

Does Primary Tumour Location Affect the Prognosis of Patients with Colorectal Cancer Peritoneal Metastases Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy?

Haipeng Chen

Cancer Hospital Chinese Academy of Medical Sciences

Sicheng Zhou

Cancer Hospital Chinese Academy of Medical Sciences

Jianjun Bi

Cancer Hospital Chinese Academy of Medical Sciences

Qiang Feng

Cancer Hospital Chinese Academy of Medical Sciences

Zheng Jiang

Cancer Hospital Chinese Academy of Medical Sciences

Jianping Xu

Cancer Hospital Chinese Academy of Medical Sciences

Wei Pei (✉ peiweifbwk@163.com)

Cancer Hospital Chinese Academy of Medical Sciences

Jianwei Liang

Cancer Hospital Chinese Academy of Medical Sciences

Zhixiang Zhou

Cancer Hospital Chinese Academy of Medical Sciences

Xishan Wang

Cancer Hospital Chinese Academy of Medical Sciences

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Abstract

Background The impact of primary tumour location on the prognosis of patients with peritoneal metastasis (PM) arising from colorectal cancer (CRC) after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is rarely discussed, and the evidence is still limited.

Methods Patients with PM arising from CRC treated with CRS and HIPEC at the China National Cancer Center and Huanxing Cancer Hospital between June 2017 and June 2019 were systematically reviewed. Clinical characteristics, pathological features, perioperative parameters, and prognostic data were collected and analysed.

Results A total of 70 patients were divided into two groups according to colonic or rectal origin (18 patients in the rectum group and 52 patients in the colon group). Patients with PM of colonic origin were more likely to develop grade 3-4 postoperative complications after CRS+HIPEC (38.9% vs 19.2%, $P=0.094$), but this difference was not statistically significant. Patients with colon cancer had a longer median overall survival (OS) than patients with rectal cancer (27.0 vs 15.0 months, $P=0.011$). On the multivariate analysis, independent prognostic factors of reduced OS were rectal origin (HR 2.03, 95% CI 1.02–4.24, $P=0.044$) and incomplete cytoreduction (HR 2.33, 95% CI 1.05-5.28, $P=0.039$).

Conclusion CRS is an originally complex and potentially life-threatening procedure, and we suggest that the indications for CRS+HIPEC in patients with PM of rectal origin be more restrictive and cautious.

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumours in the world, and its morbidity and mortality rank third and fourth, respectively^[1]. Among patients with CRC, 5%-15% have synchronous peritoneal metastasis (PM), and the incidence of metachronous PM is as high as 20–50%^[2]. PM arising from CRC is a type of tumour in the terminal stage with a very poor prognosis. Palliative surgery and systemic chemotherapy are mostly adopted, but the therapeutic effect is poor, and the median survival time is only 5 to 7 months^[3]. Currently, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown good clinical efficacy in the comprehensive treatment of various malignant peritoneal diseases, including CRC, ovarian cancer and appendiceal mucous adenocarcinoma, and it has been considered a standard therapy for prolonging the survival of patients with PM arising from CRC^[4–8].

At present, most literature has demonstrated that a high peritoneal cancer index (PCI), incomplete cytoreduction, young age and postoperative complications are poor prognostic factors after CRS + HIPEC^[9–12]. It has been well established that different primary tumour locations have different biological behaviours and prognoses^[13]. However, the impact of primary tumour location on the prognosis of patients with PM arising from CRC after CRS + HIPEC is rarely discussed, and the evidence is still limited^[14–17]. It is highly desirable to optimize patient selection for those most likely to benefit from this

complex and potentially life-threatening procedure. Therefore, the aim of this study was to explore the impact of primary tumour location according to colon or rectal origin on the prognosis of patients with PM arising from CRC treated with CRS + HIPEC in our institution.

Methods

Study design and patients

The study protocol was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences (NCC2017-YZ-026, October 17, 2017). The data of all patients with synchronous or metachronous PM arising from CRC who underwent CRS with HIPEC at the National Cancer Center and Huanxing Cancer Hospital were retrospectively obtained from a prospectively maintained database between June 2017 and June 2019. Patients with appendiceal tumours, liver metastasis, poor liver and kidney functions, and a history of other malignant tumours were excluded. According to the location of the primary tumour, all enrolled patients were divided into a colon group (n = 52) and a rectal group (n = 18).

