ORIGINAL RESEARCH

Safety Study of Raltitrexed Perfusion in Elderly Patients with Colorectal Cancer and Effect on CEA mRNA in Peritoneal Lavage Fluid

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ABSTRACT

Background • Intraperitoneal chemotherapy is an effective way to kill free tumor cells in the abdominal cavity. The safety and efficacy of raltitrexed perfusion during radical surgery for elderly patients with colorectal cancer are still unclear.

Methods • In accordance with computer-generated random allocation sequences, 116 elderly patients with colorectal cancer who received radical surgery were randomly grouped into the raltitrexed intraperitoneal perfusion group or the saline intraperitoneal perfusion group from January 2020 to December 2021 in the First Affiliated Hospital of Bengbu Medical University. *t* tests and χ^2 tests were used to analyze the difference between the two groups of the clinical characteristics, pathological features, perioperative parameters, and carcinoembryonic antigen mRNA in the peritoneal lavage fluid.

Results • No statistically significant differences in postoperative complications after radical surgery were observed between the two groups. No statistically significant differences in peripheral blood indexes were observed between the two groups before surgery or on the first and third days after surgery. One day after radical surgery, the alanine transaminase (54.33 ± 4.93 vs 51.01 ± 5.56) and aspartate transaminase (49.28 ± 4.30 vs 50.99 ± 3.88) in the peripheral blood were higher in the raltitrexed intraperitoneal perfusion group than in the saline intraperitoneal perfusion group. At the same time, no significant difference was found on the third day after surgery. No significant differences in side effects of chemotherapy were observed between the two groups. The positive rate of carcinoembryonic antigen mRNA in the raltitrexed intraperitoneal perfusion group (8.47%) was significantly lower than that in the saline intraperitoneal perfusion group (22.81%) after surgery.

Conclusion • Raltitrexed perfusion during radical surgery is safe and feasible for elderly patients with CRC and can reduce the positive rate of carcinoembryonic antigen mRNA in peritoneal lavage fluid, so it can be explored as a treatment option. (*Altern Ther Health Med.* 2024;30(10):510-515).

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INTRODUCTION

Colorectal cancer (CRC) is a common form of malignancy worldwide.[1] The common distant metastases of CRC include liver metastasis, lung metastasis and peritoneal metastasis. Peritoneal metastasis refers to the growth of cancer cells from the primary focus of CRC through blood, lymphatic duct or peritoneum directly. Peritoneal implantation metastases were found in 7%-15% of patients at the initial operation. Peritoneal metastases were found in 4%-19% of patients after radical surgery. The incidence of peritoneal metastases was 25%-30% higher in CRC patients with recurrent metastases, and the only site of metastases in 3% of patients was peritoneal metastases. Due to the unsatisfactory diagnostic and therapeutic effects of peritoneal metastasis, patients with peritoneal metastasis tend to have a worse prognosis and shorter disease-free survival and overall survival than those without peritoneal metastasis.[2,3] The extrusion of the cancer tissue or the separation of the blood vessels and lymph vessels in the nutritional tumor tissue during radical surgery may also lead to the inflow of tumor cells into the abdominal cavity. Peritoneal metastasis is a metastatic mode of CRC, with five-year Overall survival (OS) reported in 0%–3% of patients with peritoneal cancer. OS is most commonly attributed to the infiltration of intraoperative tumor cells into the abdominal cavity, resulting in abdominal implantation recurrence and metastasis.[4,5]

