Regorafenib with or without chemotherapy/immunotherapy in second-line treatment of metastatic colorectal cancer during the COVID-19 pandemic: a single-center retrospective analysis

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Background: Regorafenib, approved in China for the third-line treatment of patients with metastatic colorectal cancer (mCRC), targets multiple tyrosine kinases. We retrospectively evaluated the efficacy and safety of regorafenib, both as monotherapy and in combination with capecitabine or immune checkpoint inhibitors (ICIs), as a second-line treatment for patients unable to access hospital-based care due to limited hospital visits during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Retrospective analysis was conducted on individual patient data from Peking University Third Hospital, covering the period from January 2020 to September 2023. The primary endpoint was progression-free survival (PFS), with secondary endpoints including overall survival (OS) and safety.

Results: The study comprised 31 patients with a median age of 65 years. The median PFS (mPFS) was 6.0 months, while the median OS (mOS) was 20.0 months. Compared to those treated with regorafenib alone, patients treated with regorafenib plus capecitabine/ICIs tended to have a longer PFS (8.0 *vs.* 4.0 months) and OS (27.0 *vs.* 15.0 months). Liver metastases [hazard ratio (HR) =2.515, 95% confidence interval (CI): 1.037–6.100; P=0.04] and prior bevacizumab treatment (HR =2.613, 95% CI: 1.168–5.846; P=0.02) were identified as independent prognostic factors for PFS. Frequent grade 3/4 adverse drug reactions (ADRs) included hand-foot skin reactions (HFSRs), fatigue, hypertension, and proteinuria.

Conclusions: This single-center, retrospective study indicates that regorafenib, alone or combined with chemotherapy/immunotherapy, is a feasible and safe second-line treatment for mCRC for situations where hospital access is limited, such as during the COVID-19 pandemic. Additional prospective studies are required to investigate the advantages of combination therapies.

Keywords: Metastatic colorectal cancer (mCRC); regorafenib; second-line treatment; coronavirus disease 2019 pandemic (COVID-19 pandemic); combination therapy

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Introduction

In 2022, colorectal cancer (CRC) ranked as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide (1). In China, CRC ranks second in incidence and fourth in mortality, with approximately 517,000 new cases and 240,000 deaths each year (2). The current standard treatments for CRC in both first and second line include a combination of fluoropyrimidines with either oxaliplatin or irinotecan, supplemented by bevacizumab or cetuximab (3). Metastatic colorectal cancer (mCRC) presents a significant treatment challenge, with limited effective options for patients who progress after front-line therapy (4). For third-line treatment, regorafenib, fruquintinib, and trifluridine-tipiracil (TAS-102), with or without bevacizumab, are recommended (3,4).

The phase III CORRECT trial evaluated regorafenib, a small-molecule inhibitor of multiple kinases involved in tumor growth and angiogenesis, in pretreated mCRC patients (5-8). This trial randomized 760 patients with progressive disease on standard therapy to receive either

best supportive care with placebo or regorafenib. The trial met its primary endpoint, yielding an overall survival (OS) of 6.4 months for regorafenib and of 5.0 months for placebo [hazard ratio (HR) =0.77, 95% confidence interval (CI) 0.64–0.94; P=0.005] and also demonstrated a modest improvement in progression-free survival (PFS) (9-11). Similarly, the CONCUR trial in Asia (12) as well as other studies (13-15) showed that regorafenib prolonged OS compared to placebo in patients with mCRC who have experienced disease progression following standard therapies.

Despite the well-defined efficacy in further lines of therapy, the role of regorafenib as a second-line treatment remains to be fully determined. In this context, the STREAM trial, an academic, multicenter, single-arm, Italian phase II study (16), revealed that regorafenib monotherapy, when used as a second-line treatment for rat sarcoma viral oncogene homolog (RAS)-mutant advanced colorectal cancer, exhibited an objective response rate (ORR) of 10.9% with a disease control rate (DCR) of 54.6% and a median PFS (mPFS) of 3.6 months and median OS (mOS) of 18.9 months. Although the study did not achieve its primary endpoint, the results are clinically meaningful, particularly in those patients or in those situations where a reduction in the number of hospital admissions is required.

