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Cytoreductive surgery and HIPEC for malignant ascites from colorectal cancer - a randomized study

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Abstract

Introduction: The efficacy of different timings of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in controlling malignant ascites caused by peritoneal carcinomatosis of colorectal cancer (CRC) is not well defined. The study aims to investigate the clinical efficacy and safety of different timings of CRS with HIPEC for malignant ascites caused by peritoneal carcinomatosis from CRC.

Materials and Methods: This was a preliminary randomized controlled study performed at the Intracelom Hyperthermic Perfusion Therapy Center of the Cancer Hospital of Guangzhou Medical University (China) from December 2008 to December 2016. The patients were randomized to: CRS, followed by HIPEC (CRS+HIPEC; n = 14), and ultrasound-guided HIPEC, followed by CRS 1 to 2 weeks later (HIPEC+ delayed cytoreductive surgery (dCRS) group, n = 14). The endpoints were complete remission rate of ascites, successful complete CRS rate, and overall survival.

Results: Malignant ascites in all patients showed complete remission; the total effective rate was 100%. Complete CRS was not feasible in any patient. The median follow-up of the 2 groups was 41.9 and 42.3 months in the CRS+HIPEC and HIPEC+dCRS groups, respectively. Overall survival was 14.5 (95%CI: 7–19 months) and 14.3 months (95%CI: 4–21 months) ($P > .05$). The adverse effects of HIPEC were manageable.

Conclusions: CRS+HIPEC and HIPEC+dCRS have the same efficacy in controlling malignant ascites caused by CRC and peritoneal carcinomatosis. The timing of CRS and HIPEC does not prolong the survival of patients with peritoneal carcinomatosis from CRC, even when a complete CRS is not feasible.

Abbreviations: BMS = bone marrow suppression, CRC = colorectal cancer, CRS = cytoreductive surgery, dCRS = delayed cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, PCI = peritoneal carcinomatosis index.

Keywords: ascites, colorectal cancer, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal carcinomatosis

1. Introduction

Malignant ascites is one of the main complications in patients with peritoneal carcinomatosis originating from various malignant cancers. With the increasing amount of ascites, the patients usually present with progressive symptoms of abdominal swelling, pain, nausea, and dyspnea.[1–5] Indeed, discomfort and decreased quality of life associated with malignant ascites often exceed that of the cancer itself, resulting in detrimental physiological and psychological states.[6–11] Malignant ascites are associated with a short life expectancy, ranging from weeks to a few months.[1,12–14] A modest increase in life expectancy of up to 2 to 3 months has been observed with modern chemotherapy, depending upon the primary

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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disease.[2–4,12,13] Symptomatic treatments with paracentesis improve distension and dyspnea, but the effects are short-lived as the ascites quickly accumulate, and cognitive and emotional quality of life continues to decline.[2–4,14] Targeted therapy using catumaxomab only prolongs puncture-free survival and delays the deterioration in the quality of life.[10,11] Pressurized intraperitoneal aerosol chemotherapy[10,11] is not suitable for patients with peritoneal carcinomatosis and malignant ascites complicated with intestinal obstruction induced by tumor or with digestive duct hemorrhage. Thus, there is a need for improved treatment strategies for malignant ascites.

Despite advances in adjuvant therapy for colorectal cancer (CRC), peritoneal dissemination remains an important failure site for patients with peritoneal carcinomatosis arising from CRC.[15–21] Recently, hyperthermic intraperitoneal chemotherapy (HIPEC), developed based on intraperitoneal chemotherapy, has been shown to be a promising treatment for peritoneal carcinomatosis originating from gastrointestinal cancer, ovarian cancer, and pseudomyxoma peritonei.[22–32] This procedure uses the advantages of intraperitoneal chemotherapy and the synergistic enhancement of drug cytotoxicity induced by heat.[23–27] HIPEC with cytoreductive surgery (CRS) can offer a palliative improvement for patients with CRC and peritoneal carcinomatosis, since CRS can be used to remove bulky tumor tissue, and HIPEC can be used to eradicate residual microscopic tumors in the peritoneal cavity. CRS plus HIPEC have shown good clinical efficacy for prolonging the survival of patients with peritoneal carcinomatosis from CRC.[33–36]

Many reports demonstrated that HIPEC has the ability to reduce malignant ascites and ameliorate related symptoms.[3–11] Patients with peritoneal carcinomatosis and malignant ascites could be managed using CRS with perioperative HIPEC (CRS+HIPEC) or using B-mode ultrasound-guided HIPEC first, followed by CRS 1 to 2 weeks after HIPEC (HIPEC+ delayed cytoreductive surgery (dCRS)). These 2 therapeutic strategies are based on our experience with ovarian cancer.[8] Such cancer patients must be operated within a defined time limit, CRS is required to be completed as soon as possible after HIPEC treatment. By 1 to 2 weeks after HIPEC treatment, the patients' ascites had disappeared, their general condition was improved, and they could tolerate CRS. A previous study by our group showed that CRS+HIPEC and HIPEC+dCRS might lead to similar outcomes in patients with ovarian cancer and malignant ascites,[8] but patients with CRC usually have different clinical manifestations than patients with ovarian cancer. Indeed, CRC is often complicated with intestinal obstruction or digestive duct hemorrhage induced by the tumor. Therefore, the efficacy and safety of CRS+HIPEC or HIPEC+dCRS in patients with CRC and massive ascites have yet to be elucidated.

