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Intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin in colorectal cancer: a prospective, randomised, controlled, multicentre study

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Abstract

Background Peritoneal metastasis (PM) after radical surgery is an important cause of treatment failure in colorectal cancer (CRC). Intraoperative intraperitoneal perfusion chemotherapy may be an effective method for preventing postoperative PM in patients with CRC. This study aimed to explore the safety and feasibility of intraoperatively preventive intraperitoneal perfusion chemotherapy using lobaplatin for CRC.

Methods Between 12 December 2017 and 17 October 2019, 720 eligible CRC patients with T4 or N + clinical TNM stage were recruited from 25 hospitals in China. Eligible patients were randomised in a 1:1 ratio to undergo resection of CRC only (control group) or resection of CRC with intraperitoneal perfusion chemotherapy with lobaplatin intraoperatively (lobaplatin group). The primary endpoint of this trial was the rate of PM after surgery, while secondary endpoints included safety, overall survival (OS) time, recurrence-free survival (RFS) time, peritoneal recurrence-free survival (PRFS) time, and the rate of liver metastasis.

Results Of 716 patients included in the full analysis set (FAS), 352 were assigned to the lobaplatin group and 364 to the control group. In the FAS population, adding intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin decreased the primary end point rate of 3-year PM (3.56% vs 8.75%, $P = 0.0053$). There was no significant difference in the 3-year OS between the groups (93.2% vs 90.4%, $P = 0.1660$). The 3-year RFS rate (88.1% vs 81.6%, 0.0146) and 3-year PRFS rate (96.6% vs 91.5%, $P = 0.0053$) were significantly higher in the lobaplatin group than the control group. There were no statistically significant differences between the two groups in the incidence (69.77% vs 64.75%) or severity of adverse events (AEs) in the safety set (SS) population.

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Conclusions Initiation of intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin reduced the 3-year PM rate in CRC patients while improving both 3-year RFS and PRFS. The treatment was well tolerated, and the safety findings were comparable with those of the control group.

Trial registration Chinese Clinical Trial Registry, ChiCTR1800014617.

Keywords Peritoneal metastases, Colorectal cancer, Intraperitoneal perfusion chemotherapy, Recurrence-free survival

Background

The peritoneum is a common site of metastasis in colorectal cancer (CRC), with approximately 17% of patients with metastatic CRC exhibiting peritoneal dissemination [1–3]. Peritoneal metastasis (PM) is possible in some cases of CRC even after curative treatment for the primary tumour, and postoperative PM is believed to be connected with many high-risk factors such as right-sided colon cancer, tumour invasion of more than half circle of the bowel, poorly-differentiated cancer, invasion of the serosa or beyond the serosa, presence of lymph node metastasis, and preoperative Carcinoembryonic Antigen (CEA) level ≥ 10 ng/ml [4–6].

An increasing number of researchers believe that isolated PM can be considered a local lesion and may be treated with more aggressive local treatment modalities. A treatment regimen based on cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is gradually being recommended. However, during long-term follow-up, the demonstrable survival benefit of intraperitoneal chemotherapy is minimal once PM is identified [7]. Intraoperative preventive intraperitoneal chemotherapy in patients with PM may be an effective method for decreasing the incidence of PM.

Among the drugs commonly used for CRC in HIPEC, cisplatin exhibits low solubility and poor bioavailability, carboplatin shows reduced sensitivity in certain tumour cells, 5-FU depends on hepatic enzyme activation and is cell cycle specific, and pirarubicin is associated with significant local irritation. In contrast, lobaplatin, a third-generation platinum-based agent, is a cell cycle non-specific drug with superior solubility among platinum compounds. Additionally, it rarely forms miliary nodules on the pleura and peritoneum and causes minimal physical irritation. Its pH is closely aligned with the physiological pH of the human body, resulting in low chemical irritation. Lobaplatin has demonstrated significant antitumour efficacy against various human solid tumours including ovarian cancer, breast cancer, and CRC [8, 9]. Therefore, this study was designed to test the hypothesis that intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin can decrease the rate of PM. Within this framework, we conducted an open-label, prospective, randomised, controlled, multicentre prospective study to explore the safety and feasibility of intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin for CRC.

Methods

Study design

This open-label, prospective, randomised, controlled, multicentre prospective study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval No.: 16–147/122) and at all participating hospitals. The patients involved in this study were recruited by surgeons from 25 hospitals in China, and all hospitals participating in this study performed more than 200 operations for CRC every year. This study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent to participate. This study was reported in line with the Consolidated Standards of Reporting Trials (CONSORT) Guidelines [10]. The study began in December 2017 and the duration of inclusion was approximately 18 months.

