July 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11030-Review.doc).

Title: Diagnosis of early gastric cancer using narrow band image and acetic acid

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1

Major comments

(1) It is known that gastric cancer has heterogeneity in histology. Please explain how you handle the tumors with mixed histological type.

Answer: In our study, we have not evaluate mixed type of EGC. In future study, we will evaluate the association between endoscopic finding and histological type in mixed type of EGCs.

(2) The author should describe the reason why EME improve diagnostic yield. I guess the unclassified lesion decreased in EME (table 4).

Answer: We agree your comment. The decrease of unclassified lesion improved the diagnosis of EGCs in our study. We added the sentence 'The decrease in unclassified lesions with the NBI-EME combination resulted in improvement in the diagnosis of differentiated adenocarcinoma.' in Discussion.

Minor comments

(1) In NBI-EME combination section; The used endoscope is GIF-Q260Z. Is it right? I think it's GIF-H260Z.

Answer: We corrected Q260Z to H260Z in our manuscript.

(2) The author should mention table 1 in the manuscript.

Answer: We added the sentence 'The clinical characteristics of the patients enrolled in this study are summarized in Table 1. A total of 90 EGC lesions in 72 patients were analyzed. Histopathologically, 67 lesions (74.4%) were diagnosed as differentiated adenocarcinomas, and 23 lesions (25.6%) were undifferentiated adenocarcinomas. The depth of tumor invasion was mucosal in 93.3% (84/90) and submucosal in 6.7% (6/90).' in Result.

Reviewer 2

(1) In the Results section, two of the three figures of Figure 1 and Figure 2 are duplicated, I don't think it is necessary to separate these identical figures. All the figures should be equal in measure. In addition, the authors should provide a normal control of MV as well as MS patterns to make a comparison with their results.

Answer: We provided normal controls of MV and MS patterns and changed Figure 2B, 2C, and 2D. All Figures were almost equal in measure.

(2) The authors performed the statistical analysis for Table 2 #1 and #2, however, these results were only stated in the manuscript but not under or inside the tables, which make the results hard to read.

Answer: We added the statistical data in Table 2.

(3) In the Results section, the authors claimed: "…and 58 of 59 lesions, including 25 with fine-network patterns and 34 with MS patterns, were adequately diagnosed as differentiated adenocarcinoma (98.3%)…, I have read the paper for many times but still hard to understand the data.

Answer: We corrected the sentence 'In 59 lesions, including 25 lesions classified into fine-network patterns by NBI-ME (Table 2, #2) and 34 lesions classified into MS patterns by EME (Table 4), 58 lesions (98.3%) were adequately diagnosed as differentiated adenocarcinoma.' in Results.

(4) The authors first examined the samples with NBI-ME and then with EME for the samples cannot be classified by the former, since the authors provided the data of NBI-ME alone, I think it is necessary to provide the data for EME alone and then make an analysis for these two methods.

Answer: We agree your comments. However, we performed the study which depressed-type EGCs were classified MV patterns by NBI-ME and then EGCs unclassified by MV patterns were classified MS patterns by enhanced ME (EME). As a result, we demonstrated that 76 of the 90 (84.4%) lesions were be able to match with histological diagnosis. In future study, we will perform both NBI-ME and EME in all EGC lesions and compare the value between NBI-ME, EME, and their combination in predicting histologic diagnosis.

Reviewer 3

(1) Methods: It does not seem clear if EME was performed for ALL lesions or only for those lesions

unclassified by NBI-ME. Importance should be given to comparison between both endoscopic methods (NBI-ME and EME) and their value in predicting histologic diagnosis. The McNemar test or Kappa value is usefull to establish this analysis.

Answer: We agree your comments. However, we performed the study which depressed-type EGCs were classified MV patterns by NBI-ME and then EGCs unclassified by MV patterns were classified MS patterns by enhanced ME (EME). As a result, we demonstrated that 76 of the 90 (84.4%) lesions were be able to match with histological diagnosis. In future study, we will perform both NBI-ME and EME in all EGC lesions and compare the value between NBI-ME, EME, and their combination in predicting histologic diagnosis. The McNemar test or Kappa value will be used for establishing the analysis.

(2) Results: According to the results presented, the EME evaluation was performed only for those tumors that remained unclassified after NBI-ME. It would be much more interesting to present the results for EME if they were really performed in all lesions.

Answer: We have answered your comments in (1).

(3) Discussion: Authors should elaborate more specifically on the value of predicting histological type differentiation, since the proper histologic diagnosis in biopsy specimens is required for every treatment modality in gastric cancer. What is the contribution?

Answer: Increased accuracy of histological diagnosis of depressed-type EGCs using the combination of NBI-ME and EME is possible to decide an appropriate therapeutic approach in the early phase of EGC. The altered morphology of EGC by biopsies was occasionally caused. It sometimes interfered with ESD treatