Comparative Study on the Efficacy of Lobaplatin and Paclitaxel in the Treatment of Advanced Gastric Cancer Patients with D2 Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy

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Protocol Synopsis

Title	Comparative Study on the Efficacy of Lobaplatin and Paclitaxel in the Treatment of Advanced Gastric Cancer Patients with D2 Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy
Version.	1.0
Main inclusion criteria	Initial treatment,. Intraoperative judgment showed that the patient's T stage was T3 and above, without distant metastasis, D2 radical gastrectomy was feasible, the function of major organs was normal, and the patient was pathologically diagnosed with gastric adenocarcinoma Male or female, 18-75 years of age.
Objectives	1. Main objectives: To evaluate and compare the peritoneal metastasis rate and overall survival rate between lobaplatin and paclitaxel; 2. secondary objectives: comparison of immune status and perioperative safety assessment between lobaplatin and paclitaxel.
Design	a single-center prospective randomized controlled phase II clinical study.
Planned scale	231 cases
Organization	Wuhan Union Hospital, Tongji Medical College of HUST
Criteria	**Inclusion criteria:** 1. age 18-75 years; 2. male or non-pregnant or lactating women; 3. pathological diagnosis of gastric malignant tumor; 4. intraoperative judgment of patients requiring hyperthermic intraperitoneal chemotherapy (HIPEC); 5. normal function of major organs, that is, meeting the following criteria: routine blood tests should meet the following criteria: A. HB ≥ 90 g/L; B. ANC ≥ 1.5 x 10^9/L; C. PLT ≥ 125 × 10^9/L; Chemistry panel meeting the following criteria: A. TBIL < 1.5ULN; B. ALT and AST < 2.5 ULN; C. Serum Cr ≤ 1.25 ULN or endogenous creatinine clearance > 50 ml/min (Cockcroft-Gault formula); D. ALB ≥ 30 g/L 6. ECOG score 0-1; 7. voluntarily sign the informed consent form. **Exclusion Criteria:**

	1. the patient has a history of other malignancies within 5 years; 2. allergy to paclitaxel, lobaplatin and other related chemotherapeutic drugs; 3. suffering from epilepsy or other mental illness, unable to control behavior; 4. unable to tolerate surgery due to severe cardiac, pulmonary and vascular diseases; 5. pregnant or lactating women.
Interventions	Drug group 1: D2 surgical resection + HIPEC (paclitaxel) + systemic chemotherapy for 8 cycles Drug group 2: D2 surgical resection + HIPEC (lobaplatin) + systemic chemotherapy for 8 cycles Control group: D2 surgical resection + hyperthermic intraperitoneal therapy (HIPET) + systemic chemotherapy for 8 cycles
Primary study endpoint	overall survival (OS) and peritoneal metastasis-free survival (pRFS) observed for 3 years
Secondary study endpoints	Incidence of postoperative adverse reactions (referring to CTCAE 5.0 (including blood routine, liver and kidney function, patient response to HIPEC, adverse events), completed when the patient is discharged. (Immunology, ascites)
Safety indicators	Vital signs, laboratory parameters, adverse events (AEs), serious adverse events (SAEs)
Additional Data Analysis	Radiographic data analysis

Study Flow Chart

Item	Before randomization	Surgery	HIPEC	Post-op				Discharge
				Day 1	Day 3	Day 5	Day 7	
Informed Consent Form	×							
Physical examination	×							
ECOG score	×							
Tumor markers	×							
Chest CT/X-ray	×							
Enhanced CT/MRI of whole abdomen	×							
Colonoscope	×							
Cytological examination of washing fluid		×						
Blood routine, liver and kidney function	×		×	×	×	×	×	×
Plasma concentration				×	×			
Electrocardiogram	×							
Pregnancy test	**When necessary**							
Quality of Life Questionnaires	×							×
In-hospital adverse events								×

"×" indicates the examination currently required to be completed

List of abbreviations and definitions of terms

Abbreviations and Special Terms	Explanation
AE	Adverse events
ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Neutrophil count
CI	Confidence interval
Cr	Creatinine
CRF	Case Report Form
CRS	Cytoreductive operation
DRQ	Question and Answer Sheet
ECOG PS score	Eastern Cooperative Oncology Group Body Condition Score
EPIC	Early postoperative intraperitoneal chemotherapy
GCP	Good Clinical Practice
HB	Hemoglobin
HIPEC	Hyperthermic intraperitoneal chemotherapy
ICF	Informed Consent Form
IPC	Intraperitoneal chemotherapy
IRB	Ethics Committee
OS	Overall survival
PC	Peritoneal cancer
PFS	Progression-free survival
PLT	Platelet count
PR	Partial response
SAE	Serious adverse event
TBIL	Total bilirubin

CONTENTS

1. Research Background

1.1 Gastric Cancer

Although the prevalence and mortality of gastric cancer have a gradual decline, the mortality rate of gastric cancer (GC) is still ranked second among all kinds of tumor in the world (736,000 per year) [1, 2]. According to the latest data from the National Cancer Registry [3], the incidence and death of GC cases made up 42.6-45.0% of the global incidence and death in China. The incidence rate of china is the fifth and the mortality rate is the sixth among 183 countries in the world. In 2015, there were about 679,000 new GC cases of GC in China, including 478,000 males and 201,000 females; there were about 498,000 deaths, including 339,000 males and 159,000 females. Further, the number of patients and deaths ranked the second in all malignant tumors in China, and many patients have arrived advanced status at the time of diagnosis. A survey by the American Academy of Surgery showed that the 5-year overall survival (OS) rate of patients undergoing gastrectomy for GC was 14% [4]. In recent years, although surgical mortality and complications have been reduced with the improvement of diagnostic methods, surgical skills, perioperative care and treatment of GC, the 5-year OS rate of patients with GC is still low even after receiving standard treatment (< 40% in McDonald and Magic trials) [5, 6]. Further, the recurrence rate also remains high for advanced GCs. Therefore, it is necessary to develop more effective therapeutic measures to reduce the recurrence rate of advanced GC and mortality in addition to standard R0 resection, D2 surgery, and adjuvant therapy [7-9].

1.2 Hyperthermic Intraperitoneal Chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is traditionally applied to treat peritoneal cancer with cytoreductive surgery (CRS). In terms of GC treatment, there have been multiple randomized clinical trials assessing the efficacy of surgery + HIPEC for the treatment of locally advanced GC [11-13]. However, to date, there are still are not clearly concluded with HIPEC drugs and doses, time, combinations of drugs. Meanwhile, the standardized clinical application of intraperitoneal medication

has become an international concern. HIPEC drugs should meet the following characteristics: first, effective drugs for systemic chemotherapy of GC; second, in line with the characteristics of intraperitoneal chemotherapy, drugs must be able to effectively kill tumor cells through their own or other metabolites, higher abdominal concentration, lower abdominal permeability, less peritoneal irritation, and tumor tissue penetration ability [14]. Therefore, it is important to eplore the safety and efficacy of different chemotherapeutic drugs for HIPEC treatment of GC for improving the survive and life quality of patients with advanced GC.