Therefore, we hypothesized that both CRS+HIPEC and HIPEC +dCRS achieve good ascites control in patients with CRC and malignant ascites. The primary objective was to investigate the efficacy of different sequential approaches of HIPEC and CRS in patients with CRC and malignant ascites. The secondary objective was to examine the efficacy of CRS+HIPEC in controlling malignant ascites in patients in whom a complete CRS was attempted but not achieved because of the volume or distribution of the disease.

2. Materials and methods

2.1. Study design

This was a preliminary randomized controlled study performed at the Intracelom Hyperthermic Perfusion Therapy Center of the Cancer Hospital of Guangzhou Medical University (China) from December 2008 to December 2016. The study was approved by the Medical Ethics Committee of the Cancer Hospital of Guangzhou Medical University (no. GZMCY 20080825). Written informed consent was obtained from all patients.

2.2. Patients

The diagnosis of CRC was mainly based on colonoscopic biopsy, imaging examination, and tumor markers. The diagnostic criteria of malignant ascites were:

1) patients with abdominal malignant tumors;
2) a large volume of ascites;
3) increased tumor markers (CEA, CA199, and MMPS); and
4) exclusion of other diseases that can cause ascites such as inflammation, hepatorenal insufficiency, and portal vein or inferior vena cava obstruction.

All patients were diagnosed with malignant ascites from peritoneal carcinomatosis due to CRC by CT, MRI, and/or clinical examination. The inclusion criteria were:

1) ≥18 years of age;
2) no definite remission of ascites by other previous therapies;
3) no radiation therapy in the previous 4 weeks;
4) no chemotherapy in the previous 2 weeks; and
5) expected survival was >2 months according to the patient's general condition.

The exclusion criteria were:

1) known or possible colorectal metastasis from other organs;
2) recurrent CRC with ascites;
3) known or possible malignant tumor or metastasis tumor in other internal organs;
4) tumor-induced intestinal obstruction;
5) massive hemorrhage of the digestive tract; or
6) extensive abdominal adhesions due to multiple operations.

2.3. Grouping

According to sequential sealed envelopes prepared by an independent statistician using a computer-based random table, the patients with CRC and malignant ascites were randomized to the CRS+HIPEC group or the HIPEC+dCRS group. The CRS +HIPEC group was treated with CRS, followed by HIPEC immediately after CRS, during the operation window, while the HIPEC+dCRS group was treated with HIPEC, followed by CRS delayed by 1 to 2 weeks.

2.4. Ascites scoring system

An ascites scoring system was created based on the distribution of ascites in the peritoneal cavity on preoperative CT of the abdomen and pelvis with the patient in the supine position, as described by Randle et al.[36] The ascites were graded based on the CT scan. The abdominal cavity was divided into 9 regions, similar to those used in calculating the peritoneal carcinomatosis index (PCI). The presence of ascites in a region was scored 1; thus, ascites were graded on a scale from 0 to 9. Scores of 1 to 3, 4 to 6, and 7 to 9 were considered small, medium, and large amounts of ascites, respectively.

2.5. CRS and placement of perfusion catheters

For CRS, all patients were treated with the intention of achieving complete CRS, that is, to remove all visible nodules. Of course, patients in the HIPEC+dCRS group underwent CRS after HIPEC. All selected patients underwent CRS+HIPEC, as described in our previously published studies.[8,10] CRS was performed under general anesthesia and endotracheal intubation. After opening the abdominal wall, 200 mL of ascites were sent for cytological examination. All remaining abdominal fluid was suctioned. CRS consisted in the removal of all gross tumors and involved organs, peritoneum, or tissue, as deemed technically feasible and safe for the patient. Any tumors adhering or invading vital structures that could not be removed were cytoreduced using a cavitational ultrasonic surgical aspirator (Valleylab, Boulder, CO).

The anatomical extension of the CRC in the peritoneal cavity was evaluated using the PCI described by Sugarbaker.[37,38] The assessments of PCI and of the completeness of CRS were performed at the end of the procedure by an experienced surgeon of the study team strictly according to the Sugarbaker's standards. PCI was classified into 3 categories: CCR-0: no macroscopic residual cancer; CCR-1: no residual nodule >2.5 mm in diameter; and CCR-2: the diameter of the residual nodules was >5 mm.[39] Both CCR-0 and CCR-1 were considered as complete CRS, and CCR-2 was considered as incomplete CRS.[39]

Following CRS, an infusion catheter with multiple side holes (inner diameter of 0.8 cm, outer diameter of 1.0 cm, and 100 cm in length) was placed into the peritoneal cavity in the upper left and right quadrants, with 40 to 60 cm of the catheter inside the body. Similarly, an outflow catheter with the same dimensions was placed in the lower left and right quadrants of the pelvic cavity, respectively. The abdominal wall was sutured, and the perfusion catheter was fixed to the abdominal wall by cutaneous sutures, as shown in Figure 1B.

