

Manuscript ID: 43325

Title: Assessment of chronic radiation proctopathy and radiofrequency ablation treatment follow-up with Optical Coherence Tomography angiography: a pilot study

Response to reviewers

We thank the reviewers for their thoughtful comments and suggestions. We have made major revisions in response to address all of the reviewers' comments.

We have removed the statements regarding the clinical utility of OCTA that were not supported. We have also removed the descriptor "non-endoscopic" from the article title to avoid the possibility of miscommunicating study objectives. At the same time, we have tried to better describe the unique depth-resolved information that can be gained with OCT and OCTA in assessing CRP pathophysiology and treatment response.

We have rewritten the Abstract to more clearly describe how OCTA resolves mucosal and submucosal vascular structure that cannot be seen endoscopically, the abnormal vascular features that are present in CRP and how they normalize after treatment. We have also revised the Discussion, reordering and rewriting selected paragraphs to more clearly relate the findings to pathogenesis and treatment response. At the same time, we state the findings must be considered with caution because of the limited patient enrollment and retrospective study design. We have suggested that further larger scale, prospective, longitudinal studies are warranted to investigate the potential role of OCTA in management of CRP.

Please find below our comments and description of the revisions in point-by-point response to the reviewers.

REVIEWERS' COMMENTS TO THE AUTHOR:

Reviewer: 1

Reviewer's code: 00188507

The authors described the usage of optical coherence tomography using their prototype system for the assessment of radiation proctopathy. It is really interesting and the manuscript is well written, however, there are few concerns to be addressed before the further consideration.

We appreciate the reviewer for the positive evaluation of our study.

1. Although the authors described that the OCTA play an important role in the clinical management of, however, this study is based on the observation and analyses of patients under the treatment. Therefore, there is no information using this machine for the diagnosis of new patients or description that using this system to follow the course or for decision making for the further treatment. Based on these assessments, it is overstatement saying that the system plays an important role in the management.

We thank the reviewer for raising this point. Indeed, the scope of our study was observational and we did not use the system to guide diagnosis or therapeutic decisions. Our claim that OCTA may play a role in the clinical management of CRP was based on the observational study results

and should be considered hypothetical. In agreement with the reviewer, we have removed these statements and focused on better explaining the advantages and limitations of OCTA for studying subsurface vasculature and the mucosal and submucosal vascular alterations that are present in CRP.

Specifically, we have removed statements like “OCTA can play an important role in the clinical management of CRP and improve understanding of CRP pathophysiology” from the Abstract, Discussion and Conclusion of the text. As noted above, we have extensively revised the Abstract and Discussion.

2. If the author wants to describe the usage in management, they need to compare its usefulness with that of endoscopy.

We agree with the concern raised by the reviewer and made the changes described previously. At the same time, we have made revisions to better highlight the complementary information that can be gained with this technology, as OCTA allows assessment of superficial features which are endoscopically visible as well as deeper vasculature which cannot be seen endoscopically. We believe that has unique features which will be useful for longitudinal studies to elucidate CRP pathophysiology, the association of abnormal vasculature with CRP and treatment response. Further studies are needed to understand if OCTA can be used to predict response or target treatment.

“Submucosal vasculature is not visible endoscopically and OCT/OCTA provides a unique modality for assessing CRP. OCTA does not require injected dyes and is well suited for longitudinal studies, rapidly imaging large regions of rectum to yield integrated structural and vascular maps. These advantages suggest that it could be a viable tool for rapid assessment of CRP to elucidate pathophysiology as well as potentially plan treatment and assess response. Further larger scale, prospective, longitudinal studies are warranted.”

3. As the RFA needs the endoscopy, it is overstating to say the usefulness than endoscopy.

We agree with the reviewer and did not intend to describe our technology as a replacement of endoscopy. We have added the following sentence to the Discussion section to emphasize this point:

“OCT/OCTA imaging can be performed with a stand-alone device independent of colonoscopy, prior to colonoscopy, or with an endoscopic attachment during colonoscopy.”

It is also important to note that OCTA can visualize submucosal vasculature which is not visible endoscopically. We have tried to better emphasize this point in the Abstract, Methods and Discussion.

