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# Irinotecan plus raltitrexed as second-line treatment in locally advanced or metastatic colorectal cancer patients: a prospective open-label, single-arm, multi-center, phase II study

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## Abstract

**Background** Colorectal cancer is the third most common cancer and the second leading cause of cancer death. There are limited therapeutic options for the treatment of locally advanced or metastatic colorectal cancers which fail first-line chemotherapy. Phase I/II studies showed that the combined application of the raltitrexed and irinotecan has significant synergistic effect and acceptable toxicity. However, most of these previous studies have relatively small sample size.

**Methods** This is a prospective open-label, single-arm, multi-center, Phase II trial. Brief inclusion criteria: patients were aged 18 to 75 years with locally advanced or metastatic colorectal cancer after failure of 5-FU and oxaliplatin therapy. Enrolled patients received raltitrexed (3 mg/m$^2$, d1) and irinotecan (180 mg/m$^2$, d1) each 21-day cycle until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival, and the secondary endpoints were disease control rate, objective response rate, overall survival and safety.

**Results** A total of 108 patients were enrolled between September 2016 and May 2020. The median age was 61 years, ECOG 1 score accounts for 67.6%, the rest were ECOG 0. A total of 502 cycles were completed, with an average of 4.6 cycles and a median of 4 cycles. 108 patients were evaluated, with an objective response rate of 17.6%, and

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disease control rate of 76.9%. The median follow-up time was 27 months (range:3.1–61.0 m) at data cut-off on March 2023. Median progression-free survival was 4.9 months (95% CI 4.1–5.7) and median overall survival was 13.1 months (95% CI 12.2–15.5). The most common adverse events that were elevated are alanine aminotransferase increased, aspartate aminotransferase increased, fatigue, diarrhoea, neutrocytopenia, thrombocytopenia, hypohemoglobin, and leukocytopenia. Most of the adverse events were Grade I/II, which were relieved after symptomatic treatment, and there were no treatment-related cardiotoxicities and deaths.

**Conclusions** The combination of raltitrexed and irinotecan as second-line treatment for mCRC could be a reliable option after failure of standard 5-Fu-first-line chemotherapy in locally advanced or metastatic colorectal cancers, especially for patients with 5-FU intolerance (cardiac events or DPD deficiency patients).

**Trial registration** ClinicalTrials.gov identifier: NCT03053167, registration date was 14/2/2017.

**Keywords** Raltitrexed, Colorectal cancer, Second-line chemotherapy

## Introduction

More than 1.9 million new colorectal cancer (including anus) cases and 935,000 deaths were estimated to occur in 2020, representing about one in 10 cancer cases and deaths.

Colorectal ranks third in terms of incidence, but second in terms of mortality [1]. Surgery remains the treatment of choice for early-stage colorectal cancer (CRC) and for oligometastatic disease; however, approximately one quarter of patients present with metastatic disease at diagnosis, and another quarter eventually develop metastases during the course of their disease [2]. Although in the era of targeted and immunotherapy, the standard of care for metastatic colorectal cancer(mCRC) is chemotherapy in combination with targeted therapy, systemic chemotherapy remains the main treatment for the majority of patients with mCRC not amenable to curative-intent resection [3].

Current common systemic chemotherapeutic drugs for advanced or mCRC include fluorouracil (5-FU and capecitabine), irinotecan, oxaliplatin and TAS 102, the main treatment for mCRC has been 5-FU-based chemotherapy as either the first- or second-line treatment [4]. However, with the prolongation of the survival period of patients, some patients are clinically found to have disease progression after first-line chemotherapy is effective, and even resistant to 5-Fu. The results of randomized GERCOR study implied that second-line FOLFIRI only achieved 4% RR and 2.5 months mPFS followed FOLFOX6, and FOLFOX6 which achieved 15% RR and 4.2 months PFS followed FOLFIRI [5]. Baba et al. discovered that after FOLFOX first-line treatment, the expression of ERCC1 and DPD mRNA in mCRC patients increased significantly, which enhanced the resistance to fluorouracil in late chemotherapy [6]. Xiaowei Zhang et al. performed a randomized clinical trial involving a head-to-head comparative study between FOLFIRI and irinotecan as a second-line treatment for patients with mCRC who failed 5-FU-based regimens. The results showed that FOLFIRI was not superior to irinotecan in terms of PFS in all patients and every subgroup, and no significant differences were detected in OS and ORR between the two groups, FOLFIRI does not increases efficacy but does increase toxicity compared with single-agent irinotecan. They further demonstrated that adding 5-FU did not improve treatment efficacy and prognosis through the multivariate analysis of Cox proportional hazards model [7]. After the progression of 5-fu first-line chemotherapy, the physical fitness of a patient may decrease, or they may be complicated with cardiovascular and cerebrovascular diseases. So most recurrent patients have previously received fluoropyrimidine and oxaliplatin as adjuvant or first-line chemotherapy, we posit that other combinations of chemotherapeutic agent may be a better choice.