2.6. B-mode ultrasound-guided placement of catheters for chemotherapy

For patients in the HIPEC+dCRS group, B-mode ultrasound-guided HIPEC was performed first, and dCRS was performed 1 to 2 weeks after HIPEC. In a standard operating room, the patients were placed in the supine position. Pethidine hydrochloride (75 mg) and promethazine hydrochloride (25 mg) were administered by intramuscular injection. Propofol was given intravenously in a continuous manner at 3 to 8 mL/h, adjusted according to the patient's status. A B-mode ultrasound examination of all 4 abdominal quadrants was performed to select the best puncture location. The liquid dark region with the largest amount of ascites that were not adhering to the abdominal wall or to the peritoneal cavity was selected. In addition, the region had to be without a previous abdominal incision or tumor. A 1.2-cm incision was made after locally administering 0.5% lidocaine, and a Hasson trocar (1.2 cm in diameter) was placed into the peritoneal cavity. Then, the infusion and outflow catheters with multiple side holes (inner diameter of 0.8 cm, outer diameter of 1.0 cm, and 100 cm in length) were placed into the intraperitoneal cavity. The infusion catheters were positioned in the left and right upper quadrants of the intraperitoneal cavity with an inside length of 40 to 80 cm. The outflow catheters were placed in the pelvic cavity of the left and right lower quadrants with the same length as the infusion catheters. The ascites were extracted as completely as possible. All perfusion catheters were fixed to the abdominal wall by cutaneous sutures, as shown in Figure 1A.

2.7. HIPEC

HIPEC was performed using our self-developed "BR-TRG-II type high-precision hyperthermic intraperitoneal perfusion treatment system" (BR-TRG-II; Guangzhou Baorui Medical Instrument Co., Ltd., Guangzhou, China), which has a precision of ±0.1°C for temperature control and ±5% for flow control, and which is

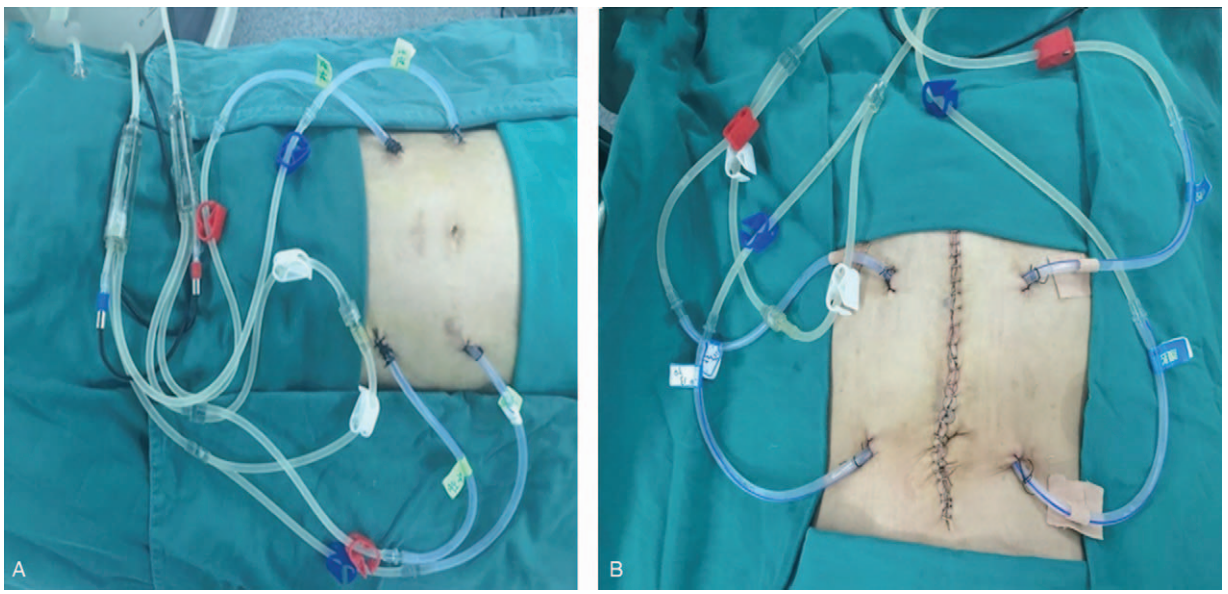

Figure 1. Placement of the infusion and outflow catheters for hyperthermic intraperitoneal chemotherapy. The red clips indicate the 2 infusion catheters, the blue clips indicate the 2 outflow catheters, and the white clips indicate the loop circuit for hyperthermic intraperitoneal chemotherapy preparation. (A) B-ultrasound-guided placement of perfusion catheters. (B) Laparotomy colorectal cancer and placement of perfusion catheters.

