Journal of Surgical Oncology 2014;109:730–739

Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Colorectal Cancer: A Case-Control Study from a Chinese Center

CHAO-QUN HUANG, MD,[1] JUE-PING FENG, MD, PhD,[2] XIAO-JUN YANG, MD, PhD,[1] AND YAN LI, MD, PhD[1]*

[1]Department of Oncology, Zhongnan Hospital of Wuhan University, Hubei Cancer Clinical Study Center & Hubei Key Laboratory of Tumor Biological Behaviors, Wuhan, P.R. China

[2]Department of Oncology, Puai Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, P.R. China

Background: Advanced colorectal cancer (CRC) is prone to developing peritoneal carcinomatosis (PC). This case-control study was to compare the efficacy and safety of cytoreductive surgery (CRS) versus CRS plus hyperthermic intraperitoneal chemotherapy (HIPEC) in Chinese patients with CRC PC.
Methods: The 62 consecutive PC patients were treated with CRS (Control group, n = 29) or CRS + HIPEC (Study group, n = 33). The primary end point was overall survival (OS), the secondary end points were perioperative safety profiles.
Results: For the comparison of Control versus Study groups, the peritoneal cancer index (PCI) ≤20 was 13 (44.8%) versus 16 (48.5%) patients ($P = 0.78$), complete cytoreduction (CC0-1) was achieved in 9 (31.0%) versus 14 (42.4%) cases ($P = 0.36$). At the median OS was 8.5 (95% confidence interval [CI] 4.7–12.4) versus 13.7 (95% CI 10.0–16.5) months ($P = 0.02$), the 1-, 2-, and 3-year survival rates were 27.5% versus 63.6%, 12.0% versus 20.0%, and 0.0% versus 16.0%, respectively. Serious adverse events in postoperative 30 days were 9.4% versus 28.6% ($P = 0.11$). Multivariate analysis revealed that CRS + HIPEC, CC0-1, adjuvant chemotherapy ≥6 cycles were independent factors for OS benefit.
Conclusion: CRS + HIPEC could improve OS for CRC PC patients, with acceptable perioperative safety.
J. Surg. Oncol. 2014;109:730–739. © 2013 The Authors. *Journal of Surgical Oncology*. Published by Wiley Periodicals, Inc.

KEY WORDS: colorectal cancer; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; peritoneal carcinomatosis

INTRODUCTION

The classic scenario for CRC progression is the lymphatic, hematogenous (to the liver, the lungs, etc) and peritoneal metastases. There have been standard treatment strategies for the first two forms of metastases, but a unified treatment guideline is yet to be formulated for the third form of metastasis, which is typically referred to as peritoneal carcinomatosis (PC). Characterized by the implantation of tumor nodules throughout the peritoneal cavity and production of refractory ascites, PC is found in about 8–15% CRC patients at first treatment [1]. At present, the conventional therapeutic approach including systemic chemotherapy, with or without palliative surgery, provides limited clinical benefit, with median overall survival (OS) no more than 6 months [2–4].

Knowledge on PC mechanisms and coping strategies has evolved considerably over the past three decades, and PC is no longer universally considered as terminal cancer metastasis, but regional tumor progression, and proactive therapeutic strategies with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotheropy (HIPEC) are hopeful to bring significant survival benefit in selected patients. Major technical advantages of this treatment approach are to maximally reduce the visible tumor burden by CRS, and to eradicate residual tumor nodules, micrometastases and free tumor cells by HIPEC [5].

Superiority of this strategy has been demonstrated by a high-level clinical study [6]. However, there has been no data from well designed studies from China. To address this clinical problem, we have conducted a series of preclinical and clinical studies on the feasibility, efficacy, and safety of this multidisciplinary treatment approach in animal models [7] and in clinical setting [8,9], and established a designated CRS + HIPEC program at our institution. This case-control study was to compare the efficacy and safety of CRS + HIPEC versus CRS alone for the treatment of PC from CRC, so as to provide rationale for more evidence-based clinical studies in Chinese patients.

PATIENTS AND METHODS

Patients Selection

This study included 62 consecutive patients of CRC PC treated from January 2004 to December 2013 at the Department of Oncology, Zhongnan Hospital of Wuhan University. The inclusion criteria were: (1) age 20–75 years old; (2) Karnofsky performance status (KPS) score > 50; (3) life expectancy >8 weeks; (4) peripheral white blood cells count ≥3,500/mm^3 and platelet count ≥80,000/mm^3; (5) acceptable liver function, with bilirubin, aspartic aminotransferase,

Grant sponsor: New Strategies to Treat Peritoneal Carcinomatosis from Hubei Sciences and Technology Bureau; Grant numbers: 2008BCC011, 2060402-542; Grant sponsor: Science Fund for Doctorate Mentors by China's Ministry of Education; Grant number: 20120141110042; Grant sponsor: Fundamental Research Fund for the Central Universities; Grant number: 2012303030212.

*Correspondence to: Yan Li, MD, PhD, Department of Oncology, Zhongnan Hospital of Wuhan University, No 169 Donghu Road, Wuchang District, Wuhan 430071, China. Fax: +86-27-67812892. E-mail: liyansd2@163.com

Received 08 September 2013; Accepted 05 December 2013

DOI 10.1002/jso.23545

Published online 27 December 2013 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Major Clinico-Pathologic Characteristics of the Patients in This Study[a]