Paclitaxel is a broad-spectrum anti-tumor drug that can fight with tumors through multiple anti-cancer mechanisms. The NCCN guidelines regard paclitaxel-based two-drug or three-drug combination as the recommended protocol for advanced GCs. In recent years, paclitaxel has been proved effective in advanced GCs combined with HIPEC, and China clinical expert consensus of HIPEC in GCs has listed it as one of infusion drugs [15]. In the HIPEC-01 clinical trial, paclitaxel was used as a HIPEC infusion drug to compare its safety and efficacy with CRS+ HIPEC. It is expected that the test results will bring more evidence-based evidence.

Platinum drugs are non-specific cell cycle anti-tumor drugs that act on the chemical structure of DNA. Oxaliplatin is unstable in sodium chloride solution. The perfusion fluid generally uses the mixture of glucose or glucose distilled water. However, recent studies have shown that glucose used for intraperitoneal hyperthermic infusion chemotherapy can increase the risk of intraoperative hyperglycemia and postoperative infection [16]. Lobaplatin is a third-generation platinum drug. It has no obvious nephrotoxicity, ototoxicity, neurotoxicity, mild gastrointestinal toxicity, and no cross-resistance with other platinum drugs, and its perfusion fluid can be normal saline. Wu et al. enrolled 50 patients of GC with peritoneal metastasis who underwent radical gastrectomy combined with hyperthermic perfusion therapy and used lobaplatin and paclitaxel in a clinical study. The results suggest that this treatment plan can improve OS [17].

There is no prospective randomized controlled clinical study on the choice of lobaplatin and paclitaxel in HIPEC of advanced GC patients in the nation. Based on the widely use of HIPEC among prevention and treatment of peritoneal cancer after surgery in the early stage，we carried out a prospective, single-center, randomized controlled clinical trial to explore the efficacy, perioperative safety and immune status evaluation of different infusion drugs in D2 surgery combined with HIPEC in the treatment of advanced GC patients. Further, this study provides clinical evidence for the clinical development of the best comprehensive treatment plan.

1.3 Expected accomplishments of the study

To evaluate the peritoneal metastasis rate, survival rate, perioperative safety and immune status of lobaplatin and paclitaxel in patients with advanced GC treated with D2 surgery + HIPEC + intravenous chemotherapy.

1.4 Risk/Benefit Assessment

1.4.1 Potential Risks

The main chemotherapeutic drugs used in this study were paclitaxel, lobaplatin and capecitabine. The hematological adverse reactions of these chemotherapeutic drugs were mainly anemia, leukopenia, granulocytopenia and thrombocytopenia; the non-hematological adverse reactions were mainly nausea, vomiting and diarrhea; the neurological toxicity was mainly manifested as peripheral neuritis, sometimes with spasm and sensory disturbance around the oral cavity, upper respiratory tract and upper gastrointestinal tract. The HIPEC treatment group must use dedicated thermal perfusion pipeline components with the risks of anastomotic leakage, delayed exhaust, intestinal adhesion, intestinal obstruction, tumor recurrence or metastasis.

1.4.2 Potential Benefits

Anticipated benefits of the Study to provide comparative results on efficacy, perioperative safety, immune effects, and reduction of cancer cell positive rate of different perfusion drugs in patients with advanced GC treated with D2 surgery + HIPEC + systemic chemotherapy. Further demonstrate the feasibility of HIPEC in

patients with advanced GC, take active treatment measures to reduce the length of hospital stay and costs, reduce mortality, improve survival outcomes, and provide real-world data for clinical practice.

2. study objectives

2.1 Primary Objectives

A prospective randomized controlled study was designed to compare the incidence of perioperative adverse reactions, overall survival rate, peritoneal metastasis-free survival rate and other indicators of different chemotherapeutic drugs (paclitaxel, lobaplatin) for intraperitoneal hyperthermic perfusion chemotherapy in patients with GC, and to evaluate its safety and efficacy

2.2 Secondary Objectives

Blood routine, biochemical, immunological parameters and ascites related tests were compared before and after HIPEC to analyze the value of relevant laboratory test results in the evaluation of HIPEC in patients with GC

Design of the study

3.1 Overall Design

Design type: This study is a prospective, randomized, single-center clinical trial, and Union Hospital, Tongji Medical College of Huazhong University of Science and Technology is the organizational unit.

Test group 1: D2 surgery + HIPEC (paclitaxel) + systemic intravenous chemotherapy

Test group 2: D2 surgery + HIPEC (lobaplatin)+ systemic intravenous chemotherapy

Control group: D2 surgery + hyperthermic intraperitoneal therapy + systemic intravenous chemotherapy

3.2 Endpoints

The study endpoint is reached if the subjects complete all stages of study or follow-up or withdraw the informed consent form according to the study protocol.

3.3 Sample Size

In a study of 1035 patients with II-IIIB GC treated with D2 surgery combined with capecitabine and adjuvant chemotherapy with oxaliplatin, patients were randomly divided into surgery alone combined with drug chemotherapy group. The 3-year PFS was 71% and 85% in stage II patients, 51% and 66% in stage IIIa patients, and 33% and 61% in stage IIIb patients, respectively. The 3-year overall survival rate in the surgery-only group was 78% (risk coefficient 0.72). Among the relevant western studies, MacDonald and Magic had the highest 5-year survival rates of 42% and 36%, respectively. In our recent study, the 5-year survival of Asian patients with T3 and T4 GC after treatment in the United States was 34% and 18%, respectively. We expect that the 3-year survival rate of patients with stage T3-4 GC treated with D2 radical resection combined with hyperthermia alone and systemic chemotherapy can reach 50%, and the 3-year survival rate of patients with stage T3-4 GC treated with D2 radical resection combined with HIPEC and systemic chemotherapy can reach 70%, and the 3-year survival rate is increased by 20%. This study is expected to complete all surgical treatments in 1 year, with an annual dropout rate of 5%. The total sample size calculated by long-rank test is 231 (77 cases in each group). The annual number of advanced GC surgeries in our center is about 300, and the study is expected to be completed in 1 year.

Steps for sample size calculation:

（1） The survival rate was 0.50 in the control group and 0.70 in the intervention group, and an alpha level of 0.1 and a beta of 0.2 were set to give a power (1 − β) of 90%.