A similar scenario involved the coronavirus disease 2019 (COVID-19) pandemic which profoundly impacted healthcare delivery worldwide, limiting patients' ability to access regular hospital-based chemotherapies (17). This situation highlighted the need for oral therapies that can be administered at home, reducing hospital visits and the associated risk of COVID-19 exposure. Regorafenib, with its oral administration and broad antitumor activity, offers a promising alternative to traditional intravenous chemotherapies (13). Moreover, combining regorafenib, a multi-kinase inhibitor also targeting the vascular endothelial growth factor receptors (VEGFR)1–3 (5), with capecitabine, a fluoropyrimidine cytotoxic drug, sounds like using other combinations, including 5-fluorouracil/capecitabine with the antiangiogenic bevacizumab that have been widely explored in AVEX (18) and AVF2107g trials (19). Besides, studies like REGONIVO have shown encouraging results for regorafenib combined with anti-programmed death 1 (PD-1) antibody in later-line treatments, suggesting the potential of this combination for enhanced therapeutic efficacy (20). Due to the relatively short infusion times, immune checkpoint inhibitors (ICIs) like anti-PD-1 antibodies can be administered conveniently in outpatient clinics or community health settings, making

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Highlight box

Key findings

• This single-center retrospective study shows that regorafenib, alone or combined with capecitabine or immune checkpoint inhibitors (ICIs), is a feasible and safe second-line treatment option for patients with metastatic colorectal cancer (mCRC) during the coronavirus disease 2019 (COVID-19) pandemic. Patients receiving combination therapy had improved progression-free survival and overall survival compared to those treated with regorafenib monotherapy.

What is known and what is new?

• It is known that regorafenib is effective as a third-line treatment for mCRC.

• This study offers new insights into the potential benefits of using regorafenib as a second-line treatment, particularly when combined with capecitabine or ICIs, in events such as the COVID-19 pandemic.

What is the implication, and what should change now?

• The findings suggest that regorafenib, especially in combination with other therapies, could be an important second-line option for patients with mCRC, particularly when intravenous chemotherapy is not feasible.

• Further prospective studies are needed to confirm these findings and guide optimal treatment strategies for mCRC in the context of limited hospital access.

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them accessible even under pandemic constraints. This study evaluated the efficacy and safety of regorafenib, alone or combined with capecitabine or ICIs, as a second-line treatment for patients with mCRC during the COVID-19 pandemic. Although the COVID-19 pandemic has ended, challenges such as minimizing hospital visits and addressing barriers to care for mCRC patients remain highly relevant. Oral therapeutic regimens like regorafenib offer a convenient alternative to intravenous chemotherapy, reducing logistical burdens and psychological stresses for patients. This study aims to explore the potential of regorafenib, alone or combined with capecitabine or ICIs, as a second-line treatment to address these unmet needs and inform future clinical strategies. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-891/rc).

Methods

Study design

This retrospective study included patients with mCRC treated at Peking University Third Hospital between January 2020 and September 2023. The eligibility criteria were histologically confirmed mCRC, progression after first-line treatment, and administration of regorafenib alone or in combination with capecitabine/anti-PD-1 antibodies (sintilimab or tislelizumab) as second-line therapy. Patients who could not regularly visit the hospital due to COVID-19 restrictions were included. Meanwhile, the exclusion criteria included patients with incomplete medical records or those who received other investigational drugs during the study period. Patients were followed up regularly through electronic medical records and scheduled clinical visits until death or the end of the study period.

