Application Evaluation of Fluorouracil Intraperitoneal Perfusion Chemotherapy in Combination with Intravenous Chemotherapy in Patients after Radical Resection of Colorectal Cancer

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Background: Colorectal cancer stands as one of the most prevalent malignant tumors affecting the digestive tract, posing a significant threat to human health. Its incidence and fatality rates rank third and second, respectively, among malignant tumors. This study seeks to analyze the efficacy of combining fluorouracil intraperitoneal perfusion chemotherapy with intravenous chemotherapy in patients following radical resection of colorectal cancer.

Methods: This retrospective study analyzed the medical records of 65 patients who underwent radical resection of colorectal cancer at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 2011 to January 2013. These patients were divided into two groups based on their treatment methods: the control group (CG, n = 31, receiving intravenous chemotherapy) and the observation group (OG, n = 32, receiving fluorouracil intraperitoneal perfusion chemotherapy + intravenous chemotherapy). After 6 cycles of treatment, the study compared clinical symptoms, Karnofsky score, body weight, adverse reactions, local recurrence, and liver metastasis between the two groups.

Results: The OG demonstrated superior efficacy in controlling recurrence and metastasis compared to the CG ($p < 0.05$). However, there were no significant differences observed in clinical symptoms, quality of life, body weight, and drug safety between the two groups ($p > 0.05$).

Conclusion: Intraperitoneal infusion chemotherapy with fluorouracil significantly impacts the control of recurrence and metastasis following radical resection of colorectal cancer. It also offers valuable references for developing clinical treatment protocols for these patients.

Keywords: fluorouracil; intraperitoneal perfusion chemotherapy; intravenous chemotherapy; radical resection of colorectal cancer

Introduction

Colorectal cancer, a malignancy affecting the digestive tract, often presents with subtle clinical symptoms in its early stages. However, as the disease progresses into the middle and late stages, symptoms such as weight loss, abdominal pain, vomiting, altered bowel habits, changes in fecal properties, and tumor metastasis become evident, posing a significant threat to patients' health [1]. Surgical intervention is frequently necessary to address these symptoms, making radical resection a pivotal approach in treating colorectal cancer. Despite surgical removal, colorectal cancer is characterized by a propensity for recurrence and metastasis. The liver is the most common site of metastasis in colorectal cancer. Studies indicate that approximately 20% to 25% of patients present with liver metastasis at initial diagnosis, and even after surgical intervention, about 50% of patients still experience liver metastasis [2]. Consequently, implementing effective measures to prevent postoperative recurrence and metastasis following radical resection of colorectal cancer is paramount.

Intraperitoneal infusion chemotherapy serves as a crucial adjunctive therapy for patients undergoing radical resection of colorectal cancer. This treatment modality helps to impede the spread of cancer cells, eradicate small malignant tumors shed within the abdominal cavity, and mitigate postoperative recurrence and metastasis to a certain extent [3]. Among the broad-spectrum chemotherapy agents utilized in clinical practice, fluorouracil stands out as one of the most prominent drugs, earning inclusion in the World Health Organization (WHO) Model List of Essential Medicines. Functioning as an antimetabolite, fluorouracil is a nucleobase analogue of uracil, featuring a fluorine atom at the fifth position of the pyrimidine unit. Its application extends across the treatment spectrum for various solid tumors, encompassing those of the gastrointestinal tract (such as pancreas and stomach) and the genitourinary system (including ovary and prostate) [4]. Through clinical trials, this study aims to further validate the benefits of combining fluorouracil intraperitoneal perfusion chemotherapy with intravenous chemotherapy in patients following radical resection of colorectal cancer.

