Comparative Study on the Efficacy of Mitomycin and Lobaplatin in the Treatment of Advanced Colorectal Cancer combined with Radical Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy

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Protocol Synopsis

Title	Comparative Study on the Efficacy of Mitomycin and Lobaplatin in the Treatment of Advanced Colorectal Cancer combined with Radical Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy
Version	1.0
Object	A total of 201 patients with advanced colorectal surgery were enrolled in the Department of Gastrointestinal Surgery, Wuhan Union Hospital, regardless of gender, 18-75 years old.
Research purposes	(1) Main purpose: To compare the incidence of perioperative adverse reactions, overall survival, and survival without peritoneal metastasis of different chemotherapy drugs (mitomycin, lobaplatin) used in colorectal and abdominal hyperthermic intraperitoneal chemotherapy by designing a prospective randomized controlled study and other indicators to evaluate its safety and effectiveness (2) Secondary purpose: To compare the blood routine, biochemical, immunological and ascites related tests before and after HIPEC, and analyze the evaluation value of relevant laboratory test results for colorectal cancer.
Research design	The study was a single-center prospective randomized controlled clinical study phase II.
Planned number of patients	201
main researcher	Professor. XXX
Research unit	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Screening criteria	Inclusion criteria: 1.18-75 years old； 2.Male and Non-pregnant or breastfeeding women； 3.Pathologically diagnosed as malignant tumor； 4. HIPEC is determined to be required during the operation； 5. The main organ function is normal, which meets the following standards： Routine blood examination standards must meet： a. HB≥90 g/L；

	b. ANC≥1.5×109/L； c. PLT≥125×109/L； Biochemical inspections must meet the following standards： a. TBIL<1.5ULN； b. ALT & AST<2.5ULN； c. serum Cr ≤1.25ULN or endogenous creatinine clearance>50ml/min（Cockcroft-Gault formula）； d. ALB≥30g／L 6.ECOG scored 0-1； 7.sign informed consent willingly. Exclusion criteria： 1.The patient has a history of other malignancies within 5 years； 2.Allergy to paclitaxel, lobaplatin, mitomycin or other related chemotherapy drugs； 3.Suffer from epilepsy or other mental illness, unable to control his own behavior； 4.Inability to tolerate the surgery due to severe heart, lung or blood vessel diseases； 5.Pregnant or breastfeeding women.
Program	This study is a single-center prospective randomized controlled clinical trial. Control group: radical resection of colorectal cancer + hyperthermic intraperitoneal chemotherapy (normal saline) + systemic intravenous chemotherapy for 8 weeks Test group 1: Radical resection of colorectal cancer + HIPEC (lobaplatin) + systemic intravenous chemotherapy for 8 weeks Test group 2: radical resection of colorectal cancer + HIPEC (mitomycin) + systemic intravenous chemotherapy for 8 weeks
Primary endpoints	Primary study endpoint: overall survival (OS) and peritoneal metastasis-free survival (pRFS) was observed for 3 years
Secondary endpoints	Secondary observation endpoint: the incidence of postoperative adverse reactions (refer to CTCAE5.0 (including blood routine, liver and kidney function, patient's reaction to HIPEC, adverse events), completed when the patient is discharged. (immunology, ascites)

CONTENTS

Flow Chart

Item	Before random	surgery	HIPEC		After the surgery				Discharged
					Day 1	Day 3	Day 5	Day 7	
Informed consent	×								
Physical examination	×								
ECOG score	×								
Tumor markers	×								
Chest scan CT	×								
Enhanced CT/MRI of the whole abdomen	×								
Enhanced CT/MRI of the pelvis	×								
Washing fluid cytology		**Option-al**							
Blood routine, liver and kidney	×		×		×	×	×	×	×

function									
Blood concentration					×	×			
ECG	×								
Pregnancy test	**when necessary**								
Quality of life questionnaire	×								×
Adverse events during hospitalization									×

"×" Indicates the examination that needs to be completed currently

Abbreviations

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 surgery
DRQ	data ready queue
ECOG Score	Eastern United States Oncology Group Physical Condition Score
EPIC	Early postoperative intraperitoneal chemotherapy
GCP	Standards for quality management of drug clinical trials
HB	Hemoglobin
HIPEC	Hyperthermic intraperitoneal chemotherapy
ICF	Informed consent
IPC	Intraperitoneal chemotherapy
IRB	Institutional Review Board
OS	Overall survival

PC	Peritoneal cancer
PFS	Progression-free survival
PLT	Platelet count
PR	Partial relief
SAE	Serious adverse event
TBIL	Total bilirubin

1. Research Background

Colorectal cancer (CRC) is the most common malignant tumor of the digestive system in the world. Its incidence rate ranks third, and its mortality rate ranks second[1]. The recurrence and metastasis of tumor is the leading cause of death in patients with colorectal cancer. Peritoneal[2] carcinomatosis (PC) is the most important causes of death in colorectal cancer patients after liver metastasis. Studies have shown that the 3-year peritoneal metastasis rate of pT4 colorectal cancer is as high as 20-36.7% [3-4]. Prevention of peritoneal metastasis is a research hotspot in the treatment of colorectal cancer.