Raltitrexed is a new-generation water-soluble TS inhibitor. In vivo and in vitro studies demonstrated that raltitrexed had no complete cross-resistance with 5-FU, and can be used in patients with mCRC who had failure with 5-FU [8]. Irinotecan combined with raltitrexed has significant synergistic effect and acceptable toxicity. A number of Phase III clinical trials proved that the efficacy of raltitrexed alone as first-line treatment for mCRC is comparable with that of 5-FU/CF [9]. Yu et al. used raltitrexed alone as second-line therapy for the treatment of mCRC, and the ORR was 28.6% and mPFS was 6.5 months [10]. The first-line treatment of mCRC with the RALOX (oxaliplatin combined with raltitrexed) regimen has an ORR of 43–54%, mPFS>6 months, and mOS of 10-14.8 months [11–14]. The first-line treatment of mCRC with the RALIRI (irinotecan combined with raltitrexed) regimen has an ORR of 27–46%, mPFS of 5-11.1 months, and mOS of 13.1–15.6 months [15–17]. Wang et al. reported a randomized controlled Phase III clinical trial of raltitrexed compared with 5-FU/CF combined with oxaliplatin in the treatment of mCRC, which included chemotherapy-naive (first-line) patients or patients in whom a 5-FU-based regimen had failed, and found that in 5-FU-based regimen-failed patients, the ORR in the raltitrexed plus oxaliplatin group was significantly higher

than that in the 5-FU/CF plus oxaliplatin group (29.4% *v*. 12.8%, $P=0.0448$) [18]. Aparicio et al. used raltitrexed combined with irinotecan as second-line therapy for the treatment of mCRC, and the ORR was 15.4%, mTTP was 4.6 months and mOS was 11.9 months [19]. These results indicated that in first-line treatment, the efficacy of raltitrexed is similar to that of 5-FU, but after failure of first-line 5-FU treatment, the combined regimen based on raltitrexed is more effective than the combined regimen based on 5-FU, indicating that there is no complete cross resistance between raltitrexed and 5-FU.

Most of the aforementioned studies have a relatively small sample size, therefore, this prospective study was performed to evaluate the efficacy and safety of the irinotecan plus raltitrexed chemotherapy regimen in patients in whom FOLFOX chemotherapy therapy had failed.

## Methods

### Phase II study design

This study was an open-label, single-arm, multi-center, Phase II study registered in clinicaltrials.gov (Registration No. NCT03053167). This clinical study was approved by Committee of Clinical Trials, The First Hospital of China Medical University. The primary outcome measures were progression-free survival (PFS). The secondary outcome measures were overall survival (OS), overall response rate (ORR), disease control rate (DCR), and toxicity.

### Patient eligibility

The main inclusion criteria were histologically confirmed colon or rectal cancer, disease progression while on first-line palliative oxaliplatin and fluoropyrimidine chemotherapy or relapse within 6 months after adjuvant oxaliplatin and fluoropyrimidine chemotherapy, washout time of 4 weeks after the last chemotherapy infusion or radiotherapy, and observed lesions not in the radiotherapy target, presence of at least one radiographically measurable target lesion using Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1, Eastern Cooperative Oncology Group(ECOG) performance status of 0–1. Pretreatment assessments included complete medical history, performance status, complete blood count, serum chemistry, electrocardiogram, and baseline measurement of tumor size based on CT/MRI. The study was conducted in compliance with the Declaration of Helsinki and all patients signed signed informed consent.

### Treatment

Although the standard of care for mCRC was chemotherapy in combination with targeted therapy, the actual accessibility of targeted drugs in China was poor because targeted drugs in China were not formally included in the national health insurance until 2020, there were still a considerable number of patients unable to afford the targeted drugs. In addition, the present study was mainly to observe the efficacy of combined irinotecan in the second-line chemotherapy regimen of mCRC after replacing conventional fluorouracil with raltitrexed, and it was hard to determine whether the change in efficacy was due to the role of raltitrexed or targeted drugs if it was combined with targeted therapy. Therefore, the treatment regimen was determined to be irinotecan in combination with raltitrexed only.