（2） $P_0 = 0.50$, $P_1 = 0.70$, test Z_{Alpha} Is 1.645, Z_{Beta} 0.842, $\overline{P} = (0.50 + 0.70)/2 = 0.6$Input Formula

$$n = \frac{\left[Z_{\alpha}\sqrt{2\overline{P}(1-\overline{P})} + Z_{\beta}\sqrt{P_1(1-P_1)+P_0(1-P_0)}\right]^2}{(P_1-P_0)^2}$$

$$N = \frac{\left[1.645\sqrt{2*0.6*0.4} + 0.842\sqrt{0.7*(1-0.7)+0.5*(1-0.5)}\right]^2}{(0.70-0.50)^2} = 73$$

Theoretical total sample size 219 (73 per arm)

（3） Consider dropout 5%

219 * 1.05 = 231

231 in total

4. Subjects

4.1 Inclusion criteria

1.1. GC patients treated with no chemoradiotherapy or other anti-tumor therapy before surgery;

1.2. Aged 18-75 years;

1.3. Male or non-pregnant or lactating women;

1.4. Pathological diagnosis of gastric adenocarcinoma;

1.5. Patients with T stage of T3 or above without distant metastasis who can be given D2 radical resection (AJCC Version 8, 2018);

1.6. Normal function of major organs, i.e. meeting the following criteria:

Routine blood tests should meet the following criteria:

A. HB ≥ 90 g/L;

B. ANC ≥ 1.5 x 10^9/L;

C. PLT ≥ 125 × 10^9/L;

Chemistry panel meeting the following criteria:

A. TBIL < 1.5ULN;

B. ALT and AST < 2.5ULN; ALB > 30 g/L

C. serum Cr ≤ 1.25 ULN or endogenous creatinine clearance > 50 ml/min (Cockcroft-Gault formula);

1.7. ECOG score 0-1;

1.8. Voluntarily signed informed consent form.

4.2 Exclusion Criteria

2.1. Patients with a history of other malignant tumors within 5 years;

2.2. Distant metastasis was found during surgery;

2.3. Allergic to paclitaxel, lobaplatin and other related chemotherapeutic drugs;

2.4. Suffering from epilepsy or other mental illness, unable to control behavior;

2.5. Inability to tolerate surgery due to severe cardiac, pulmonary and vascular disease;

2.6.Pregnant or lactating women.

2.7. Receiving anticancer drug therapy from other clinical trials.

4.3 Recruitment

Source of study subjects: Inpatients.

Recruiting place: Union Hospital, Tongji Medical College of HUST

Planned Recruitment Plan: Conversation prior to surgery.

4.4 Method of Randomization

The patients were coded by "001", "002" and "003" in turn, and randomly assigned by a scheme of generating binary categorical variables using random numbers.

5. Intervention

5.1 Administer Study Intervention

5.1.1 Description of Study Intervention

Study Intervention: Paclitaxel and lobaplatin. See Annex 1 and Annex 2 for the relevant safe use instructions.

Study Intervention Program:

1. patient screening and evaluation

Patients will be screened strictly according to the inclusion and exclusion criteria above in this study protocol.

Admission 1:

(1) Perfect medical history and physical examination

(2) Blood routine, biochemical, immunological indicators, CRP/PCT and tumor markers

(3) B ultrasound, electrocardiogram, chest radiography and gastric CT/MRI

(4) Gastroscopy

2. D2 Surgery

Surgical method: Open surgery or laparoscopic surgery

The steps are as follows: anesthesia → blood sampling → abdominal exploration and evaluation → intraoperative lottery if the criteria are met → preoperative peritoneal lavage → standard D2 surgery → cancer, paraneoplastic and normal tissue samples are obtained → the surgical area needs photography (proven as D2 surgery) → postoperative peritoneal lavage. In the abdominal exploration, "evaluation of lesion infiltration area", "evaluation of tumor size" and "intraoperative staging" were performed, and whether the patients had peritoneal cancer was decided by whether they had peritoneal cancer or not and drawing lots, and the category of the experimental group and the control group was determined.

(1) Extent of surgical resection: The distance from the gastric resection margin of localized GC to the tumor should be more than 3–4 cm, and the distance from infiltrating GC should be more than 5 cm. For esophagogastric junction cancer, the distance from the esophageal resection margin to the tumor should be more than 3 cm, and frozen pathological section examination should be performed when suspicious. For tumors invading the pyloric canal, the duodenal resection margin should be more than 3 cm from the tumor. A sufficient extent of lymph nodes was removed according to the GC staging method.

(2) Principle of tumor-free operation: First ligate veins and arteries at the root of the blood vessel, and at the same time sweep the lymph nodes, then separate and resect the specimen. The operation should be gentle, more sharp separation and less blunt separation. The tumor could not be directly touched to avoid the damage to the lymph nodes which can cause cancer cells to spread and local implantation. The serosal layer can be protected by covering method or applying various glues

(3) Remove the specimen and protect the incision to prevent tumor cell implantation in the incision.

(4) Intraoperative cytology

Before and after the resection of the primary cancer, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, and send it to the pathology department for centrifugation at 1000g ,10min. Collect nucleated cell smears for HE staining microscopy. We get two chief physicians and above pathologists using HE staining method to detect tumor cells. When two pathologists dispute the conclusion, consult the deputy chief physician and above pathologists to confirm the diagnosis.

(5) Abdominal lavage after the operation: After the operation, lavage of the abdominal cavity should be performed to remove free cancer cells in the abdominal cavity as much as possible. The lavage fluid should be normal saline.

(6) After the operation is completed, take photos or videos for archive. Photo or video must cover the following organizations:

Distal subtotal gastrectomy It shows left gastroepiploic artery ligation point, common hepatic artery, proper hepatic artery, left gastric artery ligation point, left and right gastric vein ligation point, splenic artery, right sub-pyloric artery and vein ligation point, bare lesser curvature

Gastrectomy The ligation point of left gastric artery and stump of coronary vein, common hepatic artery, splenic artery, celiac trunk and splenic hilum were shown.

Total gastrectomy It shows the ligation points of left gastric artery and vein, right gastric artery and vein, common hepatic artery, celiac trunk, splenic hilum, splenic artery, proper hepatic artery, right gastroepiploic artery and vein, and sub-pyloric artery and vein.

(7) The collection of pathological tissue samples, peripheral blood samples and lavage fluid samples should be completed during surgery, and photographs of each sample should be taken and archived.

3. Hyperthermic intraperitoneal chemotherapy (HIPEC) (with paclitaxel drugs)

The location of the drainage tube: The two drainage tubes with the tube opening in the upper abdomen are used as perfusion tubes. The tube openings are placed under the left side of the diaphragm and the liver and kidney recesses. After HIPEC is completed, the left side of the diaphragm can be used as a postoperative abdominal drainage tube. Two drainage tubes with nozzles located in the lower abdomen are used as outflow tubes, and the nozzles are placed on both sides of the pelvic floor. Each drainage tube is generally placed on the plane of the anterior axillary line, and the perfusion tube should be placed near the tumor as much as possible, while the outflow tube should be placed away from the tumor area.

Temperature Setting: 43 ±1.0 ℃.

Priming time: 60 min.

Dosage of perfusion fluid: The perfusion fluid is based on the principle of filling the abdominal cavity and unobstructed circulation.

Choice of perfusate: Normal saline.

Drug selection and dosage: Paclitaxel 75 mg/m ^{2} .