Sugarbaker et al. used cytoreductive surgery (CRS) combined with hyperthermic introperitoneal chemotherapy (HIPEC) for colorectal cancer peritoneal metastasis in the 1990s. After more than 20 years of clinical practice since the 1990s, it has been proved to extend the median survival time and improve the quality of life of patients. [5]

Intraperitoneal chemotherapy drugs need to meet the following characteristics: First: be effective for systemic chemotherapy of colorectal cancer; second, consistent with the characteristics of intraperitoneal chemotherapy, which means the drug must be able to kill tumor cells through itself or other metabolites effectively, higher intraperitoneal concentration, Lower peritoneal permeability, less peritoneal irritation, and stronger tumor tissue penetration ability [6]. So far, there are many types of drugs, dosage, time, and drug combination for intraperitoneal medication, and there is no unified conclusion. The application of standardized clinical intraperitoneal medication has become an urgent key issue [7]. Therefore, studying the safety and effectiveness of different chemotherapeutic drugs for HIPEC treatment of colorectal cancer is of great significance for improving the survival rate and quality of life of patients with advanced colorectal cancer.

According to the latest domestic expert consensus, the commonly used drugs for HIPEC treatment of colorectal cancer are mitomycin, oxaliplatin and 5-fluorouracil [8]. Mitomycin (MMC) and oxaliplatin are the most common drugs in international HIPEC. Meta-analysis shows that about 21% of patients receiving MMC treatment have serious complications, while

the rate in the oxaliplatin group is 30%. MMC is safer than oxaliplatin during the HIPEC treatment [9].

Platinum drugs and mitomycin are cell cycle non-specific antitumor drugs that act on the chemical structure of DNA. Oxaliplatin is unstable in sodium chloride solution, so the perfusion fluid generally used is glucose or a mixture of glucose and distilled water. Studies have shown that the use of glucose in intraperitoneal hyperthermic infusion chemotherapy increases the risk of intraoperative hyperglycemia and postoperative infection [10]. 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. The perfusion fluid can be normal saline. Single-center preventive studies have shown that lobaplatin does not increase the occurrence of postoperative complications during intraperitoneal lavage and it has no significant effect on bone marrow suppression, liver and kidney function, which means it has good safety [11]. There has been a clinical study registered on Clinical Trials to explore the safety of lobaplatin for the treatment of colorectal cancer HIPEC (NCT03221608).

At present, there are few domestic and international clinical studies of HIPEC treatment for colorectal cancer. But there is only one prospective randomized controlled trial registered on Clinical Trials to evaluate colorectal cancer intraperitoneal hyperthermic perfusion chemotherapy (NCT02965248). In this study, randomized controlled experiments were conducted to explore the choice of clinical drugs for colorectal cancer and their safety and effectiveness to provide references for clinical treatment.

2. Research purposes

2.1 Main purpose

By designing a prospective randomized controlled study, compare the perioperative adverse reaction rate, overall survival rate, and survival rate without peritoneal metastasis of different chemotherapy drugs (mitomycin, lobaplatin) used for colorectal and abdominal hyperthermic perfusion chemotherapy, etc. Assess its safety and effectiveness

2.2 Secondary purpose

Compare the blood routine, biochemical, immunological and ascites related tests before and after HIPEC, and analyze the evaluation value of related laboratory test results for patients with colorectal cancers.

3. Research design

This study is a single-center prospective randomized controlled clinical trial.

Control group: radical resection of colorectal cancer + intraperitoneal hyperthermic intraperitoneal chemotherapy (normal saline) + systemic intravenous chemotherapy for 8 weeks

Drug group 1: Radical resection of colorectal cancer + HIPEC (lobaplatin) + systemic intravenous chemotherapy for 8 weeks

Drug group 2: radical resection of colorectal cancer + HIPEC (mitomycin) + systemic intravenous chemotherapy for 8 weeks

Research object: Patients undergoing advanced colorectal surgery in the Department of Gastrointestinal Surgery of Wuhan Union Medical College Hospital.

Research time: September 2021 to September 2025

Patient screening: Complete the following projects within 1 week after admission: complete medical history and physical examination; Blood routine, biochemical, tumor markers; ultrasound, ECG, chest radiograph, abdominal CT/MRI; Colonoscopy

4. Selection

4.1 Inclusion criteria:

1.18-75 years old；

2.Male and Non-pregnant or breastfeeding women；

3.Pathologically diagnosed as malignant tumor；

4. HIPEC is determined to be required during the operation；

5. The main organ function is normal, which meets the following standards：

Routine blood examination standards must meet：

a. HB ≥ 90 g/L；

b. ANC ≥ 1.5×109/L；

c. PLT ≥ 125×109/L；

Biochemical inspections must meet the following standards：

a. TBIL < 1.5ULN；

b. ALT & AST < 2.5ULN；

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

d. ALB ≥ 30g / L

6. ECOG scored 0-1；

7. sign informed consent willingly.

4.2 Exclusion criteria

1. The patient has a history of other malignancies within 5 years；

2. Allergy to paclitaxel, lobaplatin, mitomycin or other related chemotherapy drugs；

3. Suffer from epilepsy or other mental illness, unable to control his own behavior；

4. Inability to tolerate the surgery due to severe heart, lung or blood vessel diseases；

5. Pregnant or breastfeeding women.

4.3 Drop/Elimination standards

4.3.1 Drop standards：

(1) Those who do not meet the entry requirements;

(2) Seriously violated this research plan or failed to perform measurement as required.

Cases that have not completed the clinical trial protocol should be considered as dropped. Including patients withdrawing by themselves (such as poor compliance, unwilling to continue treatment, etc.) and doctors ordering them to withdraw (severe cases requiring combined application of other drugs that affect the judgment of efficacy, severe adverse events requiring drug withdrawal). The reason should be explained for the dropped cases, and the CRF form of all dropped cases should be kept for future reference.

4.3.2 Elimination criteria:

Cases that should not be counted and cannot be counted should be eliminated. Such as misdiagnosis, misacceptance (subjects who do not meet the selection criteria, meet the exclusion criteria and enter the group); there is no test record or measurement record, etc. The reasons for the excluded cases should be explained, and the CRF form should be kept for future reference.

4.4 Subject's withdrawal

4.4.1 Subject withdrawal criteria

1. The subject withdrew the informed consent;

2. The subject has other complications or special physiological changes during the experiment, and it is not suitable to continue the experiment;

3. During the trial, the subjects need to combine treatments that affect the judgment of the efficacy, and the trial should be terminated in time;

4. In addition to the above, the researcher judged that it is no longer suitable to continue the experiment.

4.4.2 Treatment after subject withdrawal

For all cases of suspension/withdrawal, the completion of the trial and the reason and time of the case suspension/withdrawal shall be recorded, and the obtained information shall be filled in the record form. Subjects who discontinue/withdraw from the trial are required to complete the visit according to the visit process schedule, and at the same time, be given other treatments according to their condition.

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

4.5 Study suspension criteria

The criteria for discontinuation of research intervention: the efficacy of the experimental group is equal to or inferior to that of the control group; or the incidence of serious adverse reactions is significantly higher than that of the control group, or the overall toxicity events cannot be controlled. The basis for the suspension of research intervention comes from the interim analysis report and written recommendations of the Data Monitoring Committee.

After the decision to discontinue the research intervention is made, each researcher must convene all the subjects who are participating in the research within a reasonable period of time, up to 1 month, and tell the subjects to conduct a safety assessment, and Complete all case report forms as soon as possible.

5. Recruitment

5.1 the selection of doctor

This study is a prospective study, and we aim to obtain clinical medication safety data for intraperitoneal hyperthermic perfusion chemotherapy. We will choose clinicians who are experienced in intraperitoneal hyperthermic perfusion.

5.2 the selection of patient

The patients were enrolled continuously according to their willingness to participate in the study and the source of the research subjects (inpatients with colorectal cancer). For patients who may participate in this registration study, the possibility of enrollment should be discussed with the patients. When the patient agrees, the investigator should confirm that the patient meets all the inclusion criteria and does not meet any exclusion criteria. Patients who signed an informed consent form and met the inclusion criteria and did not meet the exclusion criteria should be included.

6. research content

6.1 research method

This study is a single-center prospective randomized controlled clinical trial.

Control group: radical resection of colorectal cancer + intraperitoneal hyperthermic intraperitoneal chemotherapy (normal saline) + systemic intravenous chemotherapy for 8 weeks

Test group 1: Radical resection of colorectal cancer + HIPEC (lobaplatin) + systemic intravenous chemotherapy for 8 weeks

Test group 2: radical resection of colorectal cancer + HIPEC (mitomycin) + systemic intravenous chemotherapy for 8 weeks

6.2 Research object

Patients undergoing advanced colorectal surgery in the Department of Gastrointestinal Surgery of Wuhan Union Medical College Hospital.

6.3 Research time

September 2020 to September 2024

6.4 Patient screening

Complete the following projects within 1 week after admission:

complete medical history and physical examination

Blood routine, biochemical, tumor markers

ultrasound, ECG, chest radiograph, abdominal CT/MRI

Colonoscopy

6.5 Intraoperative

1.Colorectal cancer surgery standard: open/laparoscopic radical resection of colorectal cancer, follow the principle of mesangectomy and the principle of no-tumor operation, refer to the "Colorectal Cancer Diagnosis and Treatment Standards (2018 Edition)" from National

Health and Family Planning Commission, surgery specimens were photographed and archived and submitted for inspection.

2.Intraoperative randomization: Whole abdomen and pelvic exploration was performed to exclude distant metastases intraoperativly, combined with preoperative examination and intraoperative exploration to estimate staging. Patients meeting the enrollment criteria was randomized, and 4 drainage tubes were placed in the control and experimental groups during the operation.

Pathological section of intraoperative exfoliated cytology:

3.Before and after the resection of the primary cancer and after HIPEC, rinse the attachment area of the primary cancer with more than 1000ml of normal saline, collect more than 500ml of rinsing solution, send it to the pathology department for 1000g centrifugation for 10min, collect nucleated cell smears, do HE stained microscopy.

6.6 Intraperitoneal hyperthermia

1.Perfusion drainage tube:

During the operation, 4 drainage tubes (2 inflow and 2 outflow) were placed in the left and right subdiaphragmatic liver and kidney recesses, liver and spleen recesses, and pelvic floor, which are generally located in the anterior axillary plane;

2.Drugs and dosage

Test group 1: Lobaplatin 50mg/m2/time

Test group 2: Mitomycin 30mg/m2/time

The dosage of HIPEC refers to the dosage of intravenous chemotherapy, the solvent is 0.9% NS (2000ml/m2+500ml),

The first time was performed after the operation, and the second time was 48 hours after the operation. The interval of HIPEC was no less than 24 hours. 43 degrees, 60 minutes.

3.Testing during treatment:

ECG monitor side blood pressure, pulse, respiration, blood oxygen saturation, and record the control parameters of perfusion chemotherapy during the HIPEC.

4. Postoperative pathological examination

Including histological classification, degree of differentiation, TNM staging

5. Postoperative complications

1) The time of first ventilating, defecation and wound healing after operation;

2) Whether there are complications such as bleeding, infection, peritonitis, anastomotic leakage, intestinal obstruction, intestinal perforation, intestinal necrosis, death, etc. in the abdominal cavity (refer to CTCAE v5.0) and unplanned secondary operations;

3) Blood routine, biochemical, tumor markers, immunological examination 1 day before and after HIPEC

4) Number of days in hospital

6.7 Perfusion fluid inspection during HIPEC

1.Intraoperative exfoliative cytology and pathological examination: Wash the appendage area of the primary cancer with more than 1000ml of normal saline before and after the resection of the primary cancer and before and after two HIPECs, collect more than 500ml washing solute, and send it to the pathology department to centrifuge at 1000g for 10 minutes to collect nucleated cells Smear, do HE stain microscopic examination.

2.Washing fluid laboratory inspection: collect the washing fluid before HIPEC and send 1 test tube of 5ml to ascites immunological examination; after HIPEC, collect 2 test tube washing fluid samples of 5ml each, and send it to ascites drug concentration inspection and ascites immunological examination respectively.

6.8 Postoperative intravenous chemotherapy

start 3-4 weeks after surgery, mFOLFOX6/XELOX is used as the chemotherapy

mFOLFOX6 chemotherapy regimen, before surgery:

On the 1st day, oxaliplatin 85mg/m2 + 500ml glucose solution, intravenous drip for 2h;

On the 1st day, leucovorin calcium 400mg/m2 + 250ml normal saline, intravenous drip for 2h;

On the 1st day, fluorouracil 400mg/m2 intravenously injected; then fluorouracil 1200mg/m2/day X 2 days (total 2400mg/m2), continuous intravenous infusion 46-48h.

Repeat every 2 weeks, 12 cycles

XELOX: Oxaliplatin 130mg/m2 IV d1+ capecitabine 1000mg/m2 po bid d1-14, q3w, 4-8 cycles

8-cycle chemotherapy monitoring: do a laboratory test before and after chemotherapy, including routine blood tests (hemoglobin Hb, red blood cell count RBC, white blood cell count WBC, platelet count Plt, neutrophil count NEUT), liver and kidney functions, etc. Biochemical indicators (glutamate aminotransferase ALT, aspartate aminotransferase AST, γ-glutamyltransferase γ-GT, lactate dehydrogenase LDH, alkaline phosphatase ALP, total protein TP, albumin ALB, white Protein/globulin ratio A/G, blood urea nitrogen BUN, blood creatinine Cr), tumor marker inspection (CEA, CA199, CA724).

6.9 Study Endpoint

Primary study endpoint: overall survival (OS) and peritoneal metastasis-free survival (pRFS) was observed for 3 years

Secondary observation endpoint: the incidence of postoperative adverse reactions (refer to CTCAE5.0 (including blood routine, liver and kidney function, patient's reaction to HIPEC, adverse events), completed when the patient is discharged. (immunology, ascites)

If the research subject completes all phases of the research and follow-up or withdraws the informed consent according to the research plan, the research end point is reached.

6.10 Sample size calculation

Based on the above research background, we estimate that the 3-year expected survival rate of patients in the control group is 60%, and the 3-year expected survival rate of patients in the experimental group is 80%. This study is expected to complete all surgical treatments in one year, and the dropout rate is 5%

The survival rate of the control group is 0.6, and the survival rate of the intervention group is 0.8. Setting the α level to 0.1 and β to 0.2, the power (1-β) is 90%.

2. P0=0.6, P1=0.8, the two-sided test Zα is 1.645, Zβ is 0.842, bring it into the formula

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

The theoretical total sample size is 192 persons (64 persons per group)

3.Considering the falling off of 5%

A total of 201 people (67 people per group)

201 people are needed

6.11 Compliance

The researcher made a detailed record of the measurement results of each subject, and the subjects who actively cooperated in each measurement were deemed to have good compliance. Subjects who do not cooperate to complete all measurements are considered to have poor compliance.

6.12 Dose adjustment and medication combined during chemotherapy

Other chemotherapy and targeted drugs are not allowed before the patient's disease progressing; use phenytoin, carbamazepine, rifampicin, barbiturate, itraconazole and other liver enzyme inducers with caution; the use of Chinese medicine for relief Symptoms of palliative treatment drugs is allowed (such as analgesics, antiemetics, bisphosphonates, etc.); white blood cell therapy can be used according to specific conditions.

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 treatment course: The following table shows the dosage adjustment when using radiotherapy and chemotherapy drugs to produce hematological toxicity. If the patient has an absolute neutrophil count> 1.5×109/L and a platelet count> 100×109/L before starting a course of treatment, a new course of 2 weeks can be started without dose adjustment. Otherwise, adjust the dose or delay the treatment until the hematological parameters return to the above-mentioned level. If the above hematological parameters have not returned to the above levels after the 3 weeks delay in administration, the patient should terminate the treatment.

2. The method of dose adjustment caused by severe hematology DLT: Dose limiting toxicity (DLT), including degree 3 and degree 4 hematology toxicity, with or without fever. If an unscheduled evaluation during a course of treatment shows dose-limiting toxicity (DLT), then capecitabine should be discontinued during the course of treatment, and the dose of ticgio and oxaliplatin should be reduced in the next course of treatment, and the dose reduction plan as follows.

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 chemothera	Consider discontinua tion

		py	
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.		

7. Description of observation indicators

7.1 Measurement standard

Preoperative

Blood routine, biochemical, tumor markers

B-ultrasound, ECG, chest radiograph, abdominal CT/MRI

Colonoscopy

Postoperative

Blood routine, biochemical and immunological index examinations 3 times each

Intraoperative

Collect ascites 3 times, before operation, after operation, and after HIPEC, send it to pathological examination and immunological examination

The primary endpoint: overall survival duration was observed (OS) and peritoneal metastasis-free survival (pRFS) 3 years

Secondary observation endpoint: the incidence of postoperative adverse reactions (refer to CTCAE5.0 (including blood routine, liver and kidney function, patient's reaction to HIPEC, adverse events), completed when the patient is discharged. (immunology, ascites)

7.2 Safety index

Vital signs, laboratory indicators, adverse events (AE) and serious adverse events (SAE).

8. Determination methods and definitions

8.1 Determination index

Collect the patient's case data during hospitalization and follow-up for 3 years after operation, combine it with imaging and laboratory examination, improve the data entry of CRF form, and evaluate the overall survival and survival rate without peritoneal metastasis.

8.2 ECOG physical fitness evaluation

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

8.3 Quality of life score

8.3.1 EORTC QLQ-C30 Questionnaire (v3.0)

We would like to know some information about you and your health. Please answer all the following questions in person. The answers here are not "right" or "wrong". We only ask you to circle on the number that best reflects your situation. The information you provide will be kept strictly confidential.