Demographic and clinical variables, as well as perioperative and long-term survival outcomes, were collected and compared. All enrolled patients underwent a routine preoperative evaluation, which included laboratory examinations, abdominal contrast-enhanced computed tomography, pelvic magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography, to assess their general condition. According to the Sugarbaker/Jacquet classification, peritoneal disease burden and the completeness of cytoreduction were assessed using the PCI and completeness of cytoreduction (CC) score, respectively^[18, 19]. All postoperative complications were graded using the Clavien-Dindo classification according to the treatment received^[20].

Surgical Technique

The surgical techniques adopted at our institution have been previously described^[9, 21]. Briefly, HIPEC was delivered in a closed fashion, with oxaliplatin (200 mg/m²) and raltitrexed (3 mg/m²), combined with or without lobaplatin (50 mg/m²). Then, patients were treated with a mixed solution of chemotherapy agents and 3 L of saline solution in the abdominal and pelvic cavity for 60 min at 42–43°C. Next, two additional HIPEC procedures were performed on the second and fourth days after surgery in both groups. Furthermore, two surgical specialists with more than 20 years of experience in gastrointestinal surgery performed the operations at the two centres, and the HIPEC technique and postoperative treatment were identical.

Statistical analysis

Data between two groups were analysed with SPSS 24.0 software (IBM, Armonk, NY, USA). Categorical data are expressed as percentages and were compared using the χ^2 test or Fisher's exact test as appropriate. Continuous data are expressed as the mean \pm standard deviation and were compared using Student's t-test and the Mann-Whitney U test for independent values with normally and nonnormally distributed values, respectively. Overall survival (OS) was defined as the time from surgery to the time of death by recurrence or metastasis or July 31, 2020, whichever came first. The Kaplan-Meier method and log-rank test were utilized to evaluate associations between individual factors and OS. Variables found to be significant (P value < 0.05) in the univariate analysis were incorporated into the multivariate analysis to identify independent predictors of OS. A P value < 0.05 was considered statistically significant.

Results

Demographic and clinical variables

A total of 70 patients with PM of CRC origin who underwent CRS + HIPEC were included in the present study. Of these patients, 18 (25.7%) had rectal cancer and 52 (74.3%) had colon cancer. The mean age of all patients was 54.5 years, and the majority (55.7%) of patients in the study were male. Patients were well balanced across the two groups in terms of age, sex, body mass index (BMI), preoperative comorbidity, preoperative chemotherapy, presentation of PM, preoperative CEA level, preoperative CA19-9 level, histology, and adjuvant chemotherapy ($P > 0.05$) (Table 1).

Table 1
Patient characteristics

Characteristics	Total (n = 70)	Rectum (n = 18)	Colon (n = 52)	<i>P</i>
Age at operation (years, mean ± SD)	54.5 ± 11.6	52.7 ± 12.2	55.2 ± 11.6	0.451
Gender (%)				0.571
Male	39 (55.7)	9 (50.0)	30 (57.7)	
Female	31 (44.3)	9 (50.0)	22 (42.3)	
Body Mass index (kg/m ² , mean ± SD)	22.7 ± 3.6	23.8 ± 3.9	22.8 ± 3.5	0.665
Comorbidity				0.936
Presence	18 (25.7)	4 (22.2)	14 (26.9)	
Absence	52 (74.3)	14 (77.8)	38 (73.1)	
Preoperative chemotherapy (%)				0.477
Presence	30 (42.9)	9 (50.0)	21 (40.4)	
Absence	40 (57.1)	9 (50.0)	31 (59.6)	
Presentation of PM (%)				0.118
Synchronous	42 (60.0)	8 (44.4)	34 (65.4)	
Metachronous	28 (40.0)	10 (55.6)	18 (34.6)	
Preoperative CEA level (ng, mean ± SD)	31.9 ± 61.5	16.6 ± 27.2	37.2 ± 69.8	0.290
Preoperative CA19-9 level (ng, mean ± SD)	75.4 ± 93.3	69.2 ± 112.4	77.5 ± 88.4	0.780
Histology (%)				0.275
Adenocarcinoma	43 (61.4)	13 (72.2)	30 (57.7)	
Mucinous	27 (38.6)	5 (27.8)	22 (42.3)	
Adjuvant chemotherapy				0.924
Presence	55 (78.6)	14 (77.8)	41 (78.8)	
Absence	15 (21.4)	4 (22.2)	11 (21.2)	
Note: <i>SD</i> standard deviation; <i>PM</i> standard peritoneal metastasis				

