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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Andrea Cavallaro, MD, PhD, Doctor, Research Assistant Professor, Researcher, Department of Surgery and Medical Surgical Specialties, University of Catania, Catania 95123, Italy. andreacavallaro@tiscali.it

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ORIGINAL ARTICLE

Observational Study

Analysis of therapeutic effect of cell reduction combined with intraperitoneal thermoperfusion chemotherapy in treatment of peritoneal pseudomyxoma

Wei-Wei Li, Xiu-Mei Ru, Hong-Yan Xuan, Qi Fan, Jing-Jing Zhang, Jun Lu

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Wei-Wei Li, Xiu-Mei Ru, Hong-Yan Xuan, Jun Lu, Department of Endocrinology, The Second Affiliated Hospital of Soochow University, Suzhou 215004, Jiangsu Province, China

Qi Fan, Jing-Jing Zhang, Department of Anus and Intestine Surgery, Xiangya Hospital of Central South University, Changsha 410008, Hunan Province, China

Corresponding author: Jun Lu, Doctor, Department of Endocrinology, The Second Affiliated Hospital of Soochow University, No. 1055 Sanxiang Road, Suzhou 215004, Jiangsu Province, China. lujun.198404@163.com

Abstract

BACKGROUND

Pseudomyxoma peritonei is a rare tumor that can produce a biological behavior similar to that of a malignant tumor. Surgical resection combined with chemotherapy is the traditional treatment method, but the effect is not good. Cell reduction (CRS) combined with intraperitoneal thermoperfusion chemotherapy (HIPEC) has become a new method for the treatment of peritoneal pseudomyxoma (PMP).

AIM

To find out if CRS and HIPEC can be used safely and effectively to treat PMP.

METHODS

This is an observational study. Clinical data of PMP patients treated with CRS + HIPEC at our hospital from January 2013 to June 2023 was collated and analyzed. The main outcome measures were overall survival (OS), and the secondary outcome measures were the incidence of surgical complications and serious adverse events. Complications were graded according to common adverse event evaluation criteria. Peritoneal tumor staging was performed using the peritoneal tumor index (PCI) scoring system, and a cell reduction degree (CCR) score was performed after CRS. CCR-0 and CCR-1 were considered satisfactory CRS.

RESULTS

A total of 186 patients with PMP were included, with a median age of 56 (48-64) years, 65 (34.9%) years in males, and 121 (65.1%) years in females. The median PCI score was 28 (20-34) points. The median operative time was 300 (211-430) minutes,

and no significant complications occurred. 91.4% (170/186) were from the appendix, 53.2% (99/186) were from the low grade, and 30.6% (57/186) were from the high grade. CCR scores showed that 55 patients (29.6%) achieved satisfactory CRS, and 113 patients (60.8%) did not achieve satisfactory CRS. The fatality rate at 30 days after surgery was 2.7% (5/186), 1.6% (3/186) needed a second operation, and the fatality rate at 90 days was 4.3% (8/186). The total incidence of III-IV complications was 43.0% (80/186), among which the higher incidence was mainly anemia (27.4%, 51/186), electrolyte disturbance (11.6%, 21/181), and albumin decrease (7.5%, 14/186). The main complications associated with abdominal surgery were gastrointestinal anastomotic leakage (2.2%, 4/186), abdominal hemorrhage (2.2%, 4/186), and abdominal infection (4.3%, 8/186). The median follow-up was 38.1 (95%CI: 31.2-45.1) months. The 5-year OS of PMP patients treated with CRS + HIPEC was 50.3% (95%CI: 40.7%-59.9%), and the median survival time was 66.1 (95%CI: 43.1-89.1) months. The results of the survival analysis showed that patients with a low pathological grade, a low PCI, and a satisfactory CCR score had a higher survival rate (all $P < 0.05$). 5-year OS was 88.9% (95%CI: 68.3%-100.0%) in CCR-0 patients, 77.6% (95%CI: 62.7%-92.5%) in CCR-1 patients, and 42.0% (95%CI: 29.5%-54.5%) in CCR-2/3 patients.

CONCLUSION

The application of CRS + HIPEC in PMP is safe and feasible, and the survival benefit is high, especially in those who achieve satisfactory CRS, which can significantly extend the OS.