In terms of dose selection, there was no consensuses about the standard recommended dose of irinotecan for the 3-week regimen in the Chinese population at the time of designing the study. It was necessary to ensure that raltitrexed was administered in accordance with the standard. A relatively safe dose of irinotecan was set for $180mg/m^2$ to reduce the risk of treatment interruption due to adverse events of the combination, which might affect the observation of the study.

Enrolled patients were treated with irinotecan plus raltitrexed as second-line treatment. Irinotecan was administered at the dose of $180mg/m^2$ in 250 ml of N/S in 90 min. After Irinotecan administered, raltitrexed was administered at the dose of $3mg/m^2$ in 100 ml of N/S in 15 min on day 1 each 21-day cycle. The efficacy was evaluated after every second cycle. The treatment would be discontinued in the event of progressive disease (PD), unacceptable adverse events, conversion surgery, patient refusal of the treatment, or by physician's decision.

### Sample size

The sample size was calculated by the median PFS of the main index, with reference to the historical data of previous studies on mCRC, the second-line median PFS of FOLFIRI was around 3.3 months(100 days), assuming that the median PFS of the experimental group was 4.5 months, in accordance with the design of superiority of the control historical data, the test efficacy of $1-\beta=0.8$, $\alpha=0.05$. The statistical analysis was performed using the One-Sample Log-rank Tests two-sided test with a sample size calculated to be 90 cases, requiring a sample size of 100 cases to take into account the 10% shedding rate.

### Statistical analysis

SPSS 26.0 software was used to analyze all data in this study. Categorical variables were calculated as percentage. The PFS and OS were calculated by using the Kaplan–Meier method. $P<0.05$ was considered as statistically significant for all tests.

## Results

### Patient characteristics and treatment

Between September 2016 and May 2020, a total of 108 patients were enrolled in this trial, received 502 cycles of chemotherapy, with an average of 4.6 cycles and a median

of 4 cycles. Their demographic and clinical data are summarized in Table 1. 72 men and 36 women were comprised with a median age of 61 years (range 38–79 years). ECOG PS was 0 in 32 patients, 1 in 77 patients. Liver was the most common site of metastasis in 71 (65.7%) patients, whereas lung and Peritoneal were involved in 48 (44.4%) and 17 (15.7%) patients.

### Efficacy

The median follow-up period was 27 months (range:3.1–61.0 m) after the last follow-up in March 2023. The ORR and the DCR were 17.6% and 76.9%. The median PFS was 4.9 months (95% CI 4.1–5.7) (Fig. 1). The median OS was 13.1 months (95% CI 12.2–15.5) (Fig. 2). Kaplan-Meier survival curves were plotted.

### Safety

The AEs are summarized in Table 2. The most common adverse reactions were mainly liver function damage, bone marrow suppression, diarrhea and fatigue. Among all AEs, the highest incidence was AST elevation (47.2%), ALT elevation (44.4%), and GGT elevation (36.1%), followed by diarrhea (31.5%), hemoglobin reduction (30.6%), thrombocytopenia (24.1%),leucopenia(24.1%) and fatigue(24.1%). Most of the adverse events were grade I/II, and could be relieved after symptomatic treatment. There was no need to stop treatment and no treatment-related death. The patients included 13 cases of abnormal electrocardiogram before treatment, but this decreased to nine cases after treatment (Table 3).

**Table 1** Baseline demographic and clinical characteristics of patients

| Variable | | No. of Patients (%) |
|---|---|---|
| Age | Median (Range) | 61 ( 38–79 ) |
| | < 60 | 48(44.4%) |
| | >=60 | 60(55.6%) |
| Gender | Male | 72(66.7%) |
| | Female | 36(33.3%) |
| Performance status (ECOG) | 0 | 32(29.6%) |
| | 1 | 76(70.4%) |
| Primary tumor site | Rectum | 54(50.0%) |
| | colon | 54(50.0%) |
| Left/right colon | Left colon | 83(76.9%) |
| | Right colon | 25(23.1%) |
| Metastatic sites | Liver | 71(65.7%) |
| | Lung | 48(44.4%) |
| | Peritoneal | 17(15.7%) |
| | pelvic cavity | 13(12.0%) |
| | Bone | 5(4.6%) |
| | Lymph nodes | 3(2.8%) |
| | Adrenal gland | 4(3.7%) |
| | stomach | 2(1.9%) |
| | Ovary | 2(1.9%) |
| | Others | 6(5.6%) |
| Primary tumor resected | Yes | 86(79.6%) |
| | No | 22(20.4%) |
| Previous adjuvant chemotherapy | Yes | 72(66.7%) |
| | No | 36(33.3%) |
| first-line regimen | FOLFOX | 27(25.0%) |
| | XELOX | 75(69.4%) |
| | SOX | 3(2.8%) |
| | Others | 3(2.8%) |