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Materials and Methods

Source and Grouping of Patients

This retrospective study analyzed the medical records of 65 patients who underwent radical resection of colorectal cancer at the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 2011 to January 2013. Two patients from the control group (CG) were excluded due to insufficient medical records, resulting in a final inclusion of 63 cases, with 31 cases in the CG and 32 cases in the observation group (OG). This study, conducted in accordance with the principles outlined in the Declaration of Helsinki (2013) [5], received approval from the ethical committee of the Logistics Management Office of Shandong College of Arts (approval No.: SDZFY-EC-H-2019-10). Patients who were aware of the purpose and significance signed an informed consent.

Inclusion Criteria and Excluded Criteria

This study included patients who met the surgical indications for colorectal cancer and underwent radical resection for stage II and stage III colorectal cancer. For patients with stage II colorectal cancer, inclusion criteria required the presence of at least one of the following risk factors for metastasis: T4 stage, poor tissue differentiation, lymphatic vessel invasion, perineural invasion, intestinal obstruction, T3 stage with local perforation, indeterminate or positive resection margin, and fewer than 12 nodes biopsied. Staging was determined according to the 2010 *AJCC TNM Staging of Colorectal Cancer* [6], while high-risk factors for metastasis were defined based on the *Guidelines for Diagnosis and Comprehensive Treatment of Colorectal Cancer Liver Metastasis* (version 2010) [7].

Patients aged 18 to 75 years with complete clinical data, an expected survival time of at least 6 months, and a Karnofsky score of 60 points or higher were eligible for inclusion. Additionally, patients enrolled one-month post-surgery were required not to have received any other treatments before enrollment and should not have experienced local recurrence or distant metastasis at the time of enrollment.

The following patients were excluded from this study: those with severe cardiac, cerebral, renal, or bone marrow hematopoietic dysfunction; individuals with mental illness or cognitive impairment; patients with known allergies to the drugs utilized in this study; participants who did not complete the treatment regimen or whose evaluation of efficacy was hindered by uncontrollable factors; individuals who were pregnant or breastfeeding; and patients with incomplete medical data.

Methods

The CG received intravenous chemotherapy post-enrollment, employing the oxaliplatin, leucovorin and flurouracil (OLF) regimen. This regimen consisted of the following components administered via intravenous infusion: 130 mg/m^2 of oxaliplatin (manufactured by Jiangsu Hengrui Medicine Co., Ltd.; NMPA approval No.: H20050962; specification: 100 mL; batch No.: 20110614; origin: Lianyungang, Jiangsu, China) on the first day, 200 mg/m^2 of leucovorin (manufactured by Jiangsu Hengrui Medicine Co., Ltd.; NMPA approval No.: H20000584; specification: 10 mL: 0.1 g; batch No.: 20111109; origin: Lianyungang, Jiangsu, China) from day 1 to day 5, and 500 mg/m^2 of fluorouracil (manufactured by Shanghai Xudong Haipu Pharmaceutical Co., Ltd.; NMPA approval No.: H31020593; specification: 10 mL: 0.25 $\times$ 5 pieces/box; batch No.: 20111215; origin: Shanghai, China) from day 1 to day 5. The treatment cycle spanned 21 days, with evaluation of therapeutic efficacy conducted after 6 consecutive cycles, totaling 126 days of continuous chemotherapy. Continuous monitoring for local recurrence and liver metastasis was performed for a duration of 2 years.

The OG underwent intraperitoneal perfusion chemotherapy. This treatment entailed the administration of 500 mL of warm physiological saline at 36 °C via intraperitoneal perfusion, followed by a combination of medications: 5 mg of dexamethasone (manufactured by Henan Runhong Pharmaceutical Co., Ltd.; NMPA approval No.: H20053754; specification: 1 mL: 5 mg $\times$ 10 pieces; batch No.: 20110910; origin: Zhengzhou, Henan, China) + 200 mg of lidocaine (manufactured by Shandong Hualu Pharmaceutical Co., Ltd.; NMPA approval No.: H37022147; specification: 0.1 g $\times$ 5 mg $\times$ 5 pieces; batch No.: 20110315; origin: Liaocheng, Shandong, China) + 500 mL of physiological saline, followed by 2.0 g of fluorouracil + 1000 mL of physiological saline administered sequentially via intraperitoneal perfusion. This procedure was completed within 1 hour, after which the patient's position was changed.

