

Article information: <https://dx.doi.org/10.21037/jgo-23-39>

Review Comments-reviewer A

- 1) First, the title needs to indicate the co-existence of mCRC and Hodgkin lymphoma.

Reply: Thanks for your advices, and we have added the co-existence of mCRC and Hodgkin lymphoma in the title (see page 1, line 3).

- 2) Second, the abstract is not adequate. The background is too simple, which did not briefly indicate the novelty, rarity and potential unique clinical contribution of this case, so it remains unclear whether this case deserves to be reported. The case presentation needs to report the first-line and second-line treatments' efficacy and safety outcomes and how the third-line treatment strategy was developed. Please also accurately describe the duration of follow up and PFS and OS status of this case. The current conclusion on "can potentially be used as a late-line therapy for mCRC" should be tone down since this is only a case report. The current case report only provided a possibility of success this third-line treatment but the findings are difficult to generalize to other similar patients.

Reply: Thanks for your advices. We have modified the abstract in our text as you advised (see page 2, line 55-64) and added the efficacy and safety outcomes of first-line and second-line treatments (see page 5-6, line 151, 176, 183). The conclusion had been toned down (see page 3, line 86-87)

- 3) Third, the introduction of the main text needs to have an extensive review on the available third-line treatments for mCRC, analyze the efficacy and safety outcomes of these treatments and their limitations, clearly indicate the clinical needs for new treatment strategies, and analyze the adjustment of the treatment strategy due to the co-existence of Hodgkin lymphoma. The authors need to describe the novelty, rarity, and potential unique clinical contribution of this case.

Reply: Thanks for your advices. We have added an extensive review on the available third-line treatments for mCRC in the introduction (see page 4, line 101-107). We have already analyzed the adjustment of the treatment strategy due to the co-existence of Hodgkin lymphoma (page 9, line 271-277) and the novelty, rarity, and potential unique clinical contribution of this case in the part of DISCUSSION (page 7, line 221-227).

- 4) Fourth, please report the follow up duration of this case and detailed data on the health status of this case until the submission of this paper such as PFS and OS.

Reply: Thanks for your advices. The last follow-up time is December 2022. The PFS of the third-line therapy is 38 months, and the OS has not yet reached. We have added the information in our text (see page 7, line 209-211).

- 5) Finally, please consider to cite the below related papers: 1. Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. *Transl Cancer Res* 2022;11(1):276-287. doi: 10.21037/tcr-20-3539. 2. Dai Y, Sun L, Zhuang L, Zhang M, Zou Y, Yuan X, Qiu H. Efficacy and safety of low-dose apatinib plus S-1 versus regorafenib and fruquintinib for refractory metastatic colorectal cancer: a retrospective cohort study. *J Gastrointest Oncol* 2022;13(2):722-731. doi: 10.21037/jgo-22-285.

Reply: Thanks for your advices. The related papers you advised are significant for our case, and we have added these references in the manuscript (see page 10-11, line 318, 340).

Review Comments-reviewer B

1. Highlight box:

- 1) Your Highlight box is too long. Please note that the highlight box should be **no more than 150 words**.

Reply: Thanks for your advices, and we have simplified the Highlight box as you advised (see page 2, line 36-49).

- 2) The below section should be divided into two points to report what is known and what is new. Please revise.

42 **What is known and what is new?** ↵

43 Patients with mCRC beyond second line treatment have a poor prognosis. The FRESCO
44 trial prompts fruquintinib as a third-line treatment in advanced colorectal cancer. A phase II
45 studies in our center reported the efficacy and safety of S-1 plus raltitrexed for the treatment
46 of chemo-refractory mCRC. The combination of the three agents has not been reported, and
47 the case demonstrated the efficacy and safety of the third-line therapy with fruquintinib,
48 raltitrexed, and S-1 in mCRC. ↵

What is known and what is new?

- Report here about what is known.
- Report here about what does this manuscript adds.

Reply: Thanks for your advices, and we have divided the above section into two points as you advised (see page 2, line 41-46).

2. Please check the below Keyword. You choose it as a Keyword but it cannot be found in the main text.

93 **Keywords:** Colorectal cancer; neoplasm metastasis; chemotherapy; vascular
94 endothelial growth factor receptor inhibitor; case report. ↵

Reply: Thanks for your advices, and we have changed the keyword (see page 3, line 90).

3. The consent statement is repeated in your text. Please delete the first one.

235 In the case report, treatment consent was obtained from the patient, and he is
236 satisfied with the therapeutic schedule and the results so far. We have de-identified
237 the details such that the identity of the patient may not be ascertained in any way. All
238 procedures performed in this study were in accordance with the ethical standards of
239 the institutional and/or national research committee(s) and with the Helsinki
240 Declaration (as revised in 2013). Written informed consent was obtained from the
241 patient for publication of this case report and accompanying images. A copy of the

Reply: Thanks for your advices, and we have deleted the first one as you advised (see page 7, line 215).

4. For Patient Perspective, patients should describe their feelings **in the first person**. Please revise the below content. Or you can delete it and fill “N/A” in item 12 of your CARE checklist.

235 In the case report, treatment consent was obtained from the patient, and he is
236 satisfied with the therapeutic schedule and the results so far. We have de-identified

Reply: Thanks for your advices, and we have deleted the content and fill “N/A” in item 12 of CARE checklist as you advised (see page 7, line 215).

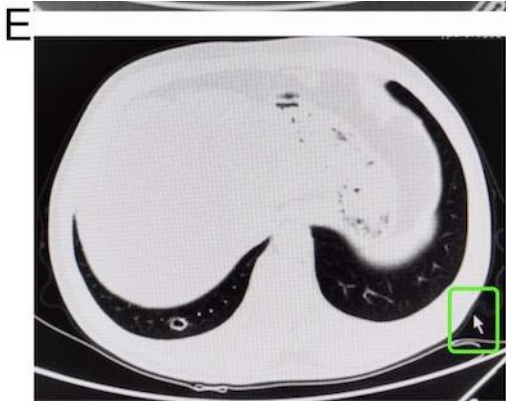
5. Figure 1:

Please provide Figure 1 in editable format (docx/ppt) to us.

Reply: Thanks for your advices. Figure 1 in editable format is put in the attachment.

6. Figure 3-4:

Please explain there is any meaning for below arrows. If no, please remove them and resubmit Figure 3-4 to us.



Reply: Thanks for your advices. The arrow in the picture is where the mouse indicates, and we have removed them and resubmitted Figure 3-4 (see page 13-14, line 388-409) .