Study population

Adults with resectable CRC without distant metastases were considered for inclusion in the study. Patients were eligible for this study when they met the following inclusion criteria: 1) Age 18–75 years; 2) pathologically diagnosed colorectal adenocarcinoma; 3) initially diagnosed without chemotherapy or radiotherapy; 4) clinical stage T4 or N(+) tumour; 5) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; 6) distance between the tumour and anal verge ≥ 10 cm in colonoscopy; 7) no present distant metastasis in chest and abdominal computed tomography (CT); 8) adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements to be conducted within 15 days prior to randomisation: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets (PLT) $\geq 100 \times 10^9$/L, haemoglobin ≥ 90 g/L, total bilirubin ≤ 1.5 upper normal limit (UNL), direct bilirubin ≤ 1.5 UNL, alanine aminotransferase (ALT) ≤ 2.5 UNL, aspartate aminotransferase (AST) ≤ 2.5 UNL, serum creatinine ≤ UNL,

endogenous creatinine clearance rate >55 ml/min; fasting blood glucose ≤7 mmol/L; 9) women of child-bearing age taking effective contraception measures; and 10) written informed consent.

Potential patients who met any of the following criteria were excluded from participation in this study: 1) Had a major operation within 4 weeks prior to inclusion or having a non-healing operative wound; 2) second primary malignancy except in situ carcinoma of the cervix, adequately treated non-melanoma skin cancer, or other malignancy treated at least 5 years prior to inclusion without evidence of recurrence; 3) serious cardiovascular disorders including uncontrollable high blood pressure, unstable angina, myocardial infarction within 6 months, congestive heart failure with New York Heart Association class III or IV; 4) serious infections needing intravenous antibiotics, antifungal drugs, or antiviral drugs; 5) psychiatric disability or interfering with compliance; 6) serious bleeding of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 within 4 weeks prior to inclusion; and 7) any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Randomization

Randomisation was performed preoperatively if the participants met all the criteria. The procedure for random allocation occurred after baseline data collection for all participants and was performed by a member of the research team who was independent of recruitment or data collection. Eligible patients were randomised in a 1:1 ratio to undergo resection of CRC only (control group) or resection of CRC with intraperitoneal perfusion chemotherapy with lobaplatin intraoperatively (lobaplatin group). Randomisation was stratified by treatment centre, sex, age, and clinical stage for comparability between the two groups. The exact sequence was generated using algorithms available at http://edc.medroad.cn/sci/login. This open-label trial involved no masking of treatment or outcomes because of the nature of the intervention, including clamping of the peritoneal drainage tubes for intraperitoneal perfusion chemotherapy.

Interventions

After randomisation, all enrolled patients underwent regular laparoscopic or open surgery. For the control group, 1000 mL of distilled water was used for peritoneal lavage after tumour removal and aspirated completely. A peritoneal drainage tube was placed in the surgical area, if necessary. Finally, the abdominal incision was closed according to routine operative procedures, and the operation ended. In the lobaplatin group, after peritoneal lavage with 1000 mL of distilled water (the distilled water was also completely aspirated intraoperatively), at least two peritoneal drainage tubes were placed in the operation area. The abdominal incision was then closed. Lobaplatin at 60–120 mg (Hainan Changan International Pharmaceutical Co., Ltd.. Haikou, China) was dissolved in 500–1000 mL of 5% aqueous glucose solution (with a lobaplatin concentration of 120 mg/L) and injected via drainage tubes. To prevent lavage fluid from flowing out, the drainage tubes were clamped for 6 h after injection and then opened to guide fluid perfusion. If needed and appropriate, all patients received routine adjuvant therapy 4 weeks after surgery according to the National Comprehensive Cancer Network (NCCN) recommendations, including chemotherapy, radiotherapy, targeted therapy, and immunological therapy. All participants were administered preventive or therapeutic antiemetics, if necessary. Granulocyte Colony-Stimulating Factor (G-CSF), Thrombopoietin (TPO), and Interleukin-11 (IL-11) were not allowed for primary prevention during the screening and perioperative periods. Symptomatic drugs were administered in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for CRC.

Follow-up

A blinded trial coordinator recorded all patient symptoms and outcomes daily during hospitalisation. Postoperative complications were calculated within 30 days of surgery, and postoperative mortality within 30 and 90 days. Outpatient follow-up visits were recommended every 3 months for 2 years and every 6 months thereafter until 3 years after randomisation. Cancer recurrence and distant metastasis were monitored based on physical and laboratory examinations including biomarkers (CEA and CA-199); CT of the chest, abdomen, and pelvis at each visit; and complete colonoscopy every year. Adverse events (AEs) and serious adverse events (SAEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTC AE *v* 4.0).

Outcome measurements

The primary endpoint of this trial was the rate of PM detected during the follow-up period. Secondary endpoints included safety, overall survival (OS) (defined as the time from randomisation to death from any cause or emigration), recurrence-free survival (RFS) (calculated from the date of randomisation until local or distant recurrence), peritoneal recurrence-free survival (PRFS), and the rate of liver metastasis after surgery. Laboratory examination results, postoperative recovery, surgical complications, AEs, and SAEs were considered significant factors related to safety.

