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ORIGINAL ARTICLE

Efficacy of postoperative intraperitoneal hyperthermic perfusion chemotherapy with oxaliplatin + 5-Fluorouracil in the treatment of gastric cancer patients with peritoneal carcinomatosis

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Summary

Purpose: *To explore the effect of palliative laparoscopic resection of gastric cancer combined with intraperitoneal hyperthermic perfusion chemotherapy (IHPC) with oxaliplatin + 5-fluorouracil (5-FU) on gastric cancer patients with peritoneal carcinomatosis (PC).*

Methods: *90 patients definitely diagnosed with gastric adenocarcinoma and PC and admitted to our hospital from March 2013 to March 2016 were collected and divided into IHPC group (n=45) and control group (n=45). In IHPC group, IHPC with oxaliplatin + 5-FU was carried out for the first time on the first day after operation, and then it was conducted once every other day for a total of 4 times. The clinical efficacy, quality of life, adverse reactions, postoperative tumor recurrence and survival of the patients were observed and recorded.*

Results: *The total effective rates in IHPC group and control group were 62.2% (28/45) and 55.6% (25/45), respectively (p>0.05). In both groups, the curative effect was the best in moderately differentiated adenocarcinoma and worst in signet ring cell carcinoma. Besides, the effective rates of Karnofsky performance status (KPS) in the two groups after operation were 82.2% (37/45) and 75.6% (34/45), respectively (p=0.606). However, the renal function indexes, serum creatinine (sCr) and blood urea nitrogen (BUN) in the two groups of patients after operation were increased, and those in the IHPC group were higher than those in the control group (p=0.016, p=0.010). Moreover, follow-up results of patients' survival revealed that the OS and PFS in the IHPC group were significantly higher than those in the control group (p=0.041, p=0.045).*

Conclusions: *Palliative laparoscopic resection of gastric cancer combined with IHPC with oxaliplatin +5-FU has a definite therapeutic effect on gastric cancer with PC, which can achieve a better short-term clinical therapeutic effect and better postoperative quality of life*

Key words: *gastric cancer, peritoneal carcinomatosis, oxaliplatin, 5-fluorouracil, intraperitoneal hyperthermic perfusion chemotherapy*

Introduction

Gastric cancer is one of the five most common cancers in the world, with the mortality rate ranking 3rd [1]. It frequently occurs in China, with the morbidity and mortality rates both ranking 3rd [2]. The detection rate of early gastric cancer in China is only 5-10%, and most patients are in advanced stage when definitely diagnosed [3,4]. Although radical resection is the only possible method to

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cure gastric cancer, the 5-year overall survival rate of advanced gastric cancer is only 23% [5]. As the common and most serious kind of metastasis of gastric cancer, peritoneal carcinomatosis (PC), is one of the primary reasons influencing the disease prognosis. The study of Preusser et al. [6] showed that the remission rate with chemotherapy for stage IV gastric cancer patients was 50%, but that of patients with PC was significantly lower. Ajani et al. [7] reported that PC is one of the common reasons for failure of intensive chemotherapy. Surgical treatment or chemotherapy alone are not enough to control gastric cancer with PC, so multidisciplinary comprehensive treatment is required. Intraperitoneal hyperthermic perfusion chemotherapy (IHPC) is a technique that organically combines hyperthermia, intraperitoneal chemotherapy and peritoneal lavage. After years of research and development, IHPC has been proved to have unique curative effects in preventing and treating a variety of abdominal malignant tumors, PC and malignant ascites [8-10].

In this study, the clinical data of 90 patients with gastric adenocarcinoma and PC admitted to our department from March 2013 to March 2016 who underwent palliative laparoscopic resection of gastric cancer combined with IHPC were retrospectively analyzed. Additionally, the safety and efficacy of IHPC in such patients were investigated, so as to provide reference for their treatment.