Considering prophylactic HIPEC during primary surgery for CRC, a study has analyzed peritoneal recurrence rates of 0-12.9%, 3-year and 5-year disease-free survival (DFS) of 67-97.5% and 54.8-84%, respectively, and 3-year and 5-year OS

of 67-100% and 84%, respectively. These oncology outcomes were superior to those in patients with early postoperative abdominal chemotherapy (EPIC) after primary surgery, early surgical reintervention, and HIPEC, HIPEC + CRS several months after primary surgery, or in patients with adjuvant systemic chemotherapy alone.[6] Currently, chemotherapeutic drugs such as cisplatin, 5-Fluorouracil (5Fu), hydroxy camptothecin, and fluorouracil sustained release agents have been used for intraperitoneal infusion chemotherapy.[7-10] Raltitrexed is an antimetabolic drug, specifically an inhibitor of thymidylate synthase. Its chemical structure is similar to folic acid in that it is an antimetabolite of folate. The drug inhibits one or more of three enzymes that use folic acid and its derivatives as substrates, including DHFR, GARFT, and thymidylate synthase. Thymidylate synthase is one of the key enzymes in the synthesis of DNA and RNA within cells (necessary for the growth and survival of normal and cancer cells). By inhibiting this enzyme, Rhatitrexed prevents the formation of DNA and RNA. In addition, the polyglutamated raltitrexed is fully active, allowing the drug to remain active within the cell. Raltitrexed, which specifically inhibits thymidylate synthase (TS) and can achieve long-term antitumor effects, is actively absorbed into cells through reductive folate transporters on the cell membrane and metabolized into a variety of polymeric glutamates.[11] As a new antitumor drug, raltitrexed has become accepted by clinicians and patients due to its long half-life and few adverse reactions. Bartoška P reported that the use of cytoreduction (CRS) + Hyperthermic Intraoperative Peritoneal Chemotherapy (HIPEC), associated with acceptable mortality and morbidity in selected patients with Peritoneal carcinomatosis (PC) of colorectal origin, results in a significant extension of OS.[12] However, compared with younger and middle-aged patients, older patients are more likely to suffer from complications in other important organs, and the physiological reserve function of the body is significantly reduced. Older patients with CRC face higher perioperative risk than younger and middle-aged patients.

Raltitrexed can selectively inhibit tumor cells and reduce damage to normal cells, thereby improving the tolerance and effectiveness of the treatment. Although increasing age is generally associated with an increased risk of CRC, the use of raltitrexed is not age-restricted. Compared with some traditional chemotherapy drugs, raltitrexed has relatively less toxic side effects, such as bone marrow suppression, nausea, vomiting, and other uncomfortable symptoms. This makes it an advantage when treating CRC patients, including older patients. A study has shown that patients with stage I-III CRC who have high carcinoembryonic antigen (CEA) in their peritoneal fluid tested intraoperatively have worse cancer-free survival, even if the peritoneal fluid is cytologically negative. Based on the results of this study, we suggest that evaluating CEA with peritoneal fluid in patients with CRC is important for predicting long-term prognosis.[13]

The the safety and efficacy of raltitrexed perfusion during radical surgery for elderly patients with colorectal cancer are still unclear. In this study, to explore the clinical safety of the intraoperative intraperitoneal lavage of raltitrexed and the effect of CEA mRNA in postoperative abdominal lavage fluid, elderly patients with CRC who underwent radical surgery and received intraperitoneal perfusion of raltitrexed were compared with patients who received intraoperative perfusion of normal saline. The aim of this study is to provide a valuable basis for the application and promotion of this treatment in elderly patients with colorectal cancer.

MATERIALS AND METHODS

Ethics statement

The Medical Ethical Committees approved this study for Ethical Review. The investigation was approved by the Ethics Committees of Bengbu Medical University (ID2019171, 2019.12.20). Written informed consent was obtained from all subjects participating in the trial. The trial protocol followed the Declaration of Helsinki. All patient were clear of mind, voluntarily accepted the investigation, and gave informed consent.The patients or guardians had the right to stop the trial at any time for any reason.

Patients

This study was conducted as a randomized patient preference trial at the First Affiliated Hospital of Bengbu Medical University. The inclusion criteria: the patients were pathologically diagnosed with colorectal cancer by endoscopic biopsy; age 65 or older; no history of serious abdominal surgery. Exclusion criteria were as follows: (a) Patients who cannot tolerate radical surgery; (b) Patients with tumors that cannot be radically resected; (c) confirmed evidence of distant metastasis and extensive peritoneal dissemination (peritoneal carcinomatosis index (PCI) >20); (d) patients received chemotherapy or radiotherapy before surgery; and (e) chronic disease-related complications that cannot be effectively controlled.

