

Dear Editor,

Thank you very much for your e-mail message dated March 6th 2014 concerning our article Ref. ESPS Manuscript NO: 9168, entitled "Poor agreement between endoscopists and pathologist for the interpretation of probe - based confocal laser endomicroscopy (pCLE) findings "

Today we submit our revised manuscript in Word format (file name: Manuscript WJG-revised.doc) following your instructions with all changes precisely indicated in the text; deletions are also obvious.

We also upload the "Copyright Assignment", the current file "Answering Reviewers", and images files in ppt format ("figure1.ppt", "figure2.ppt" and "figure3.ppt").

This work has not been published nor is under consideration elsewhere and I clearly state that all co-authors have seen and agreed with the contents of the manuscript. In addition, all authors have substantially contributed to this work and they have not any financial, consultant or institutional conflict of interest.

We are very grateful to you and the assessors for the helpful and thoughtful recommendations. We believe that we addressed all of them satisfactorily. All of us feel that our paper has now been significantly improved. Point to Point reply to reviewer comments are addresse below:

Reviewer #1) This paper aims to compare the interpretation of pCLE findings between endoscopists and gastrointestinal pathologists, in order to achieve a better diagnostic reproducibility and confirmation of interpretation of in vivo images in situations where results are indeterminate or the degree of dysplasia vs. neoplasia is unclear. The topic is of potential interest in clinical practice to define and improve the outcome in endoscopic diagnosis. The paper is only focused on the analysis of the differences in interpretation by the two specialists. Although the study is planned so correct enough, it contains limitations that make the paper a pilot study which could be supplemented with more extensive observations and rigorous statistical. Moreover, there are some methodological issues that need to be correctly and clearly explained.

We thank the reviewer for the valuable comments and agree it is an initial study in that direction.

- a) In the first paragraph of Study design is stated that "Patients underwent endoscopy with biopsy ... and were followed immediately by pCLE"; however, in the second one is stated that "pCLE interpretation was done immediately and results were recorded in

Excel worksheets. Subsequent biopsies were taken from all studied areas". A point of capital importance is that the biopsy should be collected after the detection of the lesion, after the interpretation of the image collection via pCLE, and above all in the exact site that has been documented. This is not clearly described, but a little rigorous investigation method makes the results insignificant. Which procedure was used?

This has been corrected in the study design and as pointed out biopsies were collected after the detection of the lesion and after the interpretation of the image via pCLE. The exact site where the images studied as well as the biopsies taken were documented in the excel worksheets.

- b) The assessment made by a single pathologist without a consolidated experience, may be affected by subjective elements: it is referred to a particular situation and not to an entire category. Ultimately, the data has little value as indicator and cannot be generalized. This should be reported as a main limitation of the study.

We have included this major point as a limitation in the study (discussion part)

- c) It is quite amazing the final result where pathologists have less ability to interpret the images of the lesions. The level of expertise achieved by endoscopists and pathologists in the interpretation of the images should be standardized. It should be better specified what is "the special training with formal certification" reported in the "Learning phase" chapter.

As advised the learning phase of both the groups have been expanded.

- d) It is not reported whether pathologists have viewed the images of the endoscopic lesions, as well as those collected with pCLE. This could create a gap, if endoscopists have more elements for the diagnosis, being able to take diagnostic elements also from the macroscopic aspect of the lesion.

The pathologist did not view the endoscopic images and relied solely on the pCLE images and this is mentioned as pointed out as an advantage for the endoscopist in interpreting results and thereby having more elements for diagnosis. This has been added to the discussion.

- e) For a proper assessment of the comparison between different interpretations of pCLE by endoscopists and pathologists, when there is a discrepancy, each interpretation should be assessed in the light of the histological examination of the same sample, and statistically evaluated. These results are not reported in detail in the paper; but it would be important for understanding who gives the most accurate information with respect to

the final diagnosis, and in case, for indicating what criteria can direct to a more correct interpretation.

We acknowledge this valid point, all interpretation done was assessed in the light of the histological examination of the same sample (which was kept as the gold standard for final diagnosis) the statistical analysis was done based on this. We have corrected this point in the methodology.

