

Ruo-Yu Ma
Science Editor, Editorial Office
World Journal of Gastroenterology

May 23, 2019

Re: Manuscript No.: 47352

Histologic features and genomic alterations of primary colorectal adenocarcinoma predict the growth patterns of liver metastasis,

Dear Professor Ma:

Thank you for your letter of May 14th, 2019. We have revised the manuscript based on the reviewers' comments and suggestions.

Attached please find (1) a revised version of our manuscript with changes highlighted in bold, (2) a point-by-point discussion explaining how we have addressed each of the reviewer's comments and concerns.

In addition, it should be noted that we add Dr. Peter Metrakos as one of author for his contribution to the project design. And we recalculated p values of Table 2 according to the recommendation of the biomedical statistician, however, the final conclusions are unaffected.

We sincerely hope that this revision is satisfactorily. However, if additional work needs to be done, please feel free to contact us.

Sincerely,

Zu-hua Gao, MD, PhD, FRCPC

Reply to reviewers:

1. Pathological pictures in the study may be more detailed.

Thank you for the suggestion.

To better illustrate the pathology images, we have added arrows and provided more detailed legends.

To illustrate the immunohistochemical staining features in detail, we have added a "Fig. 5: Representative immunohistochemical images."

2. In this manuscript, the author found histologic features of primary colorectal adenocarcinoma can predict the growth patterns of liver metastasis. Although clinical sample is small, the ideal seems innovative. Two minor mistakes should be revised 1) the definition of DFS should be the date of CRCLMs resection to the date of recurrence, or to the date of censoring 2) Figure 6 data should not only listed in discussion section.

Thank you for your suggestion. The definition of DFS has been changed to **the date of CRCLMs resection to the date of recurrence, or to the date of censoring (page 11, lines 7)**. The data in Figure 6 data has been added to the Results section (page 12, lines 4 to17).

3. According to the CrossCheck report, the similarity index between this manuscript and the published ones is too high, which doesn't meet the publishing requirements. Please revise the duplicated parts according to the CrossCheck report uploaded by the editor.

Thank you for the suggestion. We have revised all the duplicated parts according to the CrossCheck report uploaded by the editor.

4. Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B).For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

Most of our authors are native English speakers. In addition, our manuscript had been revised thoroughly and edited by American Journal Experts. Editorial Certificate has been

uploaded in the online submission page.

- 5. Audio core tip:**In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information. The accepted formats are mp3 or wma.

An Audio core tip has been recorded as .mp3 file and uploaded in the online submission page.

- 6. Please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - image files.ppt" on the system. Make sure that the layers in the PPT file are fully editable. For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast.**

Following your request, all the figures have been organized into a PPT file and been submitted as "Manuscript 47352 - image files" on the system. The layers in the PPT file are editable. We don't use red and green for contrast.

- 7. Your manuscript should be prepared with Word-processing Software, using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.**

The manuscript have been entirely prepared using 12 pt Book Antiqua font and 1.5 line spacing with ample margins.

- 8. The format of author contribution section should be like this: Author contributions: XXX (family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital) designed research; XXX performed research; XXX contributed new reagents or analytic tools; XXX analyzed data; XXX wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect.**

The format of author contribution has been revised to be complaint with the requirement.

9. You need to provide the grant application form(s) or certificate of funding agency for every grant, or we will delete the part of "Supported by...".

Following your request, all the grant application form has been uploaded in the online submission page.

10. Institutional Review Board Approval Form or Document

Please upload the primary version (PDF) of the Institutional Review Board's official approval, prepared in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, *etc.*

Following your request, we have uploaded the PDF version Institutional Review Board Approval document in the online submission page.

11. Signed Informed Consent Form(s) or Document(s). Please upload the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, *etc.*

All patients in our study population have signed the informed consent for the study. However, due to the presence of patient's confidential identifiable information on each consent. Original signed consents can not be provided. A letter from the surgeon who is responsible for obtaining the informed consent is attached.

12. Please distinguish between the title of the article series. Three levels of subtitles are allowed: (1) First subtitle: All in bold and capital; (2) Second subtitle: All in bold and italic; and (3) Third subtitle: All in bold.

Following your request, all titles in the manuscript has been distinguished accordingly.

- 13. Statistical significance is expressed as ^a*P* < 0.05, ^b*P* < 0.01 (*P* > 0.05 usually does not need to be denoted). If there are other series of *P* values, ^c*P* < 0.05 and ^d*P* < 0.01 are used, and a third series of *P* values is expressed as ^e*P* < 0.05 and ^f*P* < 0.01.**

Statistical significance expression in this manuscript is complaint to the guideline.

14. Article Highlight

Following the format of WJE, Article Highlight has been inserted at the end of the manuscript before the section of references.

- 15. Please check and confirm that there are no repeated references!**

We have checked all the references and no repeated references were identified.

- 16. Please add PubMed citation numbers (PMID NOT PMCID) and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI.**

We have added PubMed citation numbers and DOI citations to the reference list.

We have listed all authors in each reference.

- 17. For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast.**

Please don't include abbreviations in the title of the figure/table.

Please explain all the abbreviations in the figure/table legends as full name (abbreviation).

Please explain all the abbreviations of each figure/table under each piece of figure/table legends.

Please don't include any *, #, ...in your manuscript; Please use superscript

numbers for illustration; and for statistical significance, please use superscript letters.

Please create another file for all the supplementary figures and tables and name the file as "xxxx-Supplementary material.pdf"

All the figures have been organized into a PPT file and been submitted as "Manuscript 47352 image files" on the system. We don't use red and green for contrast. We have prepared our figures and figure legend entirely following the journal requirement. .