	Control (n = 29)	Study (n = 33)	*P*
Gender (n, %)			0.78
Male	13 (44.8)	16 (48.5)	
Female	16 (55.2)	17 (51.5)	
Median age (yr; range)	53 (17–75)	47 (25–73)	0.15
Median KPS score (range)	80 (60–90)	80 (50–100)	0.55
Primary tumor (n, %)			0.30
Carcinoma of colon	22 (75.9)	21 (63.6)	
Carcinoma of rectum	7 (24.1)	12 (36.4)	
Histopathology (n, %)			0.51
Adenocarcinoma, well/intermediately differentiated	12 (41.4)	11 (33.3)	
Adenocarcinoma, poorly/undifferentiated	17 (58.6)	22 (66.7)	
Surgical procedures-organ resection (n, %)			0.33
Resection of jejunum	0	2 (6.1)	
Resection of ileum	7 (24.1)	2 (6.1)	
Resection of ileocecus	7 (24.1)	9 (27.3)	
Ascending colectomy	5 (17.2)	10 (30.3)	
Transverse colectomy	10 (34.5)	15 (45.5)	
Descending colectomy	4 (13.8)	4 (12.1)	
Sigmoidectomy	7 (24.1)	7 (21.2)	
Rectectomy	4 (13.8)	6 (18.2)	
Splenectomy	0	1 (3.0)	
Resection ovarian/fallopian tube	4 (13.8)	9 (27.3)	
Hysterectomy	4 (13.8)	9 (27.3)	
Partial hepatectomy	0	2 (6.1)	
Cholecystectomy	0	4 (12.1)	
Organ resection area[b] (n, %)			0.30
1–3 resections	22 (75.9)	21 (63.6)	
4–5 resections	7 (24.1)	12 (36.4)	
Peritonectomy (n, %)			0.21
Greater/lesser/omentum	11 (37.9)	33 (100)	
Left diaphragmatic copula	1 (3.4)	9 (27.8)	
Right diaphragmatic copula	2 (6.9)	10 (30.3)	
Right colon gutter	1 (3.4)	12 (36.4)	
Left colon gutter	1 (3.4)	10 (30.3)	
Liver round ligament/sickle ligament	0	8 (24.2)	
Douglas pouch	0	3 (9.1)	
Anterior wall peritoneum	3 (10.3)	9 (27.3)	
Pelvic peritoneum	10 (34.5)	19 (57.6)	
Mesenteric fulguration	10 (34.5)	19 (57.6)	
Peritoneal resection area[b] (n, %)			0.002
1–3 resections	27 (93.1)	18 (54.5)	
4–6 resections	2 (6.9)	8 (24.2)	
7–10 resections	0	7 (21.2)	
Number of anastomosis[b] (n, %)			0.30
0–1	25 (86.2)[c]	31 (93.9)[d]	
2–3	4 (13.8)	2 (6.1)	
Ascites at surgery[a] (n, %)			0.06
≤1,000 ml	5 (17.2)	13 (39.4)	
>1,000 ml	24 (82.8)	20 (60.6)	
PC timing[b] (n, %)			0.002
Synchronous	23 (79.3)	13 (39.4)	
Metachronous	6 (20.7)	20 (60.6)	
PCI scores[b] (n, %)			0.78
≤20	13 (44.8)	16 (48.5)	
>20	16 (55.2)	17 (51.5)	
Median PCI score (range)	21 (6–39)	21 (6–36)	0.96
CC scores[b] (n, %)			0.36
0–1	9 (31.0)	14 (42.4)	
2–3	20 (69.0)	19 (57.6)	
Postoperative chemotherapy cycles (n, %)			0.13
<6	18 (62.1)	14 (42.4)	
≥6	11 (37.9)	19 (57.6)	
Median follow-up (Mo; range)	41.5 (11.5–70.9)	36.6 (15.5–82.9)	0.87

Mo, months.
[a]Three patients in Control group and two patients in Study group each underwent two operations.
[b]According to the first surgery.
[c]Including seven cases of stoma.
[d]Including two cases of stoma.

and alanine aminotransferase levels $<2 \times$ upper limit of normal (ULN); (6) acceptable renal function, with serum creatinine level $<1.2 \times$ ULN; (7) cardiovascular pulmonary and other major organ functions could stand major operation; and (8) with definite histological diagnosis. The exclusion criteria were: (1) age <20 or >75 years; (2) any lung, liver, or prominent retroperitoneal lymph node metastases during preoperative assessment; (3) serum bilirubin or liver enzymes $\geq 2 \times$ ULN; (4) serum creatinine level $\geq 1.2 \times$ ULN; and (5) prominent mesentery contracture as revealed by medical imaging studies. Patient information was gathered systematically from detailed medical records. Although these patients were treated in the same period at our center, they were not strictly randomized, this study was therefore defined as a case-control study, which included 29 patients receiving CRS alone (Control group) and 33 patients receiving CRS + HIPEC treatment (Study group).

CRS + HIPEC Procedure

CRS + HIPEC were performed by a designated team focusing on PC treatment. After general anesthesia, a midline xiphoid-pubic incision was made, and the PCI was evaluated according to Sugarbaker principles [10]. Subsequently, maximal CRS was performed to remove the primary tumor with acceptable margins, any involved adjacent tissue and organs, regional lymph nodes, and peritonectomy [10]. Unresectable tumors were cauterized with ball-tipped electrosurgical device at the maximal electric power (Force FX^{TM} Electrosurgical Generator, Valleylab, Surgical Solutions Group, Covidien Ltd., Boulder, CO), especially on the edge of tumor nodules. The completeness of cytoreduction (CC score) [10] was evaluated before HIPEC, which was performed by the open Colliseum technique, with 120 mg of cisplatin and 30 mg of mitomycin C each dissolved 6 L of heated saline (drug concentration cisplatin 20 μg/ml, mitomycin C 5 μg/ml, as these concentration has been confirmed to be safe and effective for HIPEC by Fujimoto et al. [11], and both drugs have been used in CRC PC [12,13]. The heated perfusion solution was infused into the peritoneal cavity at a rate of 500 ml/min through the inflow tube introduced from an automatic hyperthermia chemotherapy perfusion device (ES-6001, Wuhan E-sea Digital Engineering, Wuhan, China). The temperature of the perfusion solution in peritoneal space was kept at 43.0 ± 0.5°C and monitored with a thermometer on real time. The total HIPEC time was 90 min, after which the perfusion solution in the abdominal cavity was removed through the suction tube. Patient was delivered to the intensive care unit for recovery. When the conditions stabilized, usually 24–48 hr later, the patient was transferred to the surgical oncology ward [9].

Postoperative Chemotherapy

Adjuvant chemotherapy was delivered within 4 weeks after surgery, including systemic chemotherapy mainly with FOLFOX (oxaliplatin, leucovorin and 5-FU) or FOLFIRI (irinotecan, leucovorin and 5-FU) regimens, and perioperative intraperitoneal chemotherapy (PIC) through the intraperitoneal chemotherapy port mainly using docetaxel (75 mg/m^2, on day 1, every 3 weeks) and carboplatin (at Calvert formula: area under the curve, AUC 5; on day 1, every 3 weeks), all dosed on the base of body surface area calculation [12].