Data collection

Data were obtained from electronic medical records, including baseline clinical factors such as age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, metastatic sites, RAS/B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutation status, and prior treatment regimens. These factors were assessed to evaluate their potential impact on treatment outcomes. Treatment regimens, PFS, OS, and adverse drug reactions (ADRs)

were also collected. PFS was defined as the interval from regorafenib initiation to either disease progression or death. OS was defined as the duration from regorafenib initiation to death from any cause. ADRs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Ethical approval

This study adhered to the Declaration of Helsinki (as revised in 2013) and received approval from the Ethics Committee of Peking University Third Hospital (approval No. IRB00006761-M2023746). The Ethics Committee waived the requirement for informed consent given the retrospective design of the study. Patient data were anonymized for confidentiality.

Statistical analysis

Due to the retrospective nature of this study, no prior sample size estimation was performed. The sample size was determined based on the available patient population meeting the inclusion criteria during the study period from January 2020 to September 2023. Kaplan-Meier estimates were used to assess PFS and OS, with group differences evaluated via the log-rank test. Multivariate Cox regression analysis was performed to identify independent prognostic factors for PFS and OS. HRs and their 95% CIs were calculated. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 27 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The study included 31 patients with a median age of 65 years (range, 29–91 years), predominantly male, and with most having an ECOG performance status of 1. The metastatic sites were primarily in the liver, lungs, and peritoneum or abdominal cavity. Most patients had mutated RAS/BRAF V600E status and received chemotherapy combined with bevacizumab as their first-line regimen. For second-line treatment, regorafenib was administered as monotherapy or in combination with capecitabine or ICIs. Detailed baseline characteristics are summarized in *Table 1*.

Table 1 Basic characteristics

Characteristic	Value (n=31)
Age	
Median [range], years	65 [29–91]
<65 years, n (%)	14 (45.2)
≥65 years, n (%)	17 (54.8)
Sex, n (%)	
Male	18 (58.1)
Female	13 (41.9)
ECOG performance status, n (%)	
0	14 (45.2)
1	17 (54.8)
Metastatic sites, n (%)	
Liver	12 (38.7)
Lung	18 (58.1)
Peritoneum or abdominal cavity	11 (35.5)
RAS/BRAF V600E status, n (%)	
Mutated	20 (64.5)
Wild type	11 (35.5)
First-line regimen, n (%)	
Chemotherapy only	8 (25.8)
Chemotherapy plus bevacizumab	19 (61.3)
Chemotherapy plus cetuximab	4 (12.9)
Second-line regimen, n (%)	
Regorafenib only	19 (61.3)
Regorafenib plus chemotherapy	9 (29.0)
Regorafenib plus ICIs	3 (9.7)
Regorafenib maintenance dose, n (%)	
80 mg	24 (77.4)
120 mg	7 (22.6)

ECOG, Eastern Cooperative Oncology Group; RAS, rat sarcoma viral oncogene homolog; BRAF, B-Raf proto-oncogene, serine/threonine kinase; ICI, immune checkpoint inhibitor.

Treatment outcomes

The average follow-up time was 20.4 months (95% CI: 15.6–25.2). The mPFS for all patients was 6.0 months (95% CI: 3.6–8.4), and the mOS was 20.0 months (95% CI: 9.1–30.9) (*Figure 1A,1B*). Patients treated with regorafenib plus capecitabine or immunotherapy (combination therapy) tended to have a longer PFS compared to those treated with regorafenib alone, with an mPFS of 8.0 versus 4.0 months, respectively (P=0.31). Similarly, OS was longer in the combination therapy group than in the regorafenib-alone group, with an mOS of 27.0 versus 15.0 months, respectively (P=0.90) (*Figure 1C,1D*).

Subgroup analysis

Subgroup analysis was conducted to clarify the influence of various clinical and demographic factors on treatment outcomes (*Table 2*). Patients with liver metastases at the initiation of regorafenib therapy exhibited a trend toward shorter PFS and OS compared to those without liver metastases. The mPFS was 2.5 months for patients with liver metastases versus 7.0 months for those without (P=0.09). Similarly, the mOS was 13.0 months for patients with liver metastases, compared to 27.0 months for those without (P=0.22) (*Figure 2A,2B*).

