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Research Paper

Association between Primary Tumor Location and Prognostic Survival in Synchronous Colorectal Liver Metastases after Surgical Treatment: A Retrospective Analysis of SEER Data

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Abstract

The prognostic and predictive role of primary tumor location (PTL) in localized and metastatic colorectal cancer (CRC) is a hotspot issue in recent years. However, its prognostic role is still unclear in synchronous colorectal liver metastases (sCRLM), especially in those receiving surgical treatment of primary tumor and liver metastases. Here, a retrospective survival analysis was performed using the Surveillance, Epidemiology, and End Results Program (SEER) database between 2010 and 2014, on patients who were pathologically confirmed sCRLM, and received surgical treatment of both primary tumor and liver metastases. After stringent exclusive procedure, a total of 1508 patients with sCRLM (872 men [57.8%] and 636 women [42.2%]; mean age, 60.9 years) were eligible for the final study. Compared with sCRLM with left-sided PTL, cases with right-sided PTL were more likely to be T4 (31.3% vs. 20.1%, p<0.001), N2 (42.5% vs. 31.8%, p<0.001) and poorly differentiated (30.5% vs. 15.1%, p<0.001). Furthermore, right-sided sCRLM showed significantly shorter cancer specific survival (CSS) than those from left-side (p<0.001). After Cox hazard regression analysis, right-sided PTL still remained to be a strong independent predictor for poor prognosis in this cohort of sCRLM patients (OS, HR=1.75, 95% CI 1.34-2.29; CSS, HR=1.76, 95% CI 1.33-2.35). In conclusion, according to this population-based cohort from the SEER database, PTL was a critical prognostic factor that affect long-term OS and CSS in patients with sCRLM after surgical treatment of primary tumor and liver metastases.

Key words: synchronous, colorectal liver metastases, primary tumor location, surgical treatment, prognosis

Introduction

Colorectal cancer (CRC) is the third most common cancer type and the fourth leading cause of cancer-related deaths in the world. Traditionally, CRC was more prevalent in developed countries, while its incidence and mortality has been also on the rise in developing countries over recent decades (1, 2). Therefore, many efforts have been devoted in recent years to improve the efficacy of clinical treatment of CRC. However, great histological and molecular heterogeneity has become a major obstacle for effective prognostication and treatment stratification, raising challenges for clinical management. Recent studies have proposed that a significant part of this heterogeneity is captured by the anatomical location

of the tumor.

From the perspective of embryologic development, the right- and left-sided colon have different developmental origin. The right colon arises from the midgut and the left colon from the hindgut, which are exposed to different luminal environment(3). Accordingly, right- and left-sided CRC differs in demographical and clinical features. Furthermore, genetic studies have revealed differential gene expression patterns and gene mutation landscape between right- and left-sided colon cancers(4, 5). For these biological and molecular distinctions, the prognostic value of primary tumor location (PTL) in CRC has been proposed and attracted much attention especially in recent 10 years. On the whole, right-sided tumors was associated with a worse prognosis than left-sided tumors irrespective of tumor stages from several population-based studies worldwide(6-10). However, evidences from these studies also suggested that the prognostic value of PTL seemed to be tumor stage specific. In detail, for early-stage stage (I-II) CRC, similar prognosis was found between right-sided and left-sided CRCs(11, 12). For stage III CRC, it was found that right-sided tumors begin to show significantly worse prognosis than left-sided CRCs(11, 13). Then for unresectable stage IV CRC (mCRC), existing results supported that right-sided PTL was also associated with higher mortality regardless of chemotherapy alone or in combination with targeted therapy (BT) (eg, bevacizumab or cetuximab) (14-19). More recently, the role of PTL in predicting response to anti-EGFR based therapy in mCRC became a hotspot. In patients with wild-type KRAS tumors, treatment with cetuximab may possibly benefit only those with left-sided mCRC but not right-sided cases as recent researches have indicated.(20-25). These evidences supports the conclusion that patients with left-sided RAS wild-type mCRC should be preferentially treated with an anti-EGFR antibody, while in right-sided mCRC, anti-EGFR therapy is not recommended.