Methods

General data

In this study, a total of 90 patients with gastric cancer complicated with simple PC admitted to our hospital from March 2013 to March 2016 were included, and palliative laparoscopic resection of gastric cancer was successfully performed. Case inclusion criteria: (1) Cases with gastric adenocarcinoma combined with PC confirmed by histopathology, (2) Cases aged ≤75 years, (3) Cases with Eastern Cooperative Oncology Group (ECOG) performance status ≤2 points, (4) Cases with good bone marrow function, liver function, heart function and renal function, and (5) Cases with no serious immunosuppressive diseases or concurrent malignant tumors. Among them, there were 51 males and 39 females aged 34-71 years (mean 50.71±9.59). Age, sex, body mass index (BMI), pathological type, TNM stage, preoperative ECOG score and other basic conditions of the two groups of patients had no statistical differences ($p>0.05$), and were comparable (Table 1). All the selected patients complied with the Helsinki Declaration. They were informed over their disease and treatment planning and signed informed consent. This study was approved by the Ethics Committee of Jiangxi Cancer Hospital.

Treatment methods

All cases successfully underwent palliative laparoscopic resection of gastric cancer. In the control group, conventional drainage tubes were placed, the abdominal cavity was closed layer by layer, and conventional anti-infection, pain relief, intravenous nutrition support and

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*IHPC group (n=45) n (%)*	*Control group (n=45) n (%)*	*p value*
Age	51.24±9.55	49.33±10.11	0.359
Gender			0.671
Male	24 (53.3)	27 (60.0)	
Female	21 (46.7)	18 (40.0)	
BMI (kg/m^2), mean±SD	24.72±3.20	23.64±3.05	0.105
Pathological type			0.680
Moderately differentiated adenocarcinoma	13 (28.9)	10 (22.2)	
Poorly differentiated adenocarcinoma	23 (51.1)	27 (60.0)	
Signet ring cell carcinoma	9 (20.0)	8 (17.8)	
TNM stage			0.393
II	21 (46.7)	18 (40.0)	
III	16 (35.5)	22 (48.9)	
IV	8 (17.8)	5 (11.1)	
ECOG score			0.646
0	17 (37.8)	19 (42.2)	
1	24 (53.3)	20 (44.5)	
2	4 (8.9)	6 (13.3)	

other treatments were given after operation. In the IHPC group, a silica gel catheter with multiple lateral holes was placed on the diaphragmatic surface of the liver, splenic fossa and pelvic cavity for drainage after operation, respectively, and fixed on the right upper abdomen, left upper abdomen and left lower abdominal wall, respectively. Moreover, IHPC with oxaliplatin + 5-FU was administered for the first time on the first postoperative day, and then once every other day for a total of 4 times. After the extracorporeal circulation pipeline was connected to a hyperthermic chemoperfusion machine (BR-TRG-I type, Guangzhou Baorui Medical Technology Co., Ltd., Guangzhou, China) and the corresponding temperature measuring device was installed, 2000 mL normal saline, 150 mg oxaliplatin and 1,000 mg 5-FU were added into the perfusion bag, and the circulation pump and the heating system were started. Subsequently, the drainage was connected to the extracorporeal circulation pipeline when temperature of the chemotherapy liquid was stabilized to 38°C, the perfusion speed was adjusted to 500 mL/min, the temperature was gradually raised to allow patients to adapt to the environment, and the temperature was controlled at 43°C for 60 min. After that, the volume of the residual fluid in the abdominal cavity was allowed to be less than 1500 mL, the connection between the circulation pipeline and the drainage tube was relieved, and the drainage tube was connected to the low negative pressure drainage bag.

Observational indices

Evaluation criteria for computed tomography (CT) remission: RECIST 1.1 was adopted to evaluate the chemotherapy effect [11]: Complete remission (CR): All target lesions disappeared, and the short axis value of any pathological lymph node (whether it is the target lesion or not) must be <10 mm. Partial remission (PR): The sum of the length and diameter of all target lesions was reduced by 30% or more. Progressive disease (PD): The sum of the length and diameter of all target lesions was increased by at least 20%, and the absolute value of this sum rose up by more than 5 mm, or new lesions appear. Stable disease (SD): The changes in target lesions were between PR and PD. The effective rate of tumor remission in this study was defined as the proportion of patients with CR+PR/total.

