A Novel Bedside HIPEC as Adjuvant Therapy for Stage III Gastric Cancer Patients after D2 Radical Gastrectomy

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Research Article

Keywords: gastric cancer, hyperthermic intraperitoneal chemotherapy (HIPEC), S-1, cisplatin, surgery

Posted Date: January 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-134300/v1

Abstract

Background To investigate the efficacy and safety of a novel bedside prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced gastric cancer after radical D2 gastrectomy.

Methods Total 114 patients with stage III gastric cancer were randomly assigned to bedside HIPEC or control treatment groups two weeks after radical D2 gastrectomy. HIPEC group was treated with cisplatin (60 mg/m^2) through HIPEC, which was given on day 1 and 3 (30 mg/m^2 each time), plus oral administration of S-1 twice daily at 40–60 mg/time for 14 days. Control group was treated with cisplatin (60 mg/m^2), which was administered intravenously once, plus oral administration of S-1 twice daily, 40–60 mg/time, for 14 days. Patients in either group were given 6–8 cycles of the therapy.

Results Median of disease-free survival (DFS) was 21.0 months in the HIPEC group, which was significantly longer than that in the control group (14.0 months, $P = 0.039$). The rate of 2-year DFS in the HIPEC group was higher than that in the control group although it was not statistically significant (47.3% vs 29.4%). In contrast, incidence of peritoneal metastasis was lower in the HIPEC (6/57, 10.5%) in comparison to that in the control group (12/57, 21.1%, $P = 0.198$). Patients in both groups completed an average of 5.9 cycles of the therapy with no significant difference in the incidence of adverse effects (except thrombocytopenia).

Conclusion HIPEC with cisplatin plus oral S-1 is a safe and effective adjuvant therapy for the patients with advanced gastric cancer following radical D2 gastrectomy.

Background

It has recently been reported that prevalence of gastric cancer in 2018 reached one million, which was the third highest malignant tumor in the world (1). Worldwide mortality of gastric cancer was approximately 0.78 million, which was the third most common cause of cancer-associated death for men and fifth most common cause for women (1). Gastric cancer is the most common digestive system cancer in Chinese population. According to the most recently published data, gastric cancer is the 2nd most common cancer in Chinese population, and it is the third most common cause of death in China (2, 3).

Radical resection is still the first choice for the treatment of gastric cancer. With the development and clinical application of D2 radical surgery, prognosis of gastric cancer has been improved. However, recurrent rate of gastric cancer within 5 years after surgery is still as high as 25–40% (4, 5), especially in the stage III or higher gastric cancer patients (6). Post-surgery chemotherapy is, therefore, widely accepted as standard therapy for the treatment of gastric cancer patients in order to improve survival of the patients (7, 8).

Peritoneal metastasis is one of the common post-operative complications for advanced gastric cancer patients, and the incidence of peritoneal metastasis is as high as 60% (9). Conventional chemotherapy

through intravenous administration has limited therapeutic effect on the peritoneal metastasis. Prognosis of the patients with peritoneal metastasis after radical surgery is very poor, and average of the median survival for these patients is only 8-13.2 months (10–14). Therefore, prevention and treatment of peritoneal metastasis following the radical surgery of gastric cancer becomes crucial to improve the patients' survival and quality of life.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a topical chemotherapy applied during surgery or post-surgery for the treatment of peritoneal surface malignancies (15). The combination of hyperthermia and intraperitoneal chemotherapy has significantly increased efficacy of chemotherapeutic drugs to kill cancer cells (16). In the past decade, cytoreductive surgery (CRS) plus HIPEC has become a gold standard for the treatment of peritoneal surface malignancies including peritoneal pseudomyxoma, peritoneal mesothelioma, and colorectal peritoneal metastasis (17, 18). Recently, it was report that prophylactic HIPEC during surgery with radical D2 gastrectomy improves survival and peritoneal recurrence rates for locally advanced gastric cancer (19).

Since September 2007, a novel procedure of bedside HIPEC has been conducted in our facility. We previously reported that the safety of 5,759 times of bedside hyperthermic intra-peritoneal or intra-pleural chemotherapy (20). However, whether the bedside HIPEC after radical surgery could effectively improve the overall survival in the advanced gastric cancer patient remains to be determined. The current study was, therefore, designed to investigate the effect of bedside HIPEC plus oral S-1 in comparison to systemic chemotherapy plus oral S-1 in the treatment of stage III gastric cancer patients who received radical D2 surgery.

