Answering Reviewers

26 Jul, 2022

Thank you very much for your comments regarding our manuscript. We are grateful to reviewers for the valuable suggestions provided. Here are our point-by-point responses to the reviewer's comments. We also revised our manuscript accordingly.

Our answers are given in blue color.

Reviewer 1

Remarks to Author;

To determine the efficacy and safety of combination chemotherapy for metastatic CRC in patients aged above 80 years, 30 metastatic colorectal cancer patients were used to evaluated the effects of combination chemotherapy with TA for patients. Study showed that for the patients who aged above 80 years, combination chemotherapy with TA for metastatic CRC may be considered feasible and salvage chemotherapy can help improve overall survival rates in some selected of these elderly patients. Although this study has certain clinical guiding significance, there are still some problems as follows,

1. Overall, the manuscript was not well rationale, especially in the results and discussion section. Please carefully reorganize and rewrite it.

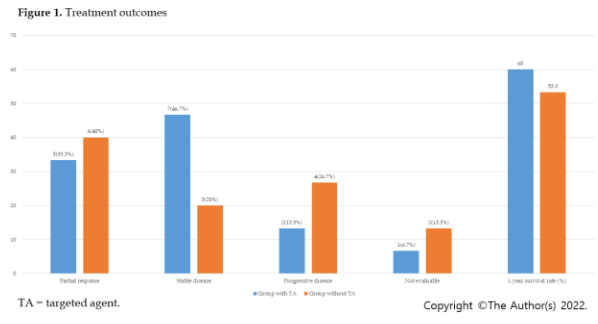
We appreciate the reviewer with valuable recommendations.
As recommended, we have reorganized and complemented the Results and Discussion section. Your suggestion reinforces our manuscript.
Result and Discussion section has been changed to the followings.

1) Result section
   (1) "Thirty consecutive patients who fulfilled the inclusion criteria were retrospectively reviewed January 2010-September 2019."
   We inserted this explanation in the top of result section.
   (2) As per your advices, we changed and revised the figures and tables.

We changed "Table 2" to "Figure 1".

Before	Revised version
Table 2. Treatment outcomes	Figure 1. Treatment outcomes

	Group with TA	Group without TA
Best response		
Partial response	5 (33.3)	6 (40.0)
Stable disease	7 (46.7)	3 (20.0)
Progressive disease	2 (13.3)	4 (26.7)
Not evaluable	1 (6.7)	2 (13.3)
1-year survival rate (%)	60.0	53.3



We also combined two figures, Figure 1 and Figure 2, as Figure 2A and Figure 2B.

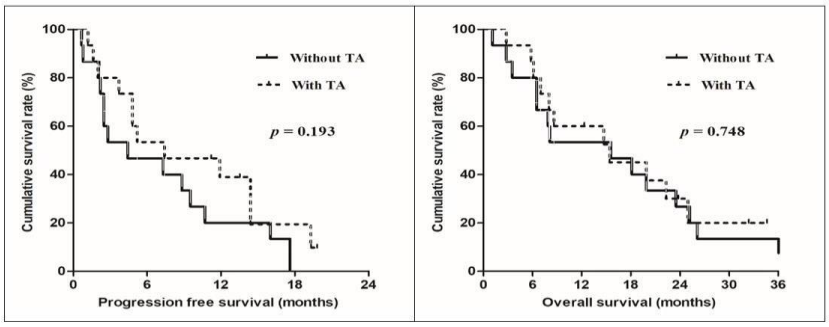


Figure 2.

A. Progression-free survival older patients with metastatic CRC treated with targeted agents.

A. Overall survival of older patients with metastatic CRC treated with targeted agents.

2) Discussion section

We revised the manuscript to emphasize the point of each paragraph of Discussion section and complement the rationale of full context.

(1) We revised the second paragraph of Discussion section

"In this study, the results of the group without TA were relatively consistent with previous findings. In a randomized study of elderly patients with metastatic CRC including 13% older than age 80, the median PFS and OS were 5.8 and 10.7 mo, respectively [25]. In another study of elderly patients (age 76-80) with metastatic CRC, modified FOLFOX regimens showed median PFS and OS of 9.0 mo and 20.7 mo, respectively, with an ORR of 59.4% [24]."

(2) We modified the third paragraph of "Discussion" section partially.

"Several studies combining TA with cytotoxic chemotherapy in older patients with metastatic CRC have been reported recently. The BEAT and BRiTE studies reported similar OS: 16.6 mo in patients age ≥75 in the BEAT study and 16.2 mo in patients age

80 in the BRiTE study [26,27].”

This explanation inserted in the third paragraph of “Discussion” section to complement rationale flow of context.