The presence of RAS/BRAF V600E mutations was not significantly associated with PFS or OS. Patients with mutated RAS/BRAF had an mPFS of 4.0 months, while those with wild-type RAS/BRAF had an mPFS of 7.0 months (P=0.62) (*Figure 2C*). The mOS was 20.0 months in patients with mutated RAS/BRAF. However, the mOS for the wild-type RAS/BRAF group could not be calculated and was recorded as "not available" (NA) because fewer than half of the patients in this group had experienced mortality at the time of analysis. This observation suggests a potential survival advantage for the wild-type RAS/BRAF group compared to the mutated group (*Figure 2D*).

Patients with prior treatment with bevacizumab had significantly shorter PFS compared to those without prior bevacizumab treatment. The mPFS was 4.0 months in patients with prior bevacizumab compared to 9.0 months in those without (P=0.01) (*Figure 2E*). For OS, there was a trend toward shorter survival in patients with prior bevacizumab treatment (13.0 *vs.* 27.0 months), although this difference did not reach statistical significance (P=0.17) (*Figure 2F*).

Multivariate analysis

Multivariate analysis was performed to identify independent prognostic factors for PFS and OS. Liver metastases (HR =2.515, 95% CI: 1.037–6.100; P=0.04) and prior treatment with bevacizumab (HR =2.613, 95% CI: 1.168–5.846;
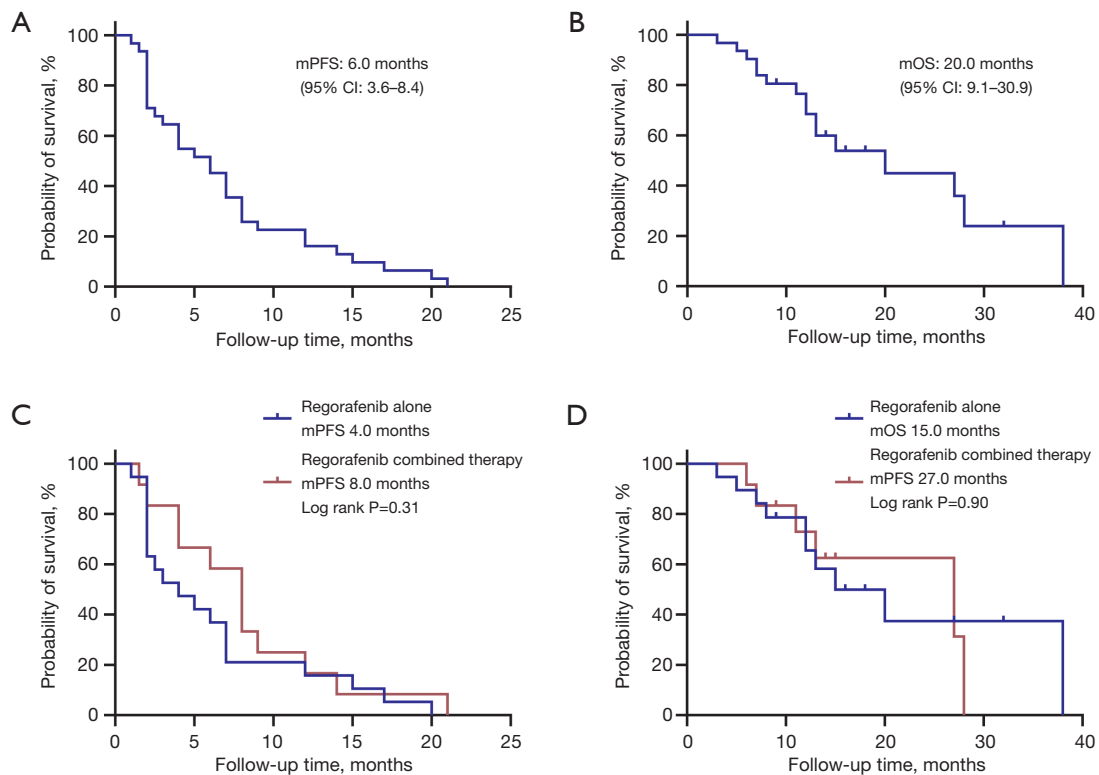
Figure 1 Kaplan-Meier curves for the overall patient population. (A) PFS for all patients treated with regorafenib, with a mPFS of 6.0 months (95% CI: 3.6–8.4). (B) OS for all patients treated with regorafenib, with an mOS of 20.0 months (95% CI: 9.1–30.9). (C) Comparison of PFS between patients treated with regorafenib alone (blue line, mPFS 4.0 months) and those treated with regorafenib combined therapy (red line, mPFS 8.0 months; P=0.31). (D) Comparison of OS between patients treated with regorafenib alone (blue line, mOS 15.0 months) and those treated with regorafenib combined therapy (red line, mOS 27.0 months; P=0.90). PFS, progression-free survival; mPFS, median PFS; OS, overall survival; mOS, median OS; CI, confidence interval.