In this study both Karnofsky performance status (KPS) and ECOG score were used. KPS is a detection tool for evaluating the performance status of cancer patients, the patients' mobility and treatment needs, especially for more accurate evaluation of survival of patients with end-stage diseases [12]. Determination of the effective rate of KPS after operation: Markedly improved: The KPS score went up by more than 20 points. Improved: The KPS score was increased by more than 10 points. Stable: The KPS core rose up by less than 10 points. Progressive: The KPS core was decreased.

On day 1 before operation and 3 days after operation, the levels of alanine aminotransferase (ALT), total bilirubin (TBIL), serum creatinine (sCr) and blood urea nitrogen (BUN) in the two groups of patients were examined. The main adverse reactions consisted of pulmonary infection, intestinal obstruction, reflux esophagitis and deep vein thrombosis. Follow-up was conducted every 3 months after operation, during which abdominal metastasis and recurrence were evaluated according to chest X-ray, abdominal B-ultrasound, abdominal CT and gastrointestinal endoscopy. Determination of tumor recurrence: Tumor recurrence was determined when gastroscopy, abdominal B ultrasound, chest X-ray or any other examinations revealed signs of tumor recurrence or metastasis in the digestive tract, lymph nodes and adjacent and distant organs. The survival time of patients was recorded, and the follow-up deadline was October 31, 2018.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. All quantitative data were expressed as mean±standard deviation (x±s), and the comparison of these data was conducted by the *t*-test. Percentage data were expressed as percentage (%), and x^2 test was used for these data analysis. Survival curves were drawn using the Kaplan-Meier method and log-rank test was used to compare differences between the two groups. $P<0.05$ showed that the difference was statistically significant.

Results

Short-term efficacy evaluation

Among 45 cases in the IHPC group, there were 19 cases of CR, 9 cases of PR, 7 cases of SD and 10 cases of PD, in which the effective (CR+PR) rate of poorly differentiated adenocarcinoma was 65.2% (15/23), that of moderately differentiated adenocarcinoma was 69.2% (9/13), and the one of signet ring cell carcinoma was 44.4% (4/9). The total effective (CR+PR) rate was 62.2% (28/45). Among 45 cases in the control group, there were 15 cases of CR, 10 cases of PR, 8 cases of SD and 12 cases of PD, in which the effective (CR+PR) rate of poorly differentiated adenocarcinoma was 59.3% (16/27), that of moderately differentiated adenocarcinoma was 60.0% (6/10), and the one of signet ring cell carcinoma was 37.5% (3/8). The total effective (CR+PR) rate was 55.6% (25/45). Therefore, there was no statistically difference in the total effective rate between the two groups of patients. In both groups, the therapeutic effect was best in moderately differentiated adenocarcinoma and worst in signet ring cell carcinoma. Besides, there were no statistical differences in the therapeutic effect between moderately and poorly differentiated adenocarcinoma and signet ring cell carcinoma in the same group ($p>0.05$) (Table 1).

Evaluation of KPS

The evaluation of the KPS score before treatment showed that of all the patients had over 50 points, including 50 points in 6 cases (6.7%), 60 points in 26 cases (28.9%), 70 points in 34 cases

(37.8%), 80 points in 16 cases (17.8%), 90 points in 4 cases (4.4%) and 100 points in 4 cases (4.4%). At 3 months after treatment, the KPS score was compared again. It was found that in IHPC group, there were 9 markedly improved cases, 16 improved cases, 12 stable cases and 8 progressive cases, and the effective (improved+stable) rate of KPS was 82.2% (37/45). In the control group, there were 7 markedly improved cases, 14 improved cases, 13 stable cases and 11 progressive cases, and the effective (improved + stable) rate of KPS was 75.6% (34/45). No statistically significant differences were found between the two groups (p=0.606) (Table 2). The above results indicate that KPS is improved in most