Please fill in your initials:

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 littl**	**Comp**	**Very**

			e	ara ble	
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

8.3.2 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

8.3.3 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**
31	Do you have frequent urination during the day?	1	2	3
32	Do you have frequent urination at night?	1	2	3
33	Do you have involuntary urine leakage?	1	2	3
34	Did you feel pain when you urinated?	1	2	3
35	Have you had abdominal pain?	1	2	3
36	Have you had pain in your buttocks, near your anus, in your rectum?	1	2	3
37	Have you had abdominal distension?	1	2	3
38	Did you have blood in your stool?	1	2	3
39	Do you have mucus in your stool?	1	2	3
40	What do you think of your mouth?	1	2	3
41	Have you lost your hair because of a disease or treatment?	1	2	3
42	Do you eat food or drink differently from before?	1	2	3
43	Are you worried about your future health?	1	2	3
44	Have you ever worried about your weight?	1	2	3
45	Are you visually less attractive because of the disease or treatment?	1	2	3
46	Do you feel less attractive for women or men	1	2	3

	because of the disease or treatment?				
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**
49	Is there involuntary venting of the ostomy bag?	1	2	3
50	Have you ever had a bowel movement from your ostomy bag?	1	2	3
51	Is there pain in the skin around the ostomy bag?	1	2	3
52	Do you often change your ostomy bag during the day?	1	2	3
53	Do you often change your ostomy bag at night?	1	2	3
54	Do you feel embarrassed about your ostomy bag?	1	2	3
55	Do you have problems with ostomy care?	1	2	3

	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

9.Safety evaluation

9.1 Adverse event observation

AE refers to any adverse medical event that occurs in subjects or clinical subjects, and may not be causally related to treatment. Therefore, AE can be any bad or unintentional signs (such as: abnormal laboratory results), symptoms or transient drug-related diseases, and it should be considered whether it is related to medication. According to management needs, adverse events that occur before and after treatment are regarded as adverse events. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be carried out from the beginning of the subjects' enrollment to the end of the study. Therefore, adverse events that occurred during the signing of the informed consent form and the start of study treatment are also considered AEs. General adverse events: the outcome of the event can be closely followed or the corresponding symptomatic treatment can be carried out according to the experimental protocol.

9.2 Assessment and management of adverse events

1.AE classification

Grade 1: mild; asymptomatic or mild: only clinical or diagnostic; no treatment is required.

Grade 2: Moderate; requires minor, local or non-invasive treatment: age-appropriate instrumental limitation of activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; cause hospitalization or prolong hospitalization; disabled; personal activities of daily living are restricted

Level 4: Life-threatening; urgent treatment is required.

Grade 5: Death related to AE.

2. AE record

Record the name, severity, time of occurrence, duration, treatment measures and outcome of various AEs that occurred during the trial in detail, and fill in the case report form (CRF) truthfully. Abnormal laboratory test data is recorded on the CRF table, and the test is repeated at least once a week, and follow-up until the return to normal or the end of the study.

3. Relevance to research intervention

Irrelevant = There is no temporal relationship with hyperthermic perfusion chemotherapy, or there is a reasonable causal relationship between AE and another treatment method, concomitant disease or environment.

Impossible = There is a temporal relationship with hyperthermic perfusion chemotherapy, but there is no reasonable causal relationship between AE and hyperthermic perfusion chemotherapy

Maybe = there is a reasonable causal relationship between AE and hyperthermic perfusion chemotherapy. The lack of stopping hyperthermic perfusion chemotherapy or is not clear.

It is possible that there is a reasonable causal relationship between AE and hyperthermic perfusion chemotherapy and drugs. Stopping hyperthermic perfusion chemotherapy has an effect on the response.

It is clearly determined that there is a reasonable causal relationship between AE and hyperthermic perfusion chemotherapy. Stopping hyperthermic perfusion chemotherapy has an impact, and when it is clinically feasible, it will happen again if hyperthermic perfusion chemotherapy is repeated.