P=0.02) were identified as independent prognostic factors for PFS in the second-line treatment. No factors were identified as independent prognostic factors for OS in the second-line setting. These findings highlight the significant impact of these factors on the prognosis of patients with mCRC receiving regorafenib.

Safety

ADRs were common but generally manageable. The most common grade 3/4 ADRs included hand-foot skin reactions (HFSRs), fatigue, hypertension, and proteinuria. Specifically, the incidence of grade 3/4 ADRs was as follows: HFSRs, 19.4%; fatigue, 16.1%; hypertension, 12.9%; and proteinuria, 9.6%. Due to the retrospective nature of this real-world study, most grade 1–2 ADRs, which are typically tolerable, were not systematically documented in the

medical records. Instead, documentation primarily focused on grade 3–4 ADRs, as these are more likely to result in dose modifications or treatment discontinuation. Three patients discontinued treatment due to ADRs, underscoring the need for careful monitoring and management of these side effects (*Table 3*).

Discussion

The COVID-19 pandemic raised the issue of quickly adapting oncological treatment protocols due to the need to drastically reduce the number of hospital admissions. The availability of oral medications and easily manageable combination therapies at home therefore represents an important unmet need in the treatment of patients with mCRC. The findings of this retrospective analysis suggest that regorafenib, particularly when combined with

Table 2 Subgroup analysis with the log-rank test

Subgroup	PFS		OS	
	Median survival, months	P value	Median survival, months	P value
Age		0.50		0.19
<65 years	7.0		28.0	
≥65 years	4.0		15.0	
Sex		0.98		0.37
Male	4.0		27.0	
Female	6.0		20.0	
ECOG performance status		0.42		0.93
0	4.0		28.0	
1	6.0		20.0	
Liver metastasis		0.09		0.22
With	2.5		13.0	
Without	7.0		27.0	
RAS/BRAF V600E status		0.62		0.33
Mutated	4.0		20.0	
Wild type	7.0		NA	
Prior treatment		0.01		0.17
With bevacizumab	4.0		13.0	
Without bevacizumab	9.0		27.0	
Second-line regimen		0.31		0.90
Regorafenib only	4.0		15.0	
Regorafenib combined therapy	8.0		27.0	
Regorafenib maintenance dose		0.95		0.67
80 mg	6.0		20.0	
120 mg	5.0		15.0	

PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; RAS, rat sarcoma viral oncogene homolog; BRAF, B-Raf proto-oncogene, serine/threonine kinase; NA, not available.

capecitabine, offered a viable second-line oral treatment option for patients with mCRC during the COVID-19 pandemic. This study also includes a small subset of patients treated with regorafenib combined with ICIs, given the relatively short infusion time that make ICIs feasible for outpatient or community-based administration. The observed mPFS of 6 months and OS of 20 months in the entire cohort are consistent with previously reported outcomes for regorafenib in patients with mCRC (16,21). Despite the lack of statistical significance in PFS and OS

improvements with combination therapy (P=0.31 and P=0.90, respectively), the indication of potential benefit merits further research.