In this parallel, double-masked trial, we need to recruit at least 100 patients. Computer-generated random allocation sequences were created by independent researchers using SPSS Statistics 24.0 at 1:1 allocation and random block size. Eligible patients were randomly divided into the raltitrexed abdominal perfusion group and the saline abdominal perfusion group, and the sealed opaque envelope was used to expose the treatment group. No patients or data collectors were aware of this grouping.

Investigation methods

Two days before radical surgery, all patients were instructed to consume a liquid diet. One day before radical surgery, the patient was given polyethylene glycol electrolyte orally to prepare the intestines. All patients underwent laparoscopic Dixon surgery, and the same group of surgeons performed all surgeries. Raltitrexed powder needles (2 mg) for the raltitrexed intraperitoneal perfusion group were produced by Nanjing Chia-Tai Tianqing Pharmaceutical Company.

After the radical surgery, the abdominal cavity was rinsed with normal saline before the abdominal incision was closed. Raltitrexed powder needles (2 mg) were dissolved in 4 ml of sterile water and diluted. Subsequently, 50mL of normal saline

containing 8 mg of dissolved raltitrexed was poured into the abdominal cavity at the site of the original tumor and the surrounding area in the raltitrexed intraperitoneal perfusion group. In contrast, 50 mL of saline solution without raltitrexed was poured into the saline intraperitoneal perfusion group. Two drainage tubes were placed in the pelvic cavity and led out through the left and right pokes. The drainage tubes were clamped and opened for 2 hours.

All patients were observed for 14 days after surgery. The perioperative exhaust time (The time from the end of surgery to the first anal exhaust after surgery) along with the occurrence of anastomotic leakage, incision infection, and postoperative fever (defined as any recording of body temperature higher than 38.5°C for 3 consecutive days after radical surgery) were evaluated in all patients through clinical observation.

Peripheral blood samples were collected before radical surgery and at one and three days after radical surgery. Hematological indexes (white blood cell count, red blood cell count, platelet count, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine (CR)) were examined and compared. Adverse gastrointestinal reactions, including abdominal pain, vomiting, and diarrhea after chemotherapy were recorded. Adverse chemotherapeutic reactions were evaluated according to the Common Terminology Criteria Adverse Events Version 3.0, developed by the National Institutes of Health.[14]

After the surgical exploration, before the excision procedure, if the volume of ascites exceeded 500 mL, the ascites were collected directly. If the volume of ascites was less than 500 mL, the ascites (if present) were rinsed with normal saline, and over 500 mL of lavage was collected in the Douglas cavity. One day after radical surgery, the patients were given a peritoneal perfusion of 500 mL of warm normal saline through the abdominal drainage tube. Change positions multiple times and collect ascites as much as we can. The drained peritoneal lavage solution (500 mL) was sent for examination after the patient was properly moved.

The peritoneal lavage solution was centrifuged at 3,000 × g for 10 min, and the supernatant was removed. RNA was extracted using the alkali lysis method, and total RNA was dissolved in ddH_2O. The RNA samples were reverse-transcribed with a reverse transcription kit according to the instructions. The primer sequences used in the PCR amplification are as follows: the forward primer is GCAGCAACACACACAAGTT, the reverse primer is TTCCAGATGCAGAGACTGTGATG, MGB probe is CCAAAATCACGCCAAATAATAACGGGACC. β-actin was used as the reference gene. The forward primers and reverse primers were added and amplified for 40 cycles. Each cycle consisted of 50°C for 2 min, 95°C for 10 min, and 60°C for 1 min. RNA concentration and quality were measured using a NanoDrop™2000 instrument. When the amplification reached the threshold, the result was interpreted as CEA mRNA positive.

Statistical analysis

Continuous data are presented as mean ± standard deviation. Statistical comparisons were performed using the two-tailed Student's *t* test for paired observations or the two-tailed chi-square test for group comparisons. Categorical data are expressed as numbers and percentages (*n*, %), and the groups were compared using χ^2 tests. The statistical significance level was set at $P < .05$.

Table 1. Comparison of peripheral blood indexes between the two groups

	Preoperative	One day after radical surgery	Three days after radical surgery
White blood cell count ($\times 10^9$/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	6.11 ± 2.39	13.16 ± 2.73	12.21 ± 1.69
Saline intraperitoneal perfusion group ($n = 57$)	5.82 ± 1.28	12.42 ± 2.01	11.64 ± 1.99
P value	.413	.100	.093
Red blood cell count ($\times 10^{12}$/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	3.81 ± 0.82	3.29 ± 0.45	3.87 ± 0.92
Saline intraperitoneal perfusion group ($n = 57$)	4.02 ± 0.39	3.45 ± 0.47	4.11 ± 0.23
P value	.083	.061	.058
Platelet count ($\times 10^9$/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	289.26 ± 56.01	194.83 ± 50.36	219.28 ± 59.92
Saline intraperitoneal perfusion group ($n = 57$)	293.11 ± 73.72	203.04 ± 55.45	214.82 ± 61.77
P value	.752	.405	.694
ALT (U/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	30.32 ± 5.91	54.33 ± 4.93[b]	39.39 ± 4.02
Saline intraperitoneal perfusion group ($n = 57$)	32.01 ± 4.22	51.01 ± 5.56[b]	37.88 ± 4.84
P value	.080	.001	.070
AST (U/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	29.89 ± 4.82	49.28 ± 4.30[a]	36.27 ± 4.45
Saline intraperitoneal perfusion group ($n = 57$)	30.19 ± 5.24	50.99 ± 3.88[a]	37.48 ± 5.31
P value	.749	.027	.186
BUN (mmol/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	6.55 ± 0.56	6.01 ± 0.73	5.93 ± 0.88
Saline intraperitoneal perfusion group ($n = 57$)	6.33 ± 1.01	5.97 ± 0.85	5.89 ± 0.79
P value	.148	.786	.797
CR (μmol/L)			
Raltitrexed intraperitoneal perfusion group ($n = 59$)	55.72 ± 4.37	59.22 ± 4.19	57.38 ± 4.00
Saline intraperitoneal perfusion group ($n = 57$)	54.80 ± 4.12	58.17 ± 4.13	56.81 ± 4.20
P value	.246	.177	.456

[a] $P < .05$
[b] $P < .01$

RESULTS

Patients

The study involved a total of 116 patients with colorectal cancer admitted to the Department of Oncological Surgery from January 2020 to December 2021, with all patients eventually completing the primary outcome analysis. The patients ranged in age from 65 to 83 years old. There were 59 cases of raltitrexed intraperitoneal perfusion group and 57 cases of saline intraperitoneal perfusion group.

Peripheral blood indexes

Comparison of peripheral blood indexes between the two groups: No statistically significant differences in peripheral blood white blood cell count, red blood cell count, platelet count, BUN, or CR were observed between the two groups before radical surgery or at one or three days after radical surgery ($P > .05$). No statistically significant differences in preoperative peripheral blood ALT or AST were found between the two groups ($P > .05$). Peripheral blood ALT (54.33 ± 4.93 vs 51.01 ± 5.56) and AST (49.28 ± 4.30 vs 50.99 ± 3.88) were higher in the raltitrexed intraperitoneal perfusion group than in the saline intraperitoneal perfusion group one day after radical surgery ($P < .05$). At three days after radical surgery, peripheral blood ALT and AST decreased in both groups compared to ALT and AST at one day after radical surgery, and no significant difference was found between the groups ($P > .05$; Table 1)

