

RESPONSE TO REVIEWER COMMENTS

Dear Editorial Board,

We are re-submitting our manuscript, “Neoadjuvant Chemotherapy for Colorectal Liver Metastases: A Contemporary Review of the Literature,” for consideration for publication in the World Journal of Gastrointestinal Oncology. We would like to thank you again for the invitation to submit this review.

In this manuscript, we endeavored to present the most recent literature examining the treatment of colorectal liver metastases using neoadjuvant chemotherapy. For these patients, neoadjuvant chemotherapy is an important treatment strategy that can facilitate curative intent surgical resection. Although it is currently recommended for patients with unresectable to borderline resectable metastases, its use in patients with initially resectable disease remains controversial. In our review, we discuss the rationale, supporting evidence, technical considerations, current indications, and alternative treatment options associated with neoadjuvant chemotherapy in this setting.

In response to the suggestions of our reviewers, we have:

1. Amended our figure captions to include all pertinent information, such as the imaging modality used and the reason for choosing the section planes displayed.
2. Created a separate section to discuss alternative treatment options such as immunotherapy and intra-arterial therapies and discussed their relationship to our main subject.

We greatly appreciate your time in reviewing our manuscript. If you have any questions, please feel free to contact us.

Best,

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Below is a point-by-point response to the review comments:

Reviewer #1:

This manuscript provides an overview on current literature on neoadjuvant chemotherapy for colorectal liver metastases. Indications and technical issues are discussed, including the problem that complete radiological response does not necessarily equate complete pathological response. Some uncertainties remain, e.g., variabilities in assessing "unresectable disease" and the question of quality of life.

We thank the reviewer for their thoughtful review of our manuscript and general favorable comments. The "uncertainties" mentioned by the reviewer have been added to the manuscript as areas where additional research is needed.

Additional comments: Surgical considerations, first paragraph: "In one large meta-analysis, resection margins >10 mm were associated with significant improvement in OS at 3 years (RR=0.86), 5 years (RR=0.91), and 10 years (RR=0.94), as well as in DFS at 3 years (R=0.93) and 5 years (R=0.88) after surgery." – "R" - "RR"?

We appreciate your detailed review of our manuscript and for pointing out this discrepancy. The appropriate abbreviation is "RR" for relative risk, which we have now corrected.

Surgical considerations, last sentence: "individuals who were received chemotherapy only" -> individuals who received chemotherapy only.

This sentence has been corrected for grammar.

Figures 1A and 1B: Are the section planes shown in these two pictures comparable?

The section planes chosen for the figure display the tumor in maximum diameter. We added this explanation to the figure legend.

Figure 2: Detailed information should be given on the imaging techniques used here.

Thank you for this feedback. The figure legends were both revised to include information on the imaging techniques used.

Reference list: Most of the references are incomplete/not consistent with the guidelines of the journal.

The reference list has been updated to include all of the elements required in accordance with the journal guidelines.

Reviewer #2:

The article describes in detail the indications, strategies, efficacy and side effects of neoadjuvant chemotherapy for colorectal cancer with liver metastasis. But there is still room for improvement, the following are suggestions:

The narrative of the article is slightly complicated, and there is content that is weakly related to the keyword neoadjuvant chemotherapy. For example, in the part of immunotherapy, the author described its mechanism in detail and pointed out that it is better than chemotherapy alone, but there is little content in describing its association with neoadjuvant chemotherapy, and there is no data to support the advantages of chemotherapy combined with immunotherapy or highlight it compared with the characteristics of immunotherapy neoadjuvant chemotherapy. Other parts also have such problems. The article is generally well written, it is recommended to be revised and published.

We thank the reviewer for this feedback. While the main purpose of this review article was to focus on the role of neoadjuvant systemic chemotherapy for colorectal liver metastases, we felt that a brief discussion of alternative preoperative approaches would be helpful for the reader. Indeed, hepatic arterial infusion therapy is commonly used as a conversion strategy for initially unresectable CRLM. In addition, there is significant interest in immunotherapy approaches for advanced MMR deficient or MSI CRLM. In response to the reviewer's feedback, we have moved these two topics to the end of the manuscript under a new section titled "Alternative Therapies." Furthermore, while scarce literature still exists on the use of neoadjuvant immunotherapy approaches for metastatic colorectal cancer, we have focused the discussion on recent relevant and ongoing clinical trials.

Editor Comments:

1 Scientific quality: The manuscript describes a review of the neoadjuvant chemotherapy for colorectal liver metastases. The topic is within the scope of the WJGO.

(1) Classification: Grade B and Grade C;

(2) Summary of the Peer-Review Report: The article describes in detail the indications, strategies, efficacy and side effects of neoadjuvant chemotherapy for colorectal cancer with liver metastasis. However, the narrative of the article is slightly complicated, and there are content that is weakly related to the keyword neoadjuvant chemotherapy. The questions raised by the reviewers should be answered;

(3) Format: There are 2 figures.

(4) References: A total of 111 references are cited, including 20 references published in the last 3 years;

(5) Self-cited references: There are 9 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated

(6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Grade B and Grade A.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJGO.

5 Issues raised:

(1) The “Author Contributions” section is missing. Please provide the author contributions;

An “Authors Contributions” section was added.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Original figure documents were uploaded with the re-submission of the manuscript.

(3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

6 Recommendation: Conditional acceptance.