PM assessment was mainly performed based on radiological findings. PM was clinically defined as the presence of nodular, confluent, or infiltrative contrast-enhancing lesions involving the peritoneum, omentum, or mesentery on contrast-enhanced CT. Diagnostic abdominal paracentesis could only be performed on patients with ascites. Fine-needle aspiration cytology or biopsy could be performed in patients with suspected PM deposits and laparoscopy may be considered if necessary.

Sample size

Based on previous research, PM is found in 7–15% of CRC patients at the first surgery, occurring in 4–19% of patients who initially underwent radical surgery [1–6, 11]. We estimated that the 3-year PM rates for the control and lobaplatin groups were 15% and 8%, respectively. With an expected 24 months accrual and 24 months of follow-up, and assuming a drop-out rate of 10%, we planned to recruit 720 patients for randomisation to the two groups, which provides 80.7% actual power to show the difference with a two-sided α level of 0.05.

Statistical analysis

The full analysis set (FAS) was used to analyse the baseline and outcome data of patients who were randomly assigned and received treatment. The per-protocol set (PPS) was used to analyse the evaluation data of patients who completed the trial without major protocol deviations. All patients who received at least one dose of the study treatment constituted the safety set (SS). Efficacy and safety were analysed using the FAS and SS, respectively.

SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to analyse the clinical data of the patients in both groups. For the primary endpoint, the rate of PM was a product-limit estimation of the cumulative hazard and was presented with a 95% confidence interval (CI). Kaplan–Meier and log-rank tests were performed to evaluate OS and RFS, and the results were presented as hazard ratios (HRs) with 95% CIs. Cox regression models were used to estimate the association between the treatment and survival. Quantitative variables were presented as mean and standard deviations and were compared with the student *t*-test, and categorical variables were compared with the χ^2 test or Fisher's exact test for probability. Ordinal categorical variables were analysed using the Wilcoxon rank-sum test. *P* values less than 0.05 were considered statistically significant.

Results

Study population

A flowchart of the study is summarized in Fig. 1. Between 12 December 2017 and 17 October 2019, 720 eligible patients were recruited and assigned to the treatment and SS analysis, 354 to the lobaplatin group, and 366 to the control group. Four cases were excluded from the analysis because of the inclusion criteria, and 716 cases were included in the FAS analysis (352 cases in the lobaplatin group and 364 cases in the control group). Eleven patients could not undergo PPS analysis because of distant metastases during intraoperative exploration or poor compliance. There were 705 cases in the PPS analysis, of which 347 and 358 were in the lobaplatin and control groups, respectively. The baseline patient characteristics are shown in Table 1. Mean (SD) patient age was 58.36 (9.92) years, and 274 patients (38.26%) were female.

Efficacy

At the predetermined data cutoff date (6 May 2023), the median follow-up durations were 1342 days (IQR 1227–1580.5) in the lobaplatin group and 1298.5 days (IQR 1213–1576) in the control group. For the primary endpoint, the 3-year efficacy analysis showed that in the FAS group, 12 cases (3.56%) of PM occurred in the lobaplatin group, while 31 cases (8.75%) occurred in the control group, (HR = 0.39; 95% CI, 0.20 to 75; P = 0.0053; Table 2). Univariate analysis of the 3-year PM rate showed that intraperitoneal chemotherapy was associated with a significantly reduced risk of PM, with an HR of 0.39 (95% CI, 0.20 to 0.75, P = 0.0053, Additional file 1: sTable 1). In the subsequent multivariate analysis, intriguingly, it was found that among all the factors considered, only intraperitoneal chemotherapy, with a HR of 0.41 (95% CI, 0.20 to 0.86; P = 0.0185), exhibited a statistically significant association with the 3-year PM rate (Additional file 1: sTable 2). In an exploratory analysis of patients in the subgroup with left hemicolon cancer, the lobaplatin group showed a benefit. The 3-year PM rate was 3.31% in the lobaplatin group, as opposed to the control group, which had a rate of 9.06% (HR = 0.35; 95% CI, 0.17 to 0.75; P = 0.0070). Additionally, the lobaplatin group demonstrated a decrease in PM among patients who did not receive adjuvant chemotherapy (HR = 0.21; 95% CI, 0.06 to 0.72; P = 0.0053; Fig. 2).