Study Parameters and Related Definitions

The following study parameters were defined: (1) Perioperative period: from the day of surgery to days 30 postoperation; (2) PCI [10]: ≤20 was defined as low PCI (LPCI), and >20 as high PCI (HPCI); (3) CC [10]: the present study set CC0-1 as complete cytoreduction, and CC2-3 as incomplete cytoreduction; (4) Synchronous PC: PC was detected synchronously at first treatment; (5) Metachronous PC: after the primary CRC had been treated, patients developed PC during follow-up; (6) Overall survival (OS): the period from first treatment to death due to the disease for synchronous PC, and from CRS to death due to the disease for metachronous PC; (7) Adverse events: complications occurred during the perioperative period directly attributable to the treatment, including SAE and other side effects; the former referred to life-threatening complications, consisting of hemorrhage, intestinal leakage, intestinal obstruction, septicemia and death directly related to the therapy; the latter consisting of hypoalbuminemia, respiratory infections, liver and kidney toxicities, and delayed incision healing; all based on NCI Common Terminology Criteria (CTC) for Adverse Events version 4.0 [14]; and (8) The survival prolong rate (SPR): worked out by OS difference of the better OS minus worse OS and divided by worse OS, calculated as:

$$\mathrm{SPR} = \frac{(\mathrm{OS}_{\text{Study group}} - \mathrm{OS}_{\text{Control group}})}{\mathrm{OS}_{\text{Control group}}} \times 100\%$$

TABLE II. Comparisons of Intraoperative Parameters Between the Two Groups[a]

	Control (n = 32[a])	Study (n = 35[a])	*P*
Fluid output volume			
Blood loss (ml)	200 (100–1,200)	800 (200–3,000)	<0.01
Urine output (ml)	300 (100–1,000)	1,000 (200–3,000)	<0.01
Ascites (ml)	100 (0–3,000)	500 (0–3,800)	<0.01
Fluid intake volume			
Plasma (ml)	0 (0–1,200)	400 (0–1,350)	<0.01
RBC (u)[b]	0 (0–8)	2 (0–8)	<0.01
Cryoprecipitation (u)[c]	0 (0–6) [d]	4 (0–8)	<0.01
Other fluids (ml)[e]	2,500 (100–4,500)	4,400 (300–7,500)	<0.01
Duration of anesthesia (min)	240 (60–360)	510 (240–900)	<0.01
Adjusted CRS time (excluding the HIPEC) (min)	175 (60–335)	405 (110–800)	<0.01

Values are in median (range).
[a]Three patients Contrl group and two patients in Study group each underwent two operations.
[b]1 u = 200 ml.
[c]1 u = 25 ml.
[d]Only one patient received 6 u of cryoprecipitation transfusion.
[e]Including colloids and electrolytes solution.

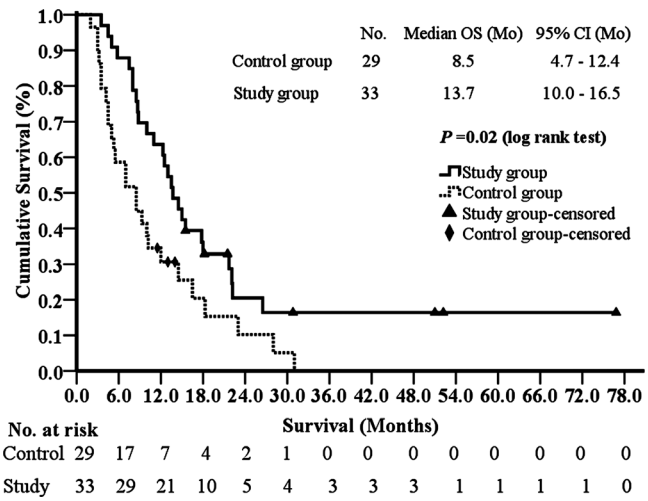

Fig. 1. The overall survival in patients with peritoneal carcinomatosis from colorectal cancer treated by CRS + HIPEC regimen compared with Control group. Mo, months.

Follow-Up

All patients received regular follow-up once every 3 months for the first 2 years, and once every 6 months thereafter. The last follow-up was on June 11, 2013, by which 1 patient in CRS group was lost for follow-up 12 months after operation, and the overall follow-up rate was 98.4%.

Statistical Analysis

The CRC PC database included major clinic-pathological information such as age, gender, KPS scores, histopathology, intraoperative resection area, input and output volume, PCI scores, CC scores, adverse events, postoperative adjuvant chemotherapy, and follow-up information. All data analyses were performed using the SPSS statistical software program, version 17.0 (SPSS, Inc., Chicago, IL) for windows. The numerical data were directly recorded, and the category data were recorded into different categories. Differences of categorical variables between the two groups were evaluated with Pearson's chi-squared test, and those of continuous variables were evaluated with Student's *t*-test. OS comparisons were analyzed with Kaplan–Meier cumulative survival curve and log rank test, and multivariate Cox regression analysis was performed to delineate the independent predictors. A two-sided $P < 0.05$ value was considered as statistically significant.

RESULTS

Baseline Data, Surgical Intervention and Perioperative Treatment

There were 62 patients including 29 patients in Control and 32 in Study groups. Five patients each received two operations due to tumor recurrence

TABLE III. OS Comparisons Between the Two Groups Stratified by Major Clinico-Pathological Factors

	Groups	n	Median OS (mo)	95% CI (mo)	*P*
Gender					0.07
Male	Control	13	7.0	3.5–10.5	0.007
	Study	16	15.0	8.5–21.5	
Female	Control	16	10.0	0.8–19.2	0.88
	Study	17	12.5	9.8–15.2	
Age (yr)					0.01
<60	Control	20	7.0	2.6–11.4	0.02
	Study	28	13.0	10.1–15.9	
≥60	Control	9	10.0	5.6–14.3	0.33
	Study	5	17.8	11.4–21.2	
Primary tumor					0.03
Carcinoma of colon	Control	22	8.5	3.1–13.9	0.11
	Study	21	13.0	10.9–15.1	
Carcinoma of rectum	Control	7	7.0	4.4–9.6	0.09
	Study	12	15.0	7.4–22.6	
Histopathology					0.01
Adenocarcinoma, well/intermediately differentiated	Control	12	9.3	1.2–17.4	0.31
	Study	11	10.0	0.0–21.1	
Adenocarcinoma, poorly/undifferentiated	Control	17	5.5	2.8–8.2	0.01
	Study	22	13.7	11.4–16.0	
PC timing					0.04
Synchronous	Control	23	8.5	5.0–12.0	0.002
	Study	13	22.2	11.5–32.9	
Metachronous	Control	6	4.2	0.0–12.4	0.51
	Study	20	12.3	9.0–15.6	
PCI scores					0.01
≤20	Control	13	16.5	7.3–23.7	0.33
	Study	16	15.5	7.5–25.5	
>20	Control	16	5.0	3.6–6.6	0.002
	Study	17	13.0	6.3–19.7	
CC scores					0.004
0–1	Control	9	18.3	13.3–23.3	0.35
	Study	14	21.7	12.2–31.2	
2–3	Control	20	5.0	3.2–6.8	0.003
	Study	19	11.0	4.9–17.1	
Postoperative chemotherapy cycles					0.08
<6	Control	18	5.0	3.3–6.7	0.21
	Study	14	8.5	7.2–9.8	
≥6	Control	11	14.5	9.5–19.5	0.21
	Study	19	21.7	16.3–27.1	
SAE[a]					0.02
No	Control	26	7.0	3.3–10.7	0.01
	Study	26	14.5	8.6–20.4	
Yes	Control	3	16.5	0.0–39.7	0.76
	Study	7	8.0	4.2–11.8	