Methods

Trial design Patients were randomly assigned to the following two treatment groups. HIPEC group: treated with HIPEC with cisplatin plus orally taken S-1. Control group: systemic chemotherapy with cisplatin IV plus orally taken S-1. One therapeutic course lasted 3 weeks, and patients received 6–8 cycles of the 3-week therapeutic courses.

Before the trial, patient's baseline condition and information were collected, including history, physical examination, quality of life evaluation (EQ-5D), laboratory tests, and radiologic images. Before and after each therapeutic course, routine blood tests, liver function tests, electrolyte panel and kidney function tests, routine urine tests, routine stool tests, and ECG examination were performed. After completion of two-therapeutic courses, radiologic imaging was conducted. After completion of the 6–8 cycles of therapy, patients were followed up every 3 months.

Patient recruitment From April 2014, patients with stage III gastric cancer, who met the diagnostic criteria of Union for International Cancer Control (UICC) as well as the 7th edition of American Joint Committee on Cancer (AJCC) staging system and received D2 radical CRS were enrolled into this study. Patients also met the following criteria: 1). Had not been treated with chemotherapy, radiotherapy, or immunotherapy before and after CRS. 2). Patient's Eastern Cooperative Oncology Group (ECOG) score was ≤ 1. 3). At 2–4

weeks period of recovery after CRS. 4). Predicted survival length was less than 6 months. 5). Patient's routine blood test, laboratory tests, electrolyte panel, liver function test, kidney function test, routine urine test, routine stool test, and ECG examination results indicated no contradiction to the chemotherapy. 6). No hepatitis B infection. 7). No deficiency in dihydropyrimidine dehydrogenase (DPD). 8). Patient signed the consent form.

HIPEC procedure Before HIPEC procedure, patients were routinely given antiemetic drugs and intravenous instillation of saline in order to prevent damage of kidney functions by the chemotherapeutic drugs. Puncture points for HIPEC-Inlet and -Outlet positions on the patients' abdominal wall were determined by bedside Ultrasonic examination. After disinfection of the skin and local anesthesia, a 16G size needle punctured into the peritoneal cavity at the Inlet point. Normal saline (2000–4000 mL) was then injected into the abdominal cavity. The 2nd needle was then punctured into the cavity at the Outlet point, hyperthermia perfusion and circulation between the patient and HIPEC machine was then established. The Inlet temperature (water temperature into the patient's peritoneal cavity) was adjusted to 41 ± 1 °C, and the Outlet temperature was at 40 ± 1 °C. Cisplatin (30 mg/m^2) was dissolved with 20–50 mL saline and injected into the HIPEC circulation system. After completion of the 60 min HIPEC treatment, most of the saline (approximately 1500 mL) containing cisplatin were left inside the peritoneal cavity (detailed parameters settings of perfusion were listed in the Table 1). Puncture needles were pulled out, and the puncture points were disinfected and sealed. Patients were told to change body position as needed. Two days later, the 2nd time HIPEC was repeated as aforementioned.

Table 1
Parameters for HIPEC

HIPEC parameters	Setting
Duration (min)	60 min
Temperature (℃)	
Input	41–43℃
Output	40–42℃
Rate of flow	180–200 ml/min
Dose of cisplatin in total	60 mg/m^2
Dose of normal saline / perfusion	2000–4000 ml

S-1 administration S-1 (Tegafur-gimeracil-oteracil potassium capsule) was purchased from Taiho Pharmaceutical (Tokushima,Japan) and it was administrated orally following the manufacture's instruction. Specifically, 40 mg/time, twice a day for a patient with < 1.25 m^2 body surface area (BSA); 50 mg/time, twice a day for a patient with ≥ 1.25 m^2, but < 1.5 m^2 BSA; and 60 mg/time, twice a day for a

patient with > 1.5 m^2 BSA. S-1 was orally taken every day for 14 days followed by 7 days break, which (21 days) was considered as one therapeutic cycle.

Systemic administration of cisplatin (Qilu Pharmaceutical, Jinan, China) was given intravenously once on day 1 (60 mg/m^2). One therapeutic cycle of systemic cisplatin was also 21 days.

Outcome evaluation Therapeutic outcome evaluation was conducted after each 2 therapeutic cycles (6 weeks).

Primary end point was to observe disease free survival (DFS), which was defined as the period starting on the date of first treatment till cancer recurrent or death.

Secondary end point was to count the number of patients with 2-year survival, which was defined as the patient survived for 2 years without cancer recurrent.

Safety was evaluated following the terms and definitions of Common Terminology Criteria for Adverse Events (CTCAE) 4.0 edition.

