Effect and safety analysis of raltitrexed peritoneal perfusion in patients with intermediate and advanced colorectal cancer

YANHUA WAN[1], XIAOYUN DAI[2] and LIANG CHAO[1]

[1]Three Branches of General Surgery, Jiujiang City Key Laboratory of Cell Therapy, Jiujiang No. 1 People's Hospital, Jiujiang, Jiangxi 332000, P.R. China; [2]First Department of Oral Medicine, Affiliated Hospital of Jiujiang University, Jiujiang, Jiangxi 332000, P.R. China

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Abstract. Colorectal cancer (CC) is a major global health burden, and effective management of intermediate and advanced stages remains a clinical challenge. The present study investigated the effect and safety of peritoneal raltitrexed infusion in patients with intermediate and advanced CC. Data from 80 patients with intermediate and advanced CC who visited the Affiliated Hospital of Jiujiang University (Jiujiang, China) between August 2018 and April 2021 were retrospectively analysed. Among them, 42 patients were administered raltitrexed peritoneal infusion as the observation group (OG), and the remaining 38 patients were administered equal amounts of saline as the control group (CG) to compare therapeutic effects. Changes in routine blood indicators [such as number of white blood cells (WBCs), neutrophils (NEs), red blood cells (RBCs) and platelets (PLTs)] and tumour markers (carcinoembryonic antigen and cancer antigen 19-9) before and after 3 days of treatment were compared. Adverse reactions that occurred during treatment were also recorded. Compared with those before surgery, WBC and NE counts were significantly lower ($P<0.05$), and RBC and PLT counts were significantly greater ($P<0.05$) in both groups after surgery. The counts in the CG were markedly greater than those in the OG after surgery ($P<0.05$). Tumour marker levels were significantly higher before surgery than after surgery in both groups ($P<0.05$). The patients in the CG had a significantly lower disease remission rate than those in the OG ($P=0.014$). In conclusion, raltitrexed peritoneal infusion chemotherapy is effective and safe for the treatment of patients with intermediate and advanced CC; it can effectively reduce serum tumour marker levels and adverse reaction incidence and improve the survival quality of patients. Raltitrexed peritoneal infusion chemotherapy thus exhibits high clinical application value.

Correspondence to: Dr Liang Chao, Three Branches of General Surgery, Jiujiang City Key Laboratory of Cell Therapy, Jiujiang No. 1 People's Hospital, 59 Changhong Avenue, Jiujiang, Jiangxi 332000, P.R. China
E-mail: liangzai6666662021@163.com; shaolan840115@163.com

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Introduction

Colorectal cancer (CC) is a common gastrointestinal malignancy of the gastrointestinal tract (1,2). The disease tends to occur in middle-aged and older men, predominantly in those aged 40-70 years (3). However, the incidence of this disease has recently been trending towards younger patients, with statistics showing that cases in adults <50 years of age has increased at an annual rate of 2% since 1994 (4). Data provided by the American Cancer Society revealed that, between 2000 and 2013, CC incidence decreased by 32% in adults >50 years of age but increased by 22% in those <50 years of age, and between 2000 and 2014, mortality decreased by 34% in adults >50 years of age, but increased by 13% in those <50 years of age (5). Early symptoms of CC are not evident, and most patients are in the middle to late stages at diagnosis (6). Although significant clinical advances have been made in the diagnosis and treatment of CC, most patients (60-70% of patients with CC in China) are still diagnosed with mid- to late-stage tumours at the time of presentation (7). Therefore, suitable treatment options for patients with intermediate and advanced CC are urgently needed.

Surgery is among the main methods for the treatment of CC, but only for early-stage patients (8). Peritoneal perfusion can effectively control tumours in the abdominal cavity and reduce the risk of metastasis, effectively prolonging the survival time of patients (9). Raltitrexed is a thymidine synthase inhibitor that inhibits cancer cell growth mainly by suppressing thymidine synthase activity (10,11). Fluorouracil can also be used to treat patients with intermediate and advanced CC, demonstrating efficacy comparable with that of raltitrexed. Compared with fluorouracil, raltitrexed has a lower incidence of side effects, is simpler to administer and is better tolerated by patients (12). Liu *et al* (13) reported that, compared with conventional 5-fluorouracil chemotherapy regimens, raltitrexed-based chemotherapy for patients with intermediate and advanced CC resulted in equivalent overall survival (HR, 1.06; 95% CI, 0.96-1.17; P=0.23) and overall response rate (RR, 1.09; 95% CI, 0.86-1.38; P=0.47) with an acceptable toxicity profile. Thus, in the present study, raltitrexed was

assessed as a therapeutic agent for the treatment of patients with intermediate and advanced CC.