Key Words: Peritoneal pseudomyxoma; Cell reduction; Intraperitoneal thermoperfusion chemotherapy; Survival prognosis; Observational study

Core Tip: This study analyzed the efficacy of cell reduction combined with intraperitoneal thermoperfusion chemotherapy in the treatment of peritoneal pseudomyxoma (PMP). We will observe and study this treatment method, compare its efficacy with traditional chemotherapy methods, and explore the possible mechanism of action and adverse reactions of this method. This study will provide new ideas and methods for the treatment of PMP.

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INTRODUCTION

Due to the rupture of mucin-secreting tumors, peritoneal pseudomyxoma (PMP) primarily results from the accumulation and redistribution of a significant amount of gelatinous ascites in the abdominal cavity[1-3]. PMP is a low-grade malignant myxoid tumor occurring in the parietal peritoneum, the omentum, and the serous membrane of the intestinal wall, about 90% of which originate from the appendix[4]. PMP is a rare clinical disease with an annual incidence of 2 to 3 in 1 million. Recent PMP epidemiological data from China's national database show that the crude prevalence of PMP is 2.47/1 million people/year, and the prevalence of women is higher than that of men[5]. The crude incidence of PMP was 1.19/1 million people/year, and the incidence of PMP was higher in females than in males[6-8]. The incidence increased with age, and the incidence was highest in people over 80 years old. The pathogenesis of this disease has not been fully defined, and it is mostly secondary lesions formed by the diffusion and metastasis of mucinous tumors from abdominal and pelvic organs to the peritoneum, that is, the so-called "tumor redistribution phenomenon[9]. In the early stages of the disease, which may be found incidentally at the time of appendectomy, it occurs in less than 1% of appendectomy cases [10]. However, once the tumor ruptures, PMP is easy to occur. In the late stage, PMP is usually caused by tumor perforation and extensive planting of tumor cells in the peritoneal cavity, which can manifest as abdominal pain, abdominal distension, ascites, intestinal obstruction, massive abdominal mass, and cachexia[11]. Patients with this disease live longer than those with other malignant tumors, but they are prone to recurrence after surgery and often require multiple surgeries to alleviate symptoms[12].

For a long time, the international understanding of PMP has been insufficient, and it is often misdiagnosed or missed in clinic. The treatment is mostly limited to repeated surgery or palliative chemotherapy, and the overall effect is not good[13]. In the 1980s, Cases of cell reduction (CRS) combined with intraperitoneal thermoperfusion chemotherapy (HIPEC) in the treatment of PMP patients and then gradually developed a comprehensive treatment strategy for PMP with CRS + HIPEC as the core[14-16].

Through retrospective and observational analysis of the clinical data of PMP patients treated with CRS combined with HIPEC in Xiangya Hospital of Central South University, this study aims to evaluate the safety and effectiveness of CRS combined with HIPEC in the treatment of PMP and summarize the experience in the diagnosis and treatment of PMP in

our center.

MATERIALS AND METHODS

Research object

This is an observational study. Inclusion criteria: (1) Non-pregnant lactating women aged 18-75 years; (2) PMP patients were confirmed by pathology; (3) Karnofsky Performance Status score > 70; (4) The function of the heart, liver, lung, kidney, and other major organs can withstand long-term major surgery; and (5) There were no signs of distant or extraperitoneal metastasis before surgery. Exclusion criteria: (1) Patients with extensive abdominal adhesions before surgery who could not tolerate surgery; and (2) Serious infectious diseases, especially severe abdominal infection.

According to the above criteria, 186 PMP patients treated with CRS + HIPEC were retrospectively collected from January 2013 to June 2023 in the Xiangya Hospital of Central South University. The median age was 56 (48-64) years. There were 65 males (34.9%) and 121 females (65.1%). This study was approved by the Ethics Committee of the hospital (Approval Number: GYZL-ZN-2023-029), and the confidentiality principle was strictly implemented during the research process to protect the privacy of each subject.

Treatment plan

CRS surgery: The median abdominal incision is made, from the xiphoid process up to the pubic symphysis down. CRS can remove the gross visible tumor in the abdominal cavity as completely as possible, reduce the tumor load, including the affected organs, tissues, peritoneum, and lymph nodes in related areas, and strive to reduce the maximum diameter of the residual tumor to less than 0.25 cm. Before CRS, the peritoneal cavity should be fully explored, and the peritoneal tumor index (PCI) should be thoroughly evaluated and recorded in detail. According to the residual lesions in the abdominal cavity after CRS, a satisfactory CRS was determined.

