Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Younger Patients with Peritoneal Metastasis from Colorectal Cancer

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Research

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Abstract

Background Currently, few studies have evaluated effectiveness of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in young patients with peritoneal metastasis (PM) of colorectal cancer (CRC) origin.

Method Clinicopathological characteristics, perioperative data and survival outcomes in young patients, defined as being 50 years or less (n=23), performing CRS+HIPEC between June 2017 to June 2019 were reviewed and compared with older patients, defined as aged over 50 years (n=47).

Results Compared with older patients, young patients were more likely to present with PM at the time of diagnosis (78.3% vs 51.1%, $P=0.029$) and exhibit a mucinous and signet-ring histology (60.9% vs 29.8%, $P=0.013$). The cancer-specific survival (CSS) after CRS+HIPEC in two groups are similar. On multivariate Cox regression, rectal origin (HR, 2.51, 95%CI, 1.11-5.67; $P=0.027$) and mucinous/signet adenocarcinoma (HR, 2.20, 95%CI, 1.02-4.74; $P=0.044$) were independent risk factors for poor CSS.

Conclusion Younger patients (aged ≤ 50 years) with PM of CRC origin presented more often with synchronous PM than older patients. Although tend to exhibit a aggressive nature, they derive similar benefit from CRS+HIPEC as older patients.

Introduction

Colorectal cancer (CRC) is the third most common malignant tumor in the world, with approximately 1.8 million newly diagnosed cases in 2018^[1]. The prevalence of colonoscopy and improved awareness of cancer prevention have led to a decline in the overall incidence of colorectal cancer, while the incidence in young patients has increased by about 2% per year over the past decade^[2-4]. Recently, an epidemiological study found that the incidence of CRC only increased in young adults (20-49 years) based on populations in nine high-income countries across three continents^[5]. Meanwhile, compared with the elderly, more patients with young-onset CRC presented with distant metastases at the time of diagnosis, due to different biological behavior and lower suspicion of CRC^[6, 7]. Currently, the prognosis of young-onset CRC patients remains controversial^[8-10].

The peritoneum metastasis (PM) is the third most common site of colorectal cancer metastasis following liver metastasis and lung metastasis, and is generally considered as end-stage disease. Synchronous PM has been reported in 8–15% of patients with CRC, while the rate of metachronous PM can reach 20–50%^[11]. For CRC patients with PM, traditional methods usually adopt palliative surgery and systemic chemotherapy, and the median survival time is only 5-7 months^[12]. In recent years, Cytoreductive Surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown good clinical efficacy in the comprehensive treatment of various malignant peritoneal diseases, and can prolong the long-term survival in appropriately specific CRS patients^[13, 14]. However, as a special population, young-onset CRC patients have unique molecular profile and aggressive nature, and whether they can also

benefit from CRS+HIPEC is currently rarely reported in the literature^[15–18]. Therefore, the purpose of this study was to investigate the clinicopathological characteristics of young-onset CRC patients(≤ 50 years) with PM, and to evaluate the long-term therapeutic effect of CRS+HIPEC.

Patients And Method

This study was a single-center retrospective study, with patients characteristics obtained from a prospectively collected database. From June 2017 to June 2019, all consecutive CRC patients presenting PM who had performed CRS and HIPEC at the National Cancer Center were enrolled in this study after the approval of our institutional multidisciplinary review committee. The inclusion criteria are as follows: (1) Age 18-75 years old; (2) Pathologically confirmed as colorectal adenocarcinoma; (3) Eastern Cooperative Group (ECOG) score ≤ 1 . The exclusion criteria were as follows: (1) Presented with liver and lung and other distant metastases;(2) History of other malignant tumors; (3) Malignant tumor of appendiceal origin.

All patients were grouped according to age at the time of diagnosis of CRC, and two cohorts were created: ≤ 50 years and 51-75 years. All patients underwent preoperative workup to rule out extra-abdominal disease, including laboratory examinations, abdominal contrast-enhanced computed tomography (CT), and pelvic magnetic resonance imaging (MRI). The final comprehensive treatment strategy was made by multidisciplinary team that incorporated radiologists and medical and surgical oncologists. According to the Sugarbaker/Jacquet classification^[19, 20], the extent of PM was assessed using the peritoneal cancer index (PCI) and the completeness of CRS was evaluated by the completeness of cytoreduction score (CC score).

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.

