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

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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).

Conclusion: CRS + HIPEC could improve OS for CRC PC patients, with acceptable perioperative safety.

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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 chemotherapy (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/mm³ and platelet count ≥ 80,000/mm³; (5) acceptable liver function, with bilirubin, aspartic aminotransferase, asparagine transaminase, and alkaline phosphatase levels acceptable for liver resection.

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| Characteristics                        | Control (n = 29) | Study (n = 33) | P    |
|---------------------------------------|-----------------|----------------|------|
| Gender (n, %)                         |                 |                |      |
| Male                                  | 13 (44.8)       | 16 (48.5)      | 0.78 |
| 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 ileocecum                 | 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 areaa (n, %)           |                 |                | 0.30 |
| 1–3 resections                        | 22 (75.9)       | 21 (63.6)      |      |
| 4–5 resections                        | 7 (24.1)        | 12 (36.4)      |      |
| Peritoneectomy (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 (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 anastomosisb (n, %)          |                 |                | 0.30 |
| 0–1                                   | 25 (86.2)%      | 31 (93.9)%     |      |
| 2–3                                   | 4 (13.8)%       | 2 (6.1)%       |      |
| Ascites at surgeryc (n, %)             |                 |                | 0.06 |
| ≤1,000 ml                             | 5 (17.2)        | 13 (39.4)      |      |
| >1,000 ml                             | 24 (82.8)       | 20 (60.6)      |      |
| PC timingd (n, %)                      |                 |                | 0.002|
| Synchronous                           | 23 (79.3)       | 13 (39.4)      |      |
| Metachronous                          | 6 (20.7)        | 20 (60.6)      |      |
| PCI scoresd (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 scoresd (n, %)                      |                 |                | 0.36 |
| 0–1                                   | 9 (31.0)        | 14 (42.4)      |      |
| 2–3                                   | 20 (69.0)       | 19 (57.6)      |      |
| Postoperative chemotherapy cycles (n, %) | 18 (62.1) | 14 (42.4) | |
| ≤6                                    | 11 (37.9)       | 19 (57.6)      |      |
| >6                                    |                 |                |      |
| Median follow-up (Mo; range)          | 41.5 (11.5–70.9) | 36.6 (15.5–82.9) | 0.87 |

*Mo, months.

aThree patients in Control group and two patients in Study group each underwent two operations.

bAccording to the first surgery.

cIncluding seven cases of stoma.

dIncluding two cases of stoma.
and alanine aminotransferase levels <2 × upper limit of normal (ULN); (6) acceptable renal function, with serum creatinine level <1.2 × 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 ≥2 × ULN; (4) serum creatinine level ≥1.2 × 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 peritoneectomy [10]. Unresectable tumors were cauterized with ball-tipped electrosurgical device at the maximal electric power (Force FX™ Electrosurgical Generator, Valleylab, Surgical Solutions Group, Coviden 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 oncolgy 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/m², 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:

\[
SPR = \left( \frac{OS_{\text{study group}} - OS_{\text{control group}}}{OS_{\text{control group}}} \right) \times 100\%
\]

**TABLE II. Comparisons of Intraoperative Parameters Between the Two Groups**

| Parameter                        | Control (n = 32) | Study (n = 35) | 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)L                         | 0 (0–8)         | 2 (0–8)       | <0.01 |
| Cryptoprecipitation (u)          | 0 (0–6)         | 4 (0–8)       | <0.01 |
| Other fluids (ml)                | 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).

*Three patients Contrl group and two patients in Study group each underwent two operations.