The efficacy and safety of raltitrexed peritoneal infusion in patients with intermediate and advanced CC have not been systematically evaluated. Therefore, the present study investigated the efficacy and safety of chemotherapy regimens using raltitrexed peritoneal infusion in patients with intermediate and advanced CC, aiming to provide a reliable basis for clinical studies.

Patients and methods

Clinical data. In this single-centre, retrospective study, the medical records of patients diagnosed with intermediate or advanced CC who underwent laparoscopic radical surgery at the Affiliated Hospital of Jiujiang University (Jiujiang, China) between August 2018 and April 2021 were screened. In total, 80 patients who met the inclusion and exclusion criteria were included. The overall cohort had a mean age of 65.0 years (range, 48.1-74.3 years), with a male-to-female ratio of 48:32 (60.0% male).Given that this study is a retrospective analysis, the sample size was determined by the total number of eligible patients during the study period, and no a priori sample size or power calculation was performed. Patients were not prospectively assigned to treatment; instead, two historical cohorts were formed based on the standard perioperative practice at their respective times of surgery. Patients who underwent surgery during the earlier phase (August 2018 to March 2020) received the then-standard peritoneal lavage with saline and formed the control group (CG; n=38). Additionally, patients who underwent surgery during the later phase (April 2020 to April 2021) received intraoperative raltitrexed peritoneal infusion in addition to lavage and formed the observation group (OG; n=42).

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Pathological diagnosis of intermediate and advanced CC; ii) surgical resection performed by imaging evaluation before surgery; iii) complete clinical data; and iv) no abnormalities in routine blood, liver and kidney function indices within 1 week before treatment.

The exclusion criteria were as follows: i) Patients with other malignancies and other diseases that affect the study; ii) patients with abnormalities in routine blood, liver and kidney function indices within 1 week before treatment; iv) patients who had allergies for drugs used in this study; and v) pregnant women.

Treatment options. All patients underwent laparoscopic radical surgery for CC under tracheal intubation anaesthesia performed by doctors in the Three Branches of General Surgery. Raltitrexed (SFDA approval no. H20090325; 2 mg/pc; Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd.) was selected as the intraperitoneal chemotherapy drug, and the dosage was calculated as 3 mg/m^2 according to the body surface area of the patient. The laparoscopic surgery procedure was as follows: i) After laparoscopic exploration to identify tumour-free tissue and determine the tumour location, normal tissue adjacent to the tumour was retracted with separating forceps to expose the diseased tissue. ii) During the operation, pulling and squeezing the tumour tissue was avoided. iii) The blood vessels were dissociated and ligated, with the vein addressed first, followed by the artery. iv) The patients underwent radical resection of the lesion, gastrointestinal reconstruction, trauma haemostasis and saline irrigation.

For the OG, before the abdomen was closed, raltitrexed was dissolved in 10 ml normal saline, diluted in 250 ml normal saline and poured into the abdominal cavity, with a focus on cleaning and irrigating the tumour site to ensure optimal effect of the drug in the abdominal cavity. The abdomen was closed, and the drainage tube was placed in the abdominal cavity and clipped for 2 h before opening.

For the CG, before the abdomen was closed, normal saline was poured directly into the abdominal cavity for repeated flushing and suction of the fluid. Abdominal closure and drainage were the same as those of the OG.

Indicator testing. For haematological analysis, blood samples were processed immediately using a Mindray automated haematology analyser (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) according to the manufacturer's instructions, with the following reagents: Diluent (cat. no. 10300031), lysing agent (cat. no. 10300032) and cleaner (cat. no. 10300033) (all Shenzhen Mindray Bio-Medical Electronics Co., Ltd.). This system employs impedance counting and flow cytometry technologies to measure the number of white blood cells (WBCs), neutrophils (NEs), red blood cells (RBCs) and platelets (PLTs).