Statistical analysis Data were analyzed using SPSS software for windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Data was presented as mean ± standard deviation (SD). The differences of age and treatment cycles between perfusion group and control group was assessed using Student's *t* test or One-way ANOVA. Pearson chi-square test or Fisher exact test was used to compare the differences of gender, ECOG score, tumor site, histopathology, tumor stage and peritoneal metastasis. Kaplan–Meier survival curve was plotted for survival analysis and the log rank test was utilized to identify difference between curves. A two-sided $P < 0.05$ was considered as statistically significant.

Results

From April 2014 through April 2018, total 114 out of the 120 patients, who signed consent form, were enrolled into the current study. Of them, 57 patients were assigned to HIPEC treatment group and 57 patients were in the control (systemic chemotherapy) group (Fig. 1). There were no significant differences in age, gender ratio, ECOG performance status, primary tumor types and histopathology, except clinical stages between the two groups ($P = 0.018$, more cases of stage IIIA in the control group, Table 2).

Table 2 Demographic characteristics of the participants

	HIPEC group (N = 57)	Control group (N = 57)	*P*
Age (years, range)	56.6(46.4–66.8)	56.7(45.5–67.9)	0.958
Gender			
Male (n, %)	46 (80.7%)	38 (66.7%)	0.136
Female (n, %)	11 (19.3%)	19 (33.3%)	
ECOG performance status (n, %)			
0	30 (52.6%)	28 (49.1%)	0.852
1	27 (47.4%)	29 (50.9%)	
Site (n, %)			
Cardia of stomach	16 (28.1%)	17 (29.8%)	0.914
Fundus of stomach	8 (14.0%)	7 (12.3%)	
Body of stomach	21 (36.8%)	23 (40.3%)	
Pylorus of stomach	12 (21.1%)	9 (15.8%)	
Total stomach	0	1 (1.8%)	
Histopathology (n, %)			
Adenocarcinoma (poor or moderately differentiated)	48 (84.2%)	46 (80.7%)	0.806
Adenocarcinoma (mucinous, signet cell or other type)	9 (15.8%)	11 (19.3%)	
Tumor stage (n, %)			
IIIA	10 (17.5%)	21 (17.5%)	0.018
IIIB	20 (35.1%)	9 (15.8%)	
IIIC	27 (47.4%)	27 (47.4%)	
ECOG: Eastern Cooperative Oncology Group			

Till April 30, 2019, total 33 patients of HIPEC group and 39 patients of the control group had recurrent cancer. Median of DFS, the primary endpoint of observation, was 21.0 months in the HIPEC group and 14.0 months in the control group, which was significantly different ($P = 0.039$, Fig. 2). The rate of two-year DFS, the 2nd endpoint of observation, was 47.3% in the HIPEC and 29.4% in the control group, respectively. Twelve of the 57 (21.1%) patients in the control group had peritoneal metastasis, which was slightly but not significantly higher than that in the patients with HIPEC treatment (6/57, 10.5%, *P* =

0.198). Risk of recurrent ascites or pleural effusion was reduced 37.9% in the HIPEC group, HR = 0.621, 95% CI: 0.389–0.989, *P* = 0.045.

As shown in Table 3, average treatment cycles were 5.9 ± 2.0 cycles in the HIPEC group and 5.9 ± 1.7 cycles in the control group, which was not significantly different (*P* = 0.959).

Table 3
Treatment cycles

	Mean cycles (range)	Std. Deviation	*P*
HIPEC group (N = 57)	5.9	2.0	0.959
Control group (N = 57)	5.9	1.7	

Majority of the participants had at least one adverse event. As shown in Table 4, the most common adverse event in the HIPEC group was leukopenia (77.2 %) followed by nausea or vomiting (61.4 %), thrombocytopenia (36.8 %), diarrhea (29.8 %), fatigue (24.6 %), and liver dysfunction (7.0 %). The most common adverse event in the control group was leukopenia (91.2 %) followed by thrombocytopenia (86.0 %), nausea or vomiting (52.6 %), diarrhea (22.8 %), fatigue (21.1 %), and liver dysfunction (8.8 %). There were no significant differences in the adverse events between the two groups (*P* > 0.05) except thrombocytopenia that was significantly higher in the control group (*P* = 0.000). In addition, there was no difference (*P* > 0.05) in the occurrence of severe adverse effects (≥ 3 grade) between the two groups (Table 4). As shown in Table 5 for the HIPEC-associated side effects, 2 out of 57 (3.5%) patients had pain at the puncture points and 1 out of 57 (1.8 %) patient had peritoneal inflammation. Neither puncture point infection, nor intestinal perforation occurred in the patients treated with HIPEC. In addition, there was no procedure-associated death in either group.