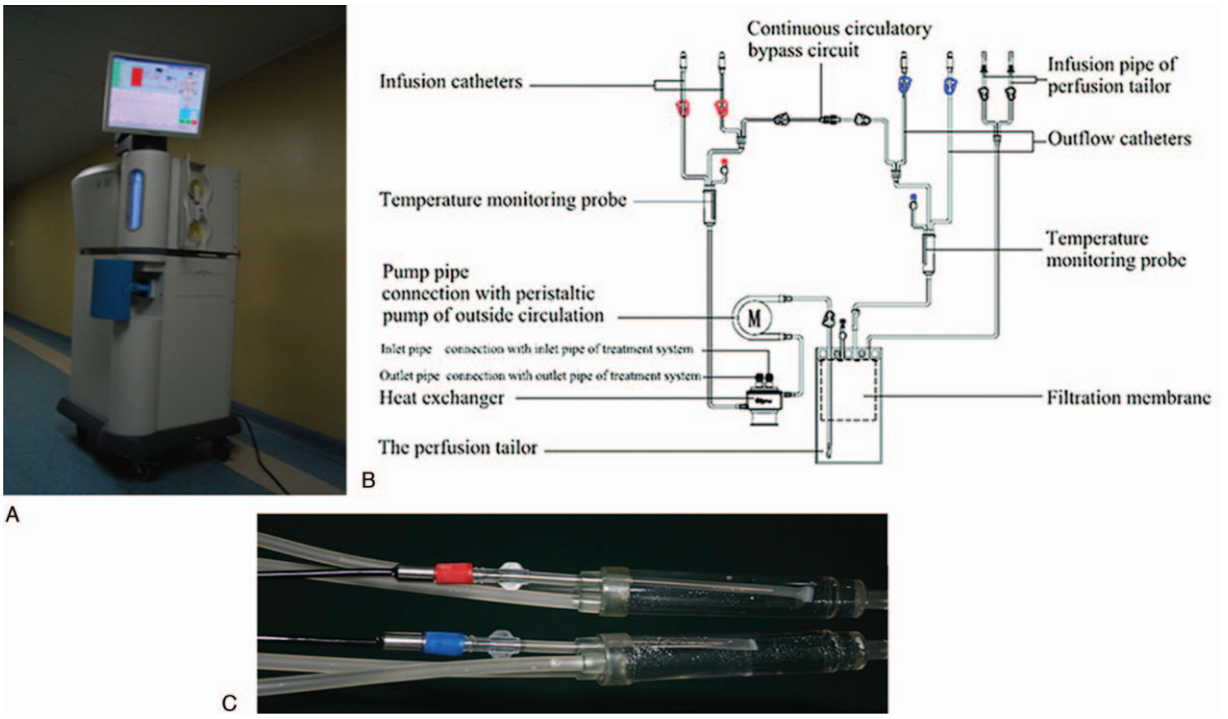

Figure 2. The BR-TRG-II high-precision body cavity hyperthermic perfusion treatment system and temperature monitoring probes. (A) The BR-TRG-II high-precision, body cavity hyperthermic perfusion treatment system. (B) Schematic diagram of the BR-TRG-II high-precision body cavity hyperthermic perfusion treatment system and temperature monitoring probes. (C) Temperature monitoring probes placed in the infusion catheter and the outflow catheter through a blind pipe in each of the catheters.

coupled to an automatic cooling function. This device, as shown in Figure 2A, the only one of its kind, has been approved by the State Food Drug Administration of China (approval number: 2009-3260924), and is covered by 2 patents in China (No. ZL2006200613779 and ZL2006200613764).[8–11] HIPEC was delivered for 3 sessions in the operating room, at a perfusion velocity of 450 to 600 mL/minute and an inflow temperature of 43°C, in order to obtain an abdominal temperature of 41° to 42°C A treatment session lasted about 90 minutes. The first session was completed with the patient under endotracheal anesthesia after the placement of perfusion catheters after CRS or after B-mode ultrasound-guided placement of catheters. Oxaliplatin (L-OHP, 125 mg/m^2 of the body surface, Sanofi (Hangzhou) Pharmaceutical Co., Ltd) was the HIPEC chemotherapeutic agent. The second and third sessions were performed on the first and second days after the first HIPEC session, using raltitrexed (Ra, 3 mg/m^2 of the body surface, Tomudex, TDX, ZD 1694) and 5-fluorouracil (5-FU, 175 mg/m^2 of the body surface, Xi'an Haixin Pharmaceutical Co., Ltd.). Intravenous propofol was administered continuously at a rate of 3 to 8 mL/h as an anesthetic agent, adjusted according to the patient's status.

When L-OHP was used as the HIPPC chemotherapeutic agent, a 5% glucose solution (approximately 4500–6000 mL, depending on the volume of the peritoneal cavity) was used as the perfusion solution. For Ra or 5-FU, 0.9% sodium chloride solution (approximately 4500–6000 mL) was selected as the carrier. All chemotherapeutic agents were added into the perfusion cocktail of HIPEC, as shown in Figure 2B.

The treatment temperature during HIPEC was measured by the BR-TRG-II treatment system using temperature-monitoring probes in the infusion and outflow catheters (Fig. 2C). Patients' vital signs (blood pressure, heart rate, respiratory rate, and blood oxygen saturation) were assessed using a multi-parameter patient monitoring machine (G3HJ20025, Shenzhen, China). After the third HIPEC session, all ascites were drained out, and the infusion catheters were removed. The outflow catheters were kept for 3 to 5 days as a closed drainage catheter.

2.8. Follow-up

All patients were followed until December 2016 or death. Follow-up was performed at 1- or 3-month intervals for 1 year and then every 3 to 6 months thereafter. Abdominal and pelvic CT were obtained at 3, 6, and 9 months after treatment or when clinically indicated. All patients received 1 to 6 cycles of FOLFOX4 systemic chemotherapy, beginning 2 weeks following all treatments, at the discretion of their oncologist.