HIPEC treatment: Closed HIPEC treatment was performed after CRS surgery, and 1 special HIPEC treatment pipe was placed in each of the 4 quadrants of the abdominal cavity and then connected to the body cavity thermal perfusion treatment equipment through the pipe. In this study, a BR-TRG-I/II type body cavity thermoperfusion therapy instrument (Guangzhou Baorui Medical Co., Ltd.) was used for HIPEC treatment. The flow rate was set at 400-600 mL/min, the volume of the perfusion solution was 2 L/m^2, the duration was 60-90 minutes. The main drugs used for HIPEC were rhatitrexer, oxaliplatin, and mitomycin, and the interval was > 24 hours for multiple HIPEC treatments.

Observation indicators and evaluation criteria

The main evaluation measure was overall survival (OS), which was defined as the time from the beginning of CRS surgery to the patient's death or last follow-up. Current survival and loss were defined as deleted data. Secondary evaluation measures were the incidence of surgical complications and serious adverse events. The evaluation of surgical complications included digestive, cardiovascular, respiratory, infectious diseases, hematological, and other adverse events, graded according to common adverse event evaluation criteria (CTCAE 5.0).

The staging of peritoneal tumors was performed by the PCI scoring system

The scoring system divided the abdomen into 13 regions: Divided into 9 regions (0-8) by the lowest level of the lateral costal arch, the highest level of the anterior superior iliac spine, and the bilateral midclavicular line, namely: Left and right upper abdomen, upper abdomen, left and right lumbar region, central region, left and right iliac fossa, and pelvic floor. The small intestine was divided into 4 regions (9-12), namely, the upper and lower jejunum segments, and the upper and lower ileum segments, with a total of 13 regions. The lesion size (LS) of each region was scored. The sum of LS scores in each area is the PCI score, and the total score ranges from 0 to 39 points. LS scoring criteria for tumors in each area: (1) No visible tumors: 0 points; (2) Tumor diameter < 0.5cm: 1 point; (3) Tumor diameter 0.5-5.0 cm: 2 points; and (4) Tumor diameter > 5.0 cm or tumor fusion: 3 points.

A cell reduction degree score was performed after CRS

The specific scoring rules are: (1) Cell reduction degree (CCR)-0 score: No tumor nodules were visible to the naked eye after surgery; (2) CCR-1 score: Residual tumor diameter < 0.25 cm; (3) CCR-2 score: Residual tumor diameter 0.25-2.5 cm; and (4) CCR-3 score: Residual tumor > 2.5 cm in diameter or unresectable lesions in any part of the abdomen. CCR-0 and CCR-1 are considered satisfactory CRSs.

Follow-up method

It is completed by the center through regular outpatient service, hospitalization, telephone, and information. The follow-up included survival, physical examination, tumor markers, imaging examination, and routine laboratory examination. Review once every 3 months for the first 2 years, once every 6 months after 2 to 5 years, and once every 5 years after 5 years. The follow-up will be completed in September 2023.

Statistical analysis

SPSS 26.0 statistical software was used for analysis. Measurement data that did not follow a normal distribution were represented by M (Q1, Q3), and counting data were represented by example (%). Statistical data were analyzed by the χ^2

test or Fisher exact probability method. The Kaplan-Meier method was used to estimate the survival curve, and the log-rank test was used to compare the survival rate between groups. Test level $\alpha = 0.05$, $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

All patients successfully completed the CRS + HIPEC treatment analysis

The median PCI score was 28 (20-34). The median operative time was 300 (211-430) minutes, and no significant complications were observed. The median first exhaustion time after surgery was 5 (3-6) days. There were 170 cases (91.4%) of appendix origin, 99 cases (53.2%) of low grade, and 57 cases (30.6%) of high grade. CCR scores showed that 55 patients (29.6%) achieved satisfactory CRS, and 113 patients (60.8%) did not achieve satisfactory CRS (Table 1).

The occurrence of adverse events

The incidence of postoperative adverse events is shown in Table 2. The fatality rate at 30 days after surgery was 2.7%, the incidence of secondary surgery was 1.6%, and the fatality rate at 90 days was 4.3%. The total incidence of III-IV complications was 43.0%, among which the high incidence was mainly anemia (27.4%), electrolyte disturbance (11.6%), and albumin decrease (7.5%). The main complications associated with abdominal surgery were gastrointestinal anastomotic leakage (2.2%), abdominal hemorrhage (2.2%), and abdominal infection (4.3%). No other serious treatment-related complications occurred. Further analysis showed that patients who underwent combined organ resection had a higher incidence of grade III-IV complications, as shown in Table 3.