Table 4
Comparison of adverse events in the two groups

	All grades			≥ 3grades		
	HIEPC (N = 57)	Control (N = 57)	*P*	HIPEC (N = 57)	Control (N = 57)	*P*
Nausea/Vomiting	35 (61.4%)	30 (52.6%)	0.449	4 (7.0%)	4 (7.0%)	1.000
Diarrhea	17 (29.8%)	13 (22.8%)	0.524	2 (3.5%)	1 (1.8%)	1.000
Leukopenia	44 (77.2%)	52 (91.2%)	0.070	8 (14.0%)	9 (15.8%)	1.000
Thrombocytopenia	21 (36.8%)	49 (86.0%)	0.000	4 (7.0%)	4 (7.0%)	1.000
Fatigue	14 (25%)	12 (21.1%)	0.824	1 (1.8%)	0 (0.0%)	1.000
Renal toxicity	0 (0.0%)	1 (1.8%)	1.000	0 (0.0%)	1 (1.8%)	1.000
Liver dysfunction	4 (7.0%)	5 (8.8%)	1.000	0 (0.0%)	0 (0.0%)	1.000

Table 5
HIPEC-associated side effects

	Patients (N = 57)
Pain at puncture point	2 (3.5 %)
Infection of puncture point	0 (0.0%)
Peritoneal inflammation	1 (1.8 %)
Intestinal perforation	0 (0.0%)
Bowel obstruction	0 (0.0%)
Perfusion failure	0 (0.0%)

Discussion

Gastric cancer is the most commonly diagnosed malignant tumor in Chinese population. While radical surgery is still the first choice for the treatment of gastric cancer, worldwide overall 5-year survival rate of gastric cancer is less than 30 % (21), especially, at stage III or later phase gastric cancer patients (6). Adjuvant chemotherapy, therefore, is used in majority of the stage III or later phase gastric cancer patient. The current study demonstrated that HIPEC with cisplatin plus orally taken S-1 was superior to systemic chemotherapy of cisplatin plus orally taken S-1 treatment after D2 radical surgery in the stage III gastric cancer patients.

Several retrospective as well as prospective clinical studies have indicated that adjuvant chemotherapy benefits stage III gastric cancer patients (8, 22–24). However, while D2 radical surgery significantly reduced occurrence of lymphatic metastasis, peritoneal metastasis becomes major recurrent location after the surgery (9, 25). In this regard, a retrospective study reported that cancer cells were found in 29.7 % of T3 and 34.8 % of T4 patients' peritoneal lavage fluid after the radical surgery; and that 59.4% of the T3 or T4 patients had peritoneal metastasis within 5 years after the surgery, while only 21.3 % had blood circulatory metastasis (9). Prognosis of the patients with peritoneal metastasis is poor, and thus, prevention of peritoneal metastasis following surgical resection of the late stage gastric cancer becomes crucial.

HIPEC has been used for the prevention of micro-transplantation of cancer cells during and after gastric surgery (18, 26). In this regard, HIPEC has been widely used during or right after cytoreductive surgery (CRS) for the prevention of peritoneal metastasis in variety kinds of cancers including gastric cancer, ovarian cancer and hepatic cancer (18, 27–30). HIPEC has also been used as palliative treatment for recurrent ascites and malignant plural effusion for the patients with variety kinds of late stage or recurrent cancers including lung cancer, breast cancer, gastric cancer and ovarian cancer (20, 31). Mechanism of HIPEC is to augment sensitivity of cancer cells to chemotherapeutic drugs at hyperthermic condition (41.5 ~ 42.5 C) in that cancer cells are more sensitive to heat than the normal cells (16, 26). In this content, it has shown that hyperthermia significantly increases efficacy of platinum-based anti-cancer drugs (32).