As a unique clinical phase of mCRC, synchronous colorectal liver metastasis (sCRLM) has attracted more and more attention. In recent years, the development of treatment concept and surgical techniques has led to revolutionary changes in clinical management of sCRLM, and it is generally accepted that surgical resection of both primary tumor and liver metastases is the only curative treatment strategy for sCRLM. However, the resection for cure is performed significantly less often in cases of sCRLM than for metachronous metastases cases (6.3% vs 16.9%, respectively), and the 5-year survival rates were lower with synchronous than with metachronous cases (3.3% vs 6.1%, respectively)(26). To date, studies concerning the prognostic value of PTL in sCRLM after resection are limited, especially in those who have metastases confined to the liver. The existing studies were mostly based on single center experience, and all of them both included synchronous and metachronous CRLM cases for study(27-31). Thus, it remains unclear whether the prognosis of sCRLM with right-sided PTL is different from left-sided cases. Here we used population-based data from the SEER database, to analyze the association between PTL and prognostic survival especially in sCRLM after surgical treatment.

Methods

Data source

Data was obtained from the Surveillance, Epidemiology, and End Results (SEER) database. The current SEER database consists of 18 population-based cancer registries that cover approximately 28% of cancer cases in the United States. This database contains no personal identifiers and is publicly available for cancer studies. And this study was also approved by our institutional review board at Huashan Hospital, Fudan University.

Cohort definition

We used the National Cancer Institute SEER*Stat software (Version 8.3.2, http://seer.cancer.gov/seer stat) to identify patients. Firstly, patients with CRC were identified with the following inclusion criteria: (1) International Classification of Diseases for Oncology (ICD-O) code 8936; (2) the year of diagnosis ranged from 2010 to 2014; (3) diagnosis was confirmed by histology; (4) aged 18 or older; (5) the cause of death and survival time were both known. Then a stringent exclusive procedure was performed to identify CRC cases with liver-limited metastases. The detailed procedure for patient selection is outlined in Figure 1.

Parameters

The following parameters were extracted from the SEER database, including sex, age, race, grade, year of diagnosis, marital status, insurance status, primary tumor location, histological type, grade, primary tumor size, neural invasion, lymph node status, tumor deposit and resection margin. The main parameter of interest was each patient's PTL at diagnosis. The division in the right- and left-sided CRC is based on its embryological origin. The embryological border between both parts of the colon is located at the proximal two-thirds of the transverse colon. However, most researchers use the splenic flexure as the demarcation line between right- and left-sided tumors (32). In our study, the right-sided

CRC includes those originate from caecum, ascending colon, hepatic flexure and transverse colon, while the left part consists of the splenic flexure, descending colon, sigmoid and rectum.

The main outcomes were 5-year overall survival (OS) and cancer specific survival (CSS). CSS was defined from the date of diagnosis to the date of cancer specific death. In this study, CSS was defined as death due to sCRLM, excluding other causes of death.

Statistical analysis

Clinicopathological parameters were analyzed by chi-square ($\chi 2$) test. Kaplan–Meier plots were used to show OS and CSS, and the differences were analyzed by log-rank test. Multivariate Cox proportional hazard models were adopted to analyze the risk factors of survival outcomes. All data analyses were performed using statistical software package SPSS (version 19.0, Inc, Chicago, IL, USA). All statistical tests were evaluated using a two tailed 95% confidence interval (CI), and a two-side P value of less than 0.05 was set for statistical significance.

