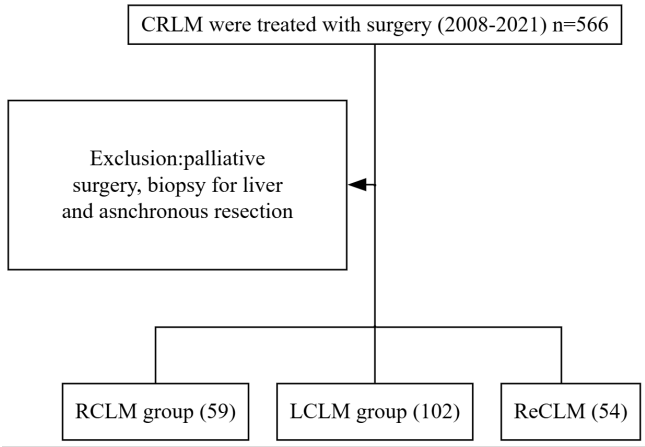
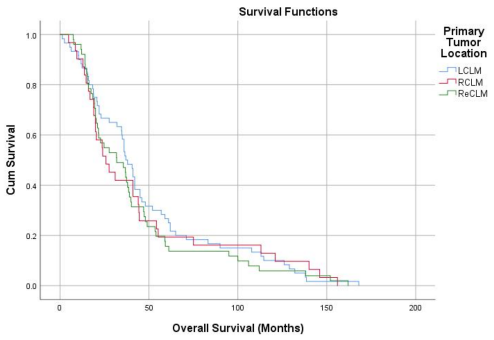


Figure 1: Flow chart summarizing patient selection. Note: CRLM: colorectal liver metastases; RCLM: right colon liver metastasis; LCLM: left colon liver metastasis; ReCLM: rectal cancer liver metastasis.



Number of included patients				
	RCLM	LCLM	ReCLM	P value
Overall Survival (OS)	40	68	32	0.016

Figure 2: Kaplan-Meier curves of the OS of the three groups. Note: CRLM: colorectal liver metastases; RCLM: right colon liver metastasis; LCLM: left colon liver metastasis; ReCLM: rectal cancer liver metastasis.

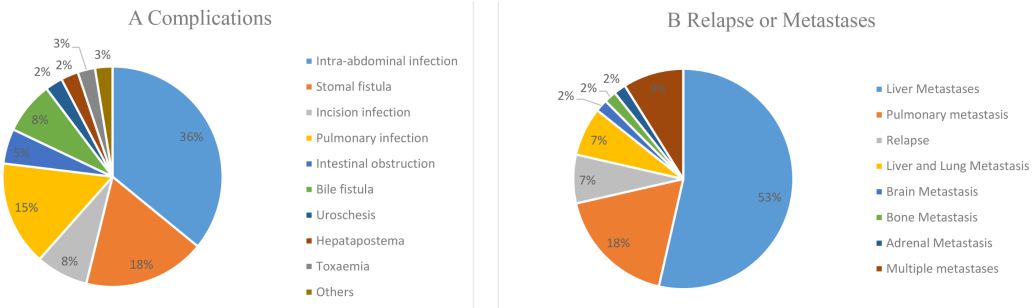


Figure 3: a. In patients who developed complications, the top three were intra-abdominal infection (36%), stomal fistula (18%), and pulmonary infection (15%). b. In patients with recurrence or metastasis, the top three were liver metastases (53%), pulmonary metastases (18%) and relapse (7%).

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