NA, not available; OS, overall survival; mo, months.
[a]In the original surgery calculation.

in Control group (n = 3) and Study group (n = 2). Major clinico-pathologic characteristics of the patients were comparable (Table I).

Surgical procedures and major intraoperative parameters were recorded and analyzed (Table II). The value of the important parameters for Study group was greater than Control group, including fluid intake and output, duration of operation.

After operation, all the 62 patients received systemic chemotherapy and 14 patients received PIC (five in Control group and nine in Study group). None of the patients in both groups received any molecular targeting agents.

Survival Analysis

By June 11, 2013, the median follow-up in Control and Study groups were 41.5 (range, 11.5–70.9) versus 36.6 (range, 15.5–82.9) months ($P = 0.87$). The primary endpoint was reached in 26 (89.7%) cases in Control group, and 26 (78.8%) cases in Study group. Ten patients are alive, 3 (10.3%) in Control group and 7 (21.2%) in Study group. Therefore, the data was mature for final analysis.

The median OS was 8.5 (95% CI: 4.7–12.4) months for Control group and 13.7 (95% CI: 10.0–16.5) months for Study group ($P = 0.02$; Fig. 1). Compared with Control group, the Study group had survival prolong rate (SPR) by 61.2%. The 1-, 2-, and 3-year survival rates were 27.5% versus 63.6%, 12.0% versus 20.0%, and 0.0% versus 16.0%, respectively, for Control versus Study groups.

The OS comparisons between the two groups were stratified based on major clinico-pathological factors (Table III). Compared with Control group, the Study group had OS advantages across all major clinico-pathological factors studied, although male patients, age <60 years, colon cancer PC, poorly/undifferentiated adenocarcinoma, synchronous PC, PCI ≤20, and CC0-1 could obtain greater OS benefit.

The OS comparison was the further stratified by subgroup analysis (Table IV), which revealed statistically greater OS benefits ($P < 0.05$) in some subgroups, such as synchronous PC in Study group (Fig. 2a), PCI ≤ 20 in Control (Fig. 2b), CC0-1 (Fig. 3a,b) and postoperative chemotherapy ≥6 cycles (Fig. 3c,d) in both groups. However, there was no statistical significance for OS improvements in other subgroups including gender, age, primary tumor, histopathology, and ascites.

Special Analysis on Long-Term Survivors

There were 12 patients surviving over 20 months in this cohort of patients, nine in Study group and three in Control group (Table V). In Study group, three patients of synchronous PC with LPCI and CCR-0 resection had a long-term OS over 50 months and still free of disease; however, three patients with HPCI and CCR-2 resection also achieved a long-term OS >20 months, and one of them was still living over 30 months with tumor. In Control group, two patients with PCI < 10 and

TABLE IV. The Subgroup Analysis Between Control and Study Groups

Groups	Subgroups	n	Median OS (mo)	95% CI (mo)	*P*
Control	Male	13	7.0	3.5–10.5	0.20
	Female	16	10.0	0.8–19.2	
Study	Male	16	15.0	8.5–21.5	0.12
	Female	17	12.5	9.8–15.2	
Control	<60 yr	20	7.0	2.6–11.4	0.54
	≥60 yr	9	10.0	5.6–14.4	
Study	<60 yr	28	13.0	10.3–16.7	0.68
	≥60 yr	5	17.8	11.4–24.2	
Control	Colon cancer	22	8.5	3.1–13.9	0.56
	Rectal cancer	7	7.0	4.4–9.6	
Study	Colon cancer	21	13.0	10.9–15.1	0.61
	Rectal cancer	12	15.0	7.4–22.6	
Control	Adenocarcinoma, well/intermediately differentiated	12	9.3	1.2–17.5	0.16
	Adenocarcinoma, poorly/undifferentiated	17	5.5	2.8–8.2	
Study	Adenocarcinoma, well/intermediately differentiated	11	10.0	0.0–21.1	0.50
	Adenocarcinoma, poorly/undifferentiated	22	13.7	11.4–16.0	
Control	Synchronous PC	23	8.5	5.0–12.0	0.43
	Metachronous PC	6	4.2	0.0–12.4	
Study	Synchronous PC	13	22.2	11.5–32.9	0.01
	Metachronous PC	20	12.3	9.0–15.6	
Control	Ascites ≤1,000 ml	24	8.5	4.9–12.1	0.67
	Ascites >1,000 ml	5	5.3	3.6–7.0	
Study	Ascites ≤1,000 ml	22	15.5	10.6–20.4	0.16
	Ascites >1,000 ml	11	10.0	6.1–13.9	
Control	PCI ≤20	13	16.5	7.5–23.5	0.001
	PCI >20	16	5.0	3.4–6.6	
Study	PCI ≤20	16	15.5	7.3–23.7	0.15
	PCI >20	17	13.0	6.3–19.7	
Control	CC0-1	9	18.3	13.3–23.3	0.000
	CC2-3	20	5.0	3.2–6.8	
Study	CC0-1	14	21.7	12.2–31.2	0.02
	CC2-3	19	11.0	4.9–17.1	
Control	<6 cycles chemotherapy	18	5.0	3.3–6.7	0.001
	≥6 cycles chemotherapy	11	14.5	9.5–19.5	
Study	<6 cycles chemotherapy	14	8.5	7.2–9.8	0.000
	≥6 cycles chemotherapy	19	21.7	16.3–27.1	

OS, overall survival; mo, months; yr, years old.