Table 2. Comparison of KPS score of patients in the two studied groups

Parameters	*HPC group (n=45) n (%)*	*Control group (n=45) n (%)*	*p value*
KPS score ↑≥20	9 (20.0)	7 (15.6)	
KPS score ↑≥10	16 (35.5)	14 (31.1)	
KPS score ↑<10	12 (26.7)	13 (28.9)	
KPS score ↓	8 (17.8)	11 (24.4)	
Effective rate	37 (82.2)	34 (75.6)	0.606
CR	19 (42.2)	15 (33.3)	
PR	9 (20.0)	10 (22.2)	
SD	7 (15.6)	8 (17.8)	
PD	10 (22.2)	12 (26.7)	
CR+PR	28 (62.2)	25 (55.6)	0.669

IHPC: intraperitoneal hyperthermic perfusion chemotherapy; KPS: Kamofsky performance status; CR: complete tesponse; PR: partial response; SD: stable disease; PD: progressive disease

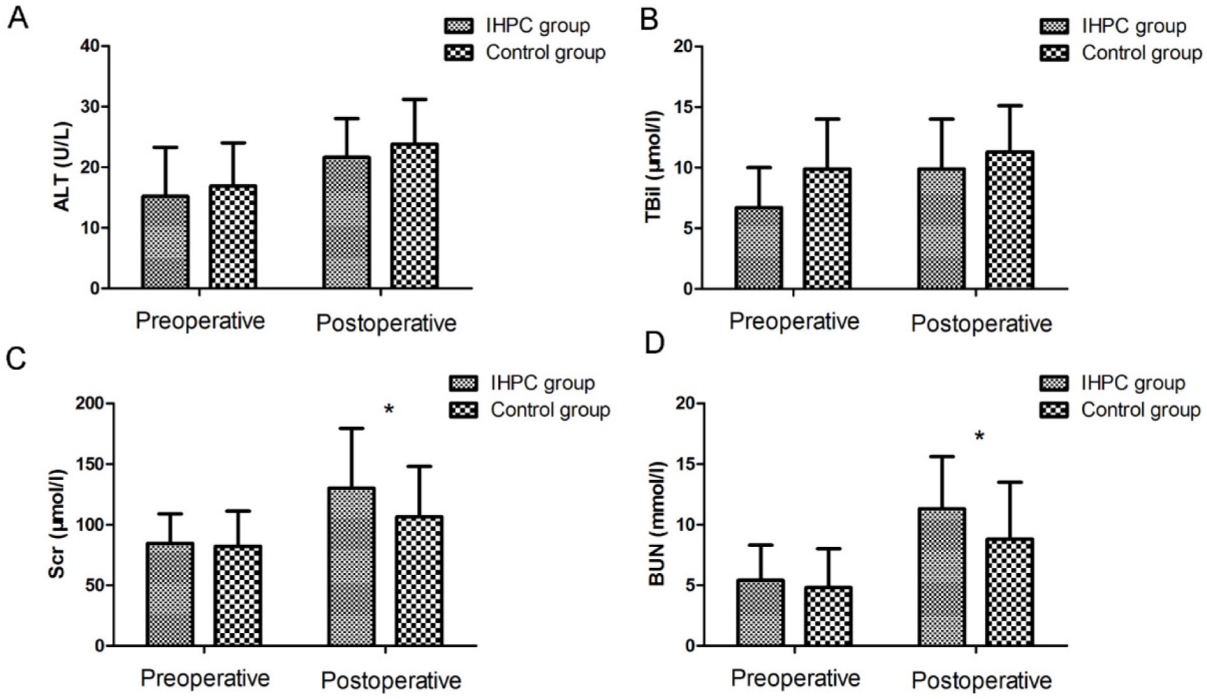

Figure 1. A: The baseline expression level of ALT of patients in the IHPC group was 15.2±8.1 U/L and increased to 21.6±6.4 U/L after treatment, while that of the control group was 16.9±7.1 U/L and increased to 23.8±7.4 U/L after treatment (p=0.135). **B:** The baseline expression level of TBIL of patients in the IHPC group was 6.7±3.3 μmol/L and increased to 9.9±4.1 μmol/L after treatment, while that of the control group was 7.8±3.6 μmol/L and increased to 11.3±3.8 μmol/L after treatment (p=0.097). **C:** The baseline expression level of Scr of patients in the IHPC group was 84.5±24.4 μmol/L and increased to 130.1±49.3 μmol/L after treatment, while that of the control group was 82.3±28.9 μmol/L and increased to 106.5±41.6 μmol/L after treatment (*p=0.016). **D:** The baseline expression level of BUN of patients in the IHPC group was 5.4±2.9 mmol/L and increased to 11.3±4.3 mmol/L after treatment, while that of the control group was 4.8±3.2 mmol/L and increased to 8.8±4.7 mmol/L after treatment (*p=0.010).

cases after palliative laparoscopic resection of gastric cancer combined with IHPC with oxaliplatin+5-FU. To some extent, the results reflect that the quality of life of most patients has been improved after treatment, which is of great significance for patients with advanced gastric cancer.