Intraperitoneal perfusion chemotherapy was administered 5–7 days after the initial intraperitoneal chemotherapy session, and the OLF regimen mirrored that of the CG. Intraperitoneal perfusion chemotherapy was performed prior to the first and second cycles of intravenous chemotherapy, with evaluation of therapeutic efficacy conducted after the completion of the sixth cycle of chemotherapy. The treatment and follow-up duration for the OG corresponded to that of the CG.

Observation Indicators

Clinical Symptoms

The clinical symptoms were scored according to *Clinical Symptomatic Grading & Quantifying Table* (Table 1).

Quality of Life

The patients' *Karnofsky* scores were assessed both before and after treatment, recorded prior to initiation of treatment and upon completion of the trial. In accordance with the *Karnofsky* Score [8], an increase or decrease of $\geq$10 points in the *Karnofsky* score following treatment indicated an im-

Table 1. Clinical symptomatic grading & quantifying table.

Symptoms	No (0)	Mild (1 point)	Moderate (2 points)	Severe (3 points)
Abdominal distension	No	Mild abdominal distension, remission after anal exhaust	Obvious abdominal fullness and less anal exhaust	Severe abdominal distension, affecting eating and rest
Abdominal pain	No	Occasional slight pain or dull pain	Dull pain or distending pain, several times a day	Sharp pain or colic, recurrent attacks every day
Loose stool	No	Occasional loose stool or loose stool once a day	Loose stool 2–3 times a day	Loose stool more than 4 times a day
Bloody stool	No	Fecal occult blood	Blood mixed with feces	Full of blood in feces
Fatigue	No	Mentally depressed, can do physical work	Mental fatigue, barely able to do physical work	Extremely mentally exhausted, unable to do daily physical work
Poor appetite	No	Loss of appetite	Food intake decreased by 1/3 to 2/3	Food intake decreased by more than 2/3
Dark purplish tongue	No	Dark reddened tongue	Blue purplish tongue	Blue purple tongue with petechia or ecchymosis

provement or decline in the quality of life, respectively. Conversely, an increase or decrease of less than 10 points denoted a stable quality of life.

Body Weight

The patients' body weights were monitored both before and after treatment, with measurements taken prior to treatment initiation and at the conclusion of the trial. An increase or decrease of $\geq$1 kg in body weight following treatment was categorized as weight gain or loss, respectively. Conversely, an increase or decrease of less than 1 kg was classified as stable weight.

Recurrence and Metastasis

Abdominal ultrasonography was conducted every 3 months during the first year post-enrollment, and subsequently every 6 months during the second year. Electronic colonoscopy was performed annually. Enhanced CT scans of the abdomen and pelvic cavity were conducted annually as well. Patients exhibiting signs suggestive of liver metastasis underwent MRI examinations to monitor for recurrence and metastasis within the 2-year period.

$$RMR = RM / T \quad (1)$$

Where: RMR = local recurrence and/or liver metastasis rate; RM = number of local recurrence and/or liver metastasis cases in each group; T = total number of cases in each group.

Safety Assessment

The medical staff monitored alterations in blood routine, liver and kidney function before and after treatment, as well as gastrointestinal reactions, chemical peritonitis, adhesive intestinal obstruction, and other treatment-related complications throughout the treatment process, and documented blood routine and blood biochemistry prior to treatment initiation and upon completion of the trial. Evaluation was conducted according to the WHO criteria for acute and subacute toxicity of antitumor drugs [9], outlined in Table 2.

