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Andrzej S Tarnawski, DSc, MD, PhD, Professor.
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Dear Editor;

We wish to re-submit the attached manuscript. The manuscript ID is 45412.

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 "Utility of Linked Color Imaging for Endoscopic Diagnosis of Early Gastric Cancer" (Manuscript NO: 45412)

Reviewer #1
Reviewer's code:03002038

Major

1. The results of the current study are similar to the previously published study on this topic (BMC Gastroenterology 2017; 17:150) and therefore I feel that the current study does not add anything significant to the current knowledge on this topic.

Reply: Thank you for all of your comments on the manuscript. In the well-known article in BMC Gastroenterology, five experts and five non-experts evaluated how much a lesion is easier to recognize using BLI-BRT and LCI compared to WLI, and concluded that it is easier to recognize the lesion with LCI, regardless of experience. Our study also showed that LCI makes it easier to recognize lesions than WLI. However, in addition to a subjective judgment, we used objective color evaluation based on CIE 1976 L*a*b* color space. Furthermore, we performed pathological analysis of the surface blood vessel density, and we found that this density in cancer lesions was significantly higher than that in non-cancer areas. Therefore, we think that this study does add significant knowledge on this topic. We have also corrected the obscure phrases and grammatical errors in the text.

2. **Main hypothesis of your article should be more carefully demonstrated with reliable references. You concluded that color differences may be diagnostic to differentiated neoplastic lesion from non- neoplastic lesion. To support this result, you showed that color differences might be resulted from the differences of vascular density between neoplastic lesion vs non neoplastic lesion. However, the related reference you showed is only one. To robust, and concreate your assertion, more reliable references and careful discussion is necessary such as vascular density is independent factors for differentiating neoplastic lesion vs non neoplastic lesion.**

Reply: Our results showed that the difference in color may result from the difference in surface blood vessel density. We have added related references in the Discussion, which were the basis for measuring the difference in surface blood vessel density.

24. Adachi Y, Mori M, Enjoji M, Sugimachi K. Microvascular architecture of early gastric carcinoma. Microvascular-histopathologic correlates. Cancer 1993; 72: 32-6. [PMID : 8508426]

25. Takemura S, Iwashita A, Yao K, Yao T. The correlation between the quantified microvascular density and the endoscopic color in elevated type of gastric neoplastic lesions. Gastroenterol Endosc 2002; 44: 745-54 [DOI : 10.11280/gee1973b.44.745]

26. Honmyo U, Misumi A, Murakami A, Mizumoto S, Yoshinaka I, Maeda M, Yamamoto S, Shimada S. Mechanisms Producing Color Change in Flat Early Gastric Cancers. Endoscopy 1997; 29: 366-371. [PMID: 9270917 DOI: 10.1055/s-2007-1004217]

3. There are enormous previous reports that not the vascular density, but the vascular architecture is the determining factor for differentiating cancer lesion from non- cancer lesion. However, in this article, you just studied the differences of vascular density. Is it reasonable to differentiate cancer lesions just with vascular density?

Reply: Previous work on vascular architecture was mainly based on magnified endoscopic images. In our study, we used non-magnified LCI and therefore the main object is the gross vasculature of the surface, rather than the single architecture of each vessel. Since a complex vessel running can cause an increase in vessel volume and density, blood vessel density in our study was probably closely related to the architecture of blood vessels. We have added comments on this issue in the Discussion section.

5. Result session, in Table 1, you did not demonstrated the characteristics of color among tumor lesions such as red, white, or isochromatic. As for the image enhanced endoscopy such as LCI is used for clinical care, LCI is to capture the differences between lesions which looks similar color though naked eyes or white light imaging.

Reply: Thank you for this comment. As suggested, we have added the subjective color category in Table 1.

6.' non neoplastic lesion' or 'neoplastic lesion' are not the right term. You did not include the adenoma or advanced gastric cancer. Non cancer lesion vs cancer lesion might be more proper in this study.

Reply: As requested, we have changed the term to "cancer/non-cancer" instead of "neoplastic/non-neoplastic" in the text and figures.

7. In this study, three of endoscopist retrospectively reviewed the images of LCI and WLI. However, it could be biased because they know what image is taken by LCI or WLI.

Reply: This is a good point, and it is one of the limitations in the study because recognition of WLI or LCI is obvious for an expert endoscopist. To overcome this bias, we used objective color evaluation based on CIE 1976 L*a*b* color space. We have added this content in the limitation part of the Discussion section.

8. When the LCI is helpful to detect cancer lesion, the margin positive rate of targeting cancer after ESD might be higher. However, in this study, not only you did not showed the successful rate of the clear resection of cancer, but also did not compared the rates between LCI and WLI.

Reply: In this study, we took both WLI and LCI images prior to ESD, and we determined the range of resection based on both images. Therefore, we could not compare the margin-positive rates of WLI and LCI. All cases were completely resected and were margin free. We have added this content in the Results section.

9. You analyzed the color differences of non neoplastic vs neoplastic lesions. What is the standard guidelines for your study to pointing the non neoplastic lesion? Non neoplastic lesion includes erosive lesion, or atrophic lesion, and so on. You should stratify and analyzed in these lesion. Because, in this lesion, erosive lesion might be

calculated red, and atrophic lesion might be calculated white. LCI also function in aforementioned lesions?

Reply: As the reviewer points out, non-cancer areas showed several colors in WLI and LCI, such as white, red, and isochromatic. For each case, we picked two regions of interest on the ESD specimen: one in a cancer lesion and one in a non-cancer area. In both the lesion and the non-cancer area, we chose an average site with no particular characteristics. Therefore, non-cancer areas did not include erosive lesions. Because most cases were differentiated cancers, the surrounding mucosa is atrophic. We added this content in the Methods section.

Reviewer #2
Reviewer's code:03017516

The authors report the use of linked color imaging for diagnosis of early gastric cancer. The manuscript is well written and the aim and methods are clear. The results are interesting. The main limitation of the study is the low number of enrolled patients. What is the impact of these findings on the clinical management of patients? Can you better detail this topic in the discussion?

Reply: Thank you very much for your comments. We agree that a limitation of the study is the small number of patients, and this has been made clear in the revised manuscript. Regarding clinical management, we believe that our finding can lead to improved diagnosis of cancer lesions, based on objective evaluation using CIE 1976 L*a*b* color space. We added this content to Discussion section.