Operative And Perioperative Data

Operative details and postoperative courses are listed in Table 2. The mean PCI of all enrolled patients was 11.1, and complete cytoreduction (CC 0–1) was achieved in most patients (68.6%). Patients in both groups experienced comparable mean operative times (255.5 vs 257.4 min, $P = 0.922$) and estimated blood loss (98.9 vs 130.2 ml, $P = 0.301$). Compared with patients in the colon group, patients in the rectum group were more likely to develop postoperative grade 3–4 complications (38.9% vs 19.2%, $P = 0.094$), but this difference was not statistically significant. Ileus (7.1%) and pelvic cavity abscesses (7.1%) were the most common postoperative complications, followed by anastomosis leakage (5.7%), wound infection (2.9%), pneumonia (5.4%), pleural effusion (1.4%), cardiac arrhythmia (1.4%), urinary retention (1.4%), and rectovaginal leakage (1.4%). Two patients (2.9%) required revision surgery due to extensive pelvic cavity abscesses, and postoperative bleeding.

Table 2
Operative and perioperative data

Characteristic	Total (n = 70)	Rectum (n = 18)	Colon (n = 52)	<i>P</i>
Operation method				0.538
Laparoscopic surgery	14 (20.0)	5 (27.8)	9 (17.3)	
Open surgery	56 (80.0)	13 (72.2)	43 (82.7)	
HIPEC regimen				0.900
Lobaplatin + Oxaliplatin + Raltitrexed	32 (45.7)	8 (44.4)	24 (46.2)	
Oxaliplatin + Raltitrexed	38 (54.3)	10 (55.6)	28 (53.8)	
PCI score (mean ± SD)	11.1 ± 6.0	11.7 ± 6.9	10.8 ± 5.8	0.600
Presence of ascites				0.693
Presence	30 (42.9)	7 (38.9)	23 (44.2)	
Absence	40 (57.1)	11 (61.1)	29 (55.8)	
CC score				0.168
CC 0–1	48 (68.6)	10 (55.5)	38 (73.1)	
CC 2–3	22 (31.4)	8 (44.5)	14 (26.9)	
Operative time, min (mean ± SD)	256.9 ± 66.0	255.5 ± 83.5	257.4 ± 60.4	0.922
Estimated blood loss, ml (mean ± SD)	122.1 ± 109.2	98.9 ± 82.9	130.2 ± 117.5	0.301
Postoperative complications (grades I,IV)	17 (24.3)	7 (38.9)	10 (19.2)	0.094
Postoperative bleeding	2 (2.9)	1 (5.6)	1 (1.9)	
Anastomosis leakage	4 (5.7)	2 (11.1)	2 (3.8)	
Pelvic cavity abscess	5 (7.1)	2 (11.1)	3 (5.8)	
Ileus	5 (7.1)	2 (11.1)	3 (5.8)	
Pneumonia	1 (1.4)	1 (5.6)	0 (0)	
Pleural effusion	1 (1.4)	1 (5.6)	0 (0)	
Cardiac arrhythmia	1(1.4)	0 (0)	1 (1.9)	

Note: *HIPEC* standard hyperthermic intraperitoneal chemotherapy; *PCI* standard peritoneal cancer index □ *CC* standard complete cytoreduction

Characteristic	Total (n = 70)	Rectum (n = 18)	Colon (n = 52)	<i>P</i>
Wound infection	2 (2.9)	1 (5.6)	1 (1.9)	
Urinary retention	1 (1.4)	0 (0)	1 (1.9)	
Rectovaginal leakage	1 (1.4)	0 (0)	1 (1.9)	
Postoperative hospital stay, day (mean ± SD)	14.6 ± 5.3	15.4 ± 4.7	14.3 ± 5.6	0.380
Re-operation	2 (2.9)	1 (5.6)	1 (5.6)	1.000
Mortality	0 (0)	0 (0)	0 (0)	-
Note: <i>HIPEC</i> standard hyperthermic intraperitoneal chemotherapy; <i>PCI</i> standard peritoneal cancer index □ <i>CC</i> standard complete cytoreduction				