In terms of secondary endpoints, there were 20 cases (5.81%) of 3-year liver metastasis in the lobaplatin group and 41 (11.70%) in the control group (P = 0.0087). However, in the subgroup analysis, we found that only among patients who did not receive adjuvant chemotherapy after surgery did the lobaplatin group have an advantage in reducing the 3-year liver metastasis (0.80% vs 10.74%, P = 0.0007). Among patients who received adjuvant chemotherapy after surgery, there was no significant difference in the incidence between the two groups (8.37% vs 12.09%, P = 0.1958). There was no statistically significant difference between the two groups in terms of 3-year

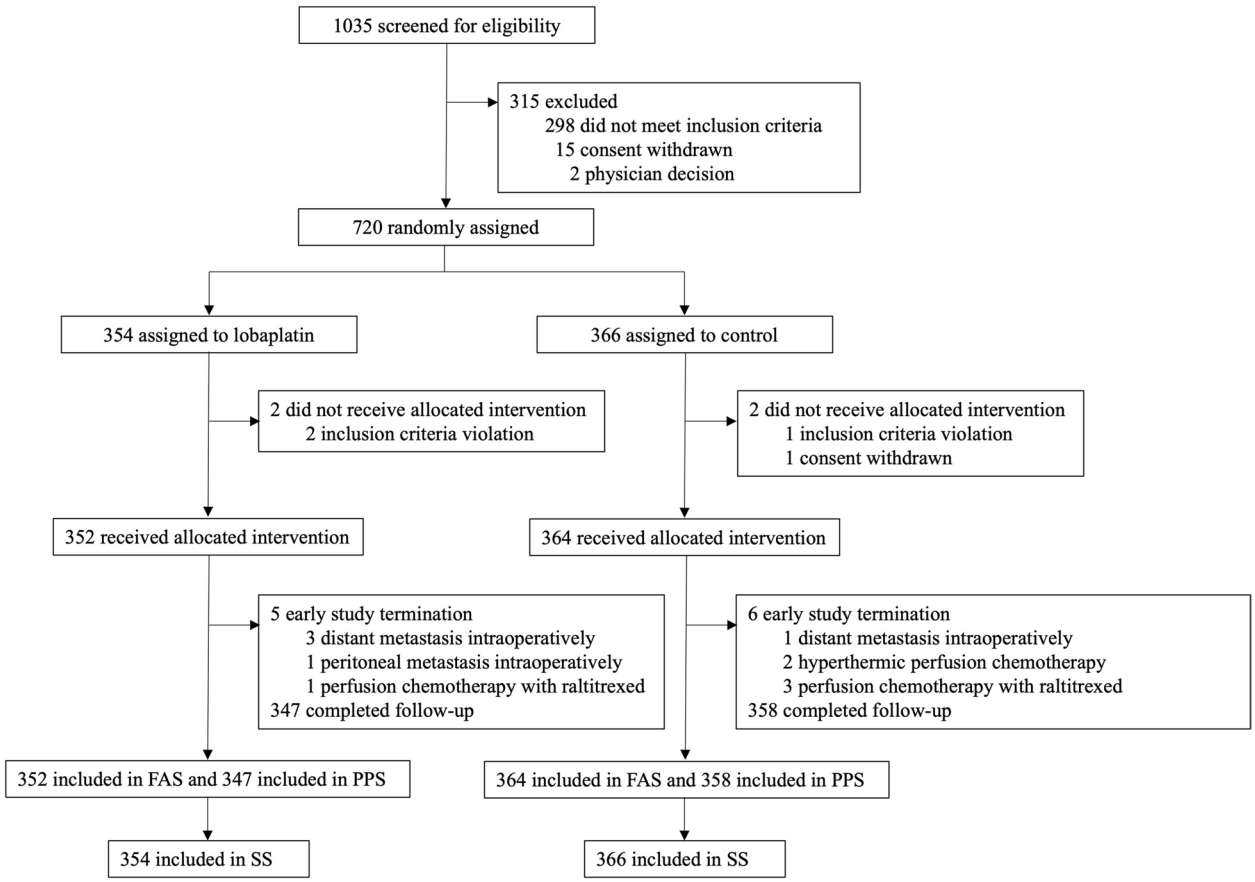

Fig. 1 Trial Profile. FAS = Full Analysis Set, PPS = Per-protocol Set, SS = Safety Set

lung, bone, or other metastases (Table 2). In the FAS, 24 patients in the lobaplatin group and 35 patients in the control group died. The 3-year OS rate was 93.2% in the lobaplatin group and 90.4% in the control group, with a HR of 0.69 (95% CI, 0.41 to 1.16; $P = 0.1660$; Fig. 3A). The 3-year RFS rate was 88.1% in the lobaplatin group and 81.6% in the control group, with an HR of 0.62 (95% CI, 0.42 to 0.91; $P = 0.0146$; Fig. 3B), indicating a statistically significant difference in RFS between the groups. Similarly, the 3-year PRFS rate was 96.6% in the lobaplatin group and 91.5% in the control group, with an HR of 0.39 (95% CI, 0.20 to 0.75; $P = 0.0053$; Fig. 3C).