a1 uL = 200 ml.
b1 uL = 25 ml.
cOnly one patient received 6 uL of cryoprecipitation transfusion.
dIncluding 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 clinicopathological 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     |    |                |             |      |
| Male       |    |                |             |      |
| Control    | 13 | 7.0            | 3.5–10.5    | 0.07 |
| Study      | 16 | 15.0           | 8.5–21.5    | 0.007|
| Female     |    |                |             |      |
| Control    | 16 | 10.0           | 0.8–19.2    | 0.88 |
| Study      | 17 | 12.5           | 9.8–15.2    | 0.88 |
| Age (yr)   |    |                |             |      |
| <60        |    |                |             |      |
| Control    | 20 | 7.0            | 2.6–11.4    | 0.02 |
| Study      | 28 | 13.0           | 10.1–15.9   | 0.02 |
| ≥60        |    |                |             |      |
| Control    | 9  | 10.0           | 5.6–14.3    | 0.33 |
| Study      | 5  | 17.8           | 11.4–21.2   | 0.33 |
| Primary tumor |  |                |             |      |
| Carcinoma of colon |   |                |             |      |
| Control    | 22 | 8.5            | 3.1–13.9    | 0.11 |
| Study      | 21 | 13.0           | 10.9–15.1   | 0.11 |
| Carcinoma of rectum |  |                |             |      |
| Control    | 7  | 7.0            | 4.4–9.6     | 0.09 |
| Study      | 12 | 15.0           | 7.4–22.6    | 0.09 |
| Histopathology       |  |                |             |      |
| Adenocarcinoma, well/intermediately differentiated | | | |
| Control    | 12 | 9.3            | 1.2–17.4    | 0.31 |
| Study      | 11 | 10.0           | 0.0–21.1    | 0.31 |
| Adenocarcinoma, poorly/undifferentiated | | | |
| Control    | 17 | 5.5            | 2.8–8.2     | 0.01 |
| Study      | 22 | 13.7           | 11.4–16.0   | 0.01 |
| PC timing |    |                |             |      |
| Synchronous |  |                |             |      |
| Control    | 23 | 8.5            | 5.0–12.0    | 0.002|
| Study      | 13 | 22.2           | 11.5–32.9   | 0.002|
| Metachronous |  |                |             |      |
| Control    | 6  | 4.2            | 0.0–12.4    | 0.51 |
| Study      | 20 | 12.3           | 9.0–15.6    | 0.51 |
| PCI scores |    |                |             |      |
| ≤20        |    |                |             |      |
| Control    | 13 | 16.5           | 7.3–23.7    | 0.33 |
| Study      | 16 | 15.5           | 7.5–25.5    | 0.33 |
| >20        |    |                |             |      |
| Control    | 16 | 5.0            | 3.6–6.6     | 0.002|
| Study      | 17 | 13.0           | 6.3–19.7    | 0.002|
| CC scores |    |                |             |      |
| 0–1        |    |                |             |      |
| Control    | 9  | 18.3           | 13.3–23.3   | 0.004|
| Study      | 14 | 21.7           | 12.2–31.2   | 0.004|
| 2–3        |    |                |             |      |
| Control    | 20 | 5.0            | 3.2–6.8     | 0.003|
| Study      | 19 | 11.0           | 4.9–17.1    | 0.003|
| Postoperative chemotherapy cycles |  |                |             |      |
| <6         |    |                |             |      |
| Control    | 18 | 5.0            | 3.3–6.7     | 0.21 |
| Study      | 14 | 8.5            | 7.2–9.8     | 0.21 |
| ≥6         |    |                |             |      |
| Control    | 11 | 14.5           | 9.5–19.5    | 0.21 |
| Study      | 19 | 21.7           | 16.3–27.1   | 0.21 |
| SAE$^a$   |    |                |             |      |
| No         |    |                |             |      |
| Control    | 26 | 7.0            | 3.3–10.7    | 0.02 |
| Study      | 26 | 14.5           | 8.6–20.4    | 0.02 |
| Yes        |    |                |             |      |
| Control    | 3  | 16.5           | 9.0–39.7    | 0.01 |
| Study      | 7  | 8.0            | 4.2–11.8    | 0.01 |

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. 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 PCI >20, and CC0-1 could obtain greater OS benefit.

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 PCI >20, and CC0-1 could obtain greater OS benefit.

**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          | 8.0–19.2    |     |
| 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.

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differentiated adenocarcinoma.

28 months. Histopathology of the 12 patients was well or intermediately

survival to metachronous PC; PCI

months; SPC, synchronous PC; MPC, metachronous PC.

have a signi

ificant survival advantage in Control group. Mo,

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CCR

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 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), septicemia (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).

DISCUSSION

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 scores, 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.

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Univariate analysis revealed 12 factors (gender, age, primary tumor,
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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
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/C20, 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 CCO-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 HPIC 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,

Fig. 3. Either Control group (a) or Study group (b), patients with CCO-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.
| 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 muscularis transversus 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 ileoceccus | 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, mesenteric fulguration | 2 | 22.2, D | |
| 8 | M/41 | Rectal ca, Metachronous PC | 20 | Rectectomy, greater omentum, left/right diaphragmatic copula resection, colon sigmoideum colectomy | 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 | | 3 | 28.0, D | |

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

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.

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**TABLE VI. Distribution of Adverse Events in Two Groups**

| SAE (grades 3–5) | Control (n = 32) | Study (n = 35) | P |
|------------------|----------------|--------------|---|
| 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) | 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 | X² | 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.
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