Follow-up data included the data of the most recent follow-up, the status of the patient (alive with ascites, alive without ascites, dead with ascites, and dead without ascites), the site of initial recurrence, and all other sites of recurrence after the initial site of recurrence.

2.9. Endpoints

Overall survival, the primary endpoint, was defined as the length of time from completing CRS+HIPEC treatment to death or end of follow-up (censored data). Clinical effectiveness (secondary endpoint), based on the remission of ascites, was classified into 3 grades according to our previous modification of the WHO criteria for effectiveness assessment.[8–11] Ascites was considered to have been successfully treated with CRS-HIPEC if ascites showed complete remission on routine 1-month postoperative

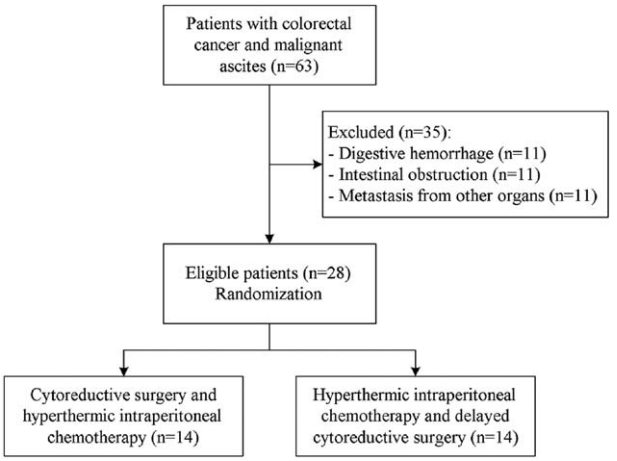

Figure 3. Patient flowchart.

CT.[8–11] Failures included all patients with re-accumulation of any ascites or recurrence of symptoms attributed specifically to ascites at 1 month.[8–11] The Karnofsky performance scores (KPS) (secondary endpoint) were calculated before treatment and at 1 month after treatment in all patients.

2.10. Safety assessment

Major complications (including grades I-IV bone marrow suppression (BMS)) were assessed according to the National Cancer Institute's Common Toxicity Criteria, version 4.0.[17]

2.11. Statistical analysis

This was a preliminary proof-of-concept study, and no formal power analysis was performed. The groups were arbitrarily set at 14 patients. Data were analyzed using SPSS 19.0 (IBM, Armonk, NY). Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. All continuous data are presented as mean ± standard deviation (SD); between-group comparisons were performed using the Student *t* tests, and paired-samples *t* tests were used to compare results before and after therapy within each group. Overall survival was analyzed and compared using the Kaplan–Meier method and the log-rank test. 2-sided *P*-values $< .05$ were considered statistically significant.

3. Results

3.1. Characteristics of the patients

As shown in Figure 3, from December 2008 to December 2016, 28 patients (mean age of 54.3 ± 3.6 years; ranging from 32–76 years) were included in the presented study. Of these 28 patients with CRC and massive ascites, 14 were assigned to the CRS +HIPEC group and 14 to the HIPEC+dCRS groups. The CRS +HIPEC group included 9 males and 5 females, aged 56.0 ± 7.2 (range, 32–78) years. There were 3 cases of transverse colon cancer, 3 of ascending colon cancer, 4 of cecum carcinoma, and 4 of sigmoid colon cancer. The pathological types included well-differentiated adenocarcinoma in 4 patients, moderately differentiated adenocarcinoma in 2, poorly differentiated adenocarcinoma in 2, and mucinous adenocarcinoma and ring cell carcinoma in 6. In the HIPEC + dCRS group, there were 8 males and 6 females, aged 58.6 ± 9.1 (36–70) years. There were 2 cases of transverse colon cancer, 4 of ascending colon cancer, 3 of cecum carcinoma, and 6 of sigmoid colon cancer. The pathological types included well-differentiated adenocarcinoma in 3 patients, moderately differentiated adenocarcinoma in 3, poorly differentiated adenocarcinoma in 3, and mucinous adenocarcinoma and signet ring cell carcinoma in 5 (Table 1).

Table 1

Clinical characteristics of the patients with malignant ascites caused by PC of colorectal cancer treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

	CRS+HIPEC (n = 14)	HIPEC+dCRS (n = 14)	Total (n = 28)	*P*
Age (yr), mean (range)	56.0 ± 7.2 (32–78)	58.6 ± 9.1 (36–70)	54.3 ± 3.6 (32–76)	.09
Sex				
Male	9	8	17	.07
Female	5	6	11	.08
Cancer site				
Transverse colon cancer	21.4% (3)	14.3% (2)	17.9% (5)	.07
Ascending colon cancer	21.4% (3)	28.6% (4)	25.0% (7)	.06
Cecum carcinoma	28.6% (4)	21.4% (3)	25.0% (7)	.08
Sigmoid colon cancer	28.6% (4)	42.9% (6)	35.7% (10)	.07
Pathological type*				
Well differentiated	28.6% (4)	21.4% (3)	25.0% (7)	.06
Moderately differentiated	14.3% (2)	21.4% (3)	17.9% (5)	.07
Poorly differentiated	14.3% (2)	21.4% (3)	17.9% (5)	.10
Mucinous adenocarcinoma and signet ring cell carcinoma	42.9% (6)	35.7% (5)	39.3% (11)	.10
Ascites (mL)	3857 ± 146 (2800–6300)	3938 ± 168 (2600–6500)	3905 ± 186 (2600–6500)	.08
Ascites scores (n)	9	9	9	.07
FCCs in the ascites, % (n)	57.1% (8)	64.2% (9)	60.7% (17)	.07
PCI	27 ± 1.3 (13–37)	26 ± 1.1 (5–29)		.06

Data are presented as the mean ± standard deviation, unless otherwise stated.