Gastric cancer is the most common cause of peritoneal metastasis after radical surgery. Therefore, prevention of peritoneal metastasis is crucial for the patients with gastrointestinal cancer. In this regard, studies have demonstrated that efficacy of CRS plus HIPEC is superior to surgical resection only in gastric cancer patients. Fujimoto first reported in 1988 that CRS plus HIPEC controlled malignant ascites in 9 out of 15 gastric cancer patients who had peritoneal metastasis after the surgery (28). Since then, HIPEC has been used as not only an adjuvant treatment for malignant ascites caused by variety kinds of abdominal cancers including colon cancer and ovarian cancer (33–35), but also a method of preventing peritoneal metastasis in the gastric cancer patients. In this regard, Fujimoto and colleagues reported in 1999 that CRS plus HIPEC could significantly increase survival rate for the patients with infiltration of gastric cancer into the gastric serosa by reducing peritoneal metastasis in comparison to the radical surgery only (36). Wansik Yu et al (37) reported that 248 stage II or III gastric cancer patients were randomly treated with either radical surgery only or CRS plus HIPEC (HIPEC starting on day 2 after surgery for 5 days with mitomycin plus fluorouracil), and they found that 5-year survival rate in the patients with CRS plus HIPEC (49.1 %) was significantly higher than that in the radical surgery only group (18.4 %). Yonemura et al (38) reported that 139 stage II-IV gastric patients were randomly assigned to a group treated with CRS plus HIPEC (42–43 °C) with mitomycin and cisplatin, a group treated with CRS plus intra-peritoneal chemotherapy at normal temperature (37 °C) with mitomycin and cisplatin, and a group treated with radical surgery only. They found the 5-year survival rates were 61 % (CRS + HIPEC), 43 % (CRS + 37 °C intra-peritoneal chemotherapy), and 42 % (CRS only) (38). Furthermore, they found that CRS plus HIPEC exerted most significant therapeutic effect in the patients, who had gastric serosa infiltration

and local lymphatic metastasis, in comparison to CRS plus normal temperature intra-peritoneal perfusion therapy (38). A meta-analysis also indicated that HIPEC could significantly increase survival rate in the advanced gastric cancer patients who had CRS plus HIPEC during the surgery or post-surgery (39). Recently, it has been reported that DFS was significantly higher in the patients received D2-CRS plus HIPEC (93%) than that of patients treated with D2-CRS only (65%, $P = 0.0054$); that peritoneal metastasis rate was significantly lower in the patients had D2-CRS plus HIPEC (3%) than that of the patients without HIPEC (23%, $P < 0.05$) (19). Consistent with these findings, the current study demonstrated that patients with stage III gastric cancer had longer median DFS when they were treated with CRS plus HIPEC and oral S-1 (21.0 months) than the patients treated with CRS plus systemic cisplatin and oral S-1 (14.0 months), suggesting HIPEC is an effective adjuvant therapy following radical surgery in the advanced gastric cancer patients, especially for the patients suffered from Bormann's type IV gastric cancer with neurovascular infiltration, $T \geq 3$, and N3. These late stage patients were highly risk in regard of peritoneal metastasis, therefore, the current study was designed to prospectively investigate the outcomes of D2-CRS plus HIPEC in comparison to the group without HIPEC.

While majority of the previous studies have compared the outcomes of HIPEC versus radical surgery only (19, 36–39), adjuvant chemotherapy following radical surgery has become standard treatment for the gastric cancer. However, outcomes of HIPEC versus systemic chemotherapy in these patients remains to be further investigated. In this regard, a retrospective study by Shi et al (40) reported that 5-year survival rate in the patients with CRS + systemic chemotherapy + HIPEC was significantly higher than that without HIPEC (60.4 % vs 42.9 %), and median progress free survival (PFS) was 60.5 and 46.2 months, respectively. Similarly, Zhang et al (41) reported that gastric cancer patients treated with CRS + systemic chemotherapy + HIPEC had significantly higher 3-year survival rate (61.8 %) but lower local recurrent rate (23.5 %) compared to that of CRS + systemic chemotherapy only (3-year survival rate: 40.0 %; local recurrent rate: 43.3 %). Furthermore, a meta-analysis on 2299 cases of late stage gastric cancer patients in 18 randomized clinical trials found that rates of post-operational recurrence and distant metastasis were significantly lower in the patients received HIPEC plus systemic chemotherapy than that of the patients received systemic chemotherapy only; that long-term survival was increased without significant adverse effect by HIPEC plus systemic chemotherapy (42). In the current study, therefore, a prospective study on the outcomes of HIPEC plus oral administration of S-1 in comparison to that of systemic chemotherapy plus oral administration of S-1 was carried out.