Statistical Analysis

SPSS software (manufactured by International Business Machines Corporation; version 25.0; origin: Armonk, NY, USA) was utilized for data analysis and processing in this study. The collected data were categorized into enumeration data and measurement data. Enumeration data were presented as [n (%)], and the appropriate test method was selected based on the "minimum expected count" criterion. Specifically, the chi-square test was employed when the "minimum expected count" was $\geq$5, whereas Fisher's exact test was utilized when the "minimum expected count" was $<$5.

The Kolmogorov-Smirnov method was employed to assess whether continuous variables adhered to a normal distribution. Continuous variables conforming to a normal distribution were expressed as ($\bar{x} \pm$ s) and subjected to the *t*-test, while continuous variables not adhering to a normal distribution were expressed as M (P_{25}, P_{75}) and analyzed using non-parametric tests. Statistical significance was set at $p < 0.05$.

Baseline Data

A total of 65 patients were selected in this study, and 2 patients in CG were excluded due to the lack of medical records. Finally, 63 cases were obtained. There was no significant difference in baseline indicators between the two groups ($p > 0.05$). See Table 3.

Results

Total Symptom Scores

After treatment, there was no significant difference in total symptom scores in both groups ($p > 0.05$), as shown in Table 4.

Comparison of Quality of Life

Both groups had no significant difference in quality of life ($p > 0.05$), as shown in Table 5.

Table 2. Safety assessment standards.

Adverse reactions	0	I	II	III	IV
Hemoglobin (g)	≥11.0	9.5–10.9	8.0–9.4	6.5–7.9	<6.5
Leucocyte (10^3)	≥4.0	3.0–3.9	2.0–2.9	1.0–1.9	<1.0
Platelet (10^3)	No	75–99	50–74	Severe	Life-threatening
Serum transaminase	≤1.25 N	1.26–2.5 N	2.6–5 N	5–10 N	>10 N
Creatinine (mg %)	≤1.2	1.3–2.0	2.1–4.0	>4.0	Symptomatic and urotoxicity
Nausea and vomiting	No	Nausea	Controllable vomiting	Vomiting requiring treatment	Uncontrollable vomiting

Notes: N represented the normal value of the index, and the normal value of serum transaminase was 0–40 U/L.

Table 3. Comparison of baseline data [M (P_{25}, P_{75}), n (%)].

Baseline indicators	CG (n = 31)	OG (n = 32)	R/Z	*p*
Gender [n (%)]			–	0.099
Male	19 (61.29)	26 (81.25)		
Female	12 (38.71)	6 (18.75)		
Average age [years, M (P_{25}, P_{75})]	55.00 (48.00, 66.00)	58.50 (52.00, 67.00)	Z = –1.060	0.289
Pathological type [n (%)]			–	–
Adenocarcinoma	31 (100)	32 (100)		
Others	0 (0)	0 (0)		
Clinical stages [n (%)]			–	0.129
Stage II	4 (12.90)	10 (31.25)		
Stage III	27 (87.10)	22 (68.75)		
Total symptom scores [points, M (P_{25}, P_{75})]	12.00 (9.00, 13.00)	12.00 (9.25, 13.00)	Z = –0.405	0.686
Karnofsky score [points, M (P_{25}, P_{75})]	79.00 (76.00, 82.00)	78.00 (76.00, 80.75)	Z = –1.032	0.303
Weight [kg, M (P_{25}, P_{75})]	68.00 (61.20, 70.00)	68.00 (56.53, 70.88)	Z = –0.151	0.880

Notes: – indicated no data in Fisher's exact test. CG, control group; OG, observation group.

Table 4. Comparison of total symptom scores before and after treatment in both groups [points, M (P_{25}, P_{75})].

Groups	Cases	Before treatment	After treatment
CG	31	9.00 (8.00, 10.00)	6.00 (4.00, 7.00)
OG	32	9.00 (8.00, 10.00)	5.00 (5.00, 7.00)
Z		–0.655	–0.267
p		0.513	0.789

Table 5. Comparison of quality of life in both groups [n (%)].