For tumour marker detection, blood samples were centrifuged at 3,000 x g for 10 min at 4˚C to obtain serum, which was stored at -80˚C until analysis. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were measured using Elecsys® CEA and CA19-9 electrochemiluminescence immunoassay kits (cat. nos. 05200067 190 and 11731676 122, respectively; Roche Diagnostics GmbH) on Roche E601 and E602 electrochemiluminescence analysers according to the manufacturer's instructions.

Outcome measures. As the main outcome measures, the therapeutic effects were compared between the OG and the CG. Changes in routine blood indicators (WBCs, NEs, RBCs and PLTs) and tumour markers (CEA and CA19-9) were observed.

As the secondary outcome measures, the basic clinical data of the patients were compared. Adverse reactions that occurred during treatment, such as nausea and vomiting, abdominal distension, diarrhoea and incisional infections, were also recorded and the reaction rates were calculated using the following formula: Total adverse reaction rate=(number of total adverse reactions/total number) x100.

Efficacy assessment criteria. A complete response (CR) was indicated by the total disappearance of the target lesions, no appearance of new lesions and the maintenance of normal tumour markers for at least 4 weeks. A partial response (PR) was indicated by a ≥30% reduction in the sum of the maximum diameter of the target lesion, which was maintained for at least 4 weeks. Progressive disease (PD) was indicated by a ≥20% increase in the total diameter of the target lesion relative to the total minimum diameter of the pretreatment lesion, an absolute increase in the total diameter ≥5 mm or the appearance

Table I. Comparison of baseline data in the CG (n=38) and the OG (n=42).

Factor	CG	OG	χ^2/t	P-value
Mean age ± SD, years	65.2±9.5	64.8±10.1	0.176	0.861
Sex, n			0.008	0.927
Male	23 (60.5)	25 (59.5)		
Female	15 (39.5)	17 (40.5)		
Tumour site, n			0.066	0.796
Rectum	17 (44.7)	20 (47.6)		
Colon	21 (55.3)	22 (52.4)		
Clinical stage, n			-	0.936[a]
II	17 (44.7)	15 (35.7)		
III	19 (50.0)	24 (57.1)		
IV	2 (5.3)	3 (7.1)		
Differentiation degree, n			1.866	0.393
Highly differentiated	7 (18.4)	10 (23.8)		
Moderately differentiated	21 (55.3)	26 (56.7)		
Poorly differentiated	10 (26.3)	6 (14.3)		

Continuous data (age) were compared using the independent samples t-test, and the statistic is presented as the t value. Categorical data were compared using the χ^2 test or Fisher's exact test (the latter when any expected cell count was <5), as appropriate, and the statistic is presented as the χ^2 value, except where noted. [a]P-value was derived from Fisher's exact test. CG, control group; OG, observation group; SD, standard deviation.

of a new lesion. Stable disease was indicated by a decrease in the sum of the maximum diameter of the target lesion without reaching a PR or an increase without reaching PD. Remission rate=(CR + PR)/total number of cases x100.

Statistical analysis. The collected data were analysed with SPSS Statistics (version 20.0; IBM Corp.) and visualised with GraphPad Prism (version 8.0; GraphPad; Dotmatics). The normality of the continuous data distribution was confirmed using the Kolmogorov-Smirnov test (all P>0.05). Continuous data are presented as the mean ± standard deviation. Baseline characteristics between the two groups were compared using independent samples t-tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. For the primary outcomes (haematological indices and tumour markers), which involved comparisons across treatment groups and time points, two-way analysis of variance (ANOVA) was employed to assess the effects of treatment groups, time and their interaction. The Šídák multiple comparisons test was used for post hoc analyses to control for the familywise error rate associated with multiple comparisons. Categorical data (for example, remission rate and adverse reaction rate) are presented as n (%) and were compared using a χ^2 or Fisher's exact tests as appropriate. A two-tailed P-value of <0.05 was considered to indicate a statistically significant difference.