S-1 is a combination of tegafur, gimeracil and oteracil potassium. Tegafur is a prodrug of the active substance fluorouracil (5-FU). Gimeracil inhibits the degradation of 5-FU by reversibly blocking the dehydrogenase enzyme dihydropyrimidine dehydrogenase (DPD), by which mechanism, higher level and prolonged half-life of 5-FU are achieved. Oteracil potassium mainly stays in the gut due to low permeability and is a highly selective inhibitor of the enzyme orotate phosphoribosyl transferase. Oteracil reduces the production of 5-FU in the gut through inhibiting phosphorylation of 5-FU, which results in a lower gastrointestinal toxicity. S-1 has been approved and used for the treatment of advanced gastric cancer by oral administration in Japan in 1999. A study, called SC-101, has been conducted in China, in which 224 cases of unresectable late phase or metastatic gastric cancer were enrolled and treated with S-

1(43). It was found that tumor remission rate was significantly higher in the patients treated with S-1 plus cisplatin (37.8%) than that of 5-FU plus cisplatin (19.2%) or S-1 only (24.7%); that median survival of the patients with S-1 plus cisplatin was 433 days (14.4 months), which was longer than that of the other two groups. Therefore, S-1 was used in the current prospective study as an adjuvant chemotherapeutic drug in addition to cisplatin, and found that DFS (21.0 months versus 14.0 months, $P = 0.039$) as well as 2-year DFS rate (47.3% versus 29.4%) were significantly longer or higher in the patients treated with HIPEC plus S-1 oral administration than that of systemic cisplatin administration plus S-1. These findings suggested that S-1 could be used as a standard chemotherapeutic drug in gastric cancer patients in China; and that HIPEC plus S-1 might be superior to systemic chemotherapy plus S-1 oral administration for the stage III gastric cancer after D2 radical surgery.

While combination of CRS and HIPEC could significantly increase survival of the cancer patients, safety is highly concerned in HIPEC procedure during surgery because adverse events associated with HIPEC may also arise by invasive procedures, high temperature, and large amount of fluid circulation. In this regard, it has been reported that HIPEC-treated patients had higher incidence rate of severe adverse events including severe bleeding and even intestinal perforation than the patients had CRS only although incidence rate of side effects and mortality were not significantly different between the two groups (37–39). In addition, incidence of leukopenia and peritoneal infection has also been reported in the patients treated with HIPEC (37, 39). In the current study, side effects including nausea/vomiting, diarrhea, leukopenia, thrombocytopenia, and fatigue were compared in the two groups, and found that incidence of these side effects was slightly lower in this novel bedside HIPEC group compared to the control group although they were not statistically different, suggesting HIPEC might reduce side effects caused by chemotherapeutic drugs. In addition, in the current study, bedside hyperthermic intra-peritoneal perfusion and circulation of chemotherapeutic drugs was established through needle puncture technique. Consistent with our previous report (20), while this technique was safe and could be performed under local anesthesia, 2 out of 57 patients (3.5 %) had HIPEC-associated pain at the puncture points and one out of 57 patients (1.8 %) had HIPEC-associated peritoneal inflammation, suggesting cautious attention be paid on these HIPEC-associated side effects.

HIPEC, especially during CRS, has been performed under systemic anesthesia of the patients with opened abdominal cavity (18). When the patients were under systemic anesthesia, it not only takes longer time to complete the HIPEC, but also may increase the opportunity of side effects such as peritoneal infection. In addition, method of previously reported HIPEC at surgical operation room was performed only once during or right after the CRS. In the current study, however, a local anesthesia followed by puncture technique and devices were used for the HIPEC. This procedure and device are especially convenient and safe to perform repeated HIPEC for multiple therapeutic cycles after CRS for the patients with recurrent peritoneal metastasis. Average time of the HIPEC performed in the current study was less than 2 hours, which rendered the patients to be easily tolerable to the procedure and could be treated multiple cycles. Furthermore, by application of multiple cycles of HIPEC plus oral S-1, the current study demonstrated that HIPEC could not only significantly increased 2-year DFS (47.3 % vs 29.4 %), but also reduced peritoneal metastasis (10.5 % vs 21.1 %), suggesting that multiple cycles of HIPEC with puncture procedure could be

safely and easily performed in the patients after RS to prevent peritoneal metastasis of gastric cancer. However, limitation of the current study was that small number of cases was enrolled into this study. A prospective and larger number of clinical trials could be performed in the future to further confirm the findings of the current study.

Conclusion

This study demonstrated that bedside HIPEC with cisplatin plus oral S-1 was an effective adjuvant therapy following D2 radical gastrectomy for the patients with stage III gastric cancer. In addition, bedside HIPEC procedure with puncture technique is safe and easily used for multiple times performance of HIPEC in the same patient.

Abbreviations

CRS: cytoreductive surgery; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group: HIPEC: hyperthermic intraperitoneal chemotherapy.

Declarations

Acknowledgments

None.