Previous studies have established regorafenib as an effective third-line treatment for mCRC in heavily pretreated populations (9,10,12). The CORRECT trial, a pivotal phase III study, reported an mPFS of 1.9 months and an OS of 6.4 months in patients receiving regorafenib compared to placebo (9). The CONCUR trial, which included Asian patients, also demonstrated a similar
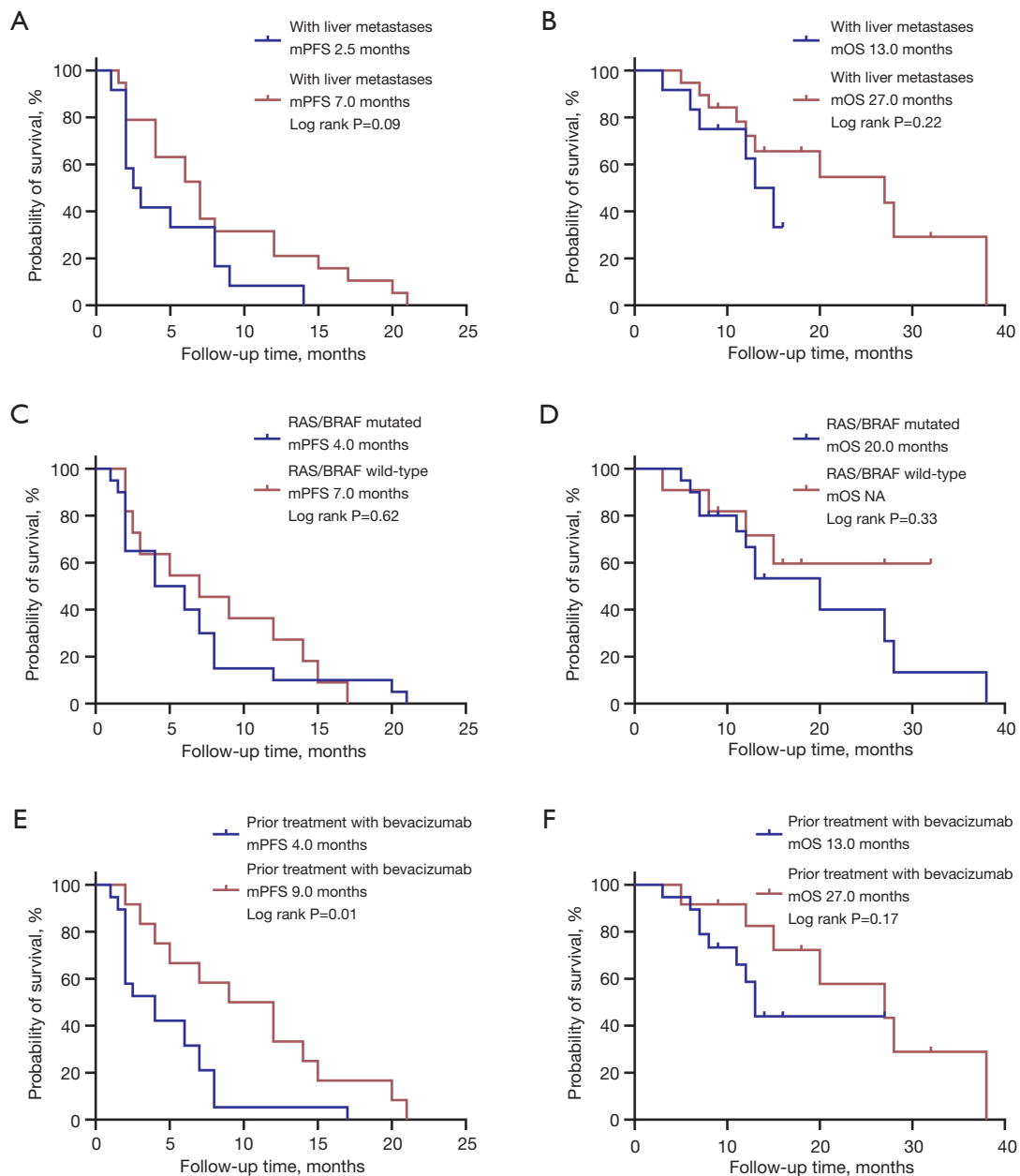
Figure 2 Subgroup analysis of PFS and OS. (A) PFS comparison between patients with liver metastasis (blue line, mPFS 2.5 months) and those without liver metastasis (red line, mPFS 7.0 months; P=0.09). (B) OS comparison between patients with liver metastasis (blue line, mOS 13.0 months) and those without liver metastasis (red line, mOS 27.0 months; P=0.22). (C) PFS comparison between patients with mutated RAS/BRAF (blue line, mPFS 4.0 months) and those with wild-type RAS/BRAF (red line, mPFS 7.0 months; P=0.62). (D) OS comparison between patients with mutated RAS/BRAF (blue line, mOS 20.0 months) and those with wild-type RAS/BRAF (red line, mOS NA; P=0.33). (E) PFS comparison between patients with prior treatment with bevacizumab (blue line, mPFS 4.0 months) and those without prior bevacizumab treatment (red line, mPFS 9.0 months; P=0.01). (F) OS comparison between patients with prior treatment with bevacizumab (blue line, mOS 13.0 months) and those without prior bevacizumab treatment (red line, mOS 27.0 months; P=0.17). PFS, progression-free survival; OS, overall survival; mPFS, median PFS; mOS, median OS; NA, not available.