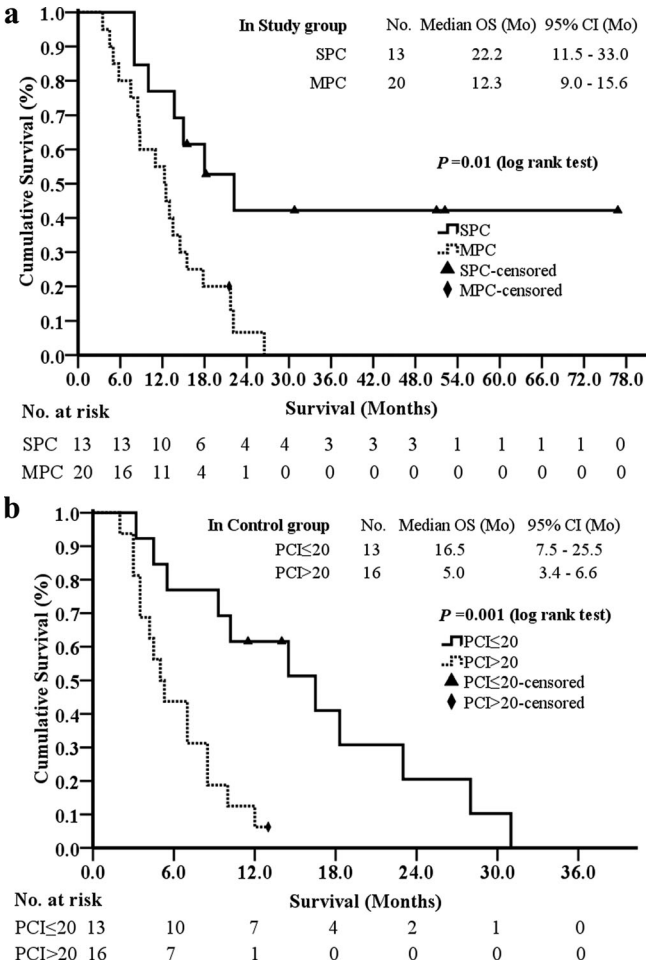

Fig. 2. **a**: the patients with synchronous PC in Study group are superior survival to metachronous PC; **b**: compared with the PCI >20, the PCI ≤20 have a significant survival advantage in Control group. Mo, months; SPC, synchronous PC; MPC, metachronous PC.

CCR-0 resection had the OS over 23 months. It was surprising that one patient (PCI = 26, CCR = 3) in this group achieved long-term OS of 28 months. Histopathology of the 12 patients was well or intermediately differentiated adenocarcinoma.

Serious Adverse Events (SAE)

SAE (grade 3–5) occurred in 13 patients, including 3 (9.4%) in Control group consisting of intestinal leakage (1 case, on day 7 postoperation) and death (2 cases, on days 7 and 22 postoperation), and 10 (28.6%) patients in Study group, consisting of postoperative hemorrhage (1 case, 4 hr postoperation), septicaemia (1 case, on day 8 postoperation), diarrhea (1 case, on day 8 postoperation, grade 3), intestinal leakage (2 cases, on days 16 and 17 postoperation), and intestinal obstruction (5 cases, on days 4, 7, 12, 13, and 13 postoperation). No statistically significant difference was found in the frequency of SAE between the two groups ($P = 0.11$; Table VI).

Detailed accounts of the 10 SAE cases in Study group were the following. One patient developed abdominal hemorrhage 4 hr postoperation, and reoperation found knot slipping on branch of right gastroepiploic artery, double ligation was made and the bleeding was immediately stopped. This patient recovered well and he is still living and active with DFS (disease free survival) of 52.2 months. The second case was a 60-year-old male patient who developed septicaemia along with inflammatory diarrhea (SAE, grade 3), abdominal pain and delirium on day 8 postoperation, which was confirmed to be infection by *Staphylococcus aureus* by blood culture. The septicaemia was controlled in 5 days after antibiotics therapy, and the patient fully recovered in about 10 days. Another two patients developed colonic stump fistula on postoperative days 16 and 17, respectively; the former had limited peritonitis syndrome and recovered after 7 days of conservative treatment; but the latter deteriorated, with sepsis, generalized peritonitis, and abdominal abscess formation due to infection by *Escherichia coli* as confirmed by bacteria culture. This patient was treated with abdominal drainage, antibiotics, and total parenteral alimentation support, and survived 3 months after the procedure. The other five patients developed ileus within 2 weeks after operation; there were not electrolyte disturbance, serious infection or sepsis after treated with conservative therapy; they had gradually recovered in about 1 week.

Multivariate Analysis

Multivariate Cox regression analysis identified three variables including therapeutic regimen, CC scores and postoperative adjuvant chemotherapy cycles as independent predictors for better survival (Table VII). Compared with Control group, Study group was about 2.2 times likely to improve survival (Hazard ratio = 2.15, 95% CI 1.18–3.93, $P = 0.01$).

DISSCUSION

Since the late 1980s, CRS + HIPEC has been gradually developed to treat CRC PC, and several phase II/III clinical studies have demonstrated the efficacy of this strategy, with median OS improved to 19.2 months from 6.0 months [13], the 3-year survival rates from 25% to 47% [15–17], and the 5-year survival rate up to 40% [18–20]. Although this new treatment strategy has gained increasing international acceptance in North American and European countries [21–23], convincing evidence is not yet available from China, where CRC ranks number five in cancer mortality list.

To address this problem, this case-control study was designed to compare the efficacy and safety of CRS + HIPEC for Chinese patients with CRC PC. The most important finding was that the median OS could be extended from 8.5 months in Control group to 13.7 months in Study group, with survival prolong rate (SPR) of 61.2%. This improvement is comparable with both experimental studies (23 vs. 40 days, SPR 60% [7]; 43 vs. 75 days, SPR 74% [24]) and clinical studies by Yang et al. [9] (6.5 vs. 11.0 months, SPR 69%), Verwaal et al. [6] (12.6 vs. 22.3 months, SPR 77%), Elias et al. [25] (23.9 vs. 62.7 months, SPR 162%), and Cashin et al. [26] (23.9 vs. 36.5 months, SPR 53%). Although this is not a strictly randomized study, and the two groups were different in terms of operation complexities, as the HIPEC group had more abdominal areas resection than the control group and thus longer operation time, there was no major selection bias in this study that could account for such big differences in OS.