Authors' contributions

L Liu, L Sun, HW Zhang, and HL Zhang designed the study and drafted the manuscript. L Sun, N Zhang, CG Liao, HC Su, J Min, and HW Zhang performed surgery. L Liu, Y Song, X Yang, XF H, DX Chen, Y Chen, and HL Zhang performed HIPEC and chemotherapy. All authors have read and approved manuscript.

Trial registration

This study was registered at the official site (ClinitalTrials.gov) on 24/03/2015. Identification number of this trial was NCT02396498.

Funding

This study was funded by The National Natural Science Fund of China, #81672742.

Availability of data and materials

All data generated in this study were included in this published article.

Ethics approval and consent to participate

The protocols of cytoreductive surgery were approved by the Ethic Committees of The Xi'an Honghui Hospital, Xi'an, China and Affiliated Suzhou Science & Technology Town Hospital of Nanjing Medical University, Suzhou, China. The protocols for HIPEC procedure and systemic chemotherapy were approved by Tangdu Hospital, Air Force Medical University, Xi'an, China. All methods were performed in accordance with the relevant guidelines and regulations of the clinical trials.

A written, informed, and signed Consent form was obtained from each participant or his/her legal guardian before enrolling into this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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Figures

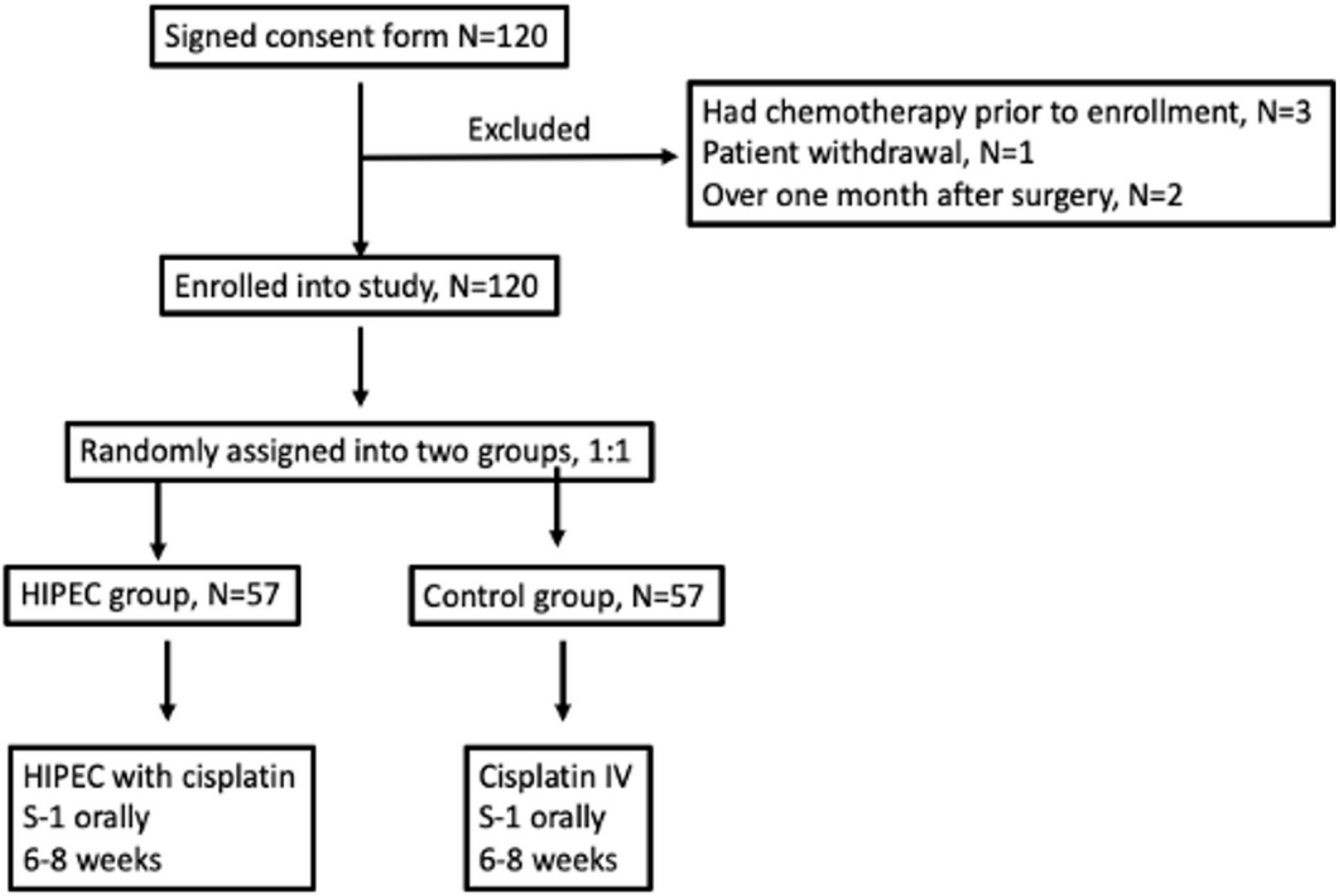

Figure 1

Schematic illustration of patient enrollment.