Groups	Cases	Increase	Stability	Decrease
CG	31	2 (6.45)	11 (35.48)	18 (58.06)
OG	32	7 (21.88)	13 (40.62)	12 (37.50)
p		0.148	0.797	0.133

Comparison of Body Weight

Both groups had no significant difference in body weight ($p > 0.05$), as shown in Table 6.

Recurrence and Metastasis

The recurrence and metastasis rates within two years were 48.39% (15/31) in the CG and 15.63% (5/32) in the OG. Notably, the recurrence and metastasis rate in the OG was significantly lower than that in the CG within the two-year timeframe ($\chi^2 = 7.800$, $p = 0.005$). Refer to Fig. 1 for visual representation.

Table 6. Comparison of body weight in both groups [n (%)].

Groups	Cases	Increase	Stability	Decrease
CG	31	3 (9.68)	6 (19.35)	22 (70.97)
OG	32	6 (18.75)	9 (28.12)	17 (53.13)
p		0.474	0.556	0.196

Notes: The weight changes of the two groups were compared by Fisher's exact test.

Safety Evaluation

Both groups exhibited no significant differences in hemoglobin, leukocyte, platelet levels, and gastrointestinal reactions (all $p > 0.05$). Additionally, renal dysfunction in both groups was mild, with no statistical difference observed between them ($p > 0.05$). Refer to Table 7 and Table 8 for detailed information.

Discussion

The incidence of colorectal cancer in China is on the rise. Current treatment methods primarily rely on surgery-based comprehensive approaches. However, postoperative abdominal recurrence and metastasis are common, significantly impacting patients' quality of life. The mechanisms underlying recurrence and metastasis after radical resection of colorectal cancer include direct infiltration of cancer cells into the serosal membrane, dissemination of cancer cells