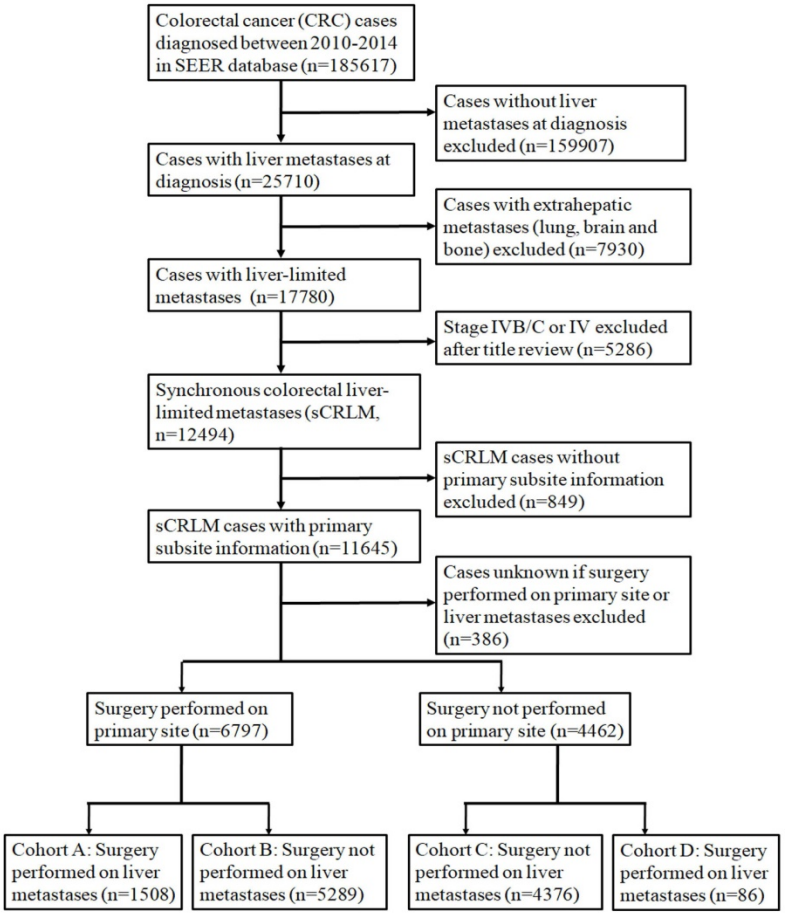

Figure 1. Flowchart of patient inclusion in this cohort study.

Results

Patient enrollment, selection and characteristics of the study cohort

In the initial enrollment stage, 22102 patients diagnosed as CRC from 2010 to 2014 were included. Then we conducted a stringent exclusion procedure as shown in Figure 1. We further grouped the patients based on information about metastasis, primary lesion and surgery as stated in Figure 1. Ultimately, 1508 patients in cohort A were selected for our study. Demographics of the 1508 subjects included in the study are listed in Table 1. The median age of the 1508 selected subjects was 61 year old (19-97), and most of them were white (75.9%, n =1145) and male (57.8%, n=872). On pathological types, the majority of patients were adenocarcinoma (93.6%, n =1412). Of subjects with known lymph nodal status, most had N1 lymph node involvement (44.2%), with 19.1% having N0 and 36.0% having N2 disease. With respect to PTL, 593 (39.3%) had right-sided tumors and 915 (60.7%) had left sided tumors, including 358 (23.7%) rectal cancer.

Comparison of clinicopathological features between right-sided and left-sided CRC with synchronous liver-limited metastases

Then we compared the clinicopathological features between right-sided and left-sided sCRLM in cohort A cases**.** As shown in Table 1, patients originating from right-sided tumors showed different baseline characteristics from left-sided cases in gender (male, 51.8% vs. 61.7%, p<0.001), age (≥60 year, 65.3% vs. 48.3%, p<0.001), race (black, 18.7% vs. 11.1%, p<0.001) and marital status (widowed, 13.3% vs. 6.2%, p<0.001). In clinicopathological parameters, the right-sided tumors showed significantly higher proportion of poor differentiation or undifferentiated (30.5% vs. 15.1%, p<0.001), mucinous change (7.3 % vs. 4.0%, p=0.005), T4 (31.3% vs. 20.1%, p<0.001) and N2 (42.5% vs. 31.8%, p<0.001) status, but lower occurrence of neural invasion (22.1% vs. 28.5%, p=0.009), compared with originally left-sided tumors. Meanwhile, more lymph nodes (LN) were examined perioperatively in cases of right-sided sCRLM compared with left-sided cases (>12 LN, 88.7% vs. 81.0%, p<0.001). Otherwise, the two subgroups did not show significant differences in proportion of CEA positive, resection margin or tumor deposits.