(3) We modified the fifth paragraph of “Discussion” section and inserted this explanation.

“As the patient's age increased, the proportion of patients receiving combination chemotherapy and median duration of treatment decreased [26]. In the BRiTE observational cohort study, the median PFS was similar across elderly subgroups (approximately 9.5 mo) but the OS decreased with increasing age [27].”

Thank you again for your suggestion. We agree with you and have incorporated your suggestion throughout the manuscript.

2. For ethics statements , “Informed consent for chemotherapy was obtained from all patients.” Such description is not appropriate, because the patients not only need to be informed about their participation in chemotherapy, they should also be informed about their participation in this study. Please provide some details about your “Informed consent”.

We appreciate your keen comments.
In general, retrospective studies are exempted from informed consent from the IRB.
This study is a retrospective study, and patient consent for study participation was waived from the IRB. (IRB No: KNUH-2021-03-008)

“Patients consent was waived from the IRB.”
We inserted this explanation in “Informed Consent” section.

Thank you again for your very important comment.

3. For experimental design, “Of 30 patients, the median age of 15 patients treated with TA was 83.0 years and that of those without TA was 81.3 years.” For what principle (or

criterion) are these patients divided into two groups? Age, or disease progression, please give a reasonable reason.

We appreciate your valuable comments.

The aim of this study is to assess the clinical outcomes and feasibility of target agent(TA) in elderly patients aged ≥ 80 years with metastatic CRC. Therefore, the criterion for dividing the patients into 2 groups is whether the target agent was used in patients who received combination chemotherapy.

"Thus, this study assessed the clinical outcomes of combination chemotherapy and feasibility of TA (bevacizumab or cetuximab) in extremely elderly patients (defined as ≥ age 80) with metastatic CRC."

We inserted this explanation to the bottom of "Introduction" section.
Thank you again for your comment.

4. For figures and tables in this study, almost all the data was presented as tables, I guess it can be presented as figures which will be more intuitively to deliver the points. (personal suggestion)

As per your advice, we changed "Table 2: Treatment outcomes" as "Figure 1".
Thank you again for your comment

Before	Revised version
Table 2. Treatment outcomes	Figure 1. Treatment outcomes

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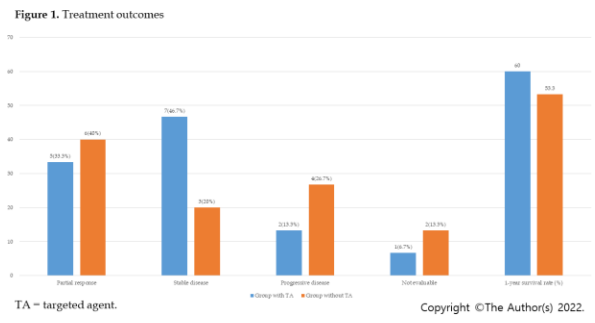

5. The impact of different treatment methods on patients requires multi-dimensional evaluation, and should not be limited to indicators such as mortality. For example, the evaluation of patients' feelings should also be displayed, e.g. quality of life.

We appreciate your keen comments and completely agree with the reviewer's comment.

"In elderly patients, it is important to improve the survival period as well as evaluate the quality of life. We believe that the comprehensive geriatric assessment (CGA) tool is useful in providing the best therapeutic option and optimal care for elderly patients most suitable for systemic chemotherapy. However, this study, which is a retrospective study, has a limitation in that it does not include quality of life and patients' feelings."

We inserted this explanation and revised the sixth paragraph of Discussion section.
Thank you again for your very important comment. Your valuable suggestion reinforced this manuscript.

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Reviewer 2

Remarks to Author;

The manuscript presented by the authors is very interesting and well written. The topic is of absolute interest as the group of very elderly patients, with of age higher than 80 years, is increasing progressively. As the authors comment this paper is only a short communication based only on 30 patients. The importance of the paper is that it shows that the combination chemotherapy with TA for metastatic CRC may be considered in highly selected elderly patients with considerable caution and with acceptable chemotherapy-related toxicity. I have not special queries.

The only observation is that authors should include at the beginning of Methods section that it is a retrospective study. In the original version, no mention to this point is shown.

We appreciate your keen comments and completely agree with the reviewer's comment.

"Medical records were retrospectively reviewed, including patients' demographic characteristics, surgeries, pathology reports showing genetic mutations, chemotherapy regimens, treatment responses, toxicity profiles, and comorbidity."

We inserted this explanation into "Materials and Methods-*Patient eligibility*" section.

Thank you again for your very important comment.

Your helpful suggestion reinforced our manuscript.