CRS = cytoreductive surgery, dCRS = delayed cytoreductive surgery, FCCs = free cancer cells, HIPEC = hyperthermic intraperitoneal chemotherapy, PCI = peritoneal carcinomatosis index.

* All cases showed concordance between the diagnoses at biopsy and on the surgical specimen.

Table 2

Analysis of the clinical effectiveness and adverse effects of patients with malignant ascites caused by PC of colorectal cancer treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

	CRS+HIPEC (n = 14)	HIPEC+dCRS (n = 14)	Total (n = 28)	*P*
Follow-up time (mo)	41.9 (6.5–110)	42.3 (10.5–99.7)		.07
OS (mo)	14.4 (4–21)	14.5 (7–19)	14.3 (4–21)	.07
Ascites remission rate (%)	100	100	100	.10
Reduction degree				
C-CRS	0	0	0	.06
I-CRS	14	14	28	.07
KPS scores				
Before treatment	50.3 ± 12.9	49.8 ± 11.3	49.2 ± 11.4	.06
After treatment	76.5 ± 14.4	76.7 ± 15.5	77.6 ± 13.3	.07
Adverse effects				
BMS	0% (0)	35.7% (5)	17.9% (5)	.001
SRF	7.1% (1)	0% (0)	3.6% (1)	.001
Hospitalization time (days)	18 (15 -21)	25 (25 -28)	22 (15 -28)	.001
Hospitalization cost (10,000¥)	8.6 (8.4–9.0)	12.5 (11.4–13.6)	10.6 (8.4–13.6)	.001

BMS = bone marrow suppression, C-CRS = complete CRS, CR = complete remission, CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, I-CRS = incomplete CRS, KPS = Karnofsky performance scale, OS = overall survival, SFR = severe renal failure.

3.2. Ascites scores and PCI

The ascites scores could be calculated in all 28 patients. All 28 patients had a score of 9,[36,38] that is, all patients had great amounts of ascites. In all patients, the amount of ascites ranged from 2600 to 6500 mL, with a mean of 3525 ± 67 mL, confirmed by exploratory laparotomy drainage or by B-mode ultrasound-guided paracentesis drainage. Free cancer cells were observed in 57.3% of the ascites samples (Table 1).

In the CRS+HIPEC group, the ascites scores were 9 in all patients.[36,38] The amount of ascites ranged from 2800 to 6300 mL, with a mean of 3857 ± 57 mL. Free cancer cells were observed in 58.2% of the ascites samples. In the HIPEC+dCRS group, ascites scores were 9 in all patients. The volume of ascites ranged from 2600 to 6500 mL, with a mean of 3938 ± 71 mL. Free cancer cells were observed in 57.7% of the ascites samples (Table 1). There were no significant differences in ascites scores, the mean amount of ascites, and the rate of free cancer cell positivity between the 2 groups.

In the CRS+HIPEC group, the mean PCI was 27 ± 1.3 (ranging from 13–37) before HIPEC, according to Sugarbaker's PCI.[14,38] In the HIPEC + dCRS group, the mean PCI was 26 ± 1.1 (ranging from 15–36), as determined 1 to 2 weeks after HIPEC. There was no significant difference in PCI between the 2 groups (Table 1).

3.3. Remission of malignant ascites and KPS score change

All patients in both groups exhibited complete remission of malignant ascites, for an objective remission rate of malignant ascites of 100%. No significant differences in ascites objective remission rates were observed between the 2 groups ($P > .05$) (Table 2).

In all patients, the KPS scores improved from 49.2 ± 1.4 before treatment to 76.4 ± 3.3 after treatment. In the CRS+HIPEC group, the KPS scores improved from 49.1 ± 2.9 before treatment to 76.3 ± 4.4 after treatment. In the HIPEC+dCRS group, the KPS scores improved from 49.7 ± 1.3 before treatment to 76.9 ± 1.5 after treatment. There were no significant differences in the KPS scores at admission and after treatments between the 2 groups (Table 2), and there were no significant differences in the changes in KPS scores between the 2 groups.

3.4. Follow-up

The median follow-up was 41.9 months (6.5–110 months) in the CRS+HIPEC group and 42.3 months (10.5–99.7 months) in the HIPEC+dCRS group ($P = .001$). Overall survival was 14.5 months (95%CI: 7–19 months) and 14.3 months (95%CI: 4–21 months), respectively ($P > .05$) (Fig. 4).