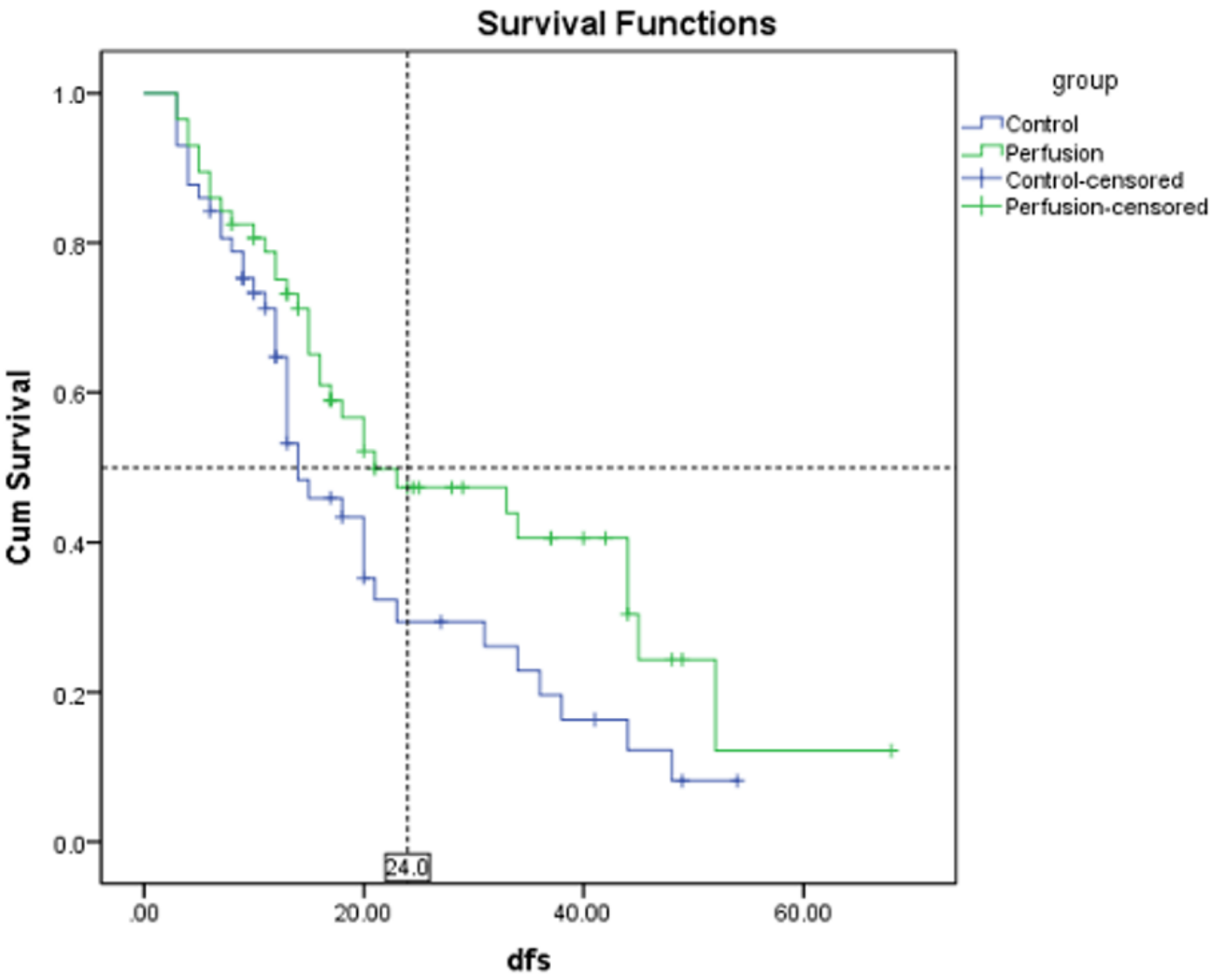

Figure 2

Kaplan-Meier plot of disease-free survival. Median DFS of HIPEC (21.0 months) Versus control group (14.0 months, P=0.039).