Table 1. Baseline clinicopathological characteristics of patients with differed sCRLM locations in SEER database

Characteristic	Primary tumor location			P-value
	All Patients (n=1508)	Right (n=593)	Left (n=915)	
Patient Related				
Sex				
Female	636 (42.2%)	286 (48.2%)	350 (38.3%)	<0.001
Male	872 (57.8%)	307(51.8%)	565 (61.7%)	
Age at diagnosis (years)				
median/mean	61/60.9			
<50	285 (18.9%)	77 (13.0%)	208 (22.7%)	<0.001
50-59	395 (26.2%)	129 (21.8%)	266 (29.1%)	
60-69	440 (29.2%)	183 (30.9%)	257 (28.1%)	
70-79	266 (17.6%)	124 (20.9%)	142 (15.5%)	
≥80	122 (8.1%)	80 (13.5%)	42 (4.7%)	
Race				
White	1145 (75.9%)	446 (75.2%)	699 (76.4%)	<0.001
Black	213 (14.1%)	111 (18.7%)	102 (11.1%)	
Other	148 (9.8%)	36 (6.1%)	112 (12.2%)	
Unknow	2 (0.1%)	0 (0%)	2 (0.2%)	
Marital status				<0.001
Married	904 (59.9%)	340 (57.3%)	564 (61.6%)	
Widowed	136 (9.0%)	79 (13.3%)	57 (6.2%)	
Single, separated, or divorced	400 (26.5%)	149 (25.1%)	251 (27.4%)	
Unknown	68 (4.5%)	25 (4.2%)	43 (4.7%)	
Insurance status				0.029
Insured	1253 (83.1%)	509 (85.8%)	744 (81.3%)	
Any Medicaid	178 (11.8%)	54 (9.1%)	124 (13.6%)	
Uninsured	57 (3.8%)	24 (4.0%)	33 (3.6%)	
unknown	20 (1.3%)	6 (1.0%)	14 (1.5%)	
Disease Related				
CEA level				0.623
Positive/elevated	840 (55.7%)	317 (53.5%)	523 (57.2%)	
Negative/normal	287 (19.0%)	113 (19.1%)	174 (19.0%)	
Unknown/Borderline	381 (25.3%)	163 (27.5%)	218 (23.8%)	
Primary tumor size (mm)				
≤50	777 (51.5%)	301 (50.8%)	510 (55.6%)	0.003
>50	408 (27.1%)	270 (45.5%)	332 (36.3%)	
Tumor deposits				0.27
Yes	393 (26.1%)	146 (24.6%)	247 (27.0%)	
No	1036 (68.7%)	418 (70.5%)	618 (67.5%)	
Unknown	79 (5.2%)	29 (4.9%)	50 (5.5%)	
Tumor differentiation(grade)				<0.001
Undifferentiated (IV)	68 (4.5%)	40 (6.7%)	28 (3.1%)	
Poor (III)	251 (16.6%)	141 (23.8%)	110 (12.0%)	
Moderate (II)	1072 (71.1%)	373 (62.9%)	699 (76.4%)	
Well (I)	40 (2.7%)	15 (2.5%)	25 (2.7%)	
Unknown	77 (5.1%)	24 (4.0%)	53 (5.8%)	
Histological subtype				0.005
Adenocarcinoma	1412 (93.6%)	540 (91.1%)	872 (95.3%)	
Mucinous adenocarcinoma	80 (5.3%)	43 (7.3%)	37 (4.0%)	
Other	16 (1.1%)	10 (1.7%)	6 (0.7%)	
Neural invasion				0.009
Yes	392 (26.0%)	131 (22.1%)	261 (28.5%)	
No	991 (65.7%)	407 (68.6%)	584 (63.8%)	
Unknown	125 (8.3%)	55 (9.3%)	70 (7.7%)	
Resection Margin				0.484
R0	993 (65.8%)	387 (65.3%)	606 (66.2%)	
R1	140 (9.3%)	59 (9.9%)	81 (8.9%)	
Unknown	375 (24.9%)	147 (24.8%)	228 (24.9%)	
T status				<0.001
T1	24 (1.6%)	3 (0.5%)	21 (2.3%)	
T2	62 (4.1%)	24 (4.0%)	38 (4.2%)	
T3	1020 (67.6%)	372 (62.7%)	648 (70.8%)	
T4a	274 (18.2%)	133 (22.4%)	141 (15.4%)	
T4b	96 (6.4%)	53 (8.9%)	43 (4.7%)	
Unknown	32 (2.1%)	8 (1.3%)	24 (2.6%)	
Nodal status				<0.001
NX	11 (0.7%)	2 (0.3%)	9 (1.0%)	
N0	288 (19.1%)	93 (15.7%)	195 (21.3%)	
N1	666 (44.2%)	246 (41.5%)	420 (45.9%)	
N2	543 (36.0%)	252 (42.5%)	291 (31.8%)	
Adequate lymph node examination (i.e., 12 nodes)				<0.001
No	224 (14.9%)	58 (9.8%)	166 (18.1%)	
Yes	1267 (84.0%)	526 (88.7%)	741 (81.0%)	
Unknown	17 (1.1%)	9 (1.5%)	8 (0.9%)	