Adverse reactions and complications

The most common adverse reaction was abdominal pain. The incidence rates of abdominal pain in the two groups of patients were 35.6% and 28.9%, respectively, in which mild pain dominated and could be relieved in most patients by themselves after treatment. The peripheral blood leukocytes decreased significantly in 3 patients (6.7%) in the IHPC group and in 1 patient (2.2%) in the control group. They were decreased from normal value to 2.68×10^9/L and 2.44×10^9/L and 2.59×10^9/L, respectively, and the leukocyte number returned to normal with the use of G-CSF. Hemoglobin reduction and thrombocytopenia occurred in 4 cases (8.9%) and 7 cases (15.6%), and in 4 cases (8.9%) and 2 cases (4.5%), respectively, in the two groups of patients. There were no statistically significant differences in liver and kidney functions between the two groups before operation (p>0.05) (Figure 1). Besides, no statistically significant differences in the levels of ALT and TBIL were found between the two groups of patients after operation (p=0.135, p=0.097). However, the levels of sCr and BUN in the IHPC group were notably higher than those in the control group (p=0.016, p=0.010). Grade 1 fever, nausea and vomiting were encountered in most cases, which were improved after symptomatic treatment. No bleeding, diarrhea, hematuria, allergy, rash, blockage or shedding of the perfusion

Table 3. Comparison of adverse reactions and complications of patients in the two studied groups

Parameters	*HPC group (n=45)* *n (%)*	*Control group (n=45)* *n (%)*	*p value*
Fever	10 (22.2)	8 (17.8)	0.793
Abdominal pain	16 (35.6)	13 (28.9)	0.652
Nausea / Vomiting	6 (13.3)	2 (4.5)	0.266
Leukocytopenia	3 (6.7)	1 (2.2)	0.616
Anemia	4 (8.9)	7 (15.6)	0.522
Thrombocytopenia	4 (8.9)	2 (4.5)	0.677
Pneumonia	1 (2.2)	3 (6.7)	0.616
Reflux esophagitis	0 (0)	1 (2.2)	1.000
Ileus	2 (4.4)	1 (2.1)	1.000
DVT	1 (2.2)	0 (0)	1.000

IHPC: intraperitoneal hyperthermic perfusion chemotherapy; DVT: deep venous thrombosis

