

## List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Comparison of optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial" (Manuscript NO: 59684). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portions are marked in red in the paper. The main corrections in the paper and the responses to the reviewer's comments are as follows:

### **Reviewer #1:**

#### ***Specific Comments to Authors:***

*This is a comparative study of ME-OE vs ME-AAC for GIM. The authors concluded that ME-OE is more efficacious for endoscopic evaluation of GIM a precancerous lesion. The article is very interesting for publication. Some issues for further clarification:*

*The main finding that LBC sign under ME-OE is a proof of GIM is already known. However this study does not add any new finding to the already known. No method to differentiate the low to high-grade dysplasia in GIM is given. GIM is important however more important is the endoscopic evaluation and identification of GIM with dysplasia. Such information is not given here.*

**REPLY:** Thanks for your comments. OE is a newly developed endoscopic technology and today commercially available. However, to the best of our knowledge, less study has been conducted to evaluate the efficacy of OE for GIM detection. In addition, there is a scarcity of data regarding the diagnosis of GIM using only acetic-acid chromoendoscopy combined with magnifying endoscopy (ME-AAC) or optical-enhanced magnifying endoscopy (ME-OE). This is also the first study to investigate the inter- and intra-observer agreement for GIM judgment using ME-OE. In spite of its limitations, the strengths of the study included the in-depth analysis of the reasons for the differences in accuracy and operation time of various endoscopic techniques on the basis of previous similar studies. As I mentioned in my article, Uedo et al have reported that the detection of LBC on the surface of gastric mucosa epithelium in ME-NBI may be a unique endoscopic manifestation related to intestinal metaplasia, the principle of ME-OE is similar to that of ME-NBI. But

they are two different technologies(such as LCI/FICE), I agree with both GIM (gastric intestinal metaplasia) and GIN (gastric intraepithelial neoplasia) are all important, the focus of this study is to highlight GIM, I'll talk more about GIN in future studies.

**Reviewer #2:**

***Specific Comments to Authors:***

*The study is aimed to directly compare the diagnostic value of white-light endoscopy, acetic-acid chromoendoscopy combined with magnifying endoscopy, and optical-enhanced magnifying endoscopy for detection of gastric intestinal metaplasia. The title is "Comparison of optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial".*

***1. Several factors influence the outcome of the study. Please discuss these.***

**REPLY:** Thanks for your comments. We are very sorry for our unclear description.

It is really true as Reviewer suggested that our aim is to directly compare the diagnostic value of WLE, ME-AAC, and ME-OE for detection of GIM. First, we compared the diagnostic accuracy of three endoscopic methods for patients with GIM, second, WLE is only a preliminary identification of abnormal areas, so the diagnosis time of WLE is not evaluated. we just compared the time required for ME-OE and ME-AAC to diagnose GIM. Due to the limitation of the number of words in the article, we made a retrospective analysis of the pictures taken with ME-OE.

We have added some words or sentences to the manuscript in the hope of reducing readers' confusion.

**Title**

Comparison of **white-light endoscopy**, optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial.

**RESULTS**

*Secondary endpoints*

**White light endoscopy is only a preliminary identification of abnormal areas, so the diagnosis time is not evaluated.**

**DISCUSSION**

Our study shows that ME-OE is more **advantage** than WLE and ME-AAC in

the diagnosis of GIM.

***2.Please review the literature and add more details in the discussion section.***

**REPLY:** Thanks for your comments. Considering the Reviewer's suggestion, we added details of the literature in the discussion section. We deleted some unnecessary sentences, and based on the data, we discussed the shortcomings of WLE and ME-AAC in the diagnosis of GIM, and explained the reasons why ME-OE can better diagnose GIM. According to the latest literature, we added the impact of practice and experience on endoscopic techniques. Finally, we re-expounded the conclusions of our study, so that readers can more clearly understand the impact of our study on clinical practice.

## **DISCUSSION**

1. As WLE cannot adequately predict the presence of GIM.
2. These results demonstrate that WLE has a low diagnosis rate of GIM, so it may not be suitable for the diagnosis of GIM.
3. According to the available data, there seems to be no significant difference between the use of AAC without magnification and the use of ME-AAC in the diagnosis of GIM. In our study, we did not use AAC without magnification to diagnose GIM, and we will confirm our speculation in future studies.
4. Due to the nature of the NBI filter, the resulting light is very weak, so the image is very dark. However, this drawback is compensated by OE. This may bring some benefits to diagnosing GIM.
5. This finding is relevant, because, at present, sufficient evidence on the usefulness of ME-OE for GIM was lacking. Our study shows higher diagnostic capability of ME-OE compared with the other two techniques, proved that LBC diagnosis of GIM is also applicable to ME-OE.
6. ESGE suggests competency in optical diagnosis can be learned by attending a validated optical diagnosis training course based on a validated classification, and self-learning with a minimum number of lesions. From a study viewpoint, in expert hands, optical diagnosis has been demonstrated to be very helpful in predicting the histology, Endoscopic experience can help to

improve the diagnostic accuracy of GIM, and does have some influence on diagnostic reliability.