Survival analysis based on primary tumor location

To determine whether the primary tumor location is associated with distinct clinical outcomes in sCRLM, we then evaluated the prognosis of the two subsite in our cohort. Of note, Kaplan-Meier plots of 5-year CSS were significantly worse in patients with right-sided sCRLM (Figure 2, p<0.001), and left-sided colon cancer and rectal cancer showed similarly better CSS (Figure 3, p<0.001). Consistently, Kaplan–Meier survival curve based on more detailed tumor subsite location are presented in Supplementary Figure 1. Splenic flexure, sigmoid colon and rectal cases had the highest overall survival estimates, descending and transverse colon cancers had intermediate survival estimates, whereas proximal cancers had the poorest survival.

Multivariate analysis of factors associated with Mortality

Next, we evaluated the association of clinicopathological factors with the outcome of sCRLM patients. On multivariable analyses after controlling for competing risk factors, several factors remained independently associated with OS and CSS, including old age (≥80) (OS, HR= 3.5, 95% CI 2.04-6.02; CSS, HR= 3.31, 95% CI 1.87-5.87), N2 status (OS, HR= 1.54, 95% CI 1.02-2.31; CSS, HR=1.73, 95% CI 1.11-2.71), resection margin (OS, HR= 1.83, 95% CI 1.29-2.59; CSS, HR=1.89, 95% CI 1.32-2.71), as well as right-sided PTL (OS, HR= 1.75, 95% CI 1.34-2.29; CSS, HR=1.76, 95% CI 1.33-2.35) (all P<0.05). While other factors such as gender, race, marital status, insurance status, CEA positive, tumor size, tumor deposit, histological type, differentiation, neural invasion and T status were not correlated with OS or CSS in this cohort (Table 2).

Discussion

During the last years, the impact of PTL in CRC has been intensively studied by multiple research groups. Now it has been recognized that the right- and left-sided CRC have different developmental origin and correspondingly diverse oncogenic

mechanism, contributing to side specific clinical outcome and therapeutic response(4, 5, 32). However, whether this prognostic distinction also exists in specific clinical stages of CRC remains obscure. In this study, using the SEER database, we confirmed the emerging notion that in stage IVA CRC with liver-limited metastases, right-sided PTL also predict worse prognosis than left-sided tumors, for cases who accepted surgical treatment of both primary and hepatic metastases.