Table 3 The incidence of grade 3/4 treatment-related adverse events

Adverse event	Grade 3/4 adverse event, n (%)
Hand-foot skin reactions	6 (19.4)
Fatigue	5 (16.1)
Hypertension	4 (12.9)
Proteinuria	3 (9.7)

efficacy profile, with an mPFS of 3.2 months and an OS of 8.8 months (12). In contrast, our study, which examined second-line treatment with regorafenib alone or combined with capecitabine/ICIs, observed a mPFS of 6 months and an mOS of 20 months, indicating a potential benefit when used earlier in the treatment continuum. However, unlike the prospective STREAM trial (16) evaluating regorafenib second-line monotherapy in RAS-mutant mCRC patients pretreated with oxaliplatin, fluoropyrimidines and bevacizumab, our study was a retrospective analysis without restrictions on RAS status or kind of first-line treatment protocol. This key methodological difference should be considered when comparing outcomes, despite similarities in PFS and OS data between the two studies. Our findings were within context of a real-world setting during the COVID-19 pandemic, highlighting the feasibility and safety of regorafenib in combination with other therapeutic modalities in a second-line context.

Several studies have evaluated the efficacy and safety of combining regorafenib with cytotoxic agents. For example, a multicenter phase II study evaluated regorafenib combined with FOLFIRI as second-line therapy, and revealed a mPFS of 6.1 months compared to 5.3 months with FOLFIRI alone, suggesting that regorafenib's efficacy could be enhanced in combination with chemotherapy (22). Furthermore, a network meta-analysis comparing regorafenib in combination with various chemotherapy agents suggests that regorafenib may perform better in terms of PFS than some other biological agents such as aflibercept and panitumumab, albeit with manageable adverse events (21). Globally, these studies and our single center experience claim the potential benefits of combining regorafenib with traditional cytotoxic agents, though larger, randomized studies are necessary to validate these findings across different combinations. Our study, however, mainly focuses on the combination of regorafenib with capecitabine, an approach that remains underexplored in the literature.

The scarcity of data on this combination limits direct comparisons, yet highlighting the need for additional studies to fully understand its clinical utility in mCRC management. Given that both regorafenib and capecitabine are differently approved for CRC treatment, exploring their combined effect could provide a meaningful alternative for patients unable to access regular intravenous chemotherapy, as was necessary during the pandemic.