Timing of treatment: Performed intra-operatively

Treatment course: the first time after surgery, the second time 48h after first time.

Intraoperative medication: give intravenous sedatives during treatment when the patient is intolerant, adjust the dose according to the patient's response, and give fluids according to the monitoring of vital signs.

Cytological examination: Before and after the resection of the primary cancer, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, and send it to the pathology department for centrifugation at 1000g ,10min. Collect nucleated cell smears for HE staining microscopy. We arrange two chief physicians and above pathologists using HE staining method to detect tumor cells. When two pathologists dispute the conclusion, consult the deputy chief physician and above pathologists to confirm the diagnosis.

Immunological examination: After HIPEC, collect patient blood samples and 5mL the above-mentioned flushing fluid samples for immunological indicators such as CD3, CD4 and CD8 lymphocyte population; IL-2, 4, 8, 10, etc.

Intraoperative monitoring: During HIPEC treatment, monitor blood pressure, body temperature, pulse, urine output, respiration, blood oxygen saturation, whether the perfusion tube is blocked and whether the outflow is smooth. If there is profuse sweating, if the heart rate is faster than 100 beats/minute etc. It is necessary to strengthen fluids after eliminating the cause of hypovolemia. If abnormalities such as breathing and blood oxygen saturation occur, pay attention to the number of anesthetics and perfusion fluid, and stop treatment if necessary.

Judgment on postoperative complications: Intra-abdominal bleeding, infection, peritonitis, anastomotic leakage, intestinal obstruction, intestinal perforation, intestinal necrosis, death and other complications (refer to CTCAE v5.0) and unplanned second surgery;

4.Postoperative systemic adjuvant chemotherapy regimen (SOX/XELOX regimen)

After the patient's condition recovered 4-6 weeks after surgery, 8 cycles of postoperative systemic adjuvant chemotherapy were started. SOX/XELOX regimen was used for chemotherapy regimen

SOX regimen: Oxaliplatin 130 mg/m2 IV d1 + Tegafur capsules: body surface area < 1.25m ^{2} 40 mg/time, bid; 1.25 m2 ≤ body surface area < 1.5m ^{2} 60 mg/time, twice a day; body surface area ≥ 1.5 m ^{2} Those, 60 mg/time, twice a day, d1-14, q3w, 4-8 cycles.

XELOX regimen: Oxaliplatin 130 mg/m ^{2} IV d1 + Capecitabine 1000 mg/m ^{2} Po bid d1-14, q3w, 4-8 cycles

Eight-cycle chemotherapy monitoring: Laboratory tests were performed once before and after chemotherapy, including blood routine tests (hemoglobin Hb, red

blood cell count RBC, white blood cell count WBC, platelet count Plt, neutrophil count NEUT), routine biochemical parameters such as liver and kidney function (glutamate aminotransferase ALT, aspartate aminotransferase AST, γ-glutamyl transferase γ-GT, lactate dehydrogenase LDH, alkaline phosphatase ALP, total protein TP, albumin ALB, albumin/globulin ratio A/G, blood urea nitrogen BUN, serum creatinine Cr), and tumor marker tests (CEA, CA199, CA724).

5.1.2 Dosage and Administration

1) mode of administration: hyperthermic intraperitoneal perfusion (HIPEC)

2) Drug and dose

Drug group 1: Paclitaxel 75 mg/m ^{2}

Drug group 2: Lobaplatin 50 mg/m ^{2} /time

The dose of HIPEC was based on the dose of intravenous chemotherapy, and the solvent was 0.9% NS (2000 ml/m2 + 500 ml),

The first time of HIPEC is performed after surgery, and the second time is performed 48 hours after surgery. The HIPEC interval is not less than 24 hours.

5.2 Preparation/Handling/Storage/Responsibility of Durgs

5.2.1 Responsibilities

The drug will be collected by the hospital pharmacy according to actual needs and random results

5.2.2 Drug composition, appearance, packaging and labeling

The experimental group lobaplatin (Hainan Chang'an International Pharmaceutical Co., Ltd., 50 mg), and paclitaxel (Haikou Pharmaceutical Factory Co., Ltd., 30 mg) were provided by the hospital pharmacy

5.2.3 Product Storage and Stability

Store the drug at room temperature, protected from light

5.2.4 Preparation

The drug is compatible with normal saline, and is perfused and administered through a hyperthermic intraperitoneal perfusion device

5.3 Measures to Reduce Bias: Randomization and Blind

The randomization process is performed by the investigator through the software, and the subjects are single-blinded

5.4 Follow-up and Compliance

• Eight follow-ups were performed at 3, 6, 9, 12, 18, 24, 30, and 36 months after surgery, and blood routine, biochemistry, and tumor markers needed to be examined during follow-up, and CT was performed once a year after surgery; postgraduates were responsible for follow-up.

5.5 Dose Modifications and Concomitant Medications During Chemotherapy

Other chemotherapy and targeted drugs are not allowed to be used before disease progression; liver enzyme inducers such as phenytoin sodium, carbamazepine, rifampicin, barbiturates and itraconazole should be used with caution; palliative drugs (such as analgesic, antiemetic and bisphosphonates, etc.) to relieve symptoms of traditional Chinese medicine are allowed; and leukocyte-elevating therapy can be used according to specific circumstances.

Absolute neutrophil count ($\times 10^9$/L)		Platelet count ($\times 10^9$/L)	Chemotherapy Dose Modification
≥ 1.5	And	≥ 100	Continue 100% of the initial dose of chemotherapy without delay Administration.

≥ 1 - < 1.5	And	≥ 100	75% of the initial dose of the chemotherapeutic agent was used and the administration was delayed.
< 1	And/or	< 100	Delay dosing until absolute neutrophil count recovers to ≥ 1 and platelet count recovers to ≥ 100; if absolute neutrophil count recovers to ≥ 1 but < 1.5, resume treatment at 75% of starting dose of chemotherapeutic agents; if absolute neutrophil count recovers to ≥ 1.5, then chemotherapeutic agents Resume treatment at 100% of the starting dose.

① Dose adjustment method at the beginning of each course of treatment: The following table shows the dose adjustment when hematological toxicity is produced by the application of chemoradiotherapy drugs. If patient has an absolute neutrophil count > 1.5 × 10 prior to starting a course ^{9}/L and platelet count > 100 × 10 ^{9}/L, then a new 2-week course may be started without dose adjustment. Otherwise, dose modification or treatment delay will occur until hematological parameters return to the above levels. If the above hematological parameters do not return to the above levels after a 3-week delay, the patient should discontinue treatment.

② Dose adjustment method caused by severe hematological DLT: dose-limiting toxicity (DLT), including grade 3 and 4 hematological toxicity, with or without fever. If an unscheduled evaluation during a treatment course revealed dose limiting toxicity (DLT), capecitabine was discontinued during that course and the dosage of tegafur and oxaliplatin was reduced in the next course with the following dose reduction regimen.