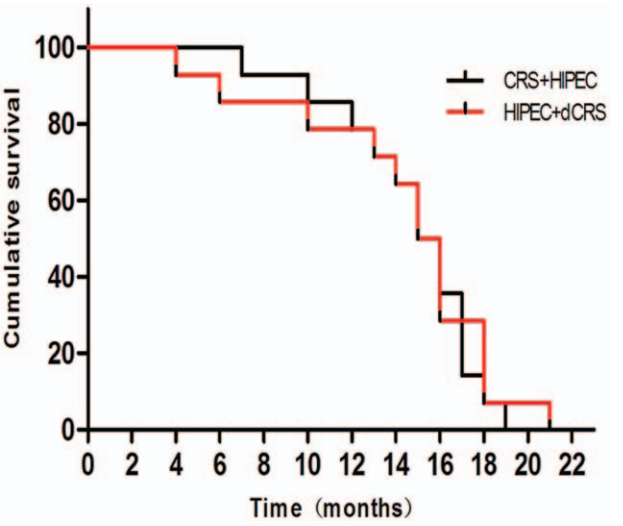

Figure 4. Kaplan–Meier survival curves for patients with malignant ascites caused by peritoneal carcinomatosis of colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). The overall survival of patients treated with cytoreductive surgery +HIPEC ranged from 7 to 19 months, with a median survival of 14.5 months (95%CI: 7–19 months). The overall survival of patients treated with HIPEC+ delayed cytoreductive surgery ranged from 4 to 21 months, with a median survival of 14.3 months (95%CI: 7–19 months). There were no significant differences in overall survival between the 2 groups ($P > .05$, log-rank test).

3.5. CRS outcomes

All patients underwent CRS with the aim of achieving CCR-0 or CCR-1 CRS. Disappointingly, only partial colon resection and anastomosis or partial excision of greater omentum could be achieved, without any case in whom satisfactory CRS of CRC tumor could be achieved (Table 2).

3.6. Hospitalization time and cost

In all patients, the total mean hospitalization time was 22 days (ranging from 15–28 days). The total mean hospitalization cost was 106,000 ¥ per patient (ranging from 84,000–136,000 ¥).

The CRS+HIPEC group had a mean hospitalization time of 18 days (ranging from 15–21 days); the HIPEC+dCRS group had a significantly longer total hospitalization time of 25 days (ranging from 20–28 days) ($P = .001$). The CRS+HIPEC group had a mean total hospitalization cost of 86,000 ¥ per patient (84,000–90,000 ¥). The HIPEC+dCRS group had a significantly higher total hospitalization cost of 125,000 ¥ per patient (114,000–136,000 ¥) ($P = .001$).

3.7. Adverse events due to HIPEC

Adverse events due to HIPEC were found in 6 patients, including 5 with grade I-II BMS and 1 with severe renal failure (SRF) that required hemodialysis. BMS of grade I-II was observed in 5 patients in the HIPEC+dCRS group. These events were resolved after 1 to 3 days of granulocyte colony-stimulating factor treatment. SRF was observed in 1 case in the CRS+HIPEC group and required hemodialysis. No other severe complications (such as visceral injury, abdominal incision infection, or adhesive bowel obstruction) were observed after HIPEC.

4. Discussion

The efficacy of different timings of CRS with HIPEC in controlling malignant ascites caused by peritoneal carcinomatosis of CRC is not defined. Therefore, this study aimed to investigate the clinical efficacy and safety of different timings of CRS with HIPEC for malignant ascites caused by peritoneal carcinomatosis from CRC. The results showed that CRS+HIPEC and HIPEC+dCRS have the same efficacy in controlling malignant ascites caused by CRC and peritoneal carcinomatosis. The timing of CRS and HIPEC does not prolong the survival of patients with peritoneal carcinomatosis from CRC, even when a complete CRS is not feasible.

Studies showed that many primary or secondary intraperitoneal tumors such as gastric cancer, ovarian cancer, breast cancer, pseudomyxoma peritonei, or gastrointestinal stromal tumor could present a large amount of malignant ascites.[2–11] In the present study, CRC patients with malignant ascites included various pathological types such as well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, and mucinous adenocarcinoma or signet ring cell carcinoma. The results showed that there were no definite relationships between the formation of malignant ascites, tumor sites, and pathological types.

The intention of CRS is to achieve complete CRS, that is, to remove all tumors seen by the naked eye, but the majority of patients with malignant ascites and peritoneal carcinomatosis caused by gastrointestinal tumors experience CRS failure because of disseminated peritoneal carcinomatosis.[9,10,38] The ascites score could estimate the rate of complete CRS before surgery. A retrospective study by Randle et al[36] suggested that the presence of malignant ascites significantly decreases the chances of achieving a complete CRS for macroscopic metastases. We previously reported that the rate of complete CRS was reduced with increasing amounts of ascites in patients with gastrointestinal cancer.[8–11] The present study suggests that complete CRS was achieved in no patient with CRC and malignant ascites, which is consistent with our previous report and Randle's study.[36] The ascites score could serve as a tool to predict the likelihood of achieving a complete CRS before attempting CRS,[38] and the high morbidity and mortality provide further support to avoid CRS as palliative therapy for these patients, except when these patients require emergency operation due to intestinal obstruction, digestive duct hemorrhage, or neoplastic intestinal perforation.[40–42]