Surgical Procedure

The surgical technique of CRS+HIPEC has been described previously^[21, 22]. Brief, various peritonectomy was selected depending on the the location of the PM, and intraperitoneal organ resection was performed according to the degree of tumor invasion. After cytoreduction, a closed HIPEC procedure was carried out with two chemotherapeutic regimens in present study: Oxaliplatin (200 mg/m²) and raltitrexed (4 mg/m²) with or without lobaplatin (50 mg/m²). A mixed solution of chemotherapy agents and 3 L of saline solution was infused in peritoneal cavity for 60 min at 43°C. After that, two more same HIPEC procedures were carried out again on the second and fourth days after surgery in the ward.

Statistical analysis

Data were compared and analyzed using SPSS 24.0 software (IBM, Armonk, NY, USA). Categorical variables were expressed as percentages frequencies and compared by the χ^2 test or Fisher's exact test as appropriate. Continuous variables were expressed as the mean $\pm$ standard deviation and using Student's t-test or the Mann-Whitney U test. Overall survival (OS) was calculated as the time from the first CRS+HIPEC to death due to tumor or July 31, 2020, whichever came first. Disease-free survival (DFS) refers to the time from CRS+HIPEC to appearance of obvious evidence of recurrence. The survival analysis was performed by Kaplan-Meier methods and compared by log-rank test. Variables yielded a *P* value <0.05 in the univariate analysis were further included into the multivariate analysis to identify independent predictors of OS and DFS. A *P* value < 0.05 was considered statistically significant.

Results

A total of 70 patients who performed CRS+HIPEC for PM of CRC origin were included in present study, 23 of whom were ≤ 50 years old. The clinicopathological characteristics are listed in Table 1. There are 39 males and 31 females in the whole group, with an average age of 54.5 ± 11.6 years. The proportion of younger patients complicated with peritoneal metastasis at the initial diagnosis of colon cancer is significantly higher (78.3% vs 51.1%, $P=0.029$). Notably, a higher proportion of younger patients pathologically confirmed mucinous/signet adenocarcinoma (60.9% vs 29.8%, $P=0.013$). Comparison of other clinical characteristics, such as BMI, preoperative chemotherapy, site of original, adjuvant chemotherapy, BRAF status, MSI, were all similar ($P>0.05$).

Table 1
The clinicopathological characteristics of 70 patients underwent CRS/HIPEC

Variables	Total (n=70)	Aged ≤ 50 years (n=23)	Aged > 50 years (n=47)	<i>P</i>
Age (years, mean±SD)	54.5 ± 11.6	40.9 ± 6.9	61.2 ± 6.7	<0.001
Gender				0.677
Male	39 (55.7)	12 (52.2)	27 (57.4)	
Female	31 (44.3)	11 (47.8)	20 (42.6)	
BMI (Kg/m ²)	22.7 ± 3.6	22.4 ± 2.4	23.1 ± 2.8	0.432
Preoperative chemotherapy				0.557
Presence	30 (42.9)	11 (47.8)	19 (40.4)	
Absence	40 (57.1)	12 (52.2)	28 (59.6)	
Presentation of PM				0.029
Synchronous	42 (60.0)	18 (78.3)	24 (51.1)	
Metachronous	28 (40.0)	5 (21.7)	23 (48.9)	
Site of original (%)				0.527
Colon	52 (74.3)	16 (69.6)	36 (76.6)	
Rectum	18 (25.7)	7 (30.4)	11 (23.4)	
Preoperative CEA level (ng, mean ± SD)	31.9 ± 61.5	36.9 ± 71.6	31.6 ± 61.7	0.782
Preoperative CA19-9 level (ng, mean ± SD)	75.4 ± 93.3	90.1 ± 106.6	70.1 ± 92.3	0.491
Histology (%)				0.013
Adenocarcinoma	43 (61.4)	9 (39.1)	33 (70.2)	
Mucinous/signet	27 (38.6)	14 (60.9)	14 (29.8)	
Adjuvant chemotherapy				0.232
Presence	55 (78.6)	20 (87.0)	35 (74.4)	
Absence	15 (21.4)	3 (13.0)	12 (25.6)	
BRAF status				0.859
Mutation	13 (18.6)	4 (17.4)	9 (19.1)	

Variables	Total (n=70)	Aged ≤ 50 years (n=23)	Aged > 50 years (n=47)	<i>P</i>
No mutation	57 (81.4)	19 (82.6)	38 (80.8)	
MSI				0.615
MSI-H	8 (11.4)	2 (8.7)	6 (12.8)	
MSS	62 (88.6)	21 (91.3)	41 (87.2)	

The perioperative data are presented in Table 2. The mean PCI score was 11.1 ± 6.0 for young patients and 11.8 ± 6.5 for older patients ($P=0.536$). The proportion of patients who achieved complete cytoreductive surgery (CC 0-1) was comparable in both groups (69.6% vs 68.1%, $P=0.900$). Mean number of organs resection also were similar (2.2 vs. 1.9, $P=0.401$). Following the operation and within 30 days, 8 patients (34.8%) developed postoperative complications in age ≤ 50 group, and 17 (36.2%) in age 51-65 group ($P=0.909$). Comparison of other perioperative indicators, such as operation time, estimated blood loss, postoperative complication rates (grade 3-4), and total hospital days, were all similar ($P>0.05$).

