

Dear Editor Wang:

Thank you very much for your decision letter and advice on our manuscript (39513), entitled “Current status of surgery for colorectal liver metastases.” We also thank you and the reviewers for the constructive and positive comments and suggestions. Accordingly, we have revised the manuscript. All amendments are highlighted in red in the revised manuscript. In addition, point-by-point responses to the comments are listed below this letter.

This revised manuscript has been edited and proofread by *Medjaden* Bioscience Limited.

We hope that the revision is acceptable for publication in your journal, and we look forward to hearing from you soon.

Yours sincerely,

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First of all, we would like to express our sincere gratitude to you and the reviewers for the constructive and positive comments.

### **Replies to editor**

1. Please add pictures and forms

**Response:** Thank you for your suggestion. We have added a table to summarize the traditional and current criteria for surgery for colorectal liver metastasis. We also have added a figure to show our management flow chart for colorectal liver metastasis.

2. Answer all of the reviewers' comments carefully (point-to-point).

**Response:** We thank you for your valuable suggestion. We have answered all of the reviewers' comments point-by-point.

3. Please provide us with the funding approval.

**Response:** We have provided the funding approval.

4. Please add 5-10 key words here words that could reflect content of the study mainly from Index Medicus.

**Response:** We have added key words reflecting the content of our study according to Index Medicus.

### **Replies to reviewers**

**Reviewer #1:** The manuscript by Feng Xu, et al. is a review on a very interesting topic on current surgical strategy for colorectal liver metastases. This topic is ever-changing in the way to improve outcome for patients who suffer from advanced colorectal malignancy. Here are concerns to strengthen the manuscript.

1. The referenced studies should be clearly described as to their year established, authors, especially article type should be put into consideration since it reflects the reliability of the data. Also, the referenced studies' quality should be carefully reviewed, best quality studies published and the time of the review can improve the review by leaps and bounds.

**Response:** We thank you for your valuable suggestion. We have corrected the description of the referenced studies by including the year of publication. In addition, we have reevaluated the referenced studies' quality; the low-quality studies have been removed so that only the best quality studies are included.

2. (Definition of resectability of CRLM) the conclusion as to whether limited indication or extended indication is currently accepted should be shown. If the author would suggest extended indication for CRLM, is it conflicting with the study quoted? Is there any explanation for worse long term outcome in extended indication in the referenced study? Is there other confounding factors for worse overall survival that should be considered? Are there other studies that answer this topic more clearly?

**Response:** We thank you for your critical comment. We have revised the manuscript by addressing all of these critical queries.

3. (Imaging modalities) The subheadings should be a) sensitivity in detection intrahepatic and extra hepatic metastases, either occult or not, as well as disappearing liver metastases, b) pre-operative anatomical localization, c) intra-operative detection. The topics were vaguely explained which may cause confusion. There is meta-analysis on this topic which gives different result especially regarding chemotherapeutic effects on imaging. In standard treatment protocol, such as NCCN, PET-CT was indicated in specific circumstance only, this issue should also be noted.

**Response:** We thank you for your valuable advice. We have added subheadings and the content of imaging selection post-chemotherapy. We have also mentioned the role of PET-CT in specific circumstances.

4. (Evaluation of the future liver remnant) Other contributing factors for postoperative liver failure other than remnant volume and function should be noted. Chemotherapy-associated liver injury is different in certain chemotherapeutic drugs and number of cycles given. These too should be explained. If ICG15 does not correlate with pathological sinusoidal injury and steatohepatitis scores, what is the clinical application? The authors' name of the referenced study was typed wrong. Please proofread. In the last paragraph of the topic, assessment of FLR function and volume is different entity.

**Response:** We thank you for your valuable comments. We have revised and added the relevant contents in this section accordingly.

5. (Treatment timing of synchronous CRLM) Selected patient suitable for simultaneous resection should be concluded. Specific circumstances, such as large bowel obstruction, should be put into consideration. Neoadjuvant chemoradiotherapy should also be stated since they play an important role in the treatment process. There is a large review regarding this topic. In the second paragraph of this topic, reference number [41] is false since it described a total different subject from what said in this manuscript.

**Response:** We thank you for your valuable suggestion. We have revised and added the relevant contents in this section. We also have deleted the false reference in the second paragraph of this topic.

6. (Resection margin) What is the suggested resection margin? What are the factors that could effect long-term outcome along with resection margin? Does postoperative chemotherapy concern with resection margin status?