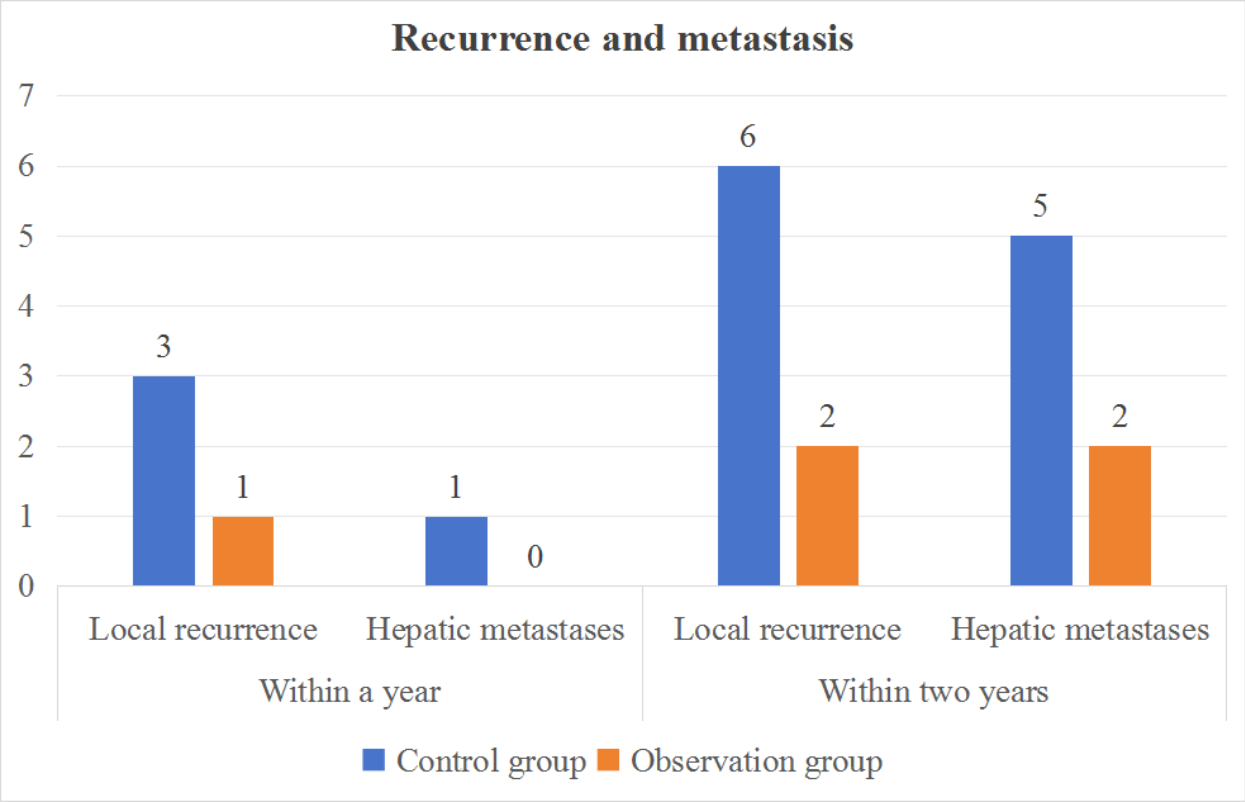

Fig. 1. Comparison of recurrence and metastasis in both groups.

Table 7. Types and degree of adverse reactions in both groups.

Adverse reactions	CG					OG				
	0	I	II	III	IV	0	I	II	III	IV
Hemoglobin	9	13	7	2	0	11	15	5	1	0
Leucocyte	7	11	11	2	0	8	12	10	2	0
Platelet	11	14	6	0	0	12	13	7	0	0
Serum transaminase	24	5	2	0	0	27	4	1	0	0
Creatinine	25	5	1	0	0	26	5	1	0	0
Nausea and vomiting	6	18	6	1	0	7	16	8	1	0

Table 8. Incidence of adverse reactions in both groups [n (%)].

Indicators	CG (n = 31)	OG (n = 32)	*p*
Hemoglobin	22 (70.97)	21 (65.63)	0.788
Leucocyte	24 (77.42)	24 (75.00)	1.000
Platelet	20 (64.52)	20 (62.50)	1.000
Serum transaminase	7 (22.58)	5 (15.63)	0.536
Creatinine	6 (19.35)	6 (18.75)	1.000
Nausea and vomiting	25 (80.65)	25 (78.13)	1.000

into the abdominal cavity via blood and lymphatic circulation, and transfer of cancer cells to the liver through the portal vein.

In cases where the tumor invades the serosal layer, presents with cancer nodules and limited ascites in the peritoneum, or undergoes extensive extrusion and resection during surgery, fluorouracil intraperitoneal perfusion chemotherapy combined with intravenous chemotherapy emerges as a straightforward and effective treatment strategy. Following intraperitoneal administration, the drug primarily enters the bloodstream through the portal vein system. Upon reaching the liver, the drug undergoes initial metabolic processing into a non-toxic or low-toxic form before entering systemic circulation, thereby minimizing toxicity, particularly bone marrow suppression and gastrointestinal reactions.

During the early postoperative period, before the formation of significant adhesions within the abdominal cavity, chemotherapy drugs can efficiently reach the abdominal cavity, where they can target free-floating cancer cells and residual microscopic cancer remnants post-surgery. This high-concentration drug exposure enhances the cytotoxic effect on cancer cells, thereby achieving effective local control.