Results

Comparison of baseline data. With respect to the basic clinical data of the two groups, there was no significant difference with regard to age, sex, tumour site, clinical stage or differentiation degree (P>0.05), as shown in Table I.

Clinical efficacy evaluation. The treatment effects for both groups were analysed and compared. The disease remission rate in the CG was significantly lower than that in the OG (P=0.014), as shown in Table II.

Changes in routine blood indicators. Two-way ANOVA revealed that while all haematological indices significantly changed over time (all P<0.0001 for time effects), no significant differences between the OG and CG were observed at either the preoperative or postoperative time points for WBC, NE, RBC or PLT (all group effects and interactions, P>0.05) (Table III). Post hoc Šídák tests confirmed that WBC and NE counts increased significantly (both P<0.0001), whereas RBC and PLT counts decreased significantly (both P<0.0001) from preoperative to postoperative measurements in both groups (Fig. 1).

Changes in tumour markers. Analysis of tumour markers using two-way ANOVA revealed significant main effects of time for both CEA and CA19-9 (both P<0.0001), with levels decreasing postoperatively in both groups (Table III). Notably, significant group effects were observed for both markers (CEA: P=0.038; CA19-9: P=0.029), and Šídák's post hoc tests confirmed that the observation group had significantly lower levels than the control group at the postoperative assessment (CEA: adjusted P=0.021; CA19-9: adjusted P=0.013). No significant differences were found between the groups preoperatively (both adjusted P>0.05) (Fig. 2).

Adverse reactions of patients. No significant differences were found with regard to the total incidence of postoperative adverse reactions between the two groups (P>0.05), as shown in Table IV.

Table II. Clinical efficacy evaluation in the CG (n=38) and the OG (n=42).

Group	CG	OG	χ^2 value	P-value
Complete response, n (%)	2 (5.26)	12 (28.57)		
Partial response, n (%)	12 (31.58)	15 (35.71)		
Progressive disease, n (%)	7 (18.42)	3 (7.14)		
Stable disease, n (%)	17 (44.7)	12 (28.57)		
Overall comparison			-	0.012[a]
Disease remission rate, %	36.84	64.28	6.014	0.014

Categorical data were compared using the χ^2 test or Fisher's exact test (the latter when any expected cell count was <5), as appropriate, and the statistic is presented as the χ^2 value, except where noted. [a]P-value was derived from Fisher's exact test. CG, control group; OG, observation group.