Dose limiting toxicity	First occurrence	Second occurrence	Third issue Raw
Grade 4 neutropenia lasting more than 5 days	75% of initial dose of chemotherapy	50% of initial dose of chemotherapy	Consider discontinuation
Grade 4 thrombocytopenia	50% of initial dose of chemotherapy	Consider discontinuation	

Grade 3 neutropenic fever (absolute neutrophil count < 1.0 and fever ≥ 38.5℃)	75% of initial dose of chemotherapy	50% of initial dose of chemotherapy	Consider discontinuation
Grade 4 neutropenic fever (absolute neutrophil count < 1.0, fever ≥ 38.5℃ with life-threatening failure Blood)	After careful consideration by the investigator, the initial dose of chemotherapy drugs can be used when the toxicity recovers to grade 0 – 1 Of 50%	Consider discontinuation	

③ Dose adjustment methods caused by non-hematological toxicity:

	Grade 2	Grade 3	Grade 4
First occurrence	Interrupt treatment until toxicity recovers to grade 0-1, followed by treatment at the same dose and, if possible, preventive measures.	Interrupt treatment until toxicity resolves to grade 0-1, then administer 75% of the initial dose, with precautions if possible.	Treatment discontinuation, 50% of the initial dose after recovery of toxicity to grade 0-1, only if the investigator believes that it is in the best interest of the patient to continue treatment Perform treatment
Second occurrence of same toxicity	Interrupt treatment until toxicity recovers to grade 0-1, followed by the initial dose 75% were treated.	Interrupt treatment until toxicity recovers to grade 0-1, followed by the initial dose 50% were treated.	
Third occurrence of the same toxicity	Interrupt treatment until toxicity recovers to grade 0-1, followed by the initial dose 50% were treated.	Discontinue treatment.	
Fourth occurrence of same toxicity	Discontinue treatment.		

5.6 Study Intervention Commitment

The investigator screened and communicated with the patient to sign the informed consent form. The postgraduate student communicated with the patient about the postoperative examination and reminded the patient to follow up. The relevant examination results of the patient were recorded by the CRF form.

6. discontinuation of study intervention and discontinuation/withdrawal of study subjects

6.1 Discontinuation of Study Intervention

Criteria for discontinuation of study intervention: the efficacy in the test group is equal to or inferior to that in the control group; or the incidence of serious adverse reactions is significantly higher than that in the control group, or the overall toxicity events are uncontrollable. The rationale for discontinuation of study intervention was derived from the interim analysis report and written recommendations from the Data Monitoring Committee.

After the decision to discontinue study intervention is made, each investigator must convene all ongoing subjects within a reasonable time, up to 1 month, and instruct the subjects to perform safety assessments and complete all case report forms as soon as possible.

6.2 Discontinuation/withdrawal of study subjects

Discontinuation/Withdrawal Criteria:

1. withdrawal of informed consent by the subject;

2. other complications or special physiological changes in subjects during the trial, which are not suitable to continue the trial;

3. During the trial, the subjects need to combine the treatment affecting the efficacy determination, and the trial should be discontinued in a timely manner;

4. in addition to the above conditions, the investigator judges that it is no longer suitable to continue this trial.

For all the suspension/withdrawal cases, it is necessary to record the completion of

trial as well as the reasons and time for case suspension/withdrawal and fill the obtained information in the record form. Subjects who discontinued/withdrew from the trial were required to complete visits according to the schedule of visit procedures, and other protocol treatments were given according to the condition.

• The medical files of the subjects are only used for this study, and only the investigators of this trial have access to this data; key new variables, medical coding and deprivacy will be generated during data processing.

6.3 Drop Out

Patients in this clinical trial will be followed up for 3 years, with a special person for follow-up and patient management. In the sample design, it is expected that 5% of the patients will drop out, and the sample size will be increased accordingly.

7. Evaluation of Study Outcomes

7.1 Evaluation of Primary and Secondary Outcomes

Primary study endpoints: Overall survival (OS) and peritoneal metastasis-free survival (pRFS) observed for 3 years

1) Peritoneal metastasis-free survival time (pRFS):

Defined as the time from the date of randomization to the date of first documentation of peritoneal metastasis (with or without metastases to other organs), ovarian metastasis, malignant ascites, death (from any cause), calculated with earlier occurrence.

2) Disease-free survival (DFS):

Defined as the time from the date of randomization to the date of first documented disease recurrence, metastasis, new GC, death (from any cause), calculated for the earlier occurrence.

3) Overall survival (OS):

Defined as the time from the date of randomization to the date of patient death (from any cause). For patients with no death information collected in the clinical database, the latest date last known to be still alive will be used as the cut-off point.

Secondary observation endpoints: The incidence of postoperative adverse reactions

(referring to CTCAE 5.0 (including blood routine, liver and kidney function, patient reaction to HIPEC, adverse events)) was completed when the patients were discharged. Analysis of immune indicator data: changes in immune indicators between groups were analyzed based on immune indicators measured at different time points. Analysis of exfoliative cytology data: According to the positive rate of exfoliative cytology cancer cells measured at different time points, the difference in the positive rate of exfoliative cytology between the groups was analyzed.

The primary outcome was recorded by 3-year follow-up after surgery, and laboratory tests were entered into the CRF form.

7.2 Safety and Other Evaluations

Laboratory tests, vital signs recording and assessment of adverse reactions during hospitalization

Laboratory tests during follow-up to assess response to chemotherapy

7.3 Performance Status and Quality of Life Scoring Tables

7.3.1 Evaluation of ECOG Performance Status

Grading	
0	Freely mobile and able to carry out all pre-disease work without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any activity of a work nature with activity of 50% or more of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Always confined to bed or chair.
5	Death

7.3.2 Quality of life score

7.3.2.1 EORTC QLQ-C30 Questionnaire (v3.0)

We would like to know about you and your health and ask you to answer all of the questions below personally. There is no "yes" or "no" answer, just circle the number that best

reflects your condition. The information provided by you will remain strictly confidential.

Please initial:

Date of birth: DD MMM YYYY Date: DD MMM YYYY

		None	**A little**	**Comparable**	**Very**
1.	Are you having trouble doing strenuous activities like lifting heavy shopping bags or suitcases?	1	2	3	4
2.	Are you having trouble walking long distances?	1	2	3	4
3.	Do you have trouble walking short distances outdoors?	1	2	3	4
4.	Do you need to stay in bed or chair during the day?	1	2	3	4
5.	Do you need help eating, dressing, bathing, or using the toilet?	1	2	3	4
	In the past week:	**None**	**A little**	**Comparable**	**Very**
6.	Were you limited in your work and daily activities?	1	2	3	4
7.	Are you limited in your hobbies or leisure activities?	1	2	3	4
8.	Have you had shortness of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Do you need a break?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Did you feel weak?	1	2	3	4
13.	Have you lost appetite (no appetite)?	1	2	3	4
14.	Did you feel sick?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Are you constipated?	1	2	3	4
17.	Do you have diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Does pain interfere with your daily activities?	1	2	3	4

20.	Do you have trouble concentrating on things, like reading a newspaper or watching TV?	1	2	3	4
21.	Did you feel nervous?	1	2	3	4
22.	Did you feel worried?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed (low mood)?	1	2	3	4
25.	Do you have difficulty remembering?	1	2	3	4
26.	Does your physical condition or treatment affect your family life?	1	2	3	4
27.	Does your medical condition or treatment affect your social activities?	1	2	3	4
28.	Do your physical condition or treatment make you financially difficult?	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you.