Table 2. Comparison of clinicopathological features between the two groups

	Raltitrexed intraperitoneal perfusion group (n = 59)	Saline intraperitoneal perfusion group (n = 57)	P value
Age (x ± s, years)	71.12 ± 5.97	73.03 ± 8.25	.155
Gender(n(%))			
Male	34 (57.63)	30 (52.63)	.589
Female	25 (42.37)	27 (47.37)	
Depth of tumor invasion(n(%))			
T3	39 (66.10)	40 (70.18)	.638
T4a	20 (33.90)	17 (29.82)	
Tumor site(n(%))			
Colon	19 (32.20)	21 (36.84)	.599
Rectum	40 (67.80)	36 (63.16)	
Lymph node metastasis(n(%))			
With	16 (27.12)	11 (19.30)	.319
Without	43 (72.88)	46 (80.70)	
Histological type(n(%))			
High-Middle differentiated adenocarcinoma	42 (71.19)	36 (63.16)	.357
Low-undifferentiated adenocarcinoma	17 (28.81)	21 (36.84)	

Table 3. Comparison of postoperative complications between the two groups

	Raltitrexed intraperitoneal perfusion group (n = 59)	Saline intraperitoneal perfusion group (n = 57)	P value
Postoperative exhaust time (h)	72.87 ± 3.91	74.12 ± 4.27	.103
Anastomotic leakage(n(%))	2 (3.39)	2 (3.51)	.972
Incision infection (n(%))	4 (6.78)	5 (8.77)	.688
Fever (n(%))	2 (3.39)	1 (1.75)	.579

Table 4. Comparison of the gastrointestinal side effects of chemotherapy between the two groups (n(%))

	Raltitrexed intraperitoneal perfusion group (n = 59)	Saline intraperitoneal perfusion group (n = 57)	P value
Abdominal pain degree			
I-II	3 (5.08)	2 (3.51)	.676
III-IV	0	0	
Vomiting degree			
I-II	2 (3.39)	1 (1.75)	.579
III-IV	0	0	
Diarrhea degree			
I-II	2 (3.39)	1 (1.75)	.579
III-IV	0	0	

Table 5. Comparison of CEAmRNA in peritoneal lavage fluid between two groups before surgery (n(%))

	raltitrexed intraperitoneal perfusion group(n=59)	saline intraperitoneal perfusion group(n=57)	P value
CEAmRNA			
positive	49(83.05)	51(89.47)	.316
negative	10(16.95)	6(10.53)	

Table 6. Comparison of CEA mRNA in peritoneal lavage fluid between two groups after surgery (n(%))

	raltitrexed intraperitoneal perfusion group (n = 59)	saline intraperitoneal perfusion group (n = 57)	P value
CEA mRNA			
positive	5 (8.47)[a]	13 (22.81)[a]	.033
Negative	54 (91.53)	44 (77.19)	

[a]$P < .05$

Clinicopathological features

No significant differences were observed in baseline clinicopathological features or postoperative complications between the two groups ($P > .05$; Table 2, 3).

Gastrointestinal side effects

Comparison of the gastrointestinal side effects of chemotherapy between the two groups: No degree III-IV adverse gastrointestinal reactions were observed in either group, and the incidences of degree I-II events (abdominal pain, vomiting, and diarrhea) were not significantly different between the two groups ($P > .05$; Table 4).

CEA mRNA

Comparison of CEA mRNA in peritoneal lavage fluid between the two groups: No significant differences were observed in CEA mRNA in peritoneal lavage fluid between the two groups before surgery ($P > .05$; Table 5). There were significant differences in CEAmRNA in peritoneal lavage fluid before and after surgery in raltitrexed intraperitoneal perfusion group(83.5% vs 8.47%, $P < .01$) and the saline intraperitoneal perfusion group(89.47% vs 22.81%, $P < .01$).

Of the 59 cases in the raltitrexed intraperitoneal perfusion group, five (8.47%) were CEA mRNA positive, whereas 13 out of the 57 cases in the saline intraperitoneal perfusion group (22.81%) were positive for CEA mRNA. The positive rate of CEA mRNA in peritoneal lavage fluid was borderline significantly lower in the raltitrexed intraperitoneal perfusion group than in the saline intraperitoneal perfusion group ($P = .033$; Table 6).