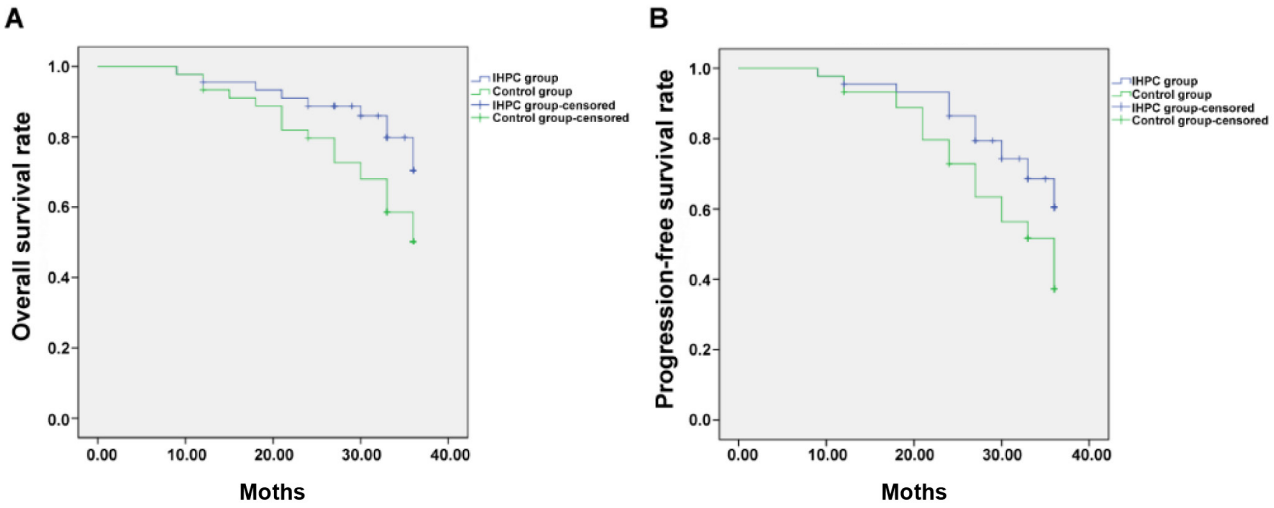

Figure 2. Kaplan-Meier survival curves of patients in the IHPC group and the control group. **A:** The overall survival rate of patients in the IHPC group was significantly higher than that of the control group (p=0.041). **B:** The progression-free survival rate of patients in the IHPC group was significantly higher than that of the control group (p=0.045).

catheter, severe infection of incision or abdominal cavity related to intraperitoneal thermal perfusion occurred in the patients. Among the two groups of patients after operation, there were 1 patient (2.2%) and 3 patients (6.7%) complicated with postoperative pulmonary infection, no patient (0%) and 1 patient (2.2%) complicated with reflux esophagitis, 2 patients (4.4%) and 1 patient (2.1%) complicated with intestinal obstruction, and 1 patient (2.1%) and no patient (0%) complicated with deep vein thrombosis. There were no statistically significant differences in postoperative complications between the two groups of patients (p>0.05) (Table 3).

Follow-up results of the patients' survival

All the patients were followed up for 24-40 months. The median follow-up time was 34.3 months in the IHPC group and 35.4 months in the control group. During follow-up, in the IHPC group, 10 patients died with overall survival of 77.8% (35/45), and the tumor recurred in 15 patients with progression-free survival of 66.7% (30/45). In the control group, 21 patients died with overall survival of 53.3% (24/45), and the tumor recurred in 26 patients with progression-free survival of 42.2% (19/45). The Kaplan-Meier survival curve of patients is shown in Figure 2. The OS and PFS of the two groups of patients were tested by log-rank test, and the differences were statistically significant. The OS and PFS in the IHPC group were remarkably higher than those in the control group (p=0.041, p=0.045).