29. How would you rate your general health over the past week?

1 2 3 4 5 6 7

Very bad Very good

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very bad Very good

7.3.2.2 Quality of life scoring methods

The QLQ-C30 (V3.0) of the EORTC is a core scale oriented to all cancer patients, with a total of 30 items. Among them, items 29 and 30 are divided into seven levels, which are scored from 1 to 7 according to their response options; other items are divided into four levels: not at all, a little, a lot, and very, which are directly scored from 1 to 4.

Calculation of EOETC QLQ-C30 domain (dimension) score (crude score):

For the convenience of statistical analysis and application, scales are often divided into certain domains. Domain is an aspect of the quality of life component, also known as dimension, which is analyzed as an independent variable. 30 items of EOETC QLQ-C30

(V3.0), which can be divided into 15 domains and count 5 functional domains

(physical, role, cognitive, emotional, and social functioning) 3 symptom domains (fatigue, pain, nausea and vomiting), 1 global health status/quality of life domain, and 6 single items (each as a domain). See the table below for classification.

The score of each domain is obtained by summing the scores of the included items and dividing by the number of included items (crude RS, Raw Score), i.e. RS = (Q1 + Q2 +... + Qn)/n.

Calculation of EOETC QLQ-C30 score

In order to make the scores of each domain compare with each other, the linear transformation is further performed using the polarization method to convert the crude score into a standardized score (SS) taking values within 0 ~ 100. In addition, the transformation has another purpose, that is, to change the direction of the score. Because the QLQ-C30 scale, except items 29 and 30, is a reverse item (the worse the quality of life), it is clearly specified in the scoring rules that: for the functional domain and overall health status domain scores, the better the functional status and quality of life, and for the symptom domain scores, the more symptoms or problems (the worse the quality of life). Therefore, it is also necessary to change the direction of calculating the standardization timescale of the functional domain. Specifically, calculate separately according to the following formula (where R is the full distance of scores in each field or item).

Functional Area: SS = [1- (RS-1)/R] 100

Symptom domain and global health status domain: SS = [(RS-1)/R] 100

7.3.2.3 EORTC QLQ-CR29 (v2.1) Questionnaire

Patients sometimes have the following symptoms or problems. Please indicate the level of symptoms or problems you have experienced during the past week and circle the number that best reflects your condition.

	In the past week:	**None**	**A little**	**Comparable**	**Very**
31	Do you have frequent urination during the day?	1	2	3	4
32	Do you have frequent urination at night?	1	2	3	4

33	Do you have involuntary urine leakage?	1	2	3	4
34	Did you feel pain when you urinated?	1	2	3	4
35	Have you had abdominal pain?	1	2	3	4
36	Have you had pain in your buttocks, near your anus, in your rectum?	1	2	3	4
37	Have you had abdominal distension?	1	2	3	4
38	Did you have blood in your stool?	1	2	3	4
39	Do you have mucus in your stool?	1	2	3	4
40	What do you think of your mouth?	1	2	3	4
41	Have you lost your hair because of a disease or treatment?	1	2	3	4
42	Do you eat food or drink differently from before?	1	2	3	4
43	Are you worried about your future health?	1	2	3	4
44	Have you ever worried about your weight?	1	2	3	4
45	Are you visually less attractive because of the disease or treatment?	1	2	3	4
46	Do you feel less attractive for women or men because of the disease or treatment?	1	2	3	4
47	Are you dissatisfied with your physical appearance?	1	2	3	4
48	Do you have a colostomy bag?	Yes		No	

In the past week:

	If you have a colostomy bag, please answer the following questions:	**None**	**A little**	**Comparable**	**Very**
49	Is there involuntary venting of the ostomy bag?	1	2	3	4
50	Have you ever had a bowel movement from your ostomy bag?	1	2	3	4
51	Is there pain in the skin around the ostomy bag?	1	2	3	4
52	Do you often change your ostomy bag during the day?	1	2	3	4
53	Do you often change your ostomy bag at night?	1	2	3	4
54	Do you feel embarrassed about your ostomy bag?	1	2	3	4

55	Do you have problems with ostomy care?	1	2	3	4

	If you do not have a colostomy bag, please answer the following questions:	**None**	**A little**	**Comparable**	**Very**
49	Have you ever had an involuntary fart?	1	2	3	4
50	Have you ever had involuntary bowel movements?	1	2	3	4
51	Have you had pain in the skin around your anus?	1	2	3	4
52	Do you need to defecate often during the day?	1	2	3	4
53	Do you need frequent bowel movements during the night?	1	2	3	4
54	Do you feel embarrassed about having too many bowel movements?	1	2	3	4

In the past four weeks:

	Male responses only:	**None**	**A little**	**Comparable**	**Very**
56.	How interested are you in having sex?	1	2	3	4
57.	Do you have trouble achieving or maintaining an erection?	1	2	3	4
	Female Responses Only:	**None**	**A little**	**Comparable**	**Very**
58.	How interested are you in having sex?	1	2	3	4
59.	Have you had pain during intercourse?	1	2	3	4

8. safety evaluation

8.1 Observation of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical subject and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events that occurred before and after treatment were considered as adverse events according to

management needs. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be performed from the beginning of the subject until the end of the study. Therefore, adverse events that occurred between signing of informed consent and initiation of study treatment were also considered as AEs. General adverse events: The outcome of the event can be closely continued or the corresponding symptomatic treatment can be given according to the trial protocol.

8.2 Assessment and Treatment of Adverse Events

① AE grading

Grade 1: Mild; asymptomatic or mild: clinical or diagnostic findings; treatment not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting personal activities of daily living

Grade 4: Life-threatening; urgent intervention indicated.

Grade 5: Death related to AE.

② AE recording

The name, severity, occurrence time, duration, handling measures and outcome of various AEs occurred during the trial shall be recorded in detail and truthfully filled in the case report form (CRF). Abnormal laboratory test data were recorded in the CRF and repeated at least once a week and followed up until recovery or the end of the study.

③ Correlation with study intervention

Not Related = There is no temporal relationship to hyperthermic perfusion chemotherapy, or there is a reasonable causal relationship between the AE and another treatment, disease, or setting.

Unlikely = Temporal relationship with hyperthermic perfusion chemotherapy but no reasonable causal relationship between the AE and hyperthermic perfusion

chemotherapy

Possibly = There is a reasonable causal relationship between the AE and the hyperthermic perfusion chemotherapy. Failure to stop hyperthermic perfusion chemotherapy or unclear.