### Subgroup analysis

#### *Single factor survival analysis*

A log-rank test was conducted on all variables, and for the PFS endpoint, there was no statistically significant difference in all variables; For the OS endpoint, there was no statistically significant difference in all variables, except for the statistically significant difference in the cumulative number of organs in the metastatic lesion (Table 4).

#### *Multifactor survival analysis*

The variables were gradually screened using AIC, and for the PFS endpoint, the final included variables were gender, ECOG score, left/right colon, number of primary and metastatic lesions. Among them, male gender was a risk factor (HR=1.47, $P$=0.085), and the difference was not statistically significant; an ECOG score of 1 is a risk factor (HR=1.60, $P$=0.035); the primary lesion in the right colon was a risk factor (HR=1.72, $P$=0.053), and the difference was not statistically significant; the primary lesion being in the colon was a protective factor (HR=0.55, $P$=0.012), while any cumulative number of organs in the metastatic lesion greater than two was a risk factor (HR=1.62, $P$=0.080), and the difference was not statistically significant (Table 5).

The variables were gradually screened using AIC, and for the OS endpoint, the final included variables were gender, ECOG score, and number of metastatic lesions. Among them, male gender was a risk factor (HR=1.46, $P$=0.063), and the difference was not statistically significant; an ECOG score of 1 is a risk factor (HR=1.40, $P$=0.137), and the difference was not statistically significant; a cumulative number of organs in metastatic lesions greater than two is a risk factor (HR=2.57, $P$=0.001) (Table 6).

## Discussion

In this study, the clinical outcomes of administration of raltitrexed and irinotecan for treating patients with unresectable recurrent CRC were evaluated. The results indicated that chemotherapy of raltitrexed and irinotecan resulted in good ORR, DCR, PFS, and OS, and the toxicity rate was within an acceptable range. The ORR and the DCR were 17.6% and 76.9%. The median PFS was