Overall Survival

The median estimated follow-up period from CRS/HIPEC for the study population was 20 months. The median survival period for all patients was 25 months, and the estimated 1-, 2- and 3-year OS rates for the entire cohort were 72.6%, 51.4%, and 40.1%, respectively (Fig. 1). The median OS for those with colon cancer was 27 months compared with 15 months for those with rectal cancer ($P = 0.011$) (Fig. 2). The median OS from CRS + HIPEC in patients undergoing incomplete cytoreduction (CC 2–3) was 12 months, while the median OS was not reached in patients undergoing complete cytoreduction (CC 0–1) (Fig. 3). On the Cox univariate regression analysis, factors found to be associated with reduced OS were increasing PCI (HR 1.09, 95% CI 1.03–1.14, $P = 0.002$), rectal origin (HR 2.54, 95% CI 1.24–5.18, $P = 0.011$), and incomplete cytoreduction (HR 3.49, 95% CI 1.77–6.87, $P < 0.001$). On the multivariate analysis, independent prognostic factors of reduced OS were rectal origin (HR 2.03, 95% CI 1.02–4.24, $P = 0.044$) and incomplete cytoreduction (HR 2.33, 95% CI 1.05–5.28, $P = 0.039$) (Table 3).

Table 3
Univariate analysis and Multivariate analysis

Variables	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P
Gender: male/female	1.32 (0.66–2.64)	0.434		
Age at operation	1.02 (0.98–1.05)	0.283		
Preoperative chemotherapy (no/yes)	1.22 (0.53–2.80)	0.635		
Synchronous/metachronous	1.46 (0.73–2.93)	0.288		
Site of original (rectum/colon)	2.54 (1.24–5.18)	0.011	2.03 (1.02–4.24)	0.044
Histology (mucinous/adenocarcinoma)	1.53 (0.78–3.00)	0.215		
Preoperative CEA level	1.00 (0.99–1.00)	0.279		
Preoperative CA19-9 level	1.00 (0.99–1.00)	0.247		
HIPEC regimen (lobaplatin/non-lobaplatin)	0.63 (0.31–1.28)	0.199		
Presence of ascites (yes/no)	1.33 (0.68–2.60)	0.410		
PCI score	1.09 (1.03–1.14)	0.002	1.05 (0.98–1.11)	0.181
CC score (2–3/0–1)	3.49 (1.77–6.87)	< 0.001	2.33 (1.05–5.28)	0.039
Grade 3–4 Postoperative complication (no/yes)	1.63 (0.77–3.42)	0.201		
Leukopenia (no/yes)	0.67 (0.28–1.63)	0.382		
Neutropenia (no/yes)	0.80 (0.33–1.94)	0.626		
Thrombocytopenia (no/yes)	0.49 (0.15–1.63)	0.245		

Discussion

Primary tumour location is recognized as one of the important prognostic factors for metastatic CRC, and it is also a selection factor for the use of different targeted medicines^[13]. However, the impact of primary tumour location on the prognosis of CRC patients undergoing CRS + HIPEC due to PM is rarely discussed, and the evidence is still limited^[14–17]. Therefore, we conducted a novel study to demonstrate the differences in different primary tumour locations among patients with PM arising from CRC and focused on their significant impacts on perioperative outcomes and long-term prognoses.

In the present study, 70 enrolled patients were divided into two groups according to the origin of the primary tumour: the colon group (52 patients) and the rectal group (18 patients). Our results revealed that patients with colon cancer-derived PM had a longer median survival after CRS + HIPEC (27.0 vs 15.0 months, $P=0.011$), and primary tumour location remained an independent predictor of OS (HR 2.03, 95% CI 1.02–4.24, $P=0.044$). In 2018, Tonello et al^[15] published a paper in which they analysed survival in patients with colorectal PM treated with CRS + HIPEC and reported that PM of rectal origin was associated with worse long-term survival outcomes than PM of colonic origin (median OS: 47.8 vs 22.0 months, $P=0.008$). Similarly, Da Silva et al^[14] also demonstrated that the median survival in patients with PM of colonic origin was significantly better than that in patients with PM of rectal origin (35.0 vs 17.0 months). The above research results are basically consistent with ours.

