

**Dear Jin-Lei Wang, Company Editor-in-Chief, Editorial Office, World Journal
of Gastrointestinal Endoscopy**

23th April 2022

We appreciate the reviewers' and editorial office's comments concerning our manuscript. The comments were constructive toward improving our manuscript. We have carefully studied the comments and revised our paper accordingly. Our point-by-point responses to their comments are appended to this letter. We believe that these modifications have made the manuscript clearer and consistent.

We hope the revised version can now be considered acceptable for publication in World Journal of Gastrointestinal Endoscopy. Please contact us if you have any questions or require any additional information. We look forward to hearing from you soon.

Sincerely

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Reply to comments of reviews and editorial office

(Manuscript NO: 75608)

First of all, we sincerely appreciate the effort of two reviewers and the editorial office in reviewing our manuscript carefully. We hereby resubmit a response to their comments formatted in the point-by-point style. We highlighted with underline where we revised within the manuscript and described the number of pages and lines.

Comments by the Reviewer 1:

The reviewer appreciates the author's work. Still, the manuscript or the work carried out is not matured for publication. Manuscript needs a good introduction, the introduction section of the paper is weak, authors are advised to improvise the introduction section. Also, result and discussion section is inadequate. Need more attention and better explanation.

Response: We wish to express our deep appreciation to the reviewer for his careful comments. We agree with your comment on our weak introduction and have dramatically changed it to stress the advantage on saving the burden of histopathologists clearly. We have revised it in the abstract, introduction, and discussion section as follows.

"The endocytoscope with ultra-high magnification (x520) allows us to observe the cellular structure of the colon epithelium during colonoscopy, known as virtual histopathology. We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists without a microscope, potentially saving the burden on histopathologists." (Page3, Line 3-7)

"The endocytoscope, which was launched in early 2018 by Olympus Medical Systems Corporation (Tokyo, Japan), can provide ultra-high magnification (x520) images in real time during colonoscopy. The endocytoscopy allows us to observe the cellular structure of the colorectal lesions, known as virtual histopathology and has provided high diagnostic performance in estimating their histopathology.^[1-5] There is growing evidence that the diagnostic

accuracy of endocytoscopy with computer-aided diagnosis (CAD) was greater than that of non-expert and comparable to expert endoscopists.^[6-12]

Based on the background of the shortage of histopathologists, we have explored a new application of endocytoscope for histopathological diagnosis of colorectal lesions.^[13] We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists themselves without a microscope. The endocyto-pathological images taken by endoscopists can be stored in the same system as the endoscopic images so that both images can be obtained as needed, making it possible to hold clinicopathological conferences efficiently even in countries with a few pathologists. Furthermore, a combination of endocyto-pathological images and the CAD system may lead to saving the burden of histopathologists in the future.

This pilot study aimed to assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis." (Page 5, Line 2-20)

"We believe the endocyto-pathological diagnosis will reduce the growing burden on histopathologists, including their time and cost, when especially made with the CAD system. Further studies will be required to prove the hypothesis."

(Page 8, Line 23 and Page 9, Line 1-3)

The contributions presented in this paper are not sufficient for possible publication in this journal. I highly suggest authors to clearly define the contributions.

Response: We appreciate your valuable suggestion regarding the author contribution. We have addressed it in detail on the title page as follows.

Author contributions:

- Study concept and design: FI, DH, MI, SH, MF, WS, YS
- Reading endocytopathological images: TS, HK, KI
- Data analysis and interpretation: FI, DH, MI, YS
- Drafting the manuscript: FI
- Critical revision of the manuscript for intellectual content: TS, HK, KI, YS

Comments

by

the

Reviewer

2:

First of all congratulations to the authors for the work. It would be important to explain the following studies to be carried out with calculation of the sample size that can demonstrate with scientific data the advantages of using this new technology.

Response: We thank the reviewer for raising the important issue of the sample size calculation. Actually, we could not find any previous data available for the sample size calculation because our pilot study is a completely brand-new exploring study. We described why this study was conducted without sample size calculation in the text. "This study was conducted as an exploratory research investigation without calculating sample size due to the lack of data in previous studies."

These advantages must be explained in terms of decreased morbidity (less need for biopsies) or improved quality of life or diagnostic certainty.

Response: We completely agree with your comment on the weak advantage of the study. As we mentioned in the comment for Reviewer1, we have enhanced the advantage of endocyto-pathological diagnosis on saving the burden of the histopathologists clearly in the introduction section. Please refer to the comment for Reviewer 1.

Within the limitations of the study, it would be relevant to address how diagnostic errors could be avoided during the learning curve.

Response: Thank you for raising this issue. We speculated leading cause of diagnostic errors would arise from the operator (endoscopist)-dependent factors. The endoscopists who take the endocyto-pathological images must learn the knowledge of histopathology enough to take the image of the correct areas in the specimens for adequate endocyto-pathlological diagnosis. We added the explanation as follows in the limitation section.

"Taking inadequate images would lead to the wrong endocyto-pathological diagnosis." (Page 9, Line 4-5)

It would also be important to explain in economic or cost terms (without being exhaustive) how the absence of pathologists is justified and the possibility of having a high-cost team, probably explaining the efficient use (by saving time) of the available pathologists.

Response: We thank the reviewer for his detailed review and comment. We added the sentences to explain the economic advantages on the pathologists in the discussion section as follows.

"We believe the endocyto-pathological diagnosis will reduce the growing burden on histopathologists, including their time and cost, when especially made with the CAD system." (Page 8, Line 21-23 and Page 9, Line 1)

Comments from Editorial Office

(1) *Science editor:*

This manuscript focused on the new application of endocytoscopy in the pathological diagnosis of colorectal diseases, which has great guiding significance in clinic. The author needs further revision to highlight the novelty and advantages of this manuscript.

Response: We thank the science editor for his detailed review and comment. We have revised the manuscript to highlight the advantage of endocyto-pathological diagnosis, as we mentioned in the comment for Reviewer1.

The form of the table in the article should adopt the form of a three-line table.

Response: We have revised the form of tables 1 and 2 in a three-line format.

The number of total references is few and a bit outdated, maybe a few more related references could also be cited. The self-referencing rate should be less than 3%. The authors should keep reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations

Response: We have deleted all self-citation articles and quoted some related articles. As a result, the total number of reference articles has increased from

9 to 13.

(2) *Company editor-in-chief:*

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Endoscopy, 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. Before its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in 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. 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. 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 reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. 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.

Response: Thank for your comments. We have attached the required files as you suggested. If you find the wrong files, please let me know soon.