The mechanism that contributed to the great prognostic discrepancy between right- and left-sided CRC has been intensively investigated. Demographically, right-sided tumors differ in gender, age and race compared to left-sided cases. Furthermore, CRC in patients over 80s are far more likely to be in the right-sided colon, as is shown in our study. Clinically, right-sided sCRLM appears to have an intent of low differentiated degrees, larger size of primary lesion and early lymph nodes invasion, indicating its relative higher malignancy degrees, which can also partly explain its negative significance in prognosis. Biologically, the differences in luminal content and bacterial flora between the right- and left-sided colon may also influence tumor biology and prognosis(32). Additionally on molecular level, right-sided carcinomas are more often KRAS/BRAF-mutated, more enriched in microsatellite instability (MSI), CpG island methylation phenotype (CIMP) and CMS1 molecular subtype. Left-sided tumors more often harbor chromosomal instability (CIN) and CMS2 molecular subtype(5, 32). Based these evidences, it is convincingly suggested that the above clinical and molecular parameters converged to contribute to the prognostic distinction between right- and left-sided sCRLM.

In recent three years, there have been several studies focusing on the association between PTL and prognostic survival in CRLM after surgical treatment based on single center data. In 2016, Sasaki K from Johns Hopkins Hospital firstly reported the prognostic implications of PTL in CRLM undergoing resection. Of note, patients with left-sided primary tumor had a shorter RFS compared with patients who had a right-sided tumor, while right-sided primary CRC tumors had a shorter OS compared with left-sided tumors(27). Interestingly, their subsequent study revealed a differential prognostic implication of KRAS status after hepatectomy for CRLM according to PTL. Among patients with a right-sided CRC, 5-year RFS and OS were not correlated with KRAS status. In contrast, among patients from a left-sided primary CRC, 5-year RFS and OS were worse among patients with mutant-type KRAS(33). Similarly, experience from MD Anderson Cancer Center found that both RFS and OS after hepatic resection were worse in patients with midgut origin tumors (right-sided)(28). Then data from MSKCC showed that right-sided CRLM had significantly worse OS compared to left-sided CRLM after resection, while the median RFS was only marginally different(29). Consistently, a study from Europe found that right-sided PTL is associated with worse OS after surgery for CLM, but seems to have no influence on PFS(30). However, two recent study from Brazil and China reported that PTL did not affect OS or DFS for patients with resected CRLM(31, 34). All the above studies in combination with our study indicate that PTL is an important prognostic factor for OS, while its role in RFS/PFS/DFS is still controversial.

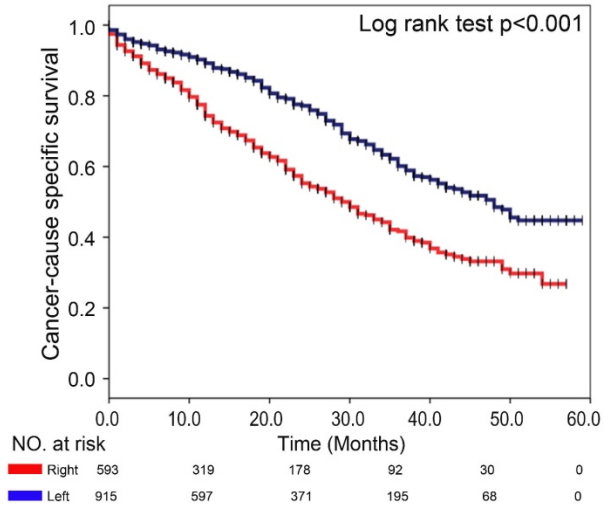

Figure 2. Comparison of CSS between left- and right-sided sCRLM patients in Kaplan-Meier survival analysis.

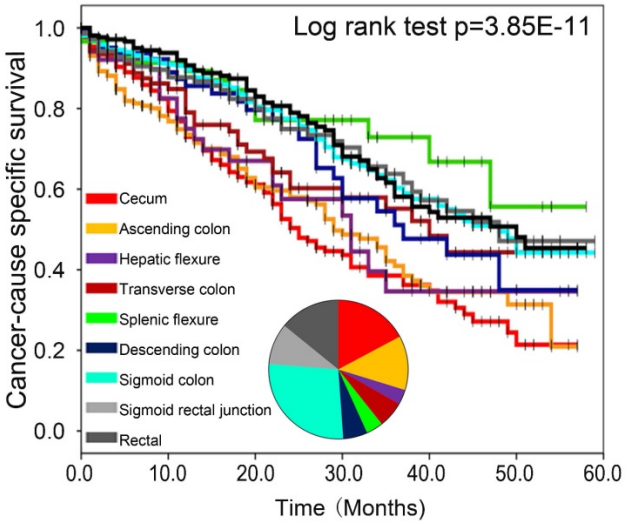

Figure 3. Comparison of CSS among right, left and rectal sCRLM patients in Kaplan-Meier survival analysis.