Univariate analysis revealed 12 factors (gender, age, primary tumor, histopathology, stage, PC timing, ascites, PCI scores, CC scores, treatment, SAE, postoperative chemotherapy cycles) associated with OS. Multivariate Cox regression analysis identified three independent factors for improving OS: Study group, CC0-1, and postoperative chemotherapy cycles ≥6. Therefore, these factors could help make better patient selection.

Although the median OS in this study was significantly better in Study group than Control group, it was shorter than most reported results [6,13,26]. Several facts could account for these differences: (1) A

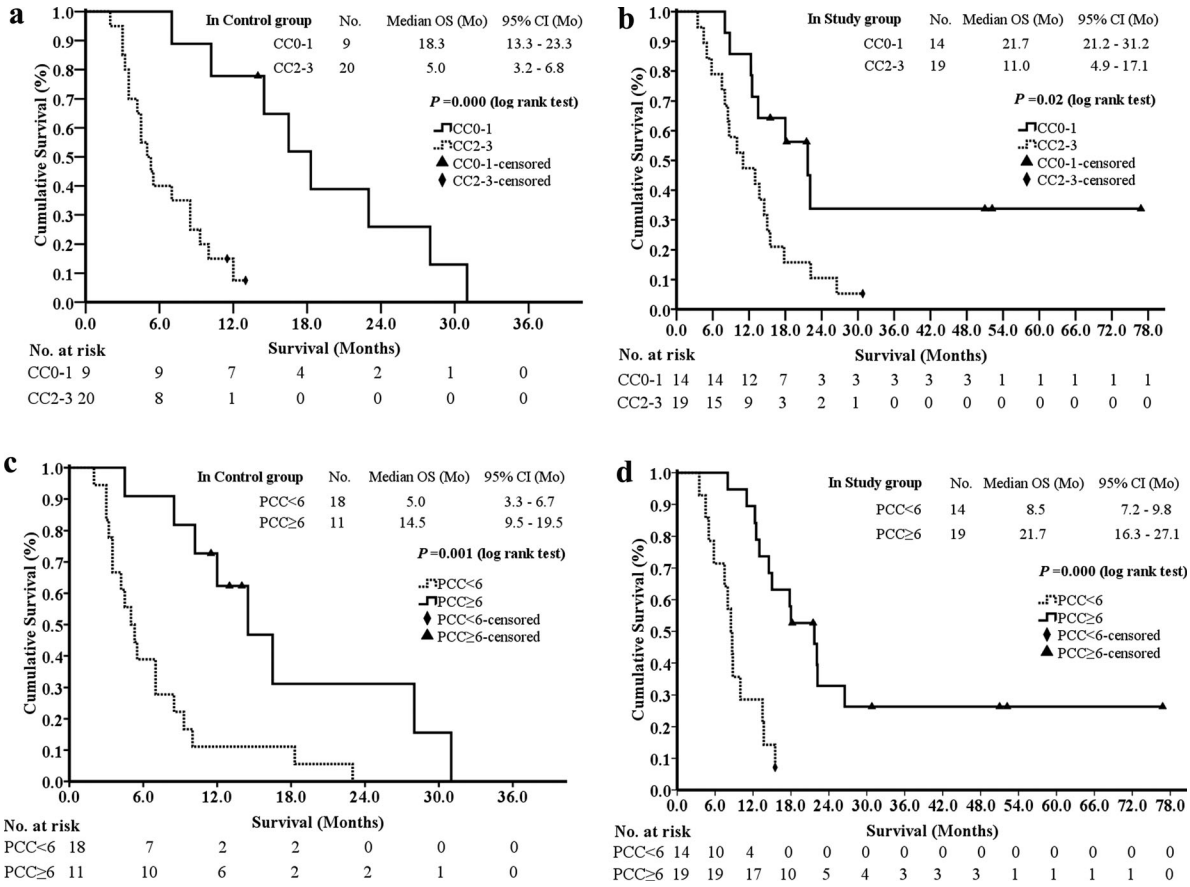

Fig. 3. Either Control group (**a**) or Study group (**b**), patients with CC0-1 cytoreduction had better survival advantage; Similarly, in both groups(**c, d**), postoperative chemotherapy ≥6 cycles provided far better survival advantage than <6 cycles, particularly in Study group (d). Mo, months; PCC, postoperative chemotherapy cycles.

majority of patients (51.5%) had high PCI scores (PCI > 20), and the median OS for such patients was 13.0 months in Study group (vs. 5.0 months in Control group, $P = 0.002$). This is comparable to most other studies [19,27,29] showing a median OS of about 12 months for patients with PCI > 20. Sugarbaker et al. [29] also reported the 5-year survival rates of 50%, 20%, and 0%, respectively for patients with PCI ≤10, 11–20, and > 20. The patients could still benefit from HIPEC procedure, even if it was high-PCI scores. (2) It is difficult to achieve complete cytoreduction for patients with high tumor burden, and in this study 57.6% of patients had CC2-3 resection. For patients with CC2-3 resection, the median OS were 8.1 and 8.4 months in two studies by Glehen et al. [13,30], 8.0 months by Cavaliere et al. [27], 12.0 months by Pestieau et al. [28], and 11.0 months in this study. Therefore, for this subgroup of patients, our results were comparable with those reported in other studies. It was worth noting that the OS of CC2-3 patients were more significantly increased in Study group than in Control group (11.0 vs. 5.0 months, $P = 0.003$). Although CC2-3 resection was not an optimal surgical outcome, HIPEC still might work to some extent after unresectable or disseminated tumor scorched by high-frequency electrotome, especially on the edge of tumor tissue. As tumor aggressiveness or proliferating activity in the periphery was more active than in the center of the tumor [31,32]. HIPEC is likely to have efficiency whatever the extent of cytoreduction, if optimal electric cauterization is delivered to the unresectable tumor. However, more importantly, the multivariate Cox regression analysis shows that CC0-1 resection is two times more likely to confer OS advantage than CC2-3 resection (Hazard ratio = 2.15, 95% CI: 1.18–3.93). Consequently, it is still necessary every effort should be made to reduce the tumor burden as much as possible. The analysis on 12 long-term survivors found that the patients in HPCI and non-CCR0 state also benefit from HIPEC indeed (OS > 21 months), although those of LPCI, CCR-0 and synchronous PC could benefited much better. Furthermore, all 12 patients have a similarity of well or intermediately differentiated adenocarcinoma in histopathology. (3) None of our patients received any molecular targeted therapy. It has been demonstrated [33,34] that if CRC PC patients received molecular targeted therapy alone, the OS could reach 18.2–23.5 months, even could reach 54.0 months if CRS + HIPEC plus conventional chemotherapy and molecular targeted therapy was administered [34]. Although our patients did not receive molecular targeted therapy in this study due to medical insurance issues, the Study group still conferred significant survival advantage over the Control group.