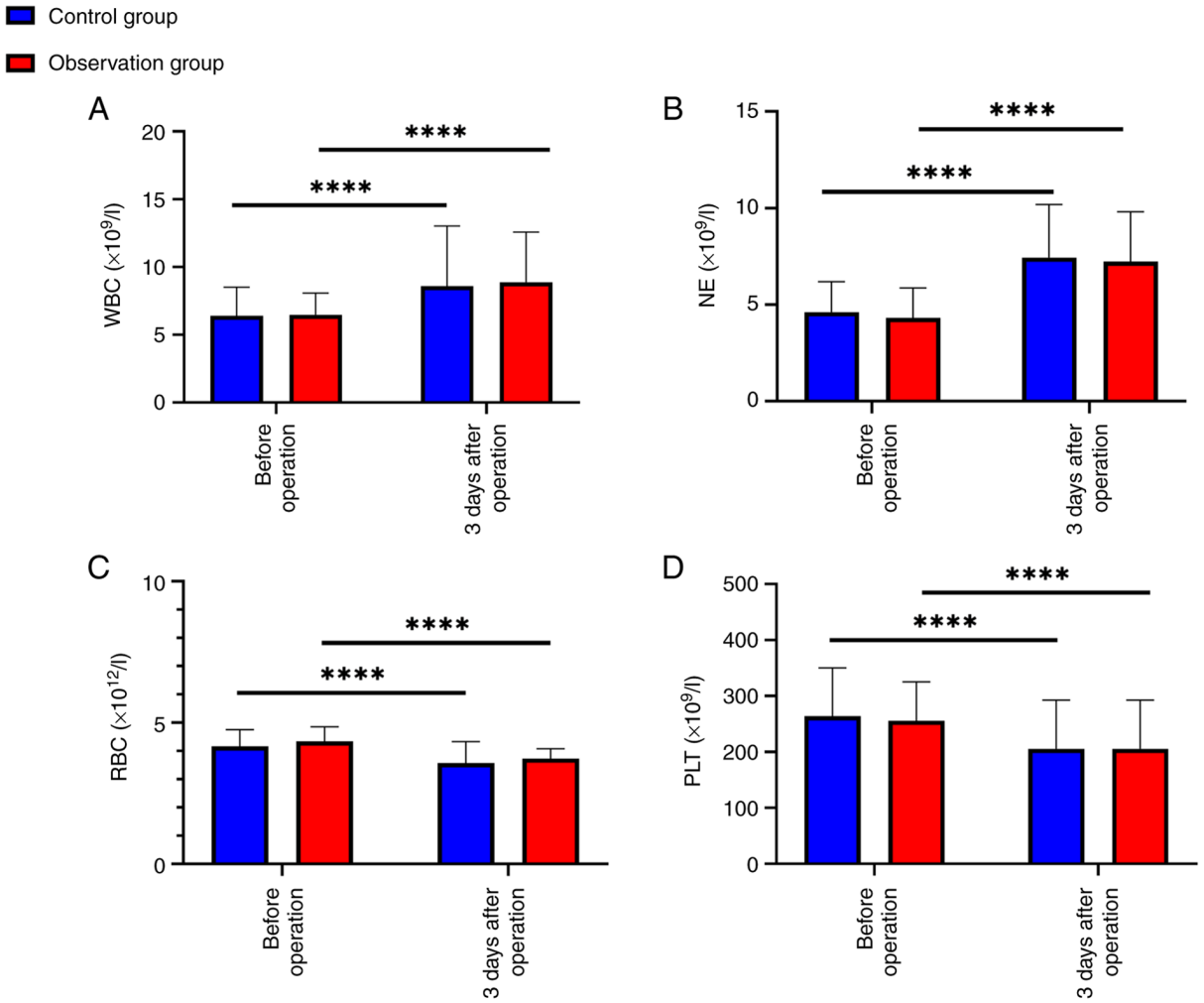

Figure 1. Changes in routine blood indicators before and 3 days after surgery. Changes in (A) WBC counts, (B) NE counts, (C) RBC counts and (D) PLT counts in patients before and 3 days after surgery. Data are presented as the mean ± standard deviation. Statistical analysis was performed using two-way analysis of variance followed by Šídák's multiple comparisons test. ****P<0.0001. WBC, white blood cell; NE, neutrophil; RBC, red blood cell; PLT, platelet.

Discussion

CC remains a major global health challenge, with its incidence increasing due to evolving environmental and dietary factors (14). The excessive and abnormal proliferation of cancer cells in CC consists of a complex pathogenic process involving a combination of multifactorial, genetic (for example, *APC*, *KRAS* and *TP53* gene mutations) and environmental (for example, dietary habits, smoking and gut microbiota dysbiosis) factors (15). As most patients are already at an intermediate to advanced stage at the time of diagnosis, the current treatments for CC are surgery and

Table III. Summary of two-way ANOVA findings.

Parameter	Time effect P-value	Group effect P-value	Interaction P-value	Key post hoc finding (Šídák-adjusted)
WBC	<0.0001	0.735	0.826	No group differences
NE	<0.0001	0.469	0.885	No group differences
RBC	<0.0001	0.060	0.911	No group differences
PLT	<0.0001	0.753	0.753	No group differences
CEA	<0.0001	0.038	0.117	OG<CG postop (P=0.021)
CA19-9	<0.0001	0.029	0.094	OG<CG postop (P=0.013)

Data were analysed using two-way ANOVA. Post hoc pairwise comparisons were performed using Šídák's multiple comparisons test when appropriate. Additionally, post hoc Šídák tests for the significant time effect confirmed that from pre- to postoperative, WBC, NE, RBC and PLT counts changed significantly (all P<0.0001) in both groups. OG, observation group; CG, control group; postop, postoperative. ANOVA, analysis of variance; WBC, white blood cell; NE, neutrophil; RBC, red blood cell; PLT, platelet; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9.