7. Despite the established association with increased gastric cancer risk, the diagnosis of GIM presents a dilemma for many gastroenterologists. WLE in the diagnosis of GIM seems impracticable, the ability to diagnose ME-AAC is modest and spend a significant amount of time. The study adds to our understanding of the diagnosis of GIM by ME-OE. And the ability of ME-OE to diagnose GIM was significantly better than that of ME-AAC and WLE, the method not only is high accuracy but also simple to perform with ME-AAC and saving time. Furthermore, endoscopic experience and education are needed to raise the diagnostic accuracy of GIM.

1 Castro R, Rodriguez M, Libanio D, Esposito G, Pita I, Patita M, Santos C, Pimentel-Nunes P, Dinis-Ribeiro M. Reliability and accuracy of blue light imaging for staging of intestinal metaplasia in the stomach. *Scand J Gastroenterol* 2019; 54(11): 1301-1305 [PMID: 31680561 DOI: 10.1080/00365521.2019.1684555]

2 Ji R, Liu J, Zhang MM, Li YY, Zuo XL, Wang X, Li YQ. Optical enhancement imaging versus acetic acid for detecting gastric intestinal metaplasia: A randomized, comparative trial. *Dig Liver Dis* 2020; 52(6): 651-657 [PMID: 32265143 DOI: 10.1016/j.dld.2020.02.010]

3 Wei N, Mulmi Shrestha S, Shi RH. Markers of gastric intestinal metaplasia under digital chromoendoscopy: systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2020 [PMID: 32675780 DOI: 10.1097/MEG.0000000000001834]

4 Dekker E, Houwen B, Puig I, Bustamante-Balen M, Coron E, Dobru DE, Kuvaev R, Neumann H, Johnson G, Pimentel-Nunes P, Sanders DS, Dinis-Ribeiro M, Arvanitakis M, Ponchon T, East JE, Bisschops R. Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy* 2020; 52(10): 899-923 [PMID: 32882737 DOI: 10.1055/a-1231-5123]

5 Huang RJ, Choi AY, Truong CD, Yeh MM, Hwang JH. Diagnosis and

Management of Gastric Intestinal Metaplasia: Current Status and Future Directions. Gut Liver 2019; 13(6): 596-603 [PMID: 31394893 DOI: 10.5009/gnl19181]

**3. What is the new knowledge from the study?**

**REPLY:** Thanks for your comments. OE is a newly developed endoscopic technology and today commercially available. However, to the best of our knowledge, less study has been conducted to evaluate the efficacy of OE for GIM detection. In addition, there is a scarcity of data regarding the diagnosis of GIM using only acetic-acid chromoendoscopy combined with magnifying endoscopy (ME-AAC) or optical-enhanced magnifying endoscopy (ME-OE). This is also the first study to investigate the inter- and intra-observer agreement for GIM judgment using ME-OE. As I mentioned in my article, Uedo et al have reported that the detection of LBC on the surface of gastric mucosa epithelium in ME-NBI may be a unique endoscopic manifestation related to intestinal metaplasia, the principle of ME-OE is similar to that of ME-NBI. But they are two different technologies. Our results also proved that LBC diagnosis of GIM is also applicable to ME-OE.

To clarify what is new about the study, I added some sentences in the discussion section.

1. As WLE cannot adequately predict the presence of GIM
2. These results demonstrate that WLE has a low diagnosis rate of GIM, so it may not be suitable for the diagnosis of GIM.
3. According to the available data, there seems to be no significant difference between the use of AAC without magnification and the use of ME-AAC in the diagnosis of GIM. In our study, we did not use AAC without magnification to diagnose GIM, and we will confirm our speculation in future studies.
4. Due to the nature of the NBI filter, the resulting light is very weak, so the image is very dark, However, this drawback is compensated by OE. This may bring some benefits to diagnosing GIM.
5. This finding is relevant, because, at present, sufficient evidence on the usefulness of ME-OE for GIM was lacking. our study shows higher diagnostic

capability of ME-OE compared with the other two techniques, proved that LBC diagnosis of GIM is also applicable to ME-OE.

6. the ability of ME-OE to diagnose GIM was significantly better than that of ME-AAC and WLE, the method not only is high accuracy but also simple to perform with ME-AAC and saving time. Furthermore, endoscopic experience and education are needed to raise the diagnostic accuracy of GIM.

***4.Finally, please recommend the readers "How to apply this knowledge for routine clinical practice?"***

**REPLY:** Thanks for your comments. We are very sorry for our negligence of apply this knowledge for routine clinical practice, In the revised manuscript, we added the importance of theoretical learning and practice to endoscopic operation.

I added some sentences in the discussion section.

ESGE suggests competency in optical diagnosis can be learned by attending a validated optical diagnosis training course based on a validated classification, and self-learning with a minimum number of lesions. From a study viewpoint, in expert hands, optical diagnosis has been demonstrated to be very helpful in predicting the histology, Endoscopic experience can help to improve the diagnostic accuracy of GIM, and does have some influence on diagnostic reliability.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.