Studies have shown that HIPEC has good clinical efficacy in controlling ascites for patients with malignant ascites originating from peritoneal carcinomatosis.[2,13,14] In the present study, CRS +HIPEC and HIPEC+dCRS demonstrated a rather good efficacy in reducing malignant ascites and alleviating related symptoms. The total ascites objective remission rate was 100%, even though a complete CRS was not achieved in any patient in the present study. Regardless of the treatment sequence, in the end, both patients underwent both procedures. The time window between the 2 procedures in the second group could allow the disease to progress, but there is a high probability that the disease was controlled by chemotherapy. Unfortunately, because of the disseminated nature of the disease and because of morphological changes after ascites drainage, CT scans were unreliable to determine the disease status. Nevertheless, the results suggest that there is no difference in survival between the 2 groups for the results suggest that eradicating peritoneal microscopic tumors using CRS-HIPEC might not be the major factor for controlling malignant ascites from CRC. Remission of ascites seemed to be independent of the resection status of CRC, suggesting that it is more likely a function of HIPEC than CRS or that HIPEC controls the ascites by yet unidentified mechanisms. Our previously published experience with laparoscopic HIPEC or ultrasound-guided HIPEC for the palliative control of malignant ascites supports this conclusion.[8–11] Our previously published study results, although in small groups of patients, indicate a high rate of alleviating ascites-related symptoms in addition to improvement in the quality of life.[8–11] In the present study, KPS scores of patients increased both in the HIPEC+dCRS and HIPEC+dCRS groups, and there were no significant differences in the changes in KPS scores between the 2 groups. These results demonstrate that CRS+HIPEC and HIPEC +dCRS have similar clinical efficacy for improving quality of life by way of improvements in KPS scores.

There is evidence of a curative effect after CRS+HIPEC in patients with peritoneal carcinomatosis originating from CRC, and 15% to 22% of patients achieved a 5-year disease-free survival. Thus, CRS should be applied with a curative and not a palliative intent.[32,41,43] Nevertheless, CRS-HIPEC improved survival of patients with peritoneal carcinomatosis originating from CRC only in cases where a successful complete CRS was achieved, and patients with peritoneal carcinomatosis and malignant ascites with incomplete CRS have a poor prognosis.[8,10,38] In the present study, the median overall survival of the patients with malignant ascites from CRC who had incomplete CRS was 14.4 months in all patients, which is in agreement with the current knowledge of survival in patients presenting with high ascites scores.

CRS+HIPEC and HIPEC+dCRS had similar effects on KPS and survival. Nevertheless, CRS+HIPEC may shorten the operation time and reduce hospitalization costs, making the treatment available to a broader patient population. Patients with massive ascites, poor health conditions, and unstable vital signs without intestinal obstruction, hemorrhage, or systemic poisoning symptoms are unsuitable for CRS+HIPEC, and they require HIPEC+dCRS. Therefore, patients with CRC and malignant ascites could receive CRS+HIPEC or HIPEC+dCRS according to their clinical manifestation or health conditions. We recommend CRC patients with massive ascites and poor health conditions and unstable vital signs without intestinal obstruction, hemorrhage, or systemic poisoning symptoms should only be treated by HIPEC, even if a CC1 or CC2 resection could be achieved, and patients with intestinal obstruction, hemorrhage, or systemic poisoning symptoms should be treated by CRS+HIPEC.

In this study, BMS was not observed in the CRS+HIPEC group (0%), but BMS of grade I-II was observed in 5 patients in the HIPEC+dCRS group (35.7%), and the high frequency of BMS in the HIPEC+dCRS group is worth mention. We think that this could be related to the stimulation of bone marrow hematopoietic function by PGE2, PGI2, IL-6, IL-1β, and TNF-α produced by CRS trauma in the CRS+HIPEC group, for these patients have a stronger regeneration ability of bone marrow white blood cells after CRS operation. The present study has limitations. First, the sample size was small due, preventing subgroup analyses. In addition, multivariable analyses evaluating the impact of treatment with CRS+HIPEC versus HIPEC+dCRS on outcomes could not be conducted. Second, since all patients achieved ascites remission, we could not analyze the factors that could be associated with treatment success. Third, the patients with an expected survival <2 months were excluded, which could lead to a healthy user bias. Finally, the study was performed in patients in whom no other treatment would have been undertaken, except probably palliative and end-of-life treatments. In addition, both groups underwent the 2 study procedures, and there was, therefore, no control group. Finally, despite a wealth of evidence regarding B-mode ultrasound catheterization, HIPEC, and CRS[1–4,6–11,15,16,23–34,36,41,42,44–47], no formal phase 1 and 2 trials have been carried out. Therefore, this study should be considered as a preliminary proof-of-concept study for the use of HIPEC and CRS for malignant ascites from CRC and peritoneal carcinomatosis. Multicenter studies are necessary to address these issues correctly.

5. Conclusion

CRS+HIPEC and HIPEC+dCRS have similar outcomes in controlling malignant ascites for patients with CRC, even though complete CRS was not achieved. Patients with CRC and malignant ascites should consider CRS+HIPEC or HIPEC+dCRS according to their clinical manifestation and health condition. The presence of voluminous malignant ascites could be a strong predictor of decreased feasibility of complete CRS for patients with CRC. HIPEC had positive effects in the treatment of malignant tumors. Nevertheless, its anti-tumor mechanism, application methods, and selection of chemotherapy drugs still need further research.

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