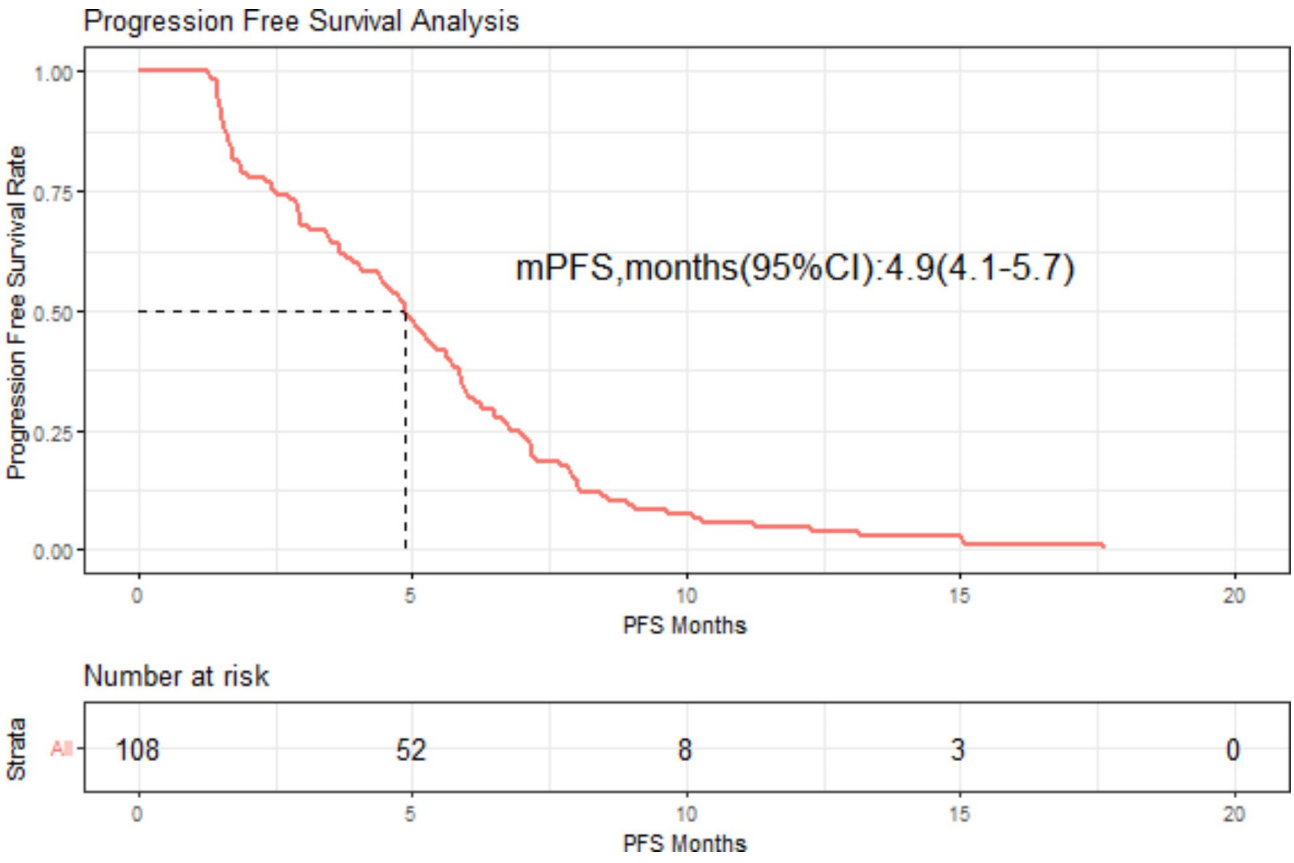


**Fig. 1** Kaplan–Meier curve for progression-free survival (PFS, months)

4.9 months and the median OS was 13.1 months, which achieved the statistical predefined results. The results were comparable to, or better than, those in previous studies which have shown that FOLFIRI as a second-line chemotherapy for mCRC has reported PFS ranging from 2 to 5.1 months, OS ranging from 8 to 15 months, and DCRs ranging from 20–61% [20, 21]. The finding implied that there is no cross resistance between raltitrexed and 5-FU; in univariate survival analysis and multivariate survival analysis, there was no statistically significant difference in all variables for the PFS endpoint, there was no statistically significant difference in all variables, except for the statistically significant difference in the cumulative number of organs in the metastatic lesion for the OS endpoint. This indicates that the efficacy of irinotecan plus raltitrexed chemotherapy regimen is unaffected by factors such as primary site, first-line chemotherapy, and primary tumor resection, or not.

The primary contraindications of 5-FU are dihydropyrimidine dehydrogenase (DPD) deficiency and severe cardiovascular comorbidities [22]. Some studies have reported that partial or complete lack of DPD activity can lead to severe or even fatal 5-FU toxicity [23, 24]. Raltitrexed is a DPD enzyme-independent drug, so raltitrexed may be considered in patients with DPD deficiency of mCRC who are particularly predisposed to develop severe adverse events associated with 5-FU. The cardiotoxicity caused by 5-FU is becoming increasingly prominent as the duration of medication increases. ARCTIC study reviewed and analyzed 42 CRC patients who switched from 5-FU cardiotoxicity to raltitrexed (single drug or combined chemotherapy). After repeated administration of fluorouracil drugs, the recurrence rate of cardiotoxicity was still 20% even after preventive anti angina treatment, while the replacement therapy of raltitrexed had no cardiotoxicity [25]. Therefore, the earlier version of the guidelines of ESMO recommend that raltitrexed can be used as an alternative treatment for patients with fluorouracil cardiotoxic intestinal cancer in the past [26]. In our study, the enrolled patients had good cardiac tolerance, including patients with baseline electrocardiogram abnormalities, and did not experience any suspension or extension of chemotherapy interval due to cardiac risk issues. In our study, the most common adverse reactions were mainly liver function damage, bone marrow suppression, diarrhea, and fatigue. The highest incidence was AST elevation (47.2%), ALT elevation (44.4%), and GGT elevation (36.1%). The toxicities seemed to be manageable and no grade 4 TAEs were observed and no treatment-related deaths occurred. Xie et al. reported that the