Table IV. Adverse reactions in the CG (n=38) and the OG (n=42).

Groups	CG, n (%)	OG, n (%)	χ^2 value	P-value
Nausea and vomiting	2 (5.26)	2 (4.76)		
Fever	5 (13.16)	5 (11.90)		
Abdominal distention	3 (7.89)	2 (4.76)		
Abdominal pain	1 (2.63)	0 (0.00)		
Diarrhoea	0 (0.00)	2 (4.76)		
Incision infection	0 (0.00)	2 (4.76)		
Total incidence	11 (28.95)	13 (30.95)	0.038	0.845

CG, control group; OG, observation group.

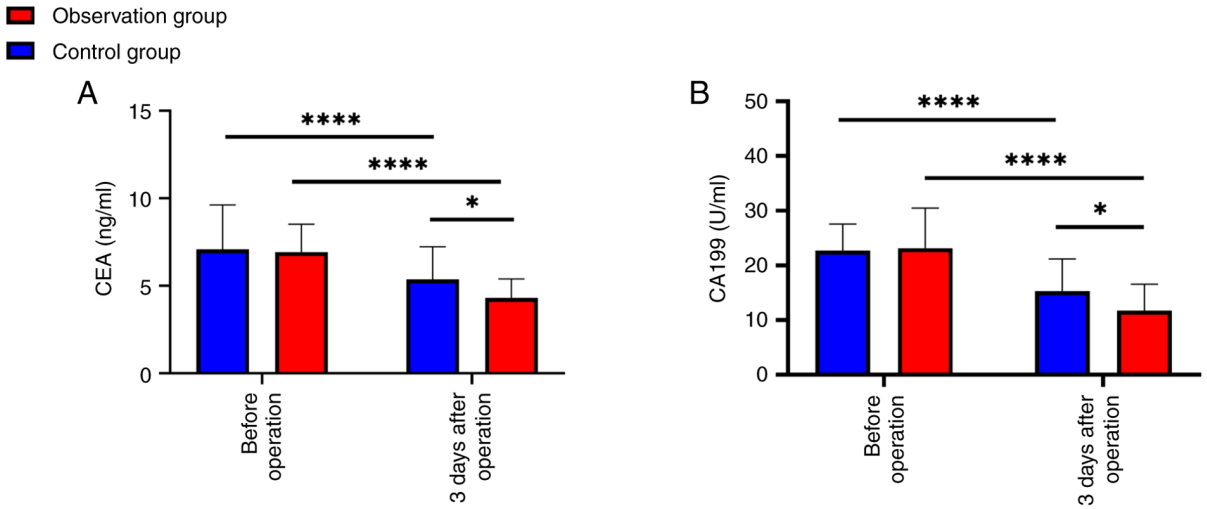

Figure 2. Changes in tumour markers before and 3 days after surgery. Changes in (A) CEA levels and (B) CA19-9 levels in patients before and 3 days after surgery. Data are presented as the mean ± standard deviation. Statistical analysis was performed using two-way analysis of variance followed by Šídák's multiple comparisons test. *P<0.05; and ****P<0.0001. CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9.

radiotherapy (16). Peritoneal infusion chemotherapy is among the most commonly used treatments for local chemotherapy, with the aims of controlling peritoneal disease and mitigating recurrence risk (17,18). McCabe-Lankford *et al* (19) reported that peritoneal perfusion has few complications when used for chemotherapy in CC mice; this study could be used as a reference for the future development of perfused mouse models.

The rationale for intraperitoneal raltitrexed administration is underpinned by sound pharmacokinetic principles, which leverage the 'peritoneal-plasma barrier' to allow for the delivery of sustained, high local concentrations of the drug directly within the abdominal cavity where residual microscopic disease may reside (20). This approach maximises the cytotoxic effects on free cancer cells and micrometastases while potentially minimising systemic exposure and its associated toxicity. Raltitrexed, a specific thymidylate synthase inhibitor, is particularly suitable for this route due to its prolonged intracellular retention, enabling a prolonged anticancer effect from a single intraoperative instillation (21). The present findings provide clinical corroboration for this strategy, showing significant improvement in the disease remission rate in the raltitrexed group. These findings align with the study by Batra *et al* (22), which reported the efficacy of systemic raltitrexed and extended its application to the intraperitoneal domain.