Safety

For the SS population, the incidences of treatment-related AEs were similar in both the lobaplatin and control groups (247 [69.77%] *vs* 237 [64.75%]), and the overall AEs of grades 1, 2, 3, and 4 that occurred in the lobaplatin group were also comparable to those in the control group. There were also no statistically significant differences between the two groups in the incidence and severity of AEs occurring in the different systems (Table 3); the most common AEs were poor metabolism and nutrition (207 [58.5%] vs 191 [52.2%]). For the SS population, patients in the lobaplatin group exhibited a decrease in the levels of ANC and PLT on POD3 compared with the control group, but these were within normal limits and recovered to levels similar to those of the control group on POD5. There were no statistically significant differences in the WBC, ALT, AST, and BUN levels between the two groups (Additional file 1: sTable 3).

For the FAS population, as shown in Additional file 1: sTable 4, no significant differences were observed between the groups in terms of the time to first flatus, first defaecation, removal of the drainage tube, wound healing, or postoperative hospitalisation. Moreover, the overall rate of surgical complications was comparable between the two groups (7.65% vs 7.34%, $P = 0.8763$). The most common postoperative surgical complication was anastomotic leakage (16 [2.23%], 10 [2.85%] in the lobaplatin group and 6 [1.66%] in the control group; sTable 4). Concomitant drug use was consistent between the lobaplatin and control groups (Additional file 1: sTable 5).

Table 1 Baseline characteristics

	Patients, No. (%)		
	Lobaplatin group (*n* = 352)	**Control group (*n* = 364)**	***P value***
Age, Mean(SD), y	58.58 ± 9.40	58.15 ± 10.41	0.5620
Sex			0.4694
Female	130(36.93)	144(39.56)	
Male	222(63.07)	220(60.44)	
ECOG performance status			0.5813
0	203(60.60)	207(58.64)	
1	132(39.40)	145(41.08)	
2	0	1(0.28)	
Clinical stage			0.8977
Stage I	0	0	
Stage II	172(49.00)	175(48.21)	
Stage III	175(49.86)	186(51.24)	
Stage IV	4(1.14)	2(0.55)	
T stage			0.6276
T3	169(49.13)	185(52.56)	
T4a	148(43.02)	139(39.49)	
T4b	27(7.85)	28(7.95)	
N stage			0.6942
N0	197(57.10)	211(59.60)	
N1	95(27.54)	96(27.12)	
N2	53(15.36)	47(13.28)	
Histological subtype			0.7779
Poorly differentiated	72(20.51)	70(19.66)	
Not poorly differentiated	279(79.49)	286(80.34)	
Surgical method			0.4447
Laparoscopic surgery	302(86.29)	305(84.25)	
Open surgery	48(13.71)	57(15.75)	
Primary tumor location			0.2417
Ascending colon	55(15.63)	47(12.91)	
Hepatic flexure	10(2.84)	11(3.02)	
Transverse colon	25(7.10)	16(4.40)	
Splenic flexure	4(1.14)	8(2.20)	
Descending colon	24(6.82)	36(9.89)	
Sigmoid colon	128(36.36)	136(37.36)	
Rectosigmoid junction & rectum	25(7.10)	34(9.34)	
Rectum	79(22.44)	70(19.23)	
Other	2(0.57)	6(1.65)	
Adjuvant chemotherapy			0.1356
Yes	227(64.49)	215(59.07)	
No	125(35.51)	149(40.93)	

Abbreviation: *ECOG* Eastern Cooperative Oncology Group

Discussion

Our preliminary findings demonstrated that the perfusion protocol used in this study was safe [12]. An in vitro study demonstrated that at a concentration of 120 mg/L, lobaplatin achieved an inhibition rate of up to 91.67 ± 2.57% on the invasion and migration capabilities of CRC cells [13]. Consequently, we maintained the 500–1000 ml lobaplatin (120 mg/L) regimen in this study, with the precise dosage tailored to each patient's body weight, nutritional status, and pre-existing medical conditions.

Table 2 Comparison of metastasis

	Patients, No. (%)			
	Lobaplatin group (*n* = 352)	**Control group (*n* = 364)**	**HR (95%CI)**	***P value***
Peritoneal metastasis	12 (3.56)	31 (8.75)	0.39 (0.20,0.75)	0.0053
Liver metastasis	20 (5.81)	41 (11.7)	0.49 (0.29,0.83)	0.0087
Lung metastasis	9 (2.73)	14 (4.01)	0.65 (0.28,1.50)	0.3128
Brain metastasis	0	0	-	-
Bone metastasis	1 (0.29)	2 (0.58)	0.51 (0.05,5.63)	0.5832
Other metastases	7 (2.13)	5 (1.44)	1.43 (0.45,4.49)	0.5444