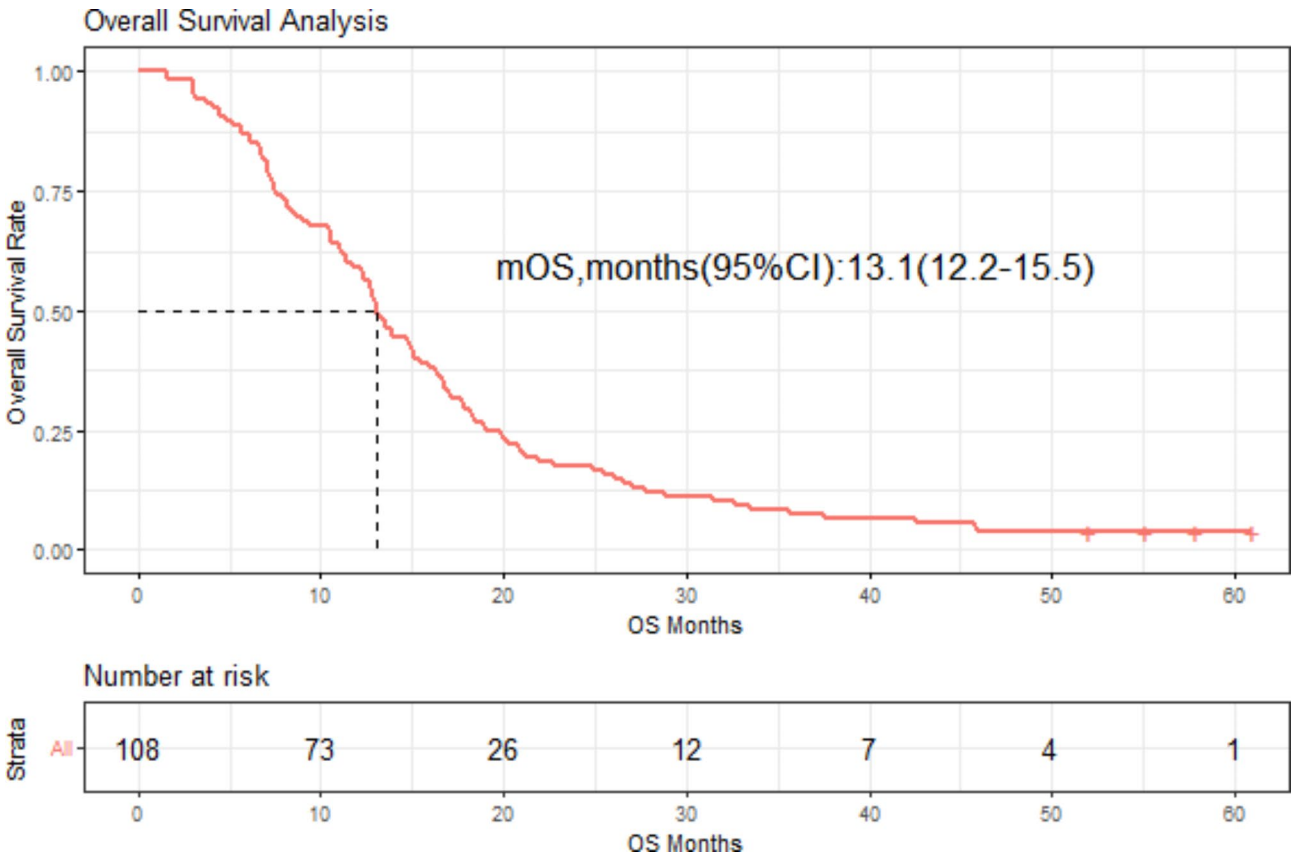


**Fig. 2** Kaplan–Meier curve for overall survival (OS, months)

**Table 2** Treatment-related adverse events

| | AE(*N* = 108) | grade I (%) | grade II(%) | grade III(%) | grade IV(%) | All grades(%) |
|---|---|---|---|---|---|---|
| Hematological toxicity | Leucopenia | 20(18.5%) | 4(3.7%) | 2(1.9%) | 0(0.0%) | 26(24.1%) |
| | Decreased hemoglobin | 25(23.1%) | 5(4.6%) | 3(2.8%) | 0(0.0%) | 33(30.6%) |
| | Neutropenia | 14(13.0%) | 3(2.8%) | 5(4.6%) | 0(0.0%) | 22(20.4%) |
| | Thrombocytopenia | 22(20.4%) | 1(0.9%) | 3(2.8%) | 0(0.0%) | 26(24.1%) |
| Liver function damage | TBiL increased | 8(7.4%) | 2(1.9%) | 2(1.9%) | 0(0.0%) | 12(11.1%) |
| | GGT increased | 16(14.8%) | 13(12.0%) | 10(9.3%) | 0(0.0%) | 39(36.1%) |
| | ALT increased | 36(33.3%) | 7(6.5%) | 5(4.6%) | 0(0.0%) | 48(44.4%) |
| | AST increased | 43(39.8%) | 5(4.6%) | 3(2.8%) | 0(0.0%) | 51(47.2%) |
| Gastrointestinal system damage | Anorexia | 5(4.6%) | 1(0.9%) | 0(0.0%) | 0(0.0%) | 6(5.6%) |
| | Nausea | 20(18.5%) | 0(0.0%) | 1(0.9%) | 0(0.0%) | 21(19.4%) |
| | Vomiting | 15(13.9%) | 0(0.0%) | 2(1.9%) | 0(0.0%) | 17(15.7%) |
| | Diarrhea | 23(21.3%) | 3(2.8%) | 8(7.4%) | 0(0.0%) | 34(31.5%) |
| | Bellyache | 9(8.3%) | 6(5.6%) | 0(0.0%) | 0(0.0%) | 15(13.9%) |
| | Mucositis/stomatitis | 2(1.9%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 2(1.9%) |
| others | Alopecia | 4(3.7%) | 1(0.9%) | 0(0.0%) | 0(0.0%) | 5(4.6%) |
| | Hand-foot syndrome | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) |
| | Fever | 7(6.5%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 7(6.5%) |
| | Fatigue | 19(17.6%) | 3(2.8%) | 4(3.7%) | 0(0.0%) | 26(24.1%) |