Table 2. Survival analysis of subgroups based on clinicopathological characteristics

Variable	Overall Survival			Cancer-Specific Survival		
	No./Total No. (%)	Hazard ratio (95 % CI)	p value	No./Total No. (%)	Hazard ratio (95 % CI)	p-value
Sex						
female	247/21 (36.0%)	1 [Reference]		232/21 (37.9%)	1 [Reference]	
male	328/32 (32.6%)	0.85 (0.65-1.11)	0.232	292/42 (38.1%)	0.79 (0.60-1.05)	0.104
Race						
White	428/34 (34.9%)	1 [Reference]		390/34 (39.0%)	1 [Reference]	
Black	100/10 (26.6%)	1.11 (0.77-1.59)	0.581	91/10 (29.9%)	1.07 (0.73-1.57)	0.741
Other	47/8 (39.3%)	1.08 (0.68-1.69)	0.756	43/8 (42.0%)	0.99 (0.61-1.61)	0.972
Age						
<50	81/10 (40.9%)	1 [Reference]		77/10 (41.8%)	1 [Reference]	
50-59	124/29 (41.0%)	0.77 (0.48-1.22)	0.266	116/29 (42.7%)	0.76 (0.47-1.24)	0.271
60-69	165/23 (35.2%)	1.29 (0.85-1.93)	0.23	149/23 (40.2%)	1.30 (0.85-2.00)	0.226
70-79	124/10 (27.6%)	1.89 (1.22-2.92)	0.004	111/14 (35.6%)	1.86 (1.18-2.96)	0.008
≥80	81/1 (7.6%)	3.5 (2.04-6.02)	<0.001	71/1 (9.6%)	3.31 (1.87-5.87)	<0.001
Marital status						
Married	306/53 (38.7%)	1 [Reference]		277/53 (42.5%)	1 [Reference]	
Widowed	77/9 (23.0%)	0.89 (0.56-1.41)	0.612	69/9 (26.7%)	0.86 (0.53-1.39)	0.531
Single/Separated/divorced	167/13 (30.1%)	1.27 (0.94-1.71)	0.127	156/13 (33.5%)	1.26 (0.92-1.73)	0.155
Insurance status						
Uninsured	24/5 (31.4%)	1 [Reference]		23/5 (32.2%)	1 [Reference]	
Insured	470/37 (34.8%)	0.66 (0.35-1.23)	0.192	425/37 (39.0%)	0.65 (0.34-1.25)	0.197
Any Medicaid	76/9 (30.3%)	1.15 (0.57-2.35)	0.694	71/9 (32.3%)	1.20 (0.57-2.53)	0.631
CEA level						
Negative	83/21 (51.3%)	1 [Reference]		78/21 (52.8%)	1 [Reference]	
Positive	333/23 (29.4%)	1.38 (0.99-1.92)	0.056	300/23 (34.3%)	1.37 (0.97-1.93)	0.078
Tumor size						
<50	238/19 (35.1%)	1 [Reference]		218/19 (37.5%)	1 [Reference]	
≥50	303/37 (31.6%)	1.11 (0.86-1.44)	0.431	278/37 (35.3%)	1.17 (0.89-1.54)	0.251
Tumor deposits						
Negative	361/35 (38.6%)	1 [Reference]		326/35 (42.5%)	1 [Reference]	
Positive	169/13 (27.6%)	1.30 (0.98-1.73)	0.071	160/13 (29.9%)	1.31 (0.97-1.77)	0.074
Histological subtype						
Mucinous adenocarcinoma	34/4 (27.8%)	1 [Reference]		32/4 (32.0%)	1 [Reference]	
Adenocarcinoma	534/42 (34.4%)	1.13 (0.64-1.98)	0.68	485/42 (38.4%)	1.14 (0.63-2.06)	0.663
Differentiation						
Well differentiated	16/7 (37.0%)	1 [Reference]		15/7 (39.5%)	1 [Reference]	
Moderately differentiated	372/32 (36.0%)	1.16 (0.52-2.59)	0.711	334/32 (40.5%)	1.01 (0.45-2.26)	0.984
Poorly differentiated	131/9 (24.3%)	2.03 (0.86-4.78)	0.106	123/9 (26.9%)	1.81 (0.76-4.32)	0.179
Undifferentiated	37/4 (18.2%)	1.79 (0.69-4.67)	0.235	34/4 (20.6%)	1.58 (0.60-4.20)	0.357
Neural invasion						