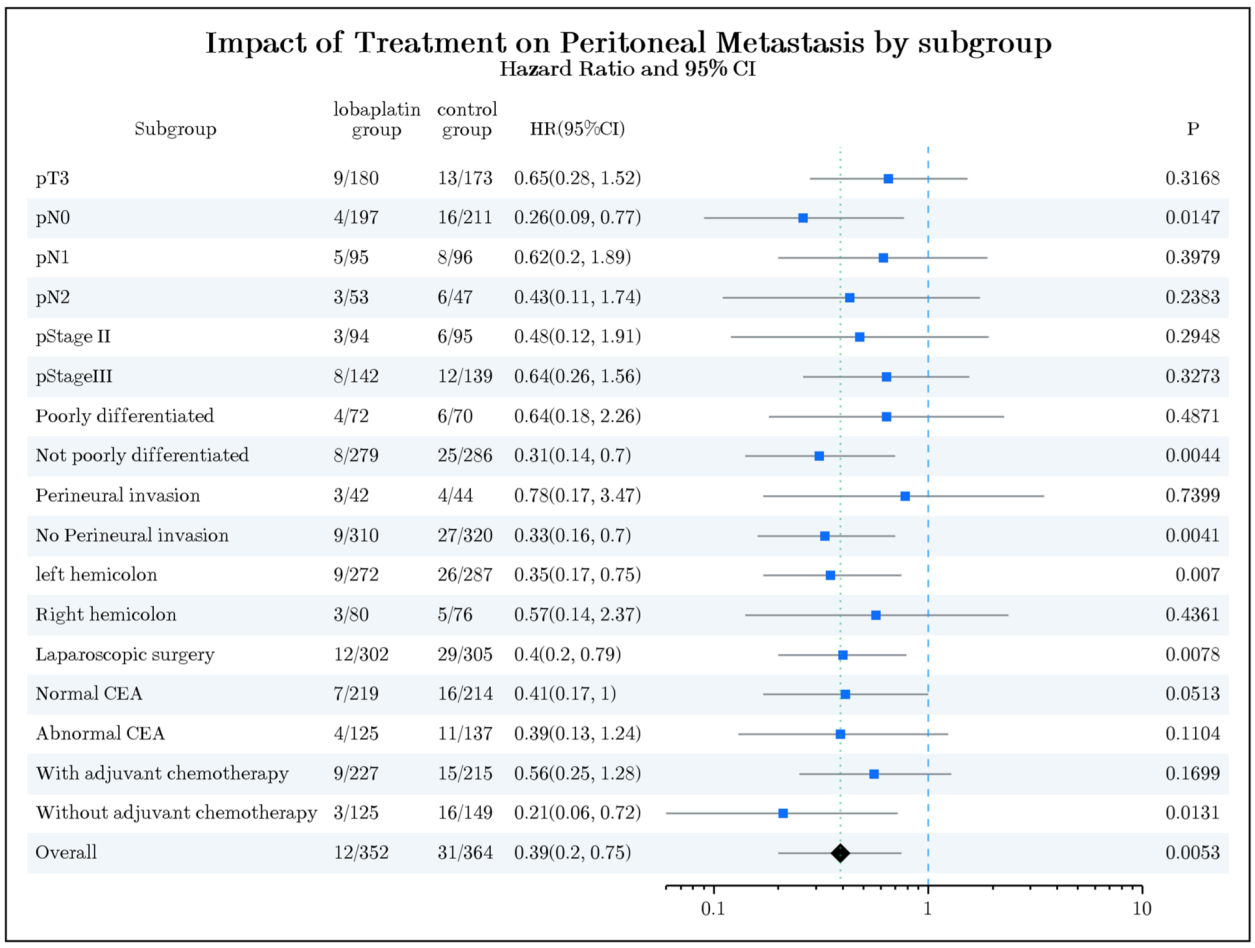

Fig. 2 Forest Plot of PM Hazard Ratios (HRs) by Subgroup

Typically, for patients weighing less than 70 kg presenting with poor nutritional status, anaemia, or multiple comorbidities, we administered a minimum dose of 500 ml of lobaplatin. Additionally, our prior research revealed that the average elimination half-life of lobaplatin in peritoneal drainage fluid was 5.99 h, which informed our decision to implement a 6-h clamping period [14].

Previous studies have presented different views on the effectiveness of preventive intraperitoneal chemotherapy for CRC. An Italian study involving 75 patients showed that preventive HIPEC could prolong the 3-year disease-free survival (DFS) and OS and reduce the rate of PM by approximately 20% [15]. A retrospective study showed that surgery plus intraoperative