total incidence rates of Grade 3 and 4 AEs were 52.6% for the patients in FOLFIRI arm [20]. Yuguo et al. reported that rates of incidence of Grade 3 and 4 AEs in the WT KRAS patients of FOLFIRI alone group were 60% and in the MU KRAS patients in the FOLFIRI-alone group were 56%[21]. They all exhibited, as the most commonly occurring side-effect, skin toxicity. Not only did Kei Muro et al. reported a treatment-related death from hypotension

**Table 3** Abnormal changes in electrocardiogram data

| Types of electrocardiogram abnormalities | Abnormal T Waves | Conduction block | ST segment change | premature beat |
|---|---|---|---|---|
| Before treatment | 5 | 3 | 2 | 3 |
| After treatment | 3 | 2 | 2 | 2 |

**Table 4** Single factor survival analysis: log-rank test results (PFS and OS)

| Items | Log-rank test *P* value(PFS) | Log-rank test *P* value(OS) |
|---|---|---|
| Age | | |
| ≥60 | 0.900 | 0.070 |
| <60 | | |
| Gender | | |
| Male | 0.200 | 0.300 |
| Female | | |
| ECOG PS | | |
| 1 | 0.200 | 0.100 |
| 0 | | |
| Primary tumor resected | | |
| Yes | 1.000 | 0.600 |
| No | | |
| Primary tumor site | | |
| Rectum | 0.060 | 0.900 |
| colon | | |
| Left/right colon | | |
| Left colon | 0.800 | 0.800 |
| Right colon | | |
| cumulative number of Metastatic sites | | |
| >2 | 0.500 | 0.002 |
| ≤2 | | |
| Previous adjuvant chemotherapy | | |
| Yes | 0.600 | 0.400 |
| No | | |
| First-line chemotherapy | | |
| FOLFOX | 0.82 | 0.51 |
| XELOX/CAPOX/SOX | | |

**Table 6** Multifactor survival analysis: Cox regression, AIC stepwise screening results (OS)

| Items | HR(95%CI) | P值 |
|---|---|---|
| Gender | | |
| Female | Ref | 0.063 |
| Male | 1.46(0.98,2.18) | |
| ECOG PS | | |
| 0 | Ref | 0.137 |
| 1 | 1.40(0.90,2.17) | |
| cumulative number of Metastatic sites | | |
| ≤2 | Ref | 0.001 |
| >2 | 2.57(1.50,4.43) | |