Table 2
The perioperative data of 70 patients underwent CRS/HIPEC

Variables	Total (n=70)	Aged ≤ 50 years (n=23)	Aged > 50 years (n=47)	<i>P</i>
Operative method				0.799
Laparoscopic surgery	14 (20.0)	5 (21.7)	9 (19.1)	
Open surgery	56 (80.0)	18 (78.3)	38 (80.9)	
HIPEC regimen				
Lobaplatin+Oxaliplatin+Raltitrexed	32 (45.7)	12 (52.2)	20 (42.6)	
Oxaliplatin+Raltitrexed	38 (54.3)	11 (47.8)	27 (57.4)	
PCI score	11.1 ± 6.0	11.8 ± 6.5	11.0 ± 5.4	0.536
Operation time (min, mean ± SD)	256.9 ± 66.4	261.5 ± 68.7	255.9 ± 66.2	0.450
Estimated blood loss (ml, mean ± SD)	122.1 ± 109.2	109.1 ± 101.9	127.2 ± 104.7	0.516
Presence of ascites	30 (42.9)	8 (34.8)	22 (46.8)	0.340
CC score				0.900
CC 0-1	48 (68.6)	16 (69.6)	32 (68.1)	
CC 2-3	22 (31.4)	7 (30.4)	15 (31.9)	
Number of organs resection	2.0 ± 1.1	2.2 ± 1.2	1.9 ± 1.1	0.401
Postoperative Complications (grade 1-4)	25 (35.7)	8 (34.8)	17 (36.2)	0.909
Postoperative Complications (grade 3-4)	17 (24.3)	5 (21.7)	12 (25.5)	0.728
Total hospital stay (day, mean ± SD)	14.6 ± 5.3	14.4 ± 5.2	15.1 ± 5.4	0.220
Re-operation	2 (2.9)	0 (0)	2 (4.3)	0.810
Mortality	0 (0)	0 (0)	0 (0)	1.000

Survival Analyses

The median follow-up period was 21.0 (range, 3-33) months. The median CCS since diagnosis were 26.0 months (95% CI, 20.7–31.3 months). The estimated 1-, 2- and 3-year CCS rates for the entire cohort were

81.3%, 58.0%, and 42.9%, respectively. CCS of patients aged ≤ 50 years who underwent CRS+HIPEC treated for PM of CRC origin are similar to those of patients aged 51-65 years (Figure 1).

On the Cox univariate regression analysis, factors found to be associated with reduced CCS were increasing PCI (HR 1.08, 95% CI 1.03–1.14, $P = 0.004$), rectal origin (HR 2.58, 95% CI 1.24-5.37, $P = 0.011$), mucinous (HR 2.13, 95% CI 1.05-4.33, $P = 0.036$), and incomplete cytoreduction (HR 2.99, 95% CI 1.47-6.10, $P = 0.003$). On multivariate Cox regression, rectal origin (HR, 2.51, 95%CI, 1.11-5.67; $P=0.027$) and mucinous/signet adenocarcinoma (HR, 2.20, 95%CI, 1.02-4.74; $P=0.044$) were independent risk factors for poor DFS (Table 3).

Table 3
Univariate and multivariate Cox regression analysis of cancer-specific survival and disease-free survival in 70 patients after CRS/HIPEC

Variables	Cancer-specific survival			
	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P	HR(95%CI)	P
Gender: male/female	1.20 (0.59-2.44)	0.606		
Age (50-65 years/ ≤ 50 years)	1.53 (0.70-3.33)	0.284		
Preoperative chemotherapy (no/yes)	0.53 (0.20-1.38)	0.191		
Synchronous/metachronous	1.03 (0.51-2.08)	0.942		
Site of original (rectum/colon)	2.58 (1.24-5.37)	0.011	2.51 (1.11-5.67)	0.027
Histology (adenocarcinoma/mucinous)	2.13 (1.05-4.33)	0.036	2.20 (1.02-4.74)	0.044
Preoperative CEA level	1.00 (0.99-1.01)	0.281		
Preoperative CA19-9 level	1.00 (0.99-1.01)	0.232		
HIPEC regimen (lobaplatin/non-lobaplatin)	1.50 (0.73-3.06)	0.268		
Presence of ascites (yes/no)	1.53 (0.75-3.10)	0.241		
PCI score	1.08 (1.03-1.14)	0.004	1.03 (0.96-1.11)	0.349
CC score (0-1/2-3)	2.99 (1.47-6.10)	0.003	1.73 (0.70-4.27)	0.231
Grade 3-4 Postoperative complication	1.11 (0.50-2.49)	0.801		