9.3 Reporting and handling of serious adverse events

1. Serious adverse events

SAE that occurs during the period from the end of the last chemotherapy to the end of the last chemotherapy for patients with serious adverse events refers to all adverse medical events that occur under any drug dose that are life threatening or cause death. "Serious" and "life-threatening" are defined as when the adverse event occurs, the subject is in danger of death; it is not assumed that more serious adverse events may lead to patient death. Usually include: the patient needs to be hospitalized or extended the current time; cause continuous and significant incapacity/disability; congenital malformations or birth defects and important medical events, some malpractices need to be treated in the emergency room; congenital malformations or Birth defects and important medical events, some malformations need to be treated in the emergency room; disability; congenital malformations or birth defects and important medical events, some malformations need to be treated in the emergency room. When important medical events occur, medical treatment and science are required to determine whether it is appropriate to report quickly, these important medical events may not immediately threaten life or cause death or require hospitalization, but may endanger the subject or may require intervention to prevent the occurrence of other results mentioned above. These should also generally be considered serious.

2. Reporting procedures for serious adverse events

The report of serious adverse events should start from the subject signing the informed consent and until 30 calendar days (including the 30th day) after the last use of the study drug. During the trial period, if a serious adverse event occurs, it must be reported to the clinical monitor and the main investigator within 24 hours, and the "Serious Adverse Event (SAE) Report Form for New Drug Clinical Research" shall be filled in, signed and dated, and faxed. The form should be immediately reported to the sponsoring unit, team leader unit, research unit ethics committee, China Food and Drug Administration (CFDA), and the food and drug administration of the region (province or city) where the investigator is located.

During the continued drug supply period after the study, any serious adverse events must be reported to the sponsor within 24 hours. The information of all serious adverse events shall be recorded in the serious adverse event table. Serious adverse events that occur during the period of continued drug delivery to 30 days after the last dose must be reported. Serious

adverse events that occur 30 days after the last administration are generally not reported unless they are suspected to be related to the study drug.

For serious adverse events, the symptoms, severity, time of occurrence, treatment time, measures taken, time and method of follow-up, and outcome should be recorded in detail. If the investigator believes that a serious adverse event is not related to the trial drug, but is potentially related to the study conditions (such as termination of the original treatment, or comorbidities during the trial), the relationship should be described on the serious adverse event page of the medical record report form Partially explained. If the intensity of an ongoing serious adverse event or its relationship with the test drug changes, the serious adverse event follow-up report should be sent to ethics immediately. All serious adverse events should be followed up until recovery or stability.

10.Data management

10.1 Filling out and handing over the case report form (CRF)

The CRF is filled in by the investigator, and each selected case must complete the CRF. After being reviewed by the researcher and handed over to the data administrator for data entry and management.

10.2 Data entry and modification

Data entry and management are handled by dedicated personnel. In order to ensure the accuracy of the data, two data administrators should independently carry out double entry, after computer verification and manual verification, it is submitted to a statistician for blind verification and statistical analysis.

For the questions in the case report form, the data manager creates a question and answer form (DRQ), and sends out inquiries to the investigator through the clinical monitor. The researcher should answer and return as soon as possible. The data manager will modify, confirm and enter the data according to the researcher's answer, and can issue a DRQ again if necessary.

10.3 Data lock

After blindly reviewing and confirming that the established database is correct, the main researchers, applicants, and statistical analysts lock the data. The locked data files will no longer be changed, and the database will be handed over to statistical analysts for statistical analysis in accordance with the requirements of the statistical analysis plan. The problems found after the data is locked will be corrected in the statistical analysis program after confirmation.

10.4 Data processing

Statistical analysis is carried out by statistical analysis professionals according to the statistical analysis plan formulated in advance. The statistical analysis is carried out in accordance with the full analysis set determined by the principle of intentionality and the principle of compliance with the plan set. After the statistical analysis is completed, the statistical analysis staff will write a statistical analysis report, and the main researcher of this experiment will write a research report.

11.Statistical analysis method

11.1 General principles

Unless otherwise specified, all statistical tests are two-sided tests, and $P<0.05$ can be considered as statistically significant differences.

Quantitative data: use the number of cases, arithmetic mean, standard deviation, median and range description. Qualitative data: use frequency, composition ratio or percentage description.

Statistical test: First consider using the parametric statistical method. If the data distribution differs greatly from the requirements of the test hypothesis, use the non-parametric statistical method.

Statistical analysis: Use statistical software for statistical analysis.

11.2 Case characteristics

Enrollment and completion status: Summarize the number of enrolled and completed cases in each center, and list the dropped cases.

Baseline characteristics of general information: The baseline is defined as the data obtained during the case screening period. Describe the patient's demographic characteristics, symptoms and signs, comorbidities, allergies, medical history, etc.

11.3 Safety evaluation

The postoperative safety evaluation was completed during the first postoperative systemic chemotherapy. Evaluation of adverse reactions during HIIPEC is carried out at discharge. For the evaluation of adverse events/adverse reactions, comprehensively refer to the CTCAEv5.0 standard. Evaluation content includes:

(1) Blood routine and liver and kidney function tests

(2) Patient's response to HIIPEC

(3) Adverse events

12.Ethical requirements

(1) The implementation of this trial protocol and trial research complies with the requirements of the "Declaration of Helsinki" and the "Quality Management Practice for Drug Clinical Trials" and other regulations.