Survival time analysis

The median follow-up was 38.1 (95%CI: 31.2 to 45.1) months. The OS of PMP patients who received CRS + HIPEC was 50.3% (95%CI: 40.7%-59.9%) at 5 years after surgery, as shown in Figure 1A. The median survival time was 66.1 (95%CI: 43.1-89.1) months. The results of the survival analysis showed that the survival rate was higher in patients with low pathologic grade and low PCI and CCR scores ranging from 0 to 1, and the difference was statistically significant (all $P < 0.05$) (Table 4; Figure 1B-D).

DISCUSSION

The treatment concept of CRS combined with HIPEC as a treatment strategy for peritoneal implantation and the spread of gastrointestinal and gynecological malignancies was first promoted and gradually popularized by Sugarbaker in the 1990s[17]. A large number of studies[18-20] have confirmed that HIPEC can significantly improve the long-term survival rate of patients with peritoneal cancers such as gastric cancer, colorectal cancer, ovarian cancer, and malignant mesothelioma. PMP is most commonly seen in intra-abdominal mucinous appendix tumor rupture, and despite the lack of prospective, multicenter, large-sample randomized controlled clinical study evidence, the combination treatment regimen of CRS + HIPEC has been considered the standard treatment for PMP[21]. However, due to its very low incidence, international studies on the safety and long-term efficacy of CRS + HIPEC in the treatment of PMP are relatively insufficient[22].

In this study, the median survival time of 186 PMP patients after CRS + HIPEC treatment was 66.1 months, and 5-year OS was 50.3%, which was consistent with previous studies and lower than the 57.8%-78.0% reported in bulk studies[23-25]. This may be related to the high tumor burden in Chinese patients (Median PCI of patients in this study was 28 points) and the lack of standard diagnosis and treatment in the past. In terms of safety, the 30-day perioperative mortality of patients was 2.7%, the incidence of secondary surgery was 1.6%, and the incidence of III-IV complications was 43.0% [26]. The high incidence of II-IV complications was mainly hematological adverse events, and the incidence of major surgical complications such as anastomotic leakage, abdominal infection, and hemorrhage was low. The incidence of grade III-IV complications was higher in patients undergoing combined organ resection, and the overall perioperative safety was acceptable[27]. The results of the survival analysis showed that the PCI score, CCR score, and pathological grade of patients were still significantly correlated with long-term survival.

New studies[28-30] show that when CRS is combined with HIPEC, it improves survival rates in people with appendicide-derived PMP. At 5 and 10 years after surgery, survival rates are 69% to 74% and 54% to 63%, respectively. Surgical complications of CRS combined with HIPEC have long been a concern for surgeons. Our study[31] shows that the CRS + HIPEC treatment strategy is not associated with the risk of patients with grade III to IV complications, does not lead to higher complication rates and mortality compared with traditional surgery, and the safety of this treatment regimen is within the acceptable range. As for the short-term perioperative safety assessment, the relevant studies showed that the postoperative mortality rate of 298 PMP patients was 2%, and 24% of patients had major surgical complications of grade III to IV, of which 12% were grade III complications and 10% were grade IV complications. Another study reported the results of 1924 PMP studies, with a mortality rate of 4.2% at 90 days and 2.1% at 30 days, a rate of 9.3% after secondary surgery, and an overall serious adverse reaction rate of 32.0%. One study[32] looked at the clinical features of 1,000 cases of appendiceal epithelial tumors. It found that the 30-day mortality rate was 0.8% in the group with satisfactory CRS and that 15.2% of people who had grade III-IV surgery had complications. In the non-satisfactory operation group, the 30-day postoperative mortality and the incidence of III-IV surgical complications were

Table 1 Status of 186 cases of pseudomyxoma of abdominal cavity treated by cell reduction combined with intraperitoneal hyperthermic chemotherapy, *n* (%)