Negative	352/29 (37.3%)	1 [Reference]		320/29 (40.4%)	1 [Reference]	
Positive	161/19 (28.6%)	1.063 (0.79-1.43)	0.684	149/19 (31.3%)	1.08 (0.80-1.48)	0.615
T status(no/yes)						
T1	7/9 (57.0%)	1 [Reference]		6/9 (62.7%)	1 [Reference]	
T2	17/11 (49.7%)	0.73 (0.09-5.91)	0.766	16/11 (52.4%)	0.58 (0.07-4.76)	0.608
T3	361/35 (36.9%)	0.87 (0.12-6.38)	0.888	320/35 (41.8%)	0.67 (0.09-4.99)	0.699
T4	180/10 (21.9%)	0.81 (0.11-6.06)	0.834	172/10 (23.2%)	0.69 (0.09-5.18)	0.714
Nodal status						
N0	83/40 (52.4%)	1 [Reference]		73/44 (57.1%)	1 [Reference]	
N1	240/16 (33.2%)	1.23 (0.84-1.81)	0.296	218/16 (36.0%)	1.37 (0.90-2.09)	0.146
N2	249/24 (26.5%)	1.54 (1.02-2.31)	0.04	230/30 (30.8%)	1.73 (1.11-2.71)	0.015
Resection Margin						
Negative	343/29 (35.2%)	1 [Reference]		303/29 (39.8%)	1 [Reference]	
Positive	82/10 (21.2%)	1.83 (1.29-2.59)	0.001	79/10 (21.9%)	1.89 (1.32-2.71)	<0.001
Primary tumor location						
Left-sided	289/55 (40.1%)	1 [Reference]		261/59 (44.8%)	1 [Reference]	
Right-sided	286/9 (24.6%)	1.75 (1.34-2.29)	<0.001	263/9 (26.8%)	1.76 (1.33-2.35)	<0.001

Traditionally, the clinical prognostication of sCRLM after surgical treatment has long been relegated to clinical staging/scoring system(35-39) or nomograms(40). A major clinically relevant finding of this study is that prognostication of sCRLM based on PTL may be predictive of prognosis (OS and RFS) and is clinically applicable. Our results indicated that adding PTL may provide an important optimization for currently used sCRLM prognosis prediction models.

Compared to the published studies including both synchronous and metachronous CRLM, our present study mainly focused on sCRLM, which

further reduced the heterogeneity. However, the limitations of our study are obvious for its nature of retrograde cohort study. Primarily, all the patients enrolled were diagnosed between 2010 and 2014 from diverse medical institutions, which means there is no standard evaluation on surgical resections, providing a confounding factor. Moreover, information about the liver metastases retrieved from the SEER database is limited, such as the number and largest size of liver lesions.

Conclusively, for sCRLM patients underwent surgical resection on both primary tumor and liver metastases, PTL can act as an effectively predictive indicator for prognosis. In the future, selectively prognostic and therapeutic stratification may be suggested in clinical practice for right- and left-sided sCRLM.

Supplementary Material

Supplementary figures.
http://www.jcancer.org/v10p1593s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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