**Response:** We thank you for your valuable advice. We have added the relevant contents in this section accordingly.

7. (Application of ablative techniques) Are there really studies conducted to advocate ablative therapy as curative intent for resectable CRLM [58-60]? The limitation of stating MWA, RFA as curative intent instead of hepatic resection should also be noted. Ablative techniques should be discussed primarily as for unresectable CRLM to not cause confusion.

**Response:** We thank you for your critical comment and valuable suggestion. We have corrected and added the relevant contents in this section accordingly.

8. (PVE PVL) Are there other publications suggest the usefulness of PVE/PVL? The descriptive use of PVE with two-stage hepatectomy should be more thorough. There are other means of dealing with tumors in FLR which have not been described. Also the referenced two-stage hepatectomy [80] was not clearly described and what is its relevance to the topic? What is your conclusion regarding the use of these techniques for manipulation of liver volume?

**Response:** We thank you for your critical comment and valuable advice. We have revised and added the contents in this section accordingly.

9. (Conversion chemotherapy) Are there predictors for patients who would benefit from this strategy? The regimen differences regarding KRAS status should be distinctly stated. Does side of primary colorectal cancer have any effect on chemotherapy regimen? What is the follow up protocol and duration of the therapy?

**Response:** We thank you for your critical comment and valuable advice. We have added the contents in this section accordingly.

10. (Liver transplantation) What is the neoadjuvant therapy for liver transplantation?

Referenced study [111], did patients underwent laparoscopic hepatectomy? What is the long term outcome compare to other modalities for unresectable CRLM? With the shortage of donors, is the transplantation more beneficial for CRLM compare to those with benign diseases who are transplantation candidates? Are there any established criteria for transplantation in patient with CRLM?

**Response:** Liver transplantation is a controversial treatment for unresectable CRLM. We thank you for your critical comment and valuable suggestion. We have revised the mistaken expression “laparoscopic hepatectomy,” and the correct expression is now “liver transplantation.” We also have added some contents in this section according to your suggestion.

11. (Repeat liver resection for recurrent CRLM) Are there other modalities feasible for recurrent patients? What kind of referenced study [121] and how does these criteria come to?

**Response:** We thank you for your critical comment. We have added content regarding the alternative treatments for recurrent CRLM. The referenced study was a systemic review and meta-analysis in which the authors proposed the criteria for a repeat hepatectomy.

12. (Extrahepatic metastatic disease) What organ containing extrahepatic metastasis does not effect resectability of CRLM? In second paragraph, what is the position of lymph nodes mentioned in second paragraph? What is the role of metastatectomy regarding extrahepatic metastases? And how does the conclusion ‘these findings reveal that resection is favorable in the absence of EHMD’ come to?

**Response:** We have revised the contents in this section according to your valuable suggestion; in particular, we have added content regarding lymph node metastases.

We have deleted the conflicting conclusion “these findings reveal that resection is favorable in the absence of EHMD.”

**Reviewer #2:** Thank you to invite me to review the manuscript entitled “Current status of surgery for colorectal liver metastases”. This is a systematic review analyzing treatment of colorectal liver metastasis. Four authors from China are listed. The article is very interesting and well-documented. I really like it. Yet, it is not that well-written; as the subject is sometimes complex, I think it should be improved. Also, I suggest a few corrections:

1. \_ a definition of resecability (page 5) and a definition of unresecability (page15).

Please, discuss discrepancy between these definitions.

**Response:** We thank you for your valuable suggestion. We have revised the manuscript to clarify the definitions of resectability and unresectability.

2. \_ in Evaluation of the future liver remnant (FLR), the authors propose that FLR > 30%; yet, 20% seems to be the cut-off leading to major increase in morbi-mortality. Please, clarify.

**Response:** We have revised the contents in this section according to your valuable suggestion.

3. \_ regarding portal vein ligation and embolization, please clarify that in case of two stages hepatectomy, PVL should be preferred. Otherwise, PVE seems to be more appropriate.

**Response:** We thank you for your critical comment of pointing out this controversial statement. We have rewritten this part and added reasons for selecting PVL or PVE.

4. \_ page 19, regarding chemotherapy in case of Wild-Kras, the paragraph is unclear. Please, clarify.

**Response:** We thank you for your valuable suggestion. We have revised the content in this paragraph accordingly.