Variable	Number of cases
Primary site	
Appendix	170 (91.4)
Ovary	15 (8.1)
Location	1 (0.5)
Pathological type	
Low-level	99 (53.2)
High level	57 (30.6)
Not quite clear	30 (16.1)
Lymph node metastasis	
Correct	19 (10.2)
Deny	151 (81.2)
Suspicious transfer	16 (8.6)
Meningeal tumor index score	
≤ 10	7 (3.8)
11-20	34 (18.3)
21-30	56 (30.1)
31-39	55 (29.6)
Not quite clear	34 (18.3)
CCR rating	
CCR-0	15 (8.1)
CCR-1	40 (21.5)
CCR-2/3	113 (60.8)
Not quite clear	18 (9.7)
Whether to combine organ resection	
Correct	123 (66.1)
Deny	63 (33.9)
HIPEC count	
1	30 (16.1)
2	48 (25.8)
3	79 (42.5)
4	25 (13.4)
5	4 (2.2)
HIPEC drugs	
Raltitrexed	47 (25.3)
Letotrexate + Oxaliplatin + Mitomycin	42 (22.6)
Platinum	32 (17.2)
Letotrexate + Oxaliplatin	25 (13.4)
Letotrexate + Mitomycin	20 (10.8)
Mitomycin	8 (4.3)
Oxaliplatin + Mitomycin	8 (4.3)

Other	4 (2.2)

HIPEC: Intraperitoneal hyperthermic chemotherapy; CCR: Cell reduction degree.

Table 2 186 patients with pseudomyxoma were treated with cell reduction combined with intraperitoneal hyperthermic chemotherapy

Incidence of complications	*n* (%)
Death 30 days after surgery	5 (2.7)
Death 90 days after surgery	8 (4.3)
Further surgery is required	3 (1.6)
Grade III-IN complications	80 (43.0)
Gastrointestinal anastomotic leakage	4 (2.2)
Urinary system complications (ureteral injury, urinary leakage, *etc.*)	1 (0.5)
Abdominal bleeding	4 (2.2)
Abdominal infection	8 (4.3)
Wound infection	2 (1.1)
Sepsis or sepsis	1 (0.5)
Urinary tract infection	1 (0.5)
Ascites	4 (2.2)
Pneumonia	10 (5.4
Pneumothorax	2 (1.1)
Cardiac insufficiency or heart failure	2 (1.1)
Renal insufficiency	1 (0.5)
Hepatic insufficiency	19 (10.2)
Septic shock	2 (1.1)
Hemorrhagic shock	2 (1.1)
Albumin reduction	14 (7.5)
Hemoglobin reduction	51 (27.4)
Thrombocytopenia	2 (1.1)
Electrolyte disturbance	21 (11.6)
Coagulopathy	11 (5.9)

1.7% and 14.5%, respectively[33-35].

PMP is a less aggressive disease, and although it is easy to relapse after surgery, almost all of the recurrence and progression of the disease occur in local areas of the abdominal cavity, and hematogenous metastasis is rare[36]. In addition, different from other peritoneal tumors, PMP patients can obtain a better prognosis through complete CRS even if the PCI score is high (31-39 points), and the thoroughness of CRS is an important factor affecting the prognosis of patients[37]. Our study showed that the 5-year OS of those who achieved satisfactory CRS was 79.5% (95%CI: 66.6%-92.4%), which was significantly better than that of CCR-2 and CCR-3[38]. However, patients with a large tumor load have a higher risk of postoperative complications, high surgical technical requirements, and a long surgical time. Therefore, the resectable tumor should be fully evaluated, and a detailed surgical plan should be formulated[39]. It is recommended that a multidisciplinary integrated diagnosis and treatment team discuss and make decisions before surgery or be referred to a specialized and experienced center for standardized diagnosis and treatment[40]. Surgery requires the removal of a large amount of "jelly-like" mucus, so standardized HIPEC treatment is essential after surgery[41]. The most recent RCT studies on HIPEC in colorectal cancer have been negative. However, the HIPEC scheme (30 minutes single drug once), HIPEC timing (5-8 weeks after surgery or 6 months after surgery), and other aspects have caused great controversy, and the conclusions drawn by the research have not been recognized by scholars at home and abroad[42]. It is recommended to adopt the accurate and standardized HIPEC treatment plan recommended in China (high precision temperature control, large capacity filling, time 60-90 minutes, frequency 3-5 times)[43,44].