**Table 5** Multifactor survival analysis: Cox regression, AIC stepwise screening results (PFS)

| Items | HR(95%CI) | *P* value |
|---|---|---|
| Gender | | |
| Female | Ref | 0.085 |
| Male | 1.47(0.95,2.29) | |
| ECOG PS | | |
| 0 | Ref | 0.035 |
| 1 | 1.60(1.03,2.47) | |
| Left/right colon | | |
| Left colon | Ref | 0.053 |
| Right colon | 1.72(0.99,2.97) | |
| Primary tumor site | | |
| Rectum | Ref | 0.012 |
| colon | 0.55(0.34,0.87) | |
| cumulative number of Metastatic sites | | |
| ≤2 | Ref | 0.080 |
| >2 | 1.62(0.94,2.77) | |

due to shock was reported in the FOLFIRI group within 28 days after the end of treatment [21]. Rui-Hua Xu et al. reported that there was one treatment-related death (lung infection) in the FOLFIRI group [27]. In contrast, our study showed milder adverse reactions. After follow-up, more than 90% of patients have received third-line or higher treatment, increasing the likelihood of prolonged survival for patients.

Raltitrexed, a direct thymidylate synthase inhibitor presenting different anticancer mechanism from that of 5-fluorouracil, has been proved promising an efficacy, favorable toxicity profile, and convenient administration schedule in patients with 5-FU–refractory conditions [28, 29]. Furthermore, the administration of FOLFIRI regimen requires a central venous catheter and continuous infusion of 5-FU for a long time, which is inconvenient for patients and reduces their quality of life. Raltitrexed can be administered intravenously for 15 min, greatly increasing its convenience. Nevertheless, there were several limitations of the study. It was difficult to compare efficacy and toxicity with standard second-line regimens such as FOLFIRI directly as a single-arm trial without a comparative group, and there were no standard targeted agents added to this combination which might limit the generalisability of the findings to a wider patient population. In addition, due to COVID-19 outbreak, although enrolment was completed in 2020, scientific follow-up and other work was delayed, final data collation and statistics were completed in 2023 after the end of the outbreak in China. Future research directions could explore combining raltitrexed with novel targeted therapies or immunotherapies in comparison to conventional chemotherapy combined with targeted therapy regimens to potentially enhance treatment outcomes, which worth a phase III study for further confirmation.

## Conclusions

In summary, the combination of raltitrexed and irinotecan as second-line treatment for mCRC could be a reliable option after failure of standard 5-Fu-first-line chemotherapy in mCRC, especially for patients refractory to or intolerant of 5-FU (patients with cardiac events or DPD deficiency).

### Abbreviations

| | |
|---|---|
| CRC | Colorectal cancer |
| PFS | Progression-free survival |
| OS | Overall survival |
| ORR | Objective response rate |
| DCR | Disease control rate |
| PD | Progressive disease |
| CI | Confidence interval |
| HR | Hazard ratio |
| 5-FU | 5-fluorouracil |
| DPD | Dihydropyrimidine dehydrogenase |
| FOLFIRI | Irinotecan combined 5-fluorouracil |
| FOLFOX | Oxaliplatin combined 5-fluorouracil |
| RALOX | Oxaliplatin combined with raltitrexed |
| RALIRI | Irinotecan combined with raltitrexed |
| XELOX | Oxaliplatin combined with capecitabine |
| SOX | Oxaliplatin combined with tegafur |
| ECOG | Eastern Cooperative Oncology Group |

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### Author contributions

Concept and design—Jinglei Qu, Xiujuan Qu, Yunpeng LiuSubject enrollment and data accrual—Yu Cheng, Zan Teng, Yanqiao Zhang, Bo Jin, Zhendong Zheng, Li Man, Zhenghua Wang, Yuee Teng, Ping Yu, Jing Shi, Ying Luo, Ying Wang, Jingdong Zhang, Huijuan Zhang, Jiwei Liu, Hao Chen, Jiawen Xiao, Lei Zhao, Lingyun Zhang, Yu Jiang, Ying Chen, Jian Zhang, Chang Wang, Sa LiuDrafting of manuscript—Yu Cheng, Zan TengStatistical analysis—Yu Cheng, Zan Teng Final approval of manuscript—all authors.

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### Data availability

The data that support the findings of this study are available upon from (Yunpeng Liu, ypliu@cmu.edu.cn) upon reasonable request and granting of permission from the journal's Editorial office.

## Declarations

### Ethics approval and consent to participate

This clinical study was approved by Committee of Clinical Trials of The First Hospital of China Medical University. Informed consent was obtained from all subjects and/or their legal guardian(s). The study was performed in accordance with the Declaration of Helsinki.

### Consent for publication

Not Applicable.

### Competing interests

The authors declare no competing interests.

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