To achieve complete cytoreduction, the CRS + HIPEC procedure is often time-consuming, technically demanding and logistically complex, which could considerably increase the risk for SAE [35]. The reported perioperative morbidity rate ranged from 14.8% to 57.0%, and mortality rate from 0.0% to 12.0% [21]. In 2 multicenter studies by Elias et al. [36] and Glehen et al. [13], the perioperative mortality rate was 4%. In our study, the 30-day SAE rate was 9.4% in Control group and 28.6% in Study group ($P = 0.11$), and the mortality rates were 6.3% and 0.0%, respectively. Some of the important parameters associated with perioperative adverse events, including the fluid output/input volume,

TABLE V. Major Treatment and Follow-Up Features of Long-Term Survivors in Both Groups

No.	Gender/age (yr)	PC origin	PCI	CRS	CCR	Survival (months)	Comments
The Study group							
1	M/36	Colon ca, Synchronous PC	6	Left hemicolectomy, greater omentum resection, left peritoneum and musculus trasversus abdominis, mesenteric fulguration	0	76.8, DFS	
2	M/36	Colon ca, Synchronous PC	15	Transverse colectomy, resection of part jejunum, greater omentum resection	0	52.2, DFS	SAE: abdominal hemorrhage 4 hr postoperation, reoperation to stop bleeding
3	M/47	Colon ca, Synchronous PC	15	Ascending colectomy, resection of ileocecus	0	51.0, DFS	
4	M/30	Colon ca, Synchronous PC	32	Right hemicolectomy, resection of part jejunum, greater omentum, left diaphragmatic copula, left/right colon gutter, liver round ligament/ sickle ligament resection, mesenteric fulguration	2	30.8, SWT	
5	M/60	Colon ca, Metachronous PC	15	Right hemicolectomy, greater omentum, pelvic peritoneum resection, mesenteric fulguration	1	21.5, SWT	
6	F/37	Colon ca, Metachronous PC	26	Descending colectomy, resection of part jejunum, left/right diaphragmatic copula, left/right colon gutter, anterior wall peritoneum, pelvic peritoneum resection, mesenteric fulguration	2	26.5, D	
7	M/26	Colon ca, Synchronous PC	28	Greater/lesser omentum, liver round ligament/ sickle ligament, anterior wall peritoneum resection, mesenteric fulguration	2	22.2, D	
8	M/41	Rectal ca, Metachronous PC	20	Rectectomy, greater omentum, left/right diaphragmatic copula resection, colon sigmoideum colostomy	1	22.1, D	
9	F/54	Colon ca, Metachronous PC	7	Sigmoidectomy, rectectomy, greater omentum, pelvic peritoneum resection	1	21.7, D	
The Control group							
1	F/50	Rectum ca, Synchronous PC	6	Sigmoidectomy, rectectomy, pelvic peritoneum resection	0	23.0, SWT	
2	F/30	Colon ca, Metachronous PC	7	Transverse colectomy, greater omentum, oophorectomy, and hysterectomy, partial hepatectomy resection (in second surgery)	0	31.0, D	Two operations
3	F/37	Colon ca, Metachronous PC	26	Right hemicolectomy	3	28.0, D	

M, male; F, female; ca, carcinomatosis; D, died; DFS, disease free survival; SWT, survival with tumor; SAE, serious adverse event.

TABLE VI. Distribution of Adverse Events in Two Groups

	Control (n = 32)[a]	Study (n = 35)[a]	*P*
SAE (grades 3–5)[b]	3	10	0.11
Hemorrhage	0	1 (2.9%)	
Intestinal leakage	1 (3.1%)	2 (5.7%)	
Intestinal obstruction	0	5 (14.3%)	
Diarrhea	0	1 (2.9%)	
Septicemia	0	1 (2.9%)	
Death	2 (6.25%)	0	
Other AE (grades 1–2)[b]	28	27	0.41
Hypoalbuminemia	16 (50.0%)	18 (51.4%)	
Liver & kidney dysfunction	8 (25.0%)	5 (14.3%)	
Respiratory infections	2 (6.3%)	0	
Hypercholesterolemia	1 (3.1%)	0	
Delayed incision healing	1 (3.1%)	3 (8.6%)	
Deep vein thrombosis	0	1 (2.9%)	

AE, adverse event.
[a]Three patients Control group and two patients in Study group each underwent two operations.
[b]Common Terminology Criteria for Adverse Events version 4.0.

TABLE VII. Multivariate Analysis on Independent Factor Influencing Survival

Covariate	χ^2	*P*	HR	HR 95% CI
Treatment (Study vs. Control)	6.16	0.01	2.15	1.18–3.93
CC score (CC0-1 vs. CC2-3)	17.91	0.000	2.98	2.10–7.52
PCC (≥6 vs.<6)	15.94	0.000	4.26	2.09–8.69

PCC, postoperative chemotherapy cycles.

duration of anesthesia/CRS and peritoneal resection rate, were more aggressive in Study group than Control group, however, the adverse events were not significant increased in Study group. These results suggest that the morbidity and mortality of Study group are comparable with conventional gastrointestinal surgery and acceptable, if patients are treated at specialized PC centers, as demonstrated in a meta-analysis by Chua et al. [37]. It is noteworthy that for patients without SAE, Study group confers greater OS advantage than Control group (14.5 vs. 7.0 months, $P = 0.01$). However, if SAE developed the OS could be considerably compromised, no matter what treatment modalities were delivered. Therefore, careful attention should be paid to minimizing SAE, including improved selection criteria, the open coliseum technique, optimal CRS and HIPEC procedure, intensified perioperative management.

CONCLUSION

In summary, this study from China has provided new evidence that CRS + HIPEC bring significant survival benefit and acceptable safety for patients with CRC PC. More knowledgeable patient selection at specialized treatment centers could ensure the value of this strategy for patients with CRC PC.