Probable = reasonable causal relationship between the AE and the hyperthermic chemotherapy and the drug. Discontinuation of hyperthermic perfusion chemotherapy has an impact on the response.

A reasonable causal relationship between AE = hyperthermic perfusion chemotherapy was clearly established. Stopping hyperthermic perfusion chemotherapy has an impact, and when clinically feasible, if hyperthermic perfusion chemotherapy occurs again.

8.3 Reporting and Handling of Serious Adverse Events

① Definition of serious adverse event

An SAE that occurs after patient enrollment but before completion of chemotherapy is defined as any untoward medical occurrence that is life-threatening or results in death at any dose. Serious "life-threatening" is defined as an adverse event in which the subject was at risk of death from the event as it occurred; it does not refer to an adverse event that hypothetically might have caused death if it were more severe. These generally include: the patient requires hospitalization or prolongation of existing time; results in persistent significant incapacity/disability; congenital anomaly/birth defect and important medical events, some requiring treatment in the emergency room for disability; congenital anomaly/birth defect and important medical events, some requiring treatment in the emergency room for disability; congenital anomaly/birth defect and important medical events, some requiring treatment in the emergency room for important medical events, requiring medical and scientific identification to decide whether prompt reporting is appropriate, these important medical events may not be immediately life-threatening or result in death or require hospitalization, but may jeopardize the subject or may require intervention to prevent the occurrence of other outcomes listed above. These should

also usually be considered serious.

② Reporting procedures of serious adverse events

Serious adverse events were reported from the time a subject signed informed consent through 30 calendar days (inclusive) after the last dose of study drug. During the trial, any SAE must be reported to the clinical research associate (CRA) and the principal investigator within 24 hours. Meanwhile, New Drug Clinical Trial Serious Adverse Event (SAE) Reporting Form should be filled in, signed and dated, and reported to the sponsor, leading site, ethics committee of the study site, China Food and Drug Administration (CFDA) and food and drug administration in the region (province or municipality) where the investigator is located immediately by fax.

During the period of continued administration after the end of the study, the occurrence of serious adverse events must be reported to the sponsor within 24 hours. Information on all serious adverse events must be recorded on the Serious Adverse Event form. Serious adverse events must be reported if they occur during continued supply and within 30 days of dosing. Serious adverse events occurring after administration of investigational product 30 are not reported unless they are suspected to be related to the study drug.

For serious adverse events, symptoms, severity, occurrence time, treatment time, measures taken, follow-up time and method and outcome should be recorded in detail. If the investigator considers a SAE to be unrelated to the investigational drug and potentially related to the study conditions (e.g. discontinuation of original treatment, or comorbidities during the trial), the relationship should be detailed in the narrative section of the SAE CRF. If the intensity of an ongoing SAE or its relationship with the investigational drug changes, the SAE follow-up report should be submitted to the ethics committee immediately. All serious adverse events should be followed up until recovery or stabilization.

9. data management

9.1 Completion and Transfer of Case Report Forms (CRFs)

CRFs are completed by the investigator and must be completed for each enrolled

case. After review by the investigator and submission to the data manager for data entry and management.

9.2 Data entry and modification

Data entry and management will be performed by a designated person. In order to ensure the accuracy of the data, two data managers independently performed double entry, which was checked by computer and manually and then submitted to a statistician for blind verification and statistical analysis.

For any question in the case report form, the data manager will prepare a question-answering form (DRQ) and ask the investigator by the CRA. The investigator should answer and return as soon as possible. The data manager modifies, confirms and enters the data according to the investigator's answers, and may send out the DRQ again if necessary.

9.3 Data Lock

After blind review and confirmation that the established database is correct, the data will be locked by the principal investigator, applicant and statistical analysis personnel. The locked data files will not be changed, and the database will be submitted to the statistician for statistical analysis according to the requirements of statistical analysis plan. Problems found after data locking will be corrected in the statistical analysis program after confirmation.

9.4 Data Processing

The professional personnel in charge of statistical analysis shall perform statistical analysis according to the statistical analysis plan prepared in advance. Statistical analysis was performed according to the principle of intention to determine the full analysis set and per protocol set. After the completion of statistical analysis, the statistical analysis personnel wrote the statistical analysis report and the principal investigator of this trial wrote the study report.

10. statistical analysis methods

(1) General principles

All statistical tests were performed and $P < 0.05$ was considered statistically significant unless otherwise noted.

Quantitative data: Number of cases, arithmetic mean, standard deviation, median and range were used for description. Qualitative data: Described by frequency, constituent ratio or percentage.

Statistical test: Parametric statistical method is considered firstly. If the data distribution is quite different from the requirements for testing hypothesis, non-parametric statistical method is used.

Statistical analysis: Statistical software was used for statistical analysis.

(2) Case characteristics

Completion of enrollment: The number of subjects who completed enrollment at each site was summarized, and a list of drop-out cases was provided.

Baseline characteristics of general information: Baseline is defined as the data obtained during the screening period of the case. The demographic characteristics, symptoms and signs, complications, allergic history and medical history of the patients were described.

(3) Safety evaluation

The postoperative surgical safety evaluation was completed during the first postoperative systemic chemotherapy

Evaluation of adverse reactions during HIIPEC, performed at discharge. For the evaluation of adverse events/adverse reactions, refer to CTCAE
V5.0 Criteria. The evaluation includes:

(1) Blood routine and liver and kidney function tests

(2) Patient response to HIIPEC

(3) Adverse events

11. ethical requirements

(1) The trial protocol and the implementation of the trial study are in accordance with the requirements of the Declaration of Helsinki and the Good Clinical Practice for Drugs.

(2) The trial protocol shall be developed before the start of the clinical trial, signed and confirmed by the investigator, and reported to the Ethics Committee for review and approval before implementation. If the protocol needs to be revised during the actual implementation of the clinical trial, it should be reported to the Ethics Committee for approval in written form before implementation. If important new information involving the study puncture needle is found, the informed consent form must be revised in writing and submitted to the Ethics Committee for approval before obtaining the consent of the subject again.

(3) Before the start of the clinical trial, the investigator must provide the subject or his/her legal representative (guardian) with details of the clinical trial, including the nature of the trial, the purpose of the trial, possible benefits and risks, other treatment options available and the rights and obligations of the subject in accordance with the Declaration of Helsinki, so that the subject or his/her legal guardian can fully understand the clinical trial. The clinical trial can only be initiated after the subject or his/her legal guardian has given consent and signed the informed consent form. The subject informed consent form was provided in duplicate, with one copy for the subject's own storage and one copy for each trial site. Each patient should leave a detailed contact address and telephone data. At the same time, the doctor should leave his/her contact number for the patient, so that the patient can contact the investigator at any time when there is a change in the condition, which is also conducive to the investigator to understand the change in the condition at any time.

(4) If adverse reactions occur during the trial, active treatment should be given to the subjects to minimize the pain of the subjects.