Several theories have been proposed to explain this difference in terms of the prognosis of PM of rectal origin. Anatomically, a rectal tumour is located in the narrow pelvic cavity, which makes resection of the primary tumour and pelvic peritoneal metastasis difficult; therefore, it is difficult to achieve complete cytoreduction, and the possibility of a residual tumour is increased^[22]. Low-middle rectal cancer (under the peritoneum) increases the risk of perforating the rectal wall, which is thicker than the colon wall and is therefore biologically more aggressive^[14].

Close attention has been given to the morbidity and mortality associated with the CRS + HIPEC procedure. Our institution confirmed that the grade 3–4 morbidity rate and mortality rate after CRS + HIPEC were 24.3% and 0%, respectively, which is basically consistent with the results reported by international centres^[7, 23–26]. Notably, we also found that patients with PM of rectal origin were more likely to develop grade 3–4 postoperative complications after CRS + HIPEC than patients with PM of colonic origin (38.9% vs 19.2%, $P=0.094$), but this difference was not statistically significant. CRS is an originally complex and potentially life-threatening procedure. Due to the special anatomical location of rectal tumours, the narrow operating space further increases the difficulty of CRS.

The limitations of this study are those inherent to a single institution with a limited sample size, which may have caused some of the differences observed between the rectal group and the colon group. Second, this study was also limited by its retrospective nature, which makes it difficult to control for bias and confounders. Therefore, we recommend caution when making any definitive conclusions, and multicentre prospective randomized controlled studies are required to further verify our results.

Conclusion

These findings demonstrated that the CC score and primary tumour location were independent prognostic factors after CRS + HIPEC in patients with PM of CRC origin. In addition, patients with PM of colonic origin were more likely to develop postoperative complications after CRS + HIPEC. We suggest that the indications for CRS + HIPEC in patients with PM of rectal origin should be more restrictive and cautious.

List Of Abbreviations

peritoneal metastasis (PM)

colorectal cancer (CRC)

cytoreductive surgery (CRS)

hyperthermic intraperitoneal chemotherapy (HIPEC)

peritoneal cancer index (PCI)

completeness of cytoreduction

Overall survival (OS)(CC)

body mass index (BMI)

Declarations

Ethics approval and consent to participate

The ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study. Prior written informed consent was obtained from all study participants.

Consent for publication

Not Applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to the data is confidential patient data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Contributions: (I) conception and design: Jianping Xu and Wei Pei; (II) administrative support: Jianwei Liang, Xishan Wang and Zhixiang Zhou; (III) provision of study materials or patients: Jianjun Bi, Qiang Feng and Zheng Jiang; (IV) collection and assembly of data: Sicheng Zhou and Haipeng Chen; (V) data analysis and interpretation: Sicheng Zhou and HaiPeng Chen. All authors read and approved the final manuscript.

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Figures

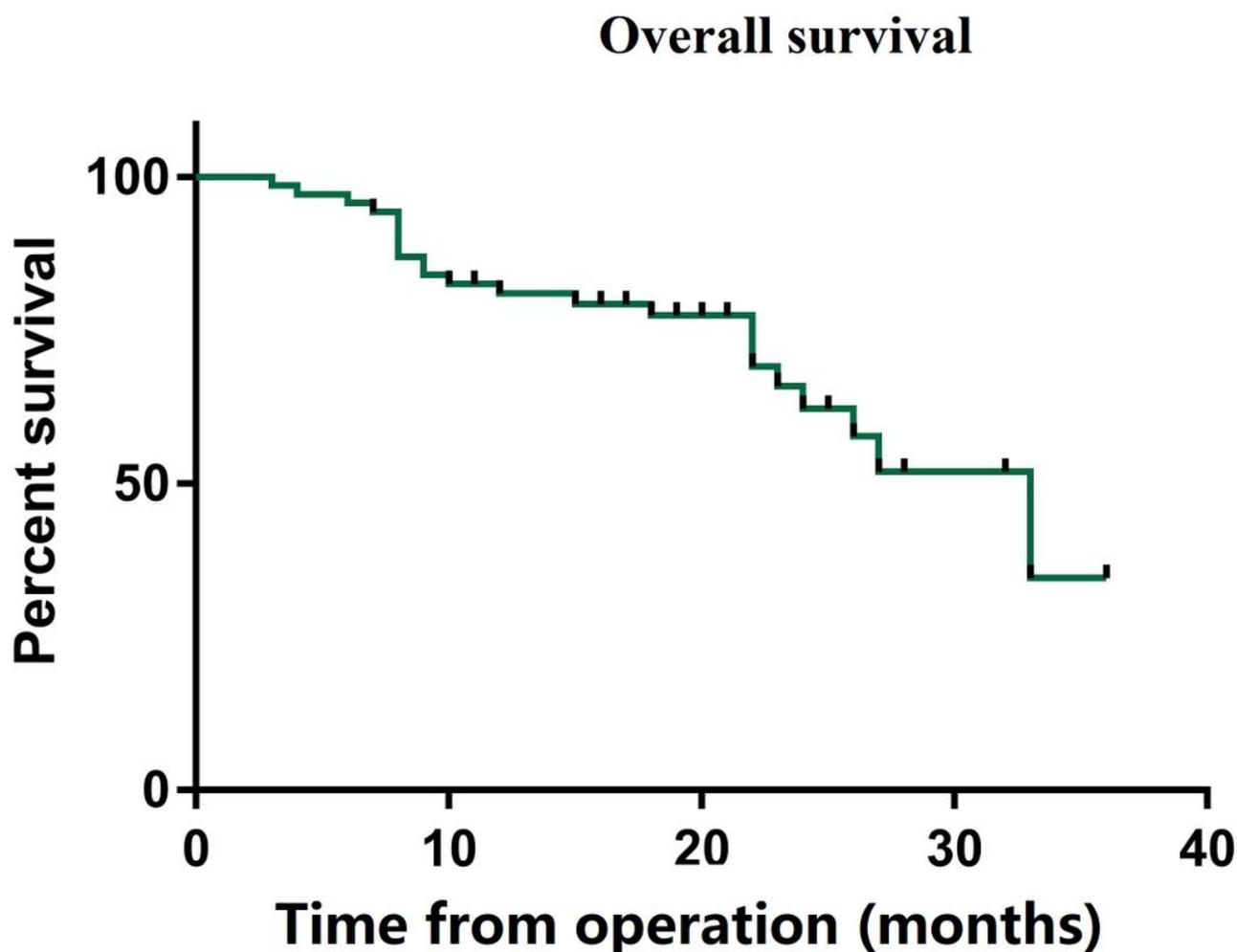


Figure 1

Overall survival of the entire cohort

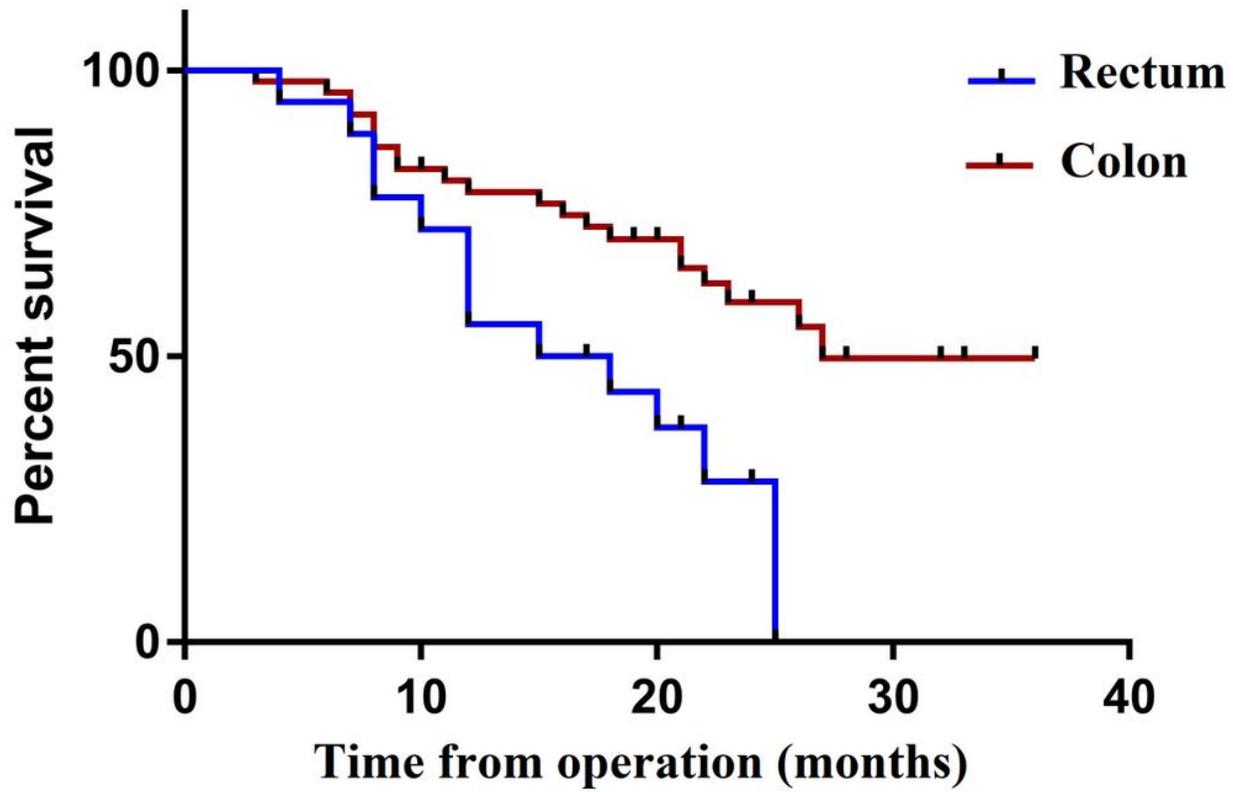


Figure 2