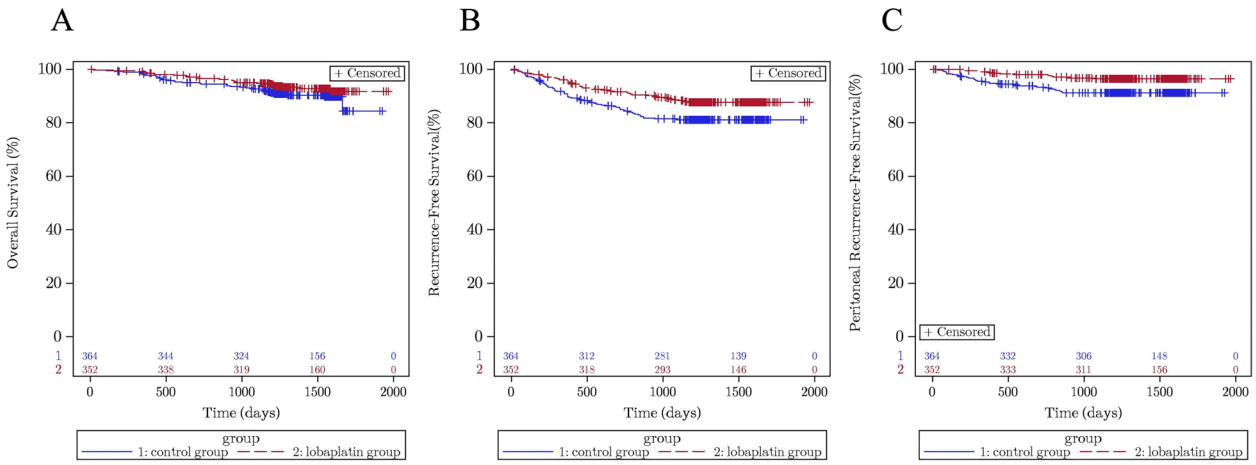

Fig. 3 A: Kaplan–Meier plot of overall survival in FAS; B: Kaplan–Meier plot of recurrence-free survival in FAS; C: Kaplan–Meier plot of peritoneal recurrence-free survival in FAS

Table 3 Treatment-related adverse events in different systems

	Patients, No. (%)							
	Lobaplatin group ($n = 354$)				Control group ($n = 366$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Poor metabolism and nutrition	131 (37.01)	62 (17.51)	14 (3.95)	0	116 (31.69)	60 (16.39)	15 (4.10)	0
Investigations	39 (11.02)	16 (4.52)	4 (1.13)	1 (0.28)	30 (8.20)	11 (3.01)	3 (0.82)	0
Hematological and lymphatic diseases	45 (12.71)	50 (14.12)	15 (4.24)	0	28 (7.65)	49 (13.39)	14 (3.83)	1 (0.27)
Neurological disease	2 (0.56)	2 (0.56)	0	0	5 (1.37)	1 (0.27)	1 (0.27)	0
Respiratory, thoracic, and mediastinal diseases	12 (3.39)	2 (0.56)	1 (0.28)	0	18 (4.92)	1 (0.27)	0	0
Local disease of application site	43 (12.15)	9 (2.54)	1 (0.28)	0	40 (10.93)	13 (3.55)	1 (0.27)	0
Gastrointestinal diseases	17 (4.80)	8 (2.26)	0	0	15 (4.10)	6 (1.64)	1 (0.27)	0
Vascular disease	2 (0.56)	2 (0.56)	3 (0.85)	0	1 (0.27)	4 (1.09)	0	0
Urinary diseases	1 (0.28)	0	0	0	0	0	0	0
Dermatologic diseases	2 (0.56)	0	0	0	1 (0.27)	0	0	0
Infectious diseases	0	1 (0.28)	3 (0.85)	0	1 (0.27)	1 (0.27)	2 (0.55)	0
Trauma, poisoning, and operational complications	0	0	1 (0.28)	0	1 (0.27)	1 (0.27)	0	0
Cardiac Disease	1 (0.28)	0	0	0	2 (0.55)	2 (0.55)	0	0

intraperitoneal chemotherapy yielded a favourable prognosis for stage III CRC patients but not for stage II patients [16]. The HIPECT4 trial also indicated that adding HIPEC to complete surgical resection for locally advanced colon cancer improved the 3-year locoregional control rate compared to surgery alone (investigational group: 98.3% vs comparator group: 82.1%) [17]. Similar to our findings, these studies demonstrated positive results. However, the COLOPEC study found that HIPEC could not reduce the rate of PM (HIPEC group: 23% vs control group: 19%), nor could it prolong DFS, OS, or PRFS [18, 19]. Nevertheless, we should also note the differences between COLOPEC and our study. First, in the COLOPEC study, HIPEC was mostly performed 5–8 weeks after surgery, whereas in our study, intraperitoneal chemotherapy was administered during the operation. Second, in the COLOPEC study, HIPEC postponed the initiation of intravenous systemic chemotherapy. In the COLOPEC study, the intravenous chemotherapy in the HIPEC group was started 10 weeks after surgery, whereas in the control group, it was started 6 weeks after surgery. In our study, intraoperative chemotherapy did not delay the administration of postoperative adjuvant chemotherapy, and patients in both groups received chemotherapy approximately 1 month after surgery.