(2) Develop a trial plan before the start of a clinical trial, which is signed by the investigator for confirmation, and implemented after being approved by the ethics committee. If this protocol needs to be revised during the actual implementation of the clinical trial, it shall be submitted to the ethics committee for approval before implementation in written form. If important new data related to the puncture needle used in the experiment is found, the informed consent form must be revised in writing and sent to the ethics committee for approval, and the subject's consent will be obtained again.

(3) Before the start of the clinical trial, the researcher must provide the subject or his legal representative (guardian) with detailed information about the clinical trial, including the nature of the trial, the purpose of the trial, the possible benefits and risks, and other treatments available. methods and the rights and obligations of subjects in accordance with the "Declaration of Helsinki" shall enable subjects or their legal guardians to fully understand the clinical trial. The clinical trial can only be started after the subject or his legal guardian has given consent and signed the informed consent form. The subject’s informed consent form is in duplicate, one of which is given to the subject to keep and the other is kept in each test center. Each patient must leave a detailed contact address and telephone information. At the same time, the doctor should leave his contact number to the patient so that the patient can contact the researcher at any time when the patient's condition changes, which is also conducive to the researcher to understand the condition at any time.

If an adverse reaction occurs during the experiment, the subject should be given active treatment to minimize the subject's suffering.

If a serious adverse reaction causes permanent damage or even death to the patient, the researcher shall make appropriate financial compensation to the subject after it has been identified and approved by a specialized agency.

13.Clinical trial quality control and quality assurance

The quality control of this clinical trial is the responsibility of the researchers in each center, and the quality control of the data and analysis is the responsibility of the statistical analysts. During the research process, ensure that all the contents of the research plan are strictly observed and fill in the research materials correctly.

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

(2) The researchers who participated in the trial carefully implemented the standard operating procedures of clinical trials before, during and after the trial;

(3) During the trial process, the clinical trial institutions of all participating units will monitor the correctness and completeness of the data in the CRF;

(4) Participating researchers must undergo unified training, unified recording methods and judgment standards;

(5) The entire clinical trial process should be conducted under strict screening;

(6) Researchers should fill in the CRF according to the requirements, truthfully, in detail and carefully record the contents of the CRF to ensure that the CRF content is true and reliable;

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

(8) All observations and findings in clinical trials should be verified to ensure the reliability of the data and to ensure that the conclusions in the clinical trials are derived from the original data. There are corresponding data management measures in clinical trials and data processing stages;

(9) Actively take measures against possible shedding to control the shedding rate of cases within 20%.

14.Data preservation

Researchers should keep all research data, including confirmation of all participating subjects (which can effectively check different records, such as CRF and original hospital records), all original signed patient informed consent forms, and all CRF records Detailed records, etc., and ensure the traceability of all laboratory inspections, are kept until 5 years after the end of the clinical study.

15.Summary

15.1 Acceptance criteria for case report forms

After the CRF is completed by the investigator during the trial period, it shall be submitted to the principal investigator of the unit for review and signature. In accordance with

the requirements of the "Clinical Trial Record", the principal investigator of each research unit shall check the original medical records and CRF and review the following items:

(1) The CRF must be checked with the original medical record. All the content recorded on the CRF should be recorded in the original medical record.

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

15.2 Preservation of case report forms

The CRF is stored in eCRF; the informed consent is in duplicate, which is kept by the subject and the investigator.

After all eCRFs were statistically processed, a clinical trial summary report is written and archived. The original medical record of the trial is kept by the medical record room of each hospital or the archives of the clinical trial institution.

15.3 Summary of the case report form

The researcher is responsible for establishing a clinical data database, collecting statistics on the data of each research unit and comprehensively collecting all the data. Each research unit writes a "Clinical Trial Subcenter Summary Table" and submits it to their respective testing unit after stamping. The statistical unit is responsible for completing the "Clinical Trial Summary Report", which is stamped and submitted to each participating unit.

16. Responsibilities of all parties and regulations of paper publication

16.1 Responsibility

The clinical research sponsor must earnestly follow the corresponding provisions of the "Clinical Trial Quality Management Standards" and undertake its due responsibilities.

16.2 Paper publishing regulations

As research results, the relevant information obtained by this research is considered confidential. Until the main researcher completes and reviews the data analysis, the research results can be published and demonstrated with the authorization and consent of the main researcher, but the confidential or proprietary information cannot be disclosed.

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