(5) Patients with permanent damage or even death caused by serious adverse reactions shall be given appropriate economic compensation by the study party after being appraised and recognized by the special institution.

12. Quality Control and Quality Assurance of Clinical Trials

The investigator of each center was responsible for the quality control of this clinical trial, and the statistical analysts were responsible for the quality control of

data and analysis. During the study process, ensure that all contents of the study protocol are strictly followed and the study data are correctly filled.

(1) The trial protocol, CRF and informed consent form shall be submitted to the clinical trial ethics committee of each participating unit for review and approval;

(2) The researchers participating in this trial should earnestly implement the standard operating procedures for clinical trials before, during and after the trial;

(3) Accept the clinical trial institutions of all participating units to monitor the correctness and completeness of the data in the CRF during the trial;

(4) The participating researchers must receive unified training, unified recording methods and judgment criteria;

(5) The whole process of clinical trials should be carried out in a strict screening state;

(6) The investigator should truthfully, detailedly and carefully record the contents of CRF according to the requirements for CRF completion, so as to ensure that the contents of CRF are true and reliable;

(7) The abnormal judgment standard of laboratory examination shall be subject to the normal reference range of the inspection institution;

(8) All observations and findings in clinical trials should be verified to ensure that the reliability of data and various conclusions in clinical trials are derived from raw data. Have corresponding data management measures in the clinical trial and data processing stage;

In view of the possible dropout, take active measures to control the dropout rate of cases within 20%.

13. Data Retention

The investigator should keep all the study data, including the confirmation of all the participating subjects (can effectively check the different record data, such as CRF and original hospital record), all the original signed ICFs, detailed records of all the CRFs, etc., and ensure the traceability of all the laboratory tests until 5 years after the end of the clinical study.

14. Summary work

14.1 Acceptance Criteria for Case Report Forms

CRF shall be submitted to the principal investigator of the unit for review and signature after being completed by the investigator during the trial. The principal investigator of each study institution examined the completion of original medical records and CRFs according to the requirements of "clinical trial records" and reviewed the following items:

(1) The CRF must be checked with the original medical records. All the contents recorded on the CRF should be recorded on the original medical records.

(2) The name, mailing address and telephone number of the subject on the medical record must be filled in to ensure its authenticity.

14.2 Retention of Case Report Forms

The CRF was kept in eCRF; the informed consent form was kept in duplicate and kept by the subject and the investigator, respectively.

After all eCRFs are statistically processed, a clinical trial summary report will be written and archived. The original medical records of the trial are kept in the medical record room of each hospital or the archive room of the clinical trial institution.

14.3 Summary of Case Report Forms

The investigator shall be responsible for establishing the database of clinical data and making statistics respectively for the data of each study institution and integrating all the data. Each study site should draft "Summary Table of Clinical Trial Sub-sites", which should be stamped and submitted to each site in one copy. The statistical unit shall be responsible for completing the "Clinical Trial Summary Report", affixing a seal on it and submitting it to each participant.

15. Duties assumed by all parties and provisions for publication of papers

15.1 Responsibilities

The sponsor of clinical study shall assume its responsibilities in accordance with the corresponding provisions of Good Clinical Practice.

15.2 Provisions for Publication

As study results, all the relevant information obtained from this study will be considered confidential. Until the principal investigator completes and reviews the data analysis, these study results can be published and demonstrated with the authorization and consent of the principal investigator, but confidential or proprietary information cannot be disclosed.

References

[1] Organization WH. Cancer, sheet Fact N °297 [D], World Health Organization Media centre, Published 2009. Reviewed January 2013.

[2] Jemal A, Siegel R, Xu J, et al. Cancer statistics [M], 2010. CA Cancer J Clin 60.277-300, 2010

[3] Peng Zhi. Interpretation of GLOBCAN Gastric Cancer Epidemiological Data [J]. Electronic Journal of Comprehensive Cancer Therapy, Vol. 4, No. 4, 2018

[4] Wanebo HJ, Kennedy BJ, Chmiel J, et al.   Cancer of the stomach. A patient care study by the American College of Surgeons [J]. Ann Surg 218.583-92, 1993

[5] Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction [J]. NEngl J Med 345.725-30, 2001

[6] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy alone versus surgery for gastroresectable esophageal cancer [J]. N Engl J Med 355.11-20, 2006

[7] Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC). a phase 3 open-label, randomised controlled trial [J]. Lancet 379.315-21, 2012

[8] Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine [J]. N Engl J Med 357.1810-20, 2007

[9] Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy or with para-nodal aortic dissection alone for gastric cancer [J]. N Engl J Med 359.453-62, 2008

[10] Kuramoto M, Shimada S, Ikeshima S, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma [J]. Ann Surg 250.242-6, 2009

[11] Yonemura Y, de Aretxabala X, Fujimura T, et al. Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer. final results of a randomized controlled study [J]. Hepatogastroenterology 48.1776-82, 2001

[12] Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study [J]. Cancer 73.2048-52, 1994

[13] Fujimoto S, Takahashi M, Mutou T, et al. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma [J]. Cancer 85.529-34, 1999

[14] Yan T D, Cao C Q, Munkholm-Larsen S. A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy [J]. World Journal of Gastrointestinal Oncology, 2010 (02): 109.

[15] Professional Committee of Peritoneal Tumor, Chinese Anti-Cancer Association, Professional Committee of Tumor Hyperthermia, Guangdong Anti-cancer Association. Chinese Expert Consensus on Clinical Application of Hyperthermic Intraperitoneal Chemotherapy (2019 Edition) [J]. Chinese Medical Journal, 2020, 100 (2). 89-96.   DOI.10.3760/cma.j.issn .0376-2491.2020.02.003.

[16] Torphy Robert J, Stewart Camille, Sharma Piyush et al. Dextrose-Containing Carrier Solution for Hyperthermic Intraperitoneal Chemotherapy. Increased Intraoperative Hyperglycemia and Postoperative Complications. [J]. Ann. Surg. Oncol., 2020.

[17] Zhong-He Ji, Kai-Wen Peng, Yang Yu, et al. Current Status and Future Prospects of Clinical Trials on CRS + HIPEC for Gastric Cancer Peritoneal Metastases [J]. Int J Hyperthermia, 2017 Aug; 33 (5). 562-570.

[18] Fujimoto S, Takahashi M, Mutou T et al. Improved JUST ACCEPTED mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoper fusion combined with surgery [J]. Cancer 1997; 79.884-91

[19] Shen P, Stewart JHT, Levine EA et al. Cytoreductive surgery and intraperitoneal hype rthermic chemotherapy for peritoneal surface malignancy. Non-colorectal indicatiions [J]. Curr Probl Cancer 2009; 33. 168-93.

[20] Glehen O, Schreiber V, Cotte E et al. Cytoreductive surgery and intraperitoneal hyperthermia for peritoneal carcinomatosis arising from gastric cancer [J]. Arch Surg 2004; 139. 20-6