Table 3 Analysis of factors of incidence of grade III to IV complications in pseudomyxoma of abdominal cavity undergoing cell reduction combined with intraperitoneal

Clinical variables	Cases	Grade III-IV complications incidence rate, *n* (%)	χ^2	*P* value
Age (years)			0.105	0.746
Up to 60	121	51 (42.1)		
Greater than 60	65	29 (44.6)		
Gender			0.088	0.766
Male	65	27 (41.5)		
Female	121	53 (43.8)		
Primary site			2.552	0.225
Appendix	170	71 (41.8)		
Ovary	15	9 (9/15)		
Other	1	0		
Pathological level			0.278	0.598
Low-level	99	46 (46.5)		
High level	57	24 (42.1)		
Lymph node metastasis			0.349	0.818
Correct	19	8 (8/19)		
Deny	151	64 (42.4)		
Suspicious transfer	16	8 (8/16)		
Peritoneal tumor index score (points)			1.332	0.536
≤ 20	41	16 (39.0)		
21-39	111	55 (49.5)		
Whether to combine organ resection			14.33	< 0.001
Correct	123	65 (52.8)		
Deny	63	15 (23.8)		
HIPEC count			4.9	0.298
1	30	17 (56.7)		
2	48	16 (33.3)		
3	79	34 (43.0)		
4	25	12 (48.0)		
5	4	1 (1/4)		

HIPEC: Intraperitoneal hyperthermic chemotherapy.

The main limitation of this study is that retrospective studies may not be able to avoid the existence of information bias and selection bias. PMP is relatively rare clinically, the number of cases in this study is still small, the domestic understanding is relatively insufficient, the tumor load of patients is high, and the satisfactory tumor reduction rate of CRS (CCR-0 and CCR-1) is lower than that reported in international studies, which may have a certain impact on the results. Some of the patients had multiple visits to other hospitals, and the specific treatment plans, such as surgery and medication, were unknown. Therefore, there is an urgent need to conduct prospective, multi-center, large-sample randomized controlled trials to provide high-quality evidence-based medical evidence to evaluate the clinical efficacy of CRS combined with HIPEC in PMP patients.

CONCLUSION

In summary, the results of this study show that CRS + HIPEC therapy can bring significant long-term survival benefits

Table 4 Efficacy of cytopenia combined with Intraperitoneal hyperthermic chemotherapy to observe the survival of patients with peritoneal pseudomyxoma with different clinical features

Variable	Cases	5-year OS (%)	95%CI (%)	*P* value
Age (years)				0.480
Up to 60	121	48.7	36.9-60.5	
Greater than 60	65	54.2	37.9-70.5	
Gender				0.139
Male	65	41.8	26.1-57.5	
Female	121	55.4	43.6-67.2	
Primary site				0.701
Appendix	170	50.6	40.6-60.6	
Ovary	15	49.5	16.8-82.2	
Other	1			
Pathological level				< 0.00
Low-level	99	68.1	54.8-81.4	
High level	57	26.3	11.0-41.6	
Lymph node metastasis				0.107
Correct	19	54.3	27.8-80.8	
Deny	151	49.4	39.2-59.6	
Suspicious transfer	16	66.7	13.4-100.0	
Peritoneal tumor index score (points)			0.001	0.001
≤ 20	41	82.1	67.4-96.8	
21-39	111	44.0	30.5-57.5	
CCR score				< 0.001
CCR-0	15	88.9	68.3-100.0	
CCR-1	40	77.6	62.7-92.5	
CCR-2/3	113	42.0	29.5-54.5	
Whether to combine organ resection				0.915
Correct	123	46.3	32.8-59.8	
Deny	63	54.7	40.8-68.6	
HIPEC treatment plan				0.597
Raltitrexed	47	67.7	51.4~84.0	
Oxaliplatin + Letotrexate + Mitomycin	42	50.8	23.8~77.8	
Platinum	32	40.2	21.4-59.0	
Oxaliplatin + Letotrexate	25	30.0	9.0-51.0	
Letotrexate + Mitomycin	20	100		
Mitomycin	8	50.0	10.0-90.0	
Oxaliplatin + Mitomycin	8	37.5	4.0-71.0	
Other	4	50.0	1.0-99.0	

HIPEC: Intraperitoneal hyperthermic chemotherapy; CCR: Cell reduction degree; OS: Overall survival.