ACKNOWLEDGMENTS

This study was supported by the grants for New Strategies to Treat Peritoneal Carcinomatosis from Hubei Sciences and Technology Bureau (Nos. 2008BCC011 and 2060402-542), the Science Fund for Doctorate Mentors by China's Ministry of Education (No. 20120141110042), and the Fundamental Research Fund for the Central Universities (No. 2012303030212). The authors thank Drs. Guoliang Yang, Yunfeng Zhou, Bin Xiong, Fulin Cheng, Guang Li, Yang Liu for their help and excellent technical support.

REFERENCES

1. Al-Shammaa HA, Li Y, Yonemura Y: Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. World J Gastroenterol 2008;14:1159–1166.
2. Glehen O, Osinsky D, Beaujard AC, et al.: Natural history of peritoneal carcinomatosis from nongynecologic malignancies. Surg Oncol Clin N Am 2003;12:729–739;xiii.
3. Sadeghi B, Arvieux C, Glehen O, et al.: Peritoneal carcinomatosis from non-gynecologic malignancies: Results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358–363.
4. Jayne DG, Fook S, Loi C, et al.: Peritoneal carcinomatosis from colorectal cancer. Br J Surg 2002;89:1545–1550.
5. Sugarbaker PH: Surgical responsibilities in the management of peritoneal carcinomatosis. J Surg Oncol 2010;101:713–724.
6. Verwaal VJ, van Ruth S, de Bree E, et al.: Randomized trial of cytoreduction and hypertherm icintraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2003;21:3737–3743.
7. Tang L, Mei LJ, Yang XJ, et al.: Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival of gastric cancer with peritoneal carcinomatosis: Evidence from an experimental study. J Transl Med 2011;9:53.
8. Yang XJ, Li Y, Hassan AHA, et al.: Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival in selected patients with peritoneal carcinomatosis from abdominal and pelvic malignancies: Results of 21 cases. Ann Surg Oncol 2009;16:345–351.
9. Yang XJ, Huang CQ, Suo T, et al.: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: Final results of a phase III randomized clinical trial. Ann Surg Oncol 2011;18:1575–1581.
10. Sugarbaker PH: Cytoreduction surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. Eur J Surg Oncol 2001;27:239–243.
11. Fujimoto S, Takahashi M, Koyabayashi K, et al.: Cytohistologic assessment of antitumor effects of intraperitoneal hyperthermic perfusion with mitomycin C for patients with gastric cancer with peritoneal metastasis. Cancer 1992;70:2754–2760.
12. Sugarbaker PH: Successful management of microscopic residual disease in large bowel cancer. Cancer Chemother Pharmacol 1999;43:S15–S25.
13. Glehen O, Kwiatkowski F, Sugarbaker PH, et al.: Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: A multi-institutional study. J Clin Oncol 2004;22:3284–3292.
14. National Cancer Institute: Common Terminology Criteria for Adverse Events version 4.0. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
15. Glehen O, Mithieux F, Osinsky D, et al.: Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: A phase II study. J Clin Oncol 2003;21:799–806.
16. Elias D, Blot F, El Otmany A, et al.: Curative treatment of peritoneal carcinomatosis arising from colorectal cancer by complete resection and intraperitoneal chemotherapy. Cancer 2001;92:71–76.
17. Witkamp AJ, de Bree E, Kaag MM, et al.: Extensive cytoreductive surgery followed by intra-operative hyperthermic intraperitoneal chemotherapy with mitomycin-C in patients with peritoneal carcinomatosis of colorectal origin. Eur J Cancer 2001;37:979–984.
18. Verwaal VJ, van Ruth S, Witkamp A, et al.: Long-term survival of peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2005;12:65–71.
19. da Silva RG, Sugarbaker PH: Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative

intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg 2006;203:878–886.
20. Elias D, Raynard B, Farkhondeh F, et al.: Peritoneal carcinomatosis of colorectal origin. Gastroenterol Clin Biol 2006;30:1200–1204.
21. Cao C, Yan TD, Black D, et al.: A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2009;16:2152–2165.
22. Esquivel J, Sticca R, Sugarbaker PH, et al.: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: A consensus statement. Ann Surg Oncol 2007;14:128–133.
23. Elias D, Gilly F, Boutitie F, et al.: Carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63–68.
24. Klaver YL, Hendriks T, Lomme RM, et al.: Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for peritoneal carcinomatosis in an experimental model. Br J Surg 2010;97:1874–1880.
25. Elias D, Lefevre JH, Chevalier J, et al.: Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27:681–685.
26. Cashin PH, Graf W, Nygren P, et al.: Intraoperative hyperthermic versus postoperative normothermic intraperitoneal chemotherapy for colonic peritoneal carcinomatosis: A case-control study. Ann Oncol 2012;23:647–652.
27. Cavaliere F, De Simone M, Virzì S, et al.: Prognostic factors and oncologic outcome in 146 patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: Italian multicenter study S.I.T.I.L.O. Eur J Surg Oncol 2011;37:148–154.
28. Pestieau SR, Sugarbaker PH: Treatment of primary colon cancer with peritoneal carcinomatosis: Comparison of concomitant vs. delayed management. Dis Colon Rectum 2000;43:1341–1346.
29. Sugarbaker TA, Chang D, Koslowe P, et al.: Patterns of spread of recurrent intra-abdominal sarcoma. Cancer Treat Res 1996;82:65–77.
30. Glehen O, Cotte E, Schreiber V, et al.: Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. Br J Surg 2004;91:747–754.
31. Chen C, Peng J, Sun SR, et al.: Tapping the potential of quantum dots for personalized oncology: Current status and future perspectives. Nanomedicine (Lond) 2012;7:411–428.
32. Nozawa T, Enomoto T, Koshida Y, et al.: Specific enhanced expression of platelel-derived endothelial cell growth factor in submucosa of human colorectal cancer. Dis Colon Rectum 2004;47:2093–2100.
33. Bokemeyer C, Van Cutsem E, Rougier P, et al.: Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012;48:1466–1475.
34. Chua TC, Morris DL, Saxena A, et al.: Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: A multicenter study. Ann Surg Oncol 2011;18:1560–1567.
35. Saxena A, Yan TD, Chua TC, et al.: Critical assessment of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol 2010;17:1291–1301.
36. Elias D: French multi-institutional registry for colorectal peritoneal carcinomatosis. 5th peritonectomy workshop. Lyon, France, Oct 2008;Abstract.
37. Chua TC, Yan TD, Saxena A, et al.: Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg. 2009;249:900–907.