DISCUSSION

The rate of early detection for CRC in China is low, and most CRCs are in the advanced stage when diagnosed. In this advanced stage, tumor cells may have fallen off from the primary site into the abdominal cavity or even spread and metastasized, and even radical surgery cannot eliminate all tumor cells. Peritoneal metastasis is present at the time of initial diagnosis in 4%-10% of patients with CRC,. Recurrent peritoneal disease occurs in 15%–20% of patients.[15,16] The efficacy of chemotherapy and palliative surgery in patients with peritoneal metastasis of CRC is unsatisfactory, with a median survival time of only 4-7 months.[17,18] Since peritoneal implantation is the main cause of peritoneal metastasis in CRC, preventing peritoneal implantation is critical. Partial chemotherapy drugs combined with HIPEC have achieved good results in the treatment of peritoneal metastasis of CRC.[19-21] However, the application of raltitrexed intraoperative perfusion to kill cancer cells after the radical resection of CRC has not been reported. Intraperitoneal chemotherapy is based on the strong absorption of the peritoneum, which allows drugs to accumulate in the peritoneum and enter the lymphatic and portal vein system to kill tumors. Chemotherapeutic drugs can come into direct contact with free tumor cells in the abdominal cavity and cause lysis. Intraperitoneal drug stimulation increases inflammatory factor substance concentrations, enhances the immune capacity of the body, and improves the role of chemotherapy drugs. Turaga K and Levine E et al. found that injecting chemotherapy drugs with very clear clinical efficacy into the abdominal cavity of patients with CRC through intraperitoneal

perfusion chemotherapy is an effective adjuvant treatment for CRC, in which the serous membrane perforation of CRC leads to the free tumor cells in the abdominal cavity and the elimination of free tumor cells, with a higher five-year survival rate and less recurrence and metastasis.[8] Raltetrexed and fluorouracil, which are both analogs of quinoline folate, are polymeric chemotherapeutic drugs with good water solubility that specifically inhibit TS. Raltetrexed enters the cell through the membrane carrier of folate methotrexate and is decomposed into polyglutamyl compounds under the action of enzymes in the cell. These polyglutamyl compounds inhibit TS much more strongly than raltetrexed itself; these compounds are 100 times more effective than raltetrexed and can remain in cells for a long time, thereby prolonging the drug half-life, extending the administration time and making treatment more convenient.[22] Zhou Sicheng found that perioperative intraperitoneal perfusion of raltitrexed (3 mg/m^2) with or without lobaplatin (50 mg/m^2) can be regarded as safe and feasible for patients with PC of colorectal origin.[23] Currently, there is no unified standard for the dose of raltetrexed intraperitoneal infusion chemotherapy. Most works refer to the recommended amount of systemic intravenous chemotherapy (3 mg/m^2). However, the plasma concentration of intraperitoneal infusion chemotherapy is significantly lower than that of systemic intravenous chemotherapy; thus, the safety of intraperitoneal infusion chemotherapy is lower than that of systemic intravenous chemotherapy at the same dose. Although the safety and efficacy of raltitrexed intraperitoneal infusion has been demonstrated in the previous studies, the safety and efficacy of raltitrexed perfusion is not clear in elderly patients, who are generally thought to have a worse response and tolerance to the drug.

In the current study, we found no significant differences in the incidence of postoperative exhaust time, anastomotic leakage, incision infection, or the incidence of fever after radical surgery between the raltitrexed intraperitoneal perfusion group and the saline intraperitoneal perfusion group. In addition, no statistically significant differences in peripheral blood, white blood cell count, red blood cell count, platelet count, BUN, or CR were observed between the two groups before radical surgery, one day after radical surgery, or three days after radical surgery. These results indicate that raltitrexed intraperitoneal perfusion had no significant effects on the white blood cell count, red blood cell count, platelet count, and renal function of elderly patients with CRC. ALT and AST in peripheral blood one day after radical surgery were higher in the raltitrexed intraperitoneal perfusion group than in the saline intraperitoneal perfusion group. However, ALT and AST decreased at three days after radical surgery in both groups. No statistically significant differences in ALT and AST were observed between the two groups three days after radical surgery. Thus, although intraoperative raltetrexed affected liver function one day after radical surgery, liver function remained within the compensable range and did not translate into serious complications. No degree III-IV adverse gastrointestinal reactions were observed in either group, and there were no significant differences in the incidence of degree I-II reactions (abdominal pain, vomiting, and diarrhea) between the two groups. These results indicate that the intraoperative use of raltetrexed is not associated with any serious systemic toxic side effects and does not increase the risk of postoperative complications. Although the study may not have had sufficient power to detect rare adverse events, we tentatively think that raltetrexed is an ideal drug for intraperitoneal chemotherapy.