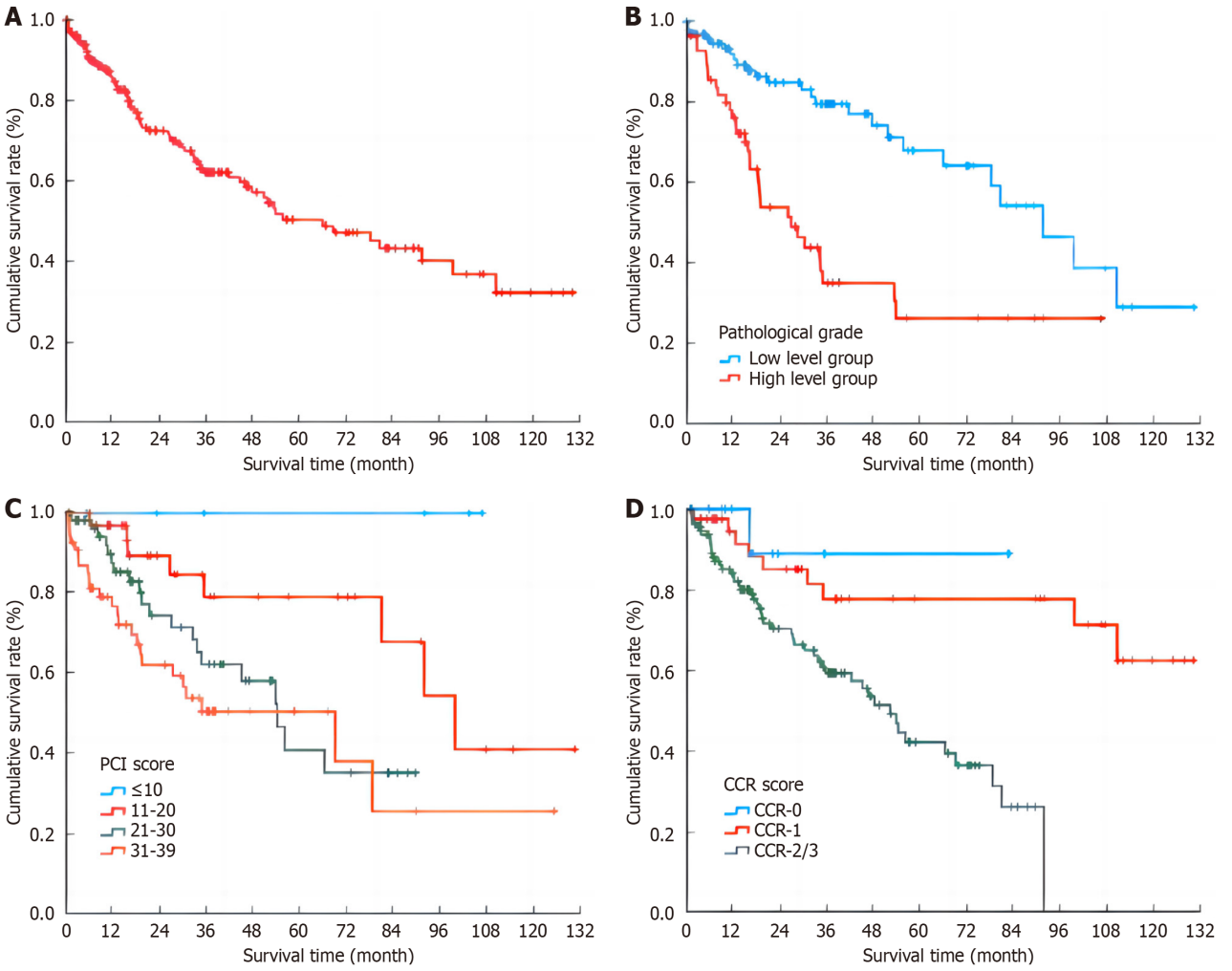

Figure 1 Analysis of survival curve of patients with peritoneal pseudomyxoma. A: Total survival time analysis; B: Pathological grade survival time analysis; C: Peritoneal tumor index score survival time analysis; D: Cell reduction degree score survival time analysis. PCI: Peritoneal tumor index; CCR: Cell reduction degree.

for PMP patients and does not increase the incidence of postoperative serious complications and mortality. Highly screened PMP patients treated with CRS + HIPEC at an experienced center, especially those who achieved satisfactory CRS, significantly extended OS.

FOOTNOTES

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