4. If the paper is prepared to show the better function of their prototype OCTA than currently available OCTA, it should be reconsidered to be submitted to the other journal.

The OCTA system used in this study does not necessarily have an improved functionality compared to previous endoscopic OCTA reports by our group cited in the text. It should also be noted that OCTA is currently not available commercially. This study is the first demonstration of

OCTA in a lower GI pathology and it is ideally suited for investigating CRP. CRP is characterized by vascular abnormalities, submucosal vasculature cannot be visualized endoscopically and biopsy is contraindicated because of bleeding risk. The following sentence in the Discussion clarifies this point: "... this is the first study demonstrating the potential clinical utility of this next-generation OCT technology in a lower gastrointestinal tract pathology."

Reviewer: 2

Reviewer's code: 03846820

Dear author, The paper represents results of the observational clinical trial (N=10, 15 OCTs) which is aiming to examine feasibility of non-endoscopic assessment of chronic radiation proctopathy and radiofrequency ablation treatment follow-up with optical coherence tomography (OCT) angiography. The article is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly.

We appreciate the reviewer for highlighting the main strengths of our study.

The most discussable options in the article are: 1) It is clear that the design of this study is mostly a feasibility-testing, but would you please kindly provide us with the sample size calculation and any understanding regarding your statistical power generally. I would remind that potentially statistical power for a number of patients and OCTs will be different.

This is a pilot study which enrolled patients at a single center and enrollment was limited by the patient demographics at the center within the study period. As noted by the reviewer, the study was intended to be feasibility-testing to identify vascular features which are potentially associated with CRP and treatment response. Enrollment size is too small for statistical analysis. Another objective of the study was to describe the unique features of OCTA for studying CRP. A prospective study with a larger enrollment is needed to achieve statistical power and the enrollment would depend upon the details of the associations that were to be tested. Potential questions would be whether specific features, mucosal or submucosal vascular alterations are associated with CRP clinical severity at any time point, if vascular alterations at baseline (treatment naïve patients) are associated with treatment response (number of RFA treatments), if mapping vascular features across the rectum can be used to guide RFA, etc. These hypotheses would require longitudinal studies with larger enrollment and are beyond the scope of this pilot study.

2) The Limitations and the Future Perspective must be comprehensively outlined.

We have made changes described previously to more clearly emphasize the limitations and future prospects for the study. The newly added section "Article Highlights" further summarizes these key aspects of the study.

Reviewer: 3

Reviewer's code: 00209021

The authors undertook a study concerning the feasibility of non-endoscopic assessment of chronic radiation proctopathy and radiofrequency ablation treatment follow-up with Optical Coherence Tomography angiography. They should be congratulated for this high quality study. The manuscript is well-written with adequate reference to the current medical literature in the field. The study can be published for educational purposes especially for clinicians in the field. However, the number of patients is not sufficient enough to draw concrete conclusions. The manuscript therefore should be shortened in a format of "brief report".

We thank the reviewer for their positive comments. We agree with the reviewer and other reviewers regarding the limitation of this study due to limited patient enrollment. As previously described in response to the other reviewers, we have made changes to disclose this limitation of the study and removed statements that could be misunderstood as concrete or comparative conclusions. We have made extensive revisions to the Abstract and Discussion in order to more clearly describe the features of OCTA which make it uniquely suited to investigate CRP, which has mucosal and submucosal vascular abnormalities as its hallmark. We also more clearly describe the features which are associated with CRP and treatment response, without speculating on future clinical utility.

Word Journal of Gastroenterology does not have a Brief Report section, and we felt that the Observational Study section fits best with our study design and objectives. Other journals that offer Brief Report format typically have limited word allowances, and we would like to publish our results in Word Journal of Gastroenterology, which preserves the meaningful Introduction, Methods and Discussion sections that would be needed to clearly describe the relatively complex OCTA technology and the preliminary findings in CRP. As noted by the reviewer, we hope that unique features of this study will be of interest for clinicians and serve as a reference for OCTA technology as well as a benchmark for planning larger scale studies.