Peritoneal-free cancer cells are an independent prognostic factor for relapse-free survival and overall survival, and positive peritoneal-free cancer cells in CRC patients can be used as a separate diagnostic indicator for stage IV CRC. CEA mRNA in peritoneal lavage was a more sensitive indicator than in peritoneal-free cancer cells.[24] CEA mRNA almost only exists in tumor cells, and the detection of CEA mRNA in ascites may indicate the existence of tumor cells expressing CEA mRNA in ascites.[24] A study showed that high CEA levels in peritoneal fluid were significantly associated with risk factors for PC in CRC. Patients with peritoneal fluid CEA higher than 5 ng/dl had significantly higher cancer-free survival than those with peritoneal fluid CEA lower than 5 ng/dl. Peritoneal fluid CEA is a predictor of PC in CRC and is significantly correlated with the prognosis of CRC.[13] In the current study, two different methods can reduce the positive rate of CEA mRNA in the peritoneal lavage fluid. The CEA mRNA-positive rate was significantly lower in the raltitrexed intraperitoneal perfusion group than in the saline intraperitoneal perfusion group. Thus, the intraperitoneal infusion of raltetrexed can reduce the loss of multiple tumor cells in patients with CRC more effectively. Based on study demonstrating the importance of CEA in peritoneal fluid for predicting the long-term prognosis of CRC patients, we can assume that patients with lower CEA in peritoneal fluid will have better survival prognosis.[13] However, better results may require a larger sample size.

Peritoneal metastasis is the most common mode of CRC recurrence and metastasis. Considering the limited effect of systemic chemotherapy on peritoneal metastasis, local peritoneal chemotherapy is being explored as a treatment option because it increases the concentration of local anticancer drugs in the peritoneum, directly exposes the peritoneal deposits and free cancer cells to these drugs, and reduces systemic reactions.

Limitations

The study was conducted at a single center, which may introduce selection bia. Our next step studies should consider using larger sample sizes. Studies with larger sample sizes can increase the statistical power of studies and be better able to capture rare side effects that may be present. Consider enrolling subjects from multiple centers or using large public databases or clinical trial registries to collect data. Further

study is required to determine if peritoneal lavage chemotherapy with raltetrexed can effectively reduce the rate of postoperative peritoneal metastasis and improve the survival rate of patients.Future studies should also consider long-term follow-up. Long-term follow-up can provide valuable information about the patient's long-term effects and possible long-term side effects. This can be done through regular follow-up of study subjects or by collecting patient data in a real-world setting. Future studies may be adjusted accordingly in light of new evidence and theories. Overall, further large-scale, long-term studies are needed to understand better and exploit the potential of peritoneal lavage chemotherapy with raltetrexed.

CONCLUSION

The findings of this study demonstrate that raltitrexed perfusion during radical surgery is safe and feasible for elderly patients with CRC and can reduce the positive rate carcinoembryonic antigen mRNA in peritoneal lavage fluid. This treatment may lead to improved patient outcomes, so it can be explored as a treatment option.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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AUTHOR CONTRIBUTIONS

Bo Xie and Yuanyuan Wang contributed equally to this work. Bo Xie: Conceptualisation, data collection and analysis, funding acquisition, investigation, methodology, and resources. Yuanyuan Wang: Conceptualisation, investigation, methodology, writing, review, and editing of the manuscript, and total project administration and supervision. Jianguang Jia: Writing, data collection, and analysis. Jing Li: Data collection. Hu Wang: Review and editing of the manuscript.

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