In contrast to the COLOPEC study, we believe that the ideal time to prevent the peritoneal seeding of free cancer cells should be during or immediately after surgery. The theoretical mechanism behind this comes from the "seed and soil" theory [20–22]. This mechanism emphasises that PM occurrence depends on the interaction between tumour cells and the peritoneal microenvironment. Various cytokines secreted by tumour cells participate in the generation and maturation of the extracellular matrix, ultimately promoting the infiltration and adhesion of free cancer cells [23–25]. Compared with intraperitoneal chemotherapy after the occurrence of PM, intraperitoneal chemotherapy during and immediately after surgery allows drugs to reach all gaps within the peritoneal cavity uniformly and effectively before adhesions form [26, 27]. This allows drugs to come into sufficient contact with potential lesions, and the optimal window of opportunity is created by curative or debulking surgery to intervene against residual cancer cells within the peritoneal cavity.

Intravenous adjuvant chemotherapy plays a crucial role in the treatment of locally advanced CRC. In our study, patients received routine adjuvant therapy 4 weeks after surgery. The implementation of intraperitoneal chemotherapy did not affect the progress of postoperative adjuvant chemotherapy, which is an advantage of the treatment regimen used in our study. The liver is the primary target organ for haematogenous metastasis in CRC, and liver metastasis is the main cause of death in patients with CRC [28, 29]. We observed a significantly lower incidence of liver metastasis in the lobaplatin group than in the control group, particularly in patients who did not receive postoperative adjuvant chemotherapy. However, it should be emphasised that the current evidence does not support the idea that a single intraperitoneal chemotherapy dose can effectively reduce liver metastasis rates. Therefore, the reduction in liver metastasis observed in our study requires caution.

Our study has several limitations. First, 25 hospitals participated in this study and there were disparities in the number of patients recruited at each site. Consequently, the study findings predominantly mirror the circumstances of a few hospitals with large patient enrolments. In practice, however, several measures have been implemented to mitigate this issue. We organised a multicentre researchers'meeting to standardise the operating procedures of the study. This initiative ensured consistency in patient inclusion, treatment protocol implementation, and data collection across all hospitals. Second, the follow-up period was relatively short. Nevertheless, we intend to conduct a future study with an extended follow-up period to comprehensively assess the efficacy and safety of this treatment. Finally, the overall number of PM cases was limited, and subsequent subgroup analyses further reduced the sample sizes, potentially introducing statistical variability. Notably, critical covariates such as adjuvant chemotherapy may substantially influence the outcomes. Future studies should incorporate strategies to minimise potential biases from these confounding factors.

Conclusions

This open-label, prospective, randomised, controlled multicentre study demonstrated that intraoperatively preventive intraperitoneal perfusion chemotherapy with lobaplatin reduced the 3-year PM rate in CRC patients while improving both the 3-year RFS and PRFS, although it did not significantly improve the 3-year OS. Importantly, the safety profile of intraperitoneal chemotherapy with lobaplatin for preventive purposes during CRC surgery was comparable with that of the control group, with no significant differences in postoperative recovery parameters or complication rates. Additionally, intraperitoneal chemotherapy with lobaplatin did not increase the utilisation of accompanying treatments.

Abbreviations

CRC	Colorectal cancer
PM	Peritoneal metastases
CEA	Carcinoembryonic antigen
HIPEC	Hyperthermic intraperitoneal chemotherapy
ECOG	Eastern Cooperative Oncology Group
CT	Computed tomography
ANC	Absolute neutrophil count
PLT	Platelets
HB	Hemoglobin
TBIL	Total bilirubin
DBIL	Direct bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
UNL	Upper normal limit
CTCAE	Common terminology criteria for adverse events
G-CSF	Granulocyte colony-stimulating factor
TPO	Thrombopoietin
IL-11	Interleukin-11
NCCN	National Comprehensive Cancer Network
AEs	Adverse events
SAEs	Serious adverse events
OS	Overall survival
RFS	Recurrence-free survival
PRFS	Peritoneal recurrence-free survival
FAS	Full analysis set
PPS	Per-protocol set
SS	Safety set
CI	Confidence interval
HRs	Hazard ratios
DFS	Disease-free survival

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04180-1.

Additional file 1: Table S1: Univariate analysis on PM. Table S2: Multivariate analysis on PM. Table S3: The bone marrow, liver, and renal function.

Table S4: Comparison of surgical recovery and complications. Table S5: Concomitant treatment

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Authors' contributions
HS, RZ, YL and YL contributed equally to this trial. HZ, and XW were responsible for the conception and design of the study. HS, RZ, YL, YL, WP, GJ, ZL, MH, JZ, QJ, MX, GW, WZ, ML, JC, ZW, KW, XZ, GL, XZ, XL, XS, JW, DZ, CZ, HZ and XW contributed to the collection of data. HS was responsible for directing the statistical analysis. All authors were responsible for the interpretation of data and writing the manuscript, as well as reviewing and approving the manuscript for submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval No.: 16–147/122) and at all participating hospitals. Written informed consent was obtained from all patients.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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