**Dear editor,**

Please find enclosed the revised version of our manuscript NO. 75162 with the title "Clinical implications and mechanism of histopathological growth pattern in colorectal cancer liver metastases" to the World Journal of Gastroenterology (WJG) by Bing-Tan Kong, et al., and the point-to-point response letter. We sincerely thank you for your time in reviewing the manuscript and your positive and constructive comments with helpful suggestions on the merits. We appreciate your clear and detailed feedback, and hope the response below has fully addressed all of your concerns. All individual issues have been addressed below in italic and in blue, with the corresponding response in black.

**From science editor**

**Comments:**

*Liver metastasis of colorectal cancer shows different histopathological growth patterns. The authors summarized their clinical significance, including prognostic value, treatment response and related vascularization. Extensive and comprehensive review, but there is no special innovation and own point of view. The figures and tables are good, the text is properly refined, and its clinical significance should be clearly explained.*

**Response :**

Though some tumoral phenotype and molecular drivers of rHGP were reported in current studies, there is still no systematic explanation for its formation. In our minireview, besides clinical implications, we also dwell on the underlying mechanism of HGP and highlight rHGP due to poorer outcomes. We therefore propose a novel "advance under camouflage" hypothesis to explain formation of rHGP and describe it at length (page 16 line 19-29 and page 17). In addition, we summarize and highlight this innovation in part 1 of "conclusion" (page 18 line 2-18) and our own point view in part 3 of "conclusion" (page 19 line 13-28).

To make the text more concise, we intensively prune the chapter "underlying mechanism of HGPs", delete the section "entry-points hypothesis" and preserve the key mechanism and molecular drivers. Moreover, we revise the chapter "prognostic

value of HGPs", "HGP and therapy", "HGP and vascularization" and "identifying HGPs in noninvasive methods" to make them more concise. Finally, we have refined the whole text from 6178 words to 5048 words.

To explain the clinical implications more clearly, three relevant chapters "prognostic value of HGPs", "HGP and therapy" and "identifying HGPs in noninvasive methods" have been addressed. Finally, we propose clinical significance of HGP and summarized them by three aspects in part 2 of "conclusion" (page18 line 19-29 and page 19 line 1-12).

**Reviewer #1:**

*Scientific Quality: Grade C (Good)*

*Language Quality: Grade B (Minor language polishing)*

*Conclusion: Major revision*

*Comment 1: The title reflects the main subject of the manuscript, and the absctract summarizes the study. As a review, the manuscript describes the background of the study. Nevertheless, as a review, the manuscript makes no original contributions in the field.*

**Response :**

Though some tumoral phenotype and molecular drivers of rHGP were reported in other studies, there is still no systematic explanation for formation of rHGP. Here, in this minireview, the clinical implications and the underlying mechanism of HGP and highlighting rHGP because of poorer outcomes have been discussed. We proposed a novel "advance under camouflage" hypothesis to explain formation of rHGP and describe the process at length (page 16 line 19-29 and page 17). In addition, we summarize and highlight this innovation in part 1 of "conclusion" (page 18 line 2-18).

*Comment 2: The manuscript becomes cumbersome in extension. It might be good to reduce the too long text to adequate to the Journal review and make it more attainable to the reader. On the contrary, the Discussion fall short in the manuscript and more*

*extension will be desirable.*

**Response:**

Thank you for the constructive suggestions to improve the manuscript. In order to make the article more attainable, we have thoroughly simplified the text, omitted some details of the study (e.g. detailed results from clinical studies, technology tool and parameters in noninvasive methods, detailed molecular interaction in mechanism of HGP, etc.), and squeezed out some less relative and essential chapters (e.g. the section "entry-points hypothesis"). Finally, we have refined the whole text from 6178 words to 5048 words.

To polish and enrich the discussion and conclusion, in this revision, the following adjustment has been made: our innovation in part 1 "conclusion" have been summarized and highlighted, the clinical significance of HGP has been proposed and summarized by three aspects in part 2 of "conclusion", and our own point views in part 3 of "conclusion" have been given. This part is extended from 347 words to 670 words

**Comment 3:** *The tables are well displayed. References are appropriately cited, updated, and self-cited are correct. The phrase ", and noninvasive methods identifying HGP futher" in the Abstract is not clear. IN page 6, in HGPS AND THERAPIES "Yet, previous study showed..." must be "studies".*

**Response:**

We have revised the interpretation of this phrase and modified abstract to make it clearer. We have corrected "study" to "studies", and checked the whole text to make sure no spelling errors.