The survival rate for colorectal cancer remains relatively low. While modern western medicine primarily employs surgery supplemented by postoperative intraperitoneal perfusion chemotherapy, the high likelihood of recurrence and metastasis, along with poor prognosis, necessitates the exploration of effective methods to enhance postoperative efficacy and reduce recurrence and metastasis rates [10–12]. Intraperitoneal perfusion chemotherapy effectively eradicates or kills free cancer cells and small lesions within the abdominal cavity, thereby preventing and treating peritoneal tumors and improving patient survival rates, quality of life, and prognosis. In some carefully selected cases, clinical cure is achievable [13]. Fluorouracil, utilized in intraperitoneal perfusion chemotherapy, alleviates patient conditions to a certain extent. Through a series of reactions in the human body, fluorouracil induces DNA double-strand breaks, interferes with protein synthesis, and crucially, inhibits thymine synthesis, DNA synthesis, and prompts apoptosis. Fluorouracil is widely employed in treating malignant tumors such as breast cancer, liver cancer, and pancreatic cancer [14–16].

Intravenous chemotherapy, a conventional treatment approach, is associated with faster drug metabolism and susceptibility to drug resistance. However, when combined with intraperitoneal perfusion chemotherapy, it complements the latter's effects, enhances chemotherapy efficacy, and improves patient survival rates.

This retrospective study evaluated the clinical effects of both treatment regimens. The results indicate that fluorouracil intraperitoneal perfusion chemotherapy combined with intravenous chemotherapy effectively controlled recurrence and metastasis in patients following radical resection of colorectal cancer, surpassing the efficacy of intravenous chemotherapy alone. Fluorouracil, administered via intraperitoneal perfusion, temporarily accumulates between the parietal and visceral peritoneum before gradual absorption into the capillary bed beneath the visceral peritoneum. The mesentery, a component of the visceral peritoneum, contains capillary beds that absorb chemotherapy drugs into the superior and inferior mesenteric veins, eventually reaching the hepatic portal vein and hepatic sinusoids directly [17]. Intraperitoneal perfusion chemotherapy optimally utilizes the hepatic portal vein, enhancing the therapeutic effect of chemotherapy drugs on tumor cells by increasing drug concentration and contact time with tumor cells [18].

Both treatment groups exhibited no significant differences in total symptom score, quality of life, body weight, or adverse reactions, indicating that the addition of fluorouracil in the treatment of patients after radical resection of colorectal cancer did not notably impact these indicators. However, the recurrence and metastasis rate in the OG was lower than that in the CG, with a significant difference observed between the two groups. This finding suggests that fluorouracil can effectively reduce the recurrence and metastasis rates of colorectal cancer. Furthermore, both groups displayed no significant differences in hemoglobin, leukocyte, platelet levels, renal dysfunction, or gastrointestinal reactions. These results demonstrate that implementing fluorouracil intraperitoneal perfusion chemotherapy in conjunction with intravenous chemotherapy effectively controls the recurrence and metastasis rate without significantly increasing chemotherapy-related symptoms in patients following radical resection of colorectal cancer. This sets a foundation for subsequent clinical applications. However, this treatment scheme did not substantially improve clinical treatment outcomes or patient quality of life.

Limitation of the Study

The study is subject to several limitations. Firstly, the sample size is small, which may not fully represent the entire population, thereby potentially reducing the reliability of the conclusions. This limitation also hampers the replication and validation of the study findings and lacks repeatability. Therefore, future studies should enhance the experimental design, increase the sample size, and conduct multicenter clinical trials to further enhance the objectivity and accuracy of the research results. This approach will facilitate the attainment of more robust and convincing conclusions.

Conclusion

In summary, the combined regimen of fluorouracil intraperitoneal perfusion chemotherapy with intravenous chemotherapy effectively manages recurrence and metastasis in patients following radical resection of colorectal cancer. This treatment approach holds promise for improving the prognosis of such patients.

Availability of Data and Materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

WJW designed the research study, analyzed the data, wrote the article and contributed to editorial changes in the manuscript. The author read and approved the final manuscript and has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study conforming to the principles of Declaration of Helsinki (2013) has been approved by the ethical committee of Logistics Management Office of Shandong College of Arts approval (No.: SDZFY-EC-H-2019-10). Patients who were aware of the purpose and significance signed an informed consent.

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Conflict of Interest

The author declares no conflict of interest.

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