Discussion

PC caused by abdominal dissemination of advanced gastric cancer is a condition that is extremely difficult to control. However, there are a large number of such patients in China, and many attempts have been made by Chinese and foreign researchers who concluded that overall efficacy is still unsatisfactory [13,14], leading to no standard treatment at present. Some patients with abdominal implantation metastasis need palliative gastrectomy due to tumor-related obstruction, hemorrhage and perforation, which can relieve symptoms and reduce tumors, thus providing favorable conditions for further treatment after operation. However, palliative gastric cancer resection has a limited effect on improving the prognosis of patients. It is often necessary to combine other comprehensive treatment methods to control peritoneal implantation metastasis as much as possible. Early sequential IHPC is one of the options [15].

The anti-tumor effect of hyperthermic chemoperfusion has the following characteristics [16,17]: Hyperthermia directly kills tumor cells and activates immune responses to kill tumor cells. The synergistic effect of hyperthermia and chemotherapy exists. A large number of cancer cells are washed away by mechanical action. It provides constant and lasting high drug concentration in the abdominal cavity and its detoxification can be achieved through the liver to reduce systemic toxic and side effects. In addition, hyperthermic chemoperfusion can circulate the chemotherapy drug and perfusion liquid, and utilize the fluidity of water and the characteristics of heat carriers to enable the warm and anti-tumor drugs to fully and uniformly contact the organs and tissues in the abdominal cavity, thus killing PC cells effectively. However, intraperitoneal chemotherapy drugs can only penetrate <2 mm below the tumor surface [18]. Therefore, the macroscopic lesions can be controlled to the greatest extent by the combination of cytoreductive surgery (CRS) and IHPC. Related systematic evaluation and phase III randomized controlled studies have proved that CRS combined with IHPC has a better effect in the treatment of PC from advanced gastric cancer [19-21].

In this study, the clinical efficacy and adverse reactions of palliative laparoscopic resection of gastric cancer combined with IHPC with oxaliplatin + 5-FU were comparatively analyzed. The results revealed that the short-term effective rate in the IHPC group was better than that in the control group, but without statistical difference. KPS scores of the two groups of patients showed that the effective rate in the IHPC group (82.2%) was higher than that in the control group (75.6%), but again without statistical significance. Besides, there were no statistically significant differences in hematological toxicity, liver function, adverse reactions and complications between the two groups of patients, indicating that IHPC with oxaliplatin + 5-FU can achieve better short-term clinical efficacy and postoperative patients' quality of life without increasing adverse reactions. In this study, sCr and BUN were increased postoperatively in the two groups of patients, and were higher in the IHPC group compared to the control group (p=0.016, p=0.010), indicating that hyperthermic chemotherapy negatively impacted the renal function. The reason may be that renal perfusion insufficiency was caused by peripheral capillary network dilatation and a relatively insufficient blood volume due to the warming effect as well as elevated intra-abdominal pressure due to compresses to renal vessels and ureters. However, all renal failure cases recovered within 3 months after operation in this study. Therefore, it can be considered that the effect of IHPC on renal function is mainly functional rather than organic. Follow-up

results of the patients' survival revealed that the OS and PFS in the IHPC group were significantly higher than those in the control group (p=0.041, p=0.045), suggesting that IHPC with oxaliplatin+5-FU can evidently improve the patient survival.

To sum up, palliative laparoscopic resection of gastric cancer combined with IHPC with oxaliplatin + 5-FU has a definite therapeutic effect on gastric cancer with PC. Moreover, patients show better tolerance, and their OS and PFS are remarkably better than those of patients in the control group. However, the number of cases in this study was small and the follow-up period was short, so the long-term efficacy needs to be confirmed by multicenter clinical studies with a large-sample size.

Conclusions

Palliative laparoscopic resection of gastric cancer combined with IHPC with oxaliplatin+5-FU has a definite therapeutic effect on gastric cancer with PC, a better short-term clinical therapeutic effect and better postoperative quality of life. Moreover, patients show good tolerance, and their OS and PFS are remarkably better than those of patients undergoing simple surgery, so it is worthy of clinical promotion.

Conflict of interests

The authors declare no conflict of interests.

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