**Reviewer #2:**

*Scientific Quality: Grade C (Good)*

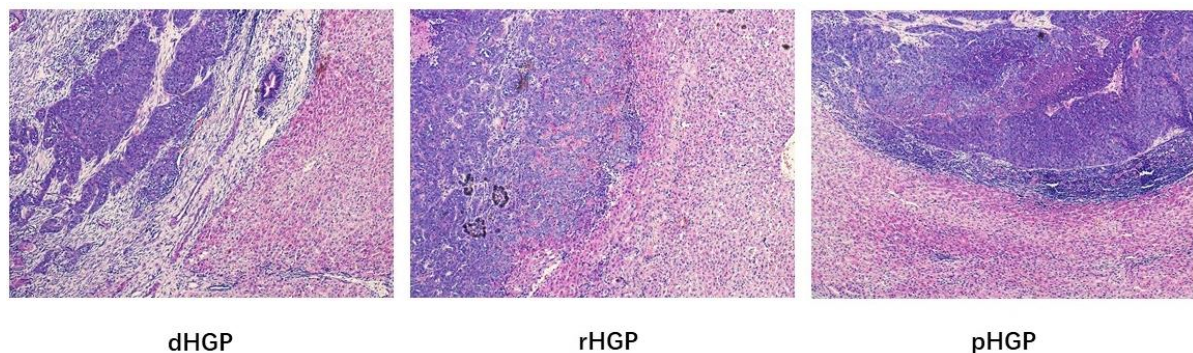*Language Quality: Grade A (Priority publishing)*

*Conclusion: Accept (General priority)*

**Comments:** *The authors demonstrated the clinical importance of histopathological*

*growth pattern (HGP) in patients with colorectal cancer liver metastases (CRCLM). Although this minireview has the clinical importance, there are several comments. Comments 1. Representative hematoxylin and eosin staining for dHGP and rHGP should be indicated as Figure.*

**Response:**

Thank you for your encouraged and constructive comments. HE staining figure is indeed a common form in describing HGP. Below are the representative HE staining figures from our own study. Considering there is slight difference among primary tumors of liver metastases, also the tumor hosts (rat, mice, human, rabbit) in different studies, HE from any studies cannot be the most vivid, representative, and universal one, we prefer the schematic diagrams to address the essential elements and descript characteristics of dHGP and rHGP in the manuscript.



dHGP                    rHGP                    pHGP

**Comment 2:** *Table 1 should be modified. The authors should indicate the real date of OS, PFS, and DFS.*

**Response:**

The data about OS, PFS, DFS and recurrence rate have been added into Table1 in the revise manuscript.

**Comment 1:** *The paper deals with an interesting argument and it is well written. Even if it does not produce any original finding, it could fit with the minireview form. The arguments are well exposed. I would change the title: it cannot be put in the foreground the clinical aspects, because in the text you show only future and not established clinical implications for HGP.*

**Response:**

Thank you for your helpful comments to polish the minireview and give us the further chance to improve the manuscript. The title "*Clinical implications and mechanism of histopathological growth pattern in colorectal cancer liver metastases*" is our original intention and purpose of this review. To make the framework, logic and contents of this manuscript fit for the title, structural adjustments have been made: three chapters "prognostic value of HGPs", "HGP and therapy" and "identifying HGPs in noninvasive methods" have been enriched and addressed in clinical significance of HGP. Furthermore, the clinical implications of HGP have been proposed, and summarized by three aspects in part 2 of "conclusion".

**Comment 2:** *I would also modify both the abstract (the entire second part of the abstract is a sort of general summary of the argument, not of your paper) and the conclusions in order to be less generic and more incisive: underline more practical aspects as well as true future perspectives in clinical practice.*

**Response:**

We modify the abstract to fit the whole manuscript in the revised version. We have proposed clinical significance of HGP and summarized them by three aspects namely risk stratification, biomarker of therapy and developing new therapeutic approaches in part 2 of "conclusion" (page18 line 19-29 and page 19 line 1-12), and describe their application in detail. Finally, we give our own point views in part 3 of "conclusion" (page 19 line 13-28).

**Comment 3:** *References are good, I would add a reference in page 21 when you talk about therapy of colorectal liver metastases (survival, therapy of choice). Only minor*

*revision.*

**Response:**

This part has been modified and complete references (76-79) have been provided.

*Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: https://www.referencecitationanalysis.com/. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the*

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**Response:**

We thank you very much for giving us the possibility to revise our manuscript and further improve it. We have carefully reread our manuscript, addressed all comments, made all the suggested revisions to further improve our review, and provided all needed files as suggested.

Nevertheless, our manuscript was proofread and corrected by a professional English language editing company and a new language certificate was provided along with the manuscript.

We thank you very much for giving us the possibility to revise our manuscript. We hope that our revision complies with your remarks and comments. We would like to thank you for analyzing our revised manuscript and hope that it will now be

acceptable for publication in the World Journal of Gastroenterology.

Sincerely,

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