- f) The discussion needs to be better written. Some sentences are unclear; there are repetition and redundancy; reading becomes difficult and often unclear. Minor revisions:- P value has a cross in the last three strips of table 2: what does the cross mean?- There are some type errors.

As advised, the discussion has been modified, we have removed the repetition of sentences to make it clearer. Also the type errors as pointed out are checked again. The cross in the P values have been corrected and interpretations given.

Reviewer #2) Review of "Poor agreement between endoscopists and pathologists for the interpretation of probe-based confocal laser endomicroscopy (pCLE) findings" Dear editor: Thank you for inviting me to review this interesting manuscript. The authors should be commended for conducting a well thought out study bringing to light the "real world" differences one might encounter with the interpretation of images using the confocal laser endomicroscopy (pCLE) technology if the pathologist is not present in the room during the procedure. The study is broad and covers much different pathology, not choosing to focus on specific pathologic locations or lesions but assessing the sensitivity, specificity and accuracy of confocal microscopy for endoscopists and pathologists, then comparing those rates. It is interesting and surprising that the endoscopist might be better able to define the nature of the lesion in real time compared with the pathologist. Obviously, this is an initial study and further, larger studies are needed to clarify the sensitivity and specificity of this technology in specific lesions and pathologies based upon the thought provoking results presented here.

We thank the reviewer for the valuable comments and have addressed the corrections as shown below:

- a) Introduction: The last paragraph does not flow well or clearly state the goals of the study. Please rework and revise. Also, the sentence starting with "While we postulated..." the term latter is misspelled as "later." In the same sentence, following therefore, I do not think the word "either" belongs. It appears it should be deleted.

As pointed out, we have modified the paragraph to clearly state the goals of the study. The corrections of the sentence have been made

- b) Methods: Next to the heading “Study Design” there is a period that needs to be deleted. Please expand the learning phase paragraph. As a gastroenterologist reading the article, readers will likely be interested in what the learning curve for this tool might be. Specifically, what are some of the topics of the videos? Is this a standardized training set from the Cellvizio Company? How many hours (approximately) does it take to train for this technique? Please comment on the endoscopists previous utilization of this technology. Was everyone naive to this tool? Please also comment on whether the pathologist has had any experience with this prior to the study.

As advised this part “Study Design” of the manuscript has been modified accordingly.

- c) Results: Table 2: The p-values appear to have a cross but there is no definition for what the cross signifies. Please define this.

This has been corrected and defined.

- d) Discussion: There appears to be a redundancy in the second sentence of the first paragraph of the discussion. Specifically, “for malignant and dysplastic lesions,” should be deleted prior to “the concordance for benign lesions was suboptimal.” Otherwise, the sentence does not make sense. The fifth paragraph needs to be re-written (Paragraph starting with “The findings may be interpreted...”) This paragraph is trying to convey important ideas, but they remain unclear. Specifically, the sentence starting with “We did not try to replace their individual potential roles...by specific targeting of relevant areas.” The point of the sentence is unclear and needs clarification. Please add a space between in and apparent in the paragraph highlighting Dunbar et al. (5th line prior to “BE neoplasia”). In the same paragraph, last sentence seems to be saying the same thing as the sentence prior. Please either reword the two sentences or combine into one. One thing that should also be addressed in the discussion is that the endoscopist has the advantage of viewing the lesion macroscopically prior to the application of the confocal microscopy and although these lesions are indeterminate previously, the endoscopist has the benefit to control the scope, the angles of visualization (addressed in manuscript) and the knowledge of what they saw. Please address this in the discussion as well. Consider moving the paragraph regarding the pathologist being present in the room with the endoscopist to later in the discussion as this seems to be an essential take home message from this study.

These valid points have been addressed and corrections made as advised in the discussion part.

All corrections are highlighted when the revised manuscript

Once again, I would like to thank you and the referees for your helpful suggestions and for giving us the opportunity to submit our revised manuscript in the World Journal of Gastroenterology.

Sincerely yours,

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