While fluorouracil derivatives have been the cornerstone of CC chemotherapy (23), the present study contributes to the growing body of evidence supporting raltitrexed as a valuable alternative, as also demonstrated by recent clinical trials (24,25). The observed efficacy, coupled with its favourable safety profile in the present cohort, is consistent with the literature suggesting that compared with fluorouracil-based regimens, raltitrexed may result in a reduced incidence of cardiotoxicity (26). This advantage makes it a particularly appealing option for patients with preexisting cardiovascular risk factors. Although the CG failed to receive an active chemotherapeutic agent, precluding a direct efficacy comparison with standard intraperitoneal drugs such as 5-fluorouracil, the present results robustly establish the significant additive benefit of raltitrexed over surgical intervention alone. Future head-to-head randomised controlled trials against other intraperitoneal agents are warranted to definitively position raltitrexed within the treatment hierarchy.

The significant reduction in serum CEA and CA19-9 levels observed in the raltitrexed group underscores its potent biological activity against CC cells. The postoperative dynamics of haematological indices, specifically the increase in WBCs/NEs and the decrease in RBCs/PLTs, were expected and comparable between groups, reflecting the systemic inflammatory response to major surgery. This type of systemic inflammation and the patient's nutritional status are critical determinants of cancer prognosis (27). Recent studies have highlighted the prognostic value of composite biomarkers, such as the albumin-to-globulin ratio and the prognostic nutritional index, in CC (28,29). Although the present study did not calculate these specific indices, the observed haematological changes provide a contextual background for the perioperative state of the patients. Future investigations can explore whether these novel inflammation-nutrition biomarkers predict which patients derive the greatest benefit from intraperitoneal chemotherapy.

The safety profile of intraperitoneal raltitrexed in this study is highly reassuring. The absence of severe adverse events, such as anastomotic leakage or abdominal bleeding, coupled with an overall incidence of common complications (e.g., nausea and vomiting) comparable with that in the CG, strongly indicates that the drug does not exacerbate postoperative morbidity. This finding is crucial, as the safety of any adjuvant local therapy is paramount following radical surgery. The observed favourable tolerability supports the feasibility of integrating raltitrexed peritoneal infusion into standard surgical practice.

The present study has several limitations that must be acknowledged. First, its retrospective and single-centre design introduces the potential for selection bias and limits the generalisability of the findings. Second, the sample size was relatively modest and was not based on a prespecified power calculation. Third, the lack of an active control arm (e.g., intraperitoneal 5-fluorouracil) means that it can only be concluded that raltitrexed is superior to no additional chemotherapy but not to the current standard. Finally, and perhaps most significantly, the short follow-up period and the assessment of efficacy on the basis of early (3-day post-operative) biomarker changes preclude conclusions regarding long-term outcomes, such as disease-free survival and overall survival. The early decrease in the expression of tumour markers, while encouraging, is a surrogate endpoint; its correlation with improved survival requires validation through long-term follow-up studies.

In conclusion, raltitrexed peritoneal infusion chemotherapy is effective and safe for the treatment of patients with intermediate to advanced CC. The treatment can effectively reduce serum tumour marker levels and adverse reaction incidence and improve the survival quality of patients. Raltitrexed peritoneal infusion chemotherapy thus has high clinical application value.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YW was responsible for the study conception and design. XD was responsible for writing the manuscript. LC was responsible for the collection and assembly of data. YW, XD and LC were responsible for data analysis and interpretation. All authors were responsible for writing the manuscript. All authors have read and approved the final manuscript. YW, XD and LC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Jiujiang No. 1 People's Hospital (Jiujiang, China; approval no. JISDYRMYY-YXLL-220132). The study was conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants.

Patient consent for publication

Written informed consent was obtained from all patients for publication of this study.

Competing interests

The authors declare that they have no competing interests.

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