Administering regorafenib at home, in fact, offers significant advantages, particularly during pandemics or other situations where regular hospital visits are challenging (23). The ability to maintain effective cancer treatment while minimizing exposure to healthcare settings is crucial for vulnerable patient populations (24). Although infection rates, hospitalization rates, and COVID-related treatment delays were not analyzed due to the study's retrospective nature, the observations in our study suggest that combining regorafenib with capecitabine or ICIs may enhance treatment efficacy without significantly increasing toxicity, making it a promising approach for mCRC management especially under pandemic constraints (25-29). The safety profile of regorafenib observed in our study aligns previously reported adverse effects (13,29-31), with HFSR, fatigue, hypertension, and proteinuria being the most common. The incidence of grade 3/4 ADRs was manageable, leading to treatment discontinuation in only three patients, indicating that regorafenib is generally well-tolerated when administered in a real-world setting. Due to the small sample size, a sub-group analysis for safety exploring the association with capecitabine or ICIs was not possible. The retrospective nature of this study resulted in limited documentation of grade 1–2 ADRs, which are generally tolerable and less likely to lead to treatment modifications. Instead, the focus was on grade 3–4 ADRs, which are clinically significant and more likely to require intervention. While this approach aligns with routine clinical practice, it limits the ability to fully assess the overall safety profile of regorafenib-based therapies. Future studies should aim to comprehensively capture data on all grades of ADRs to provide a more complete understanding of the safety of regorafenib in combination with other therapies.

Subgroup analysis revealed that patients with liver metastases at the initiation of regorafenib therapy showed a trend toward worse outcomes compared to those without liver metastases. Presence of liver metastases was identified as an independent predictor of PFS in the multivariate analysis. This finding underscores the aggressive nature of liver metastases in mCRC (32) and highlights the need

for tailored therapeutic strategies for this subgroup of patients. Future studies with larger sample sizes are needed to confirm the impact of liver metastases on treatment outcomes.

Similarly, patients with prior treatment with bevacizumab also showed significantly poorer PFS compared to those without such treatment. For OS, a trend toward shorter survival was observed but did not reach statistical significance (P=0.17). The poorer outcomes in this subgroup may be attributed to the high *RAS/BRAF* mutation rate, which is known to confer resistance to certain therapies and is associated with a worse prognosis (33,34). This highlights the need for novel therapeutic approaches for patients with a history of bevacizumab treatment.

The main limitations of this study are its retrospective nature and the small sample size, which potentially affected the generalizability of the results. Additionally, the study did not account for all potential confounding factors, and the results should be interpreted with caution. Moreover, the COVID-19 pandemic itself might have adversely influenced treatment adherence and follow-up, further complicating the interpretation of results. Future prospective, randomized controlled trials are necessary to confirm these results and offer stronger evidence for the use of regorafenib combined with chemotherapy or immunotherapy as a second-line treatment for mCRC. Such studies should also explore the potential biomarkers that predict response to regorafenib and combination therapies, enhancing the personalization of treatment strategies. Additionally, long-term follow-up studies are required to evaluate the sustainability of responses and the long-term safety profile of regorafenib, particularly when used in combination with other agents. The ongoing impact of the COVID-19 pandemic on cancer treatment access and outcomes should continue to be monitored, with a focus on developing flexible and effective treatment strategies that can be administered with minimal hospital visits.

Conclusions

This single-center, retrospective study conducted under pandemic-specific conditions indicates that regorafenib, either as monotherapy or in combination with chemotherapy/immunotherapy, may be considered a safe and feasible second-line treatment option for mCRC in situations such as the COVID-19 pandemic. Prospective studies are warranted to explore the benefits of combination

therapies and to optimize treatment strategies for this patient population.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-891/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-891/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-891/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-891/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study adhered to the Declaration of Helsinki (as revised in 2013) and received approval from the Ethics Committee of Peking University Third Hospital (approval No. IRB00006761-M2023746). The Ethics Committee waived the requirement for informed consent given the retrospective design of the study.

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(English Language Editor: J. Gray)