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Damian Garcia-Olmo, MD, PhD
Editor-in-Chief
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Dear Editor;

We wish to re-submit the attached manuscript. The manuscript ID is 35182.

The manuscript has been rechecked and appropriate changes have been made in accordance with the reviewers' suggestions. The responses to their comments have been prepared and attached herewith. The manuscript has also been reviewed by native speaker.
We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a better and more balanced account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

Thank you for your consideration. I look forward to hearing from you.

Yours sincerely,

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Revision for "In vivo histological diagnosis for gastric cancer using endocytoscopy" (ESPS Manuscript NO: 35182)

Reviewer #1
Reviewer's code:02954023

1. Even though it is a normal gastric mucosa, it is different in the antrum and the body part (Page 8). Please clarify. In addition, gastric inflamed mucosa with H.pylori infection is not "normal". The status of H.pylori infection should be written.

As you point out, the surface structure of the antrum and the body are different even in normal mucosa. The reason for this difference is that in the normal mucosa, the antrum image shows pyloric gland mucosa while that of the body shows fundic gland mucosa. We have added an encocytoscopic image and a histopathological image of the fundic gland mucosa as Figs 1A and 1B.
I agree, as you mention, that the patient's H. pylori infection status is very important. We have added this information to Table 1.

2. The authors present estimates of sensitivity and specificity – they should be presented with 95%CI – especially given the limited sample size. Further, the calculations should be specified and described in the Statistical analysis section.

Thank you very much for your valuable comment. We have added the 95%CI numbers pertaining to the sensitivity, specificity, PPV, NPV, and accuracy parameters. In accordance with your comments, we have revised the description in the "Statistical analysis" sub-section.

3. This study did not include patients with adenoma. This is also a limitation.

Thank you very much for the important observation. We have added a sentence mentioning that adenomas were not included in our study, and acknowledged this as a study limitation.

4. The usefulness of endocytoscopy in the diagnosis of ulcerative colitis (e.g., Nakazato et al. 2017 Endoscopy) and lung cancer (e.g., Shah et al. 2017 Respiration) has been reported as well as that of esophageal, gastric and colorectal cancers. To strengthen your claim of usefulness of endocytoscopy, how about describing these information (Page 6)?

Thank you. Based on your comment, we have quoted two relevant articles, one each, by Shah et al. (reference 8), and by Nakazato et al (reference 9.)

5. Please indicate the Ethics Committee approval number (Page 6).

The Ethics Committee approval number was 911, and this information has been added to the revised manuscript in the "MATERIALS AND METHODS" section.

6. In addition to references 8-9, other literature (Kumagai et al. 2017 Endoscopy) also assessed 11 cases of gastric cancer (Page 6 and 10).

Thank you very much for your valuable comment. we have now quoted the relevant paper by Kumagai et al. as reference 12.

7. The experience of a single expert endoscopist (I.T.) should be written (Page 7).

We have provided the necessary information in the revised manuscript. The endoscopist is a Board certified fellow of the Japan Gastroenterological Endoscopy Society.

Reviewer #2
Reviewer's code:02445538

Major
1. What is the primary endpoint of this study? Diagnostic accuracy of histology by endocytoscopy? Diagnostic concordance rate between endoscopist and pathologist?

Thank you very much for the detailed review and suggestion. The primary endpoint of our study was diagnostic accuracy, and the secondary endpoint was diagnostic concordance rate between the endoscopist and the pathologist. To clarify this point, we added a sub-section entitled "Outcome measures" to the "MATERIALS AND METHODS" section of the revised manuscript.

2. In the results section, the authors showed some demonstrable, endocytoscopic and histologic images of the background mucosa with and without intestinal metaplasia and gastric cancer area. I don't think these are "results". If the authors want to emphasize these as results, they should define the grade of atypia by endocytoscopy prior to this study (in the methods section), and subsequently the comparison between histology and endocytoscopic atypia should be evaluated in the results section. Sample numbers of normal mucosa and intestinal metaplastic

mucosa should be also shown in Table 1. I think that the “results” which the authors described in the result section should be moved to the “methods” section as definitions of endocytoscopic findings...

Thank you very much for your valuable comment. We have created a sub-section called “Definitions of endocytoscopic findings compared to histopathological images” and moved it from the “RESULTS” section to the “MATERIALS AND METHODS” section.
Sample numbers of normal mucosa and intestinal metaplastic mucosa have been added to Table 1.

3. Since this is a retrospective study, the title “In vivo real-time histological diagnosis…” seems to be strange as the authors mentioned in the limitations. The title should be changed.

I agree with your comment. Endocytoscopic images were obtained in vivo but the diagnosis was not made real-time. We have omitted the word “real-time” from the title.