Discussion

Three consecutive years of tumor epidemiological data in the United States show that the overall incidence of CRC is on the decline, but an rising incidence of young-onset CRC was noted^[2–4]. Due to different biological behavior and lower suspicion of CRC, young patients are more often present

advanced stage at diagnosis^[6, 7]. In present study, we found that more young-onset patients present with PM at the initial diagnosis, while older patients more likely develop metachronous PC. This finding is mainly attributed to the lack of sufficient health care awareness and lower suspicion of CRC in younger age group. A cohort study in the United States found that the median time from the onset of symptoms to treatment for rectal patients younger than 50 years old was significantly longer than that of patients older than 50 years old (217 vs 29.5 days)^[23]. Therefore, it is necessary to universally recommend screening for patient aged < 50 years who was at elevated risk of CRC because of high risk personal and family history.

Different molecular changes contribute to the heterogeneity of young-onset CRC, which often exhibit more aggressive nature compared with late-onset CRC^[25]. National Cancer Database showed that young-onset patients are typically associated with poor pathological features such as mucinous and signet ring carcinoma. Our study also showed that patients in younger age group more likely present mucinous/signet adenocarcinoma (60.9% vs 29.8%, $P=0.013$).

Few studies have been reported on the survival outcomes of CRS/HIPEC in treatment for PM of CRC origin in younger patients^[18, 27]. Young patients tend to have strong aggressive biological profile due to a higher incidence of signet ring cells and mucinous adenocarcinoma, and they more likely presented with advanced stage at the time of diagnosis, so in theory they tend to have a poor prognosis. However, our study demonstrated that OS and DFS of patients aged ≤ 50 years who underwent CRS+HIPEC treated for PM of CRC origin are similar to those of patients aged over 50 years. Multivariate analysis showed that rectal origin (HR, 2.51, 95%CI, 1.11-5.67; $P=0.027$) and mucinous/signet adenocarcinoma (HR, 2.20, 95%CI, 1.02-4.74; $P=0.044$) were independent risk factors for poor CCS. A subgroup analysis of 237 patients with CRC conducted by Dhir and colleagues revealed that 37 patients aged 15-39 years underwent CRS+HIPEC, and no difference in median survival was found compared with the older controls (28.7 vs 38.9 months, $P=0.509$)^[18], which is basically consistent with our results. CRS+HIPEC is a life-threatening procedure, and the incidence of postoperative complications in older patients is higher, which affects subsequent treatment. In addition, younger patients tend to receive more radical treatments. The above-mentioned reasons may be responsible for similar long-term survival. However, Solomon et al. analyzed the survival outcomes of 98 patients with PM of CRC origin in different ages (<50 years or ≥ 50 years) after CRS+HIPEC, their results showed that patients <50 years survived significantly longer than older controls, both from time of initial diagnosis and from CRS/HIPEC. The reason for the different results may be that patients over 65 years old were not included in this study, because the proportion of elderly patients over 65 years old was relatively low, and such patients have more organic diseases. Relevant literature reported that patients with PM of CRC origin over 65 years old benefited less from CRS+HIPEC^[28].

There were several limitations in this study. The present study is a retrospective analysis of only 70 patients from a single center database, retrospective cohort design and relatively small numbers potentially generating selection bias. However, we believe our results are reliable and data collection was complete. Multi-center large sample studies are required to further verify our conclusions.

In conclusion, younger patients (aged ≤ 50 years) with PM of CRC origin presented more often with synchronous PM than older patients (aged over 50 years). Although tend to exhibit a aggressive nature, they derive similar benefit from CRS+HIPEC as older patients. There should be a raise in awareness of the young-onset CRC, especially for those with high risk personal and family history.

Declarations

Ethics approval

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 to participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and materials

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: JPX, SCZ, and WP; (II) administrative support: JPX and XSW and JWL; (III) provision of study materials or patients: YJJ and ZXZ and QL and ZL ; (IV) collection and assembly of data: SCZ and HPC; (V) data analysis and interpretation: SCZ and HPC. All authors read and approved the final manuscript.

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Figures

Figure 1

CCS of patients aged ≤ 50 years who underwent CRS+HIPEC treated for PM of CRC vs those of patients aged over 50 years