The median OS for those with colon cancer vs those with rectal cancer.

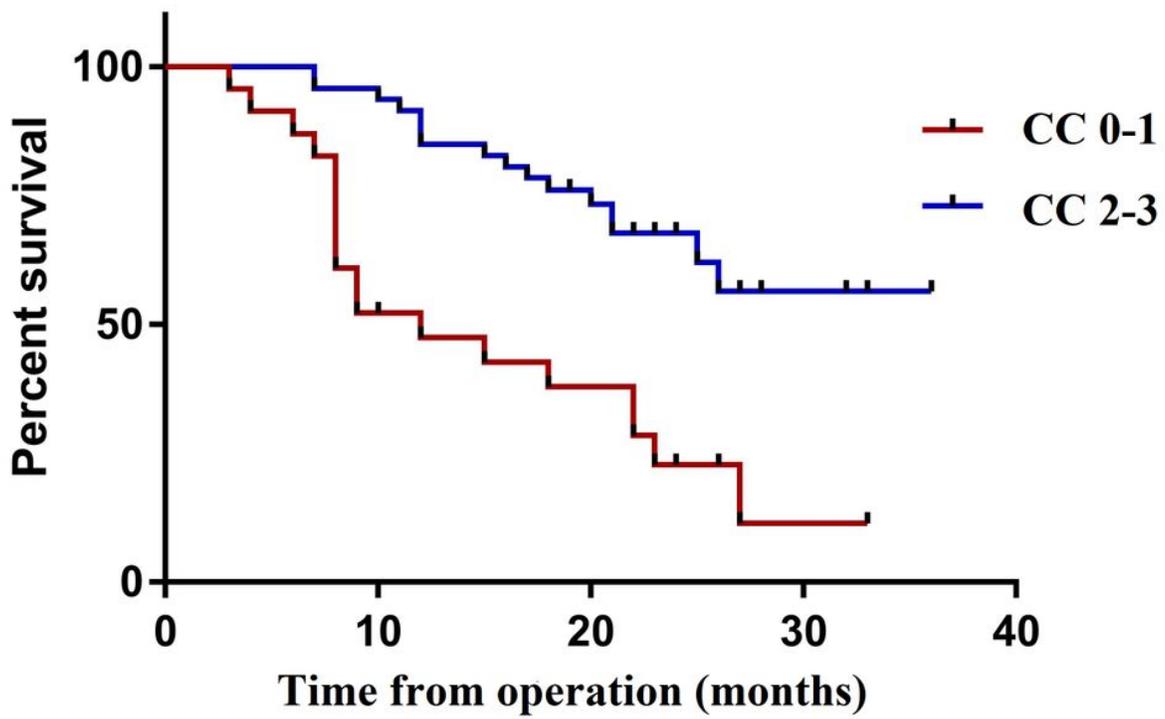


Figure 3

The median OS from CRS+HIPEC in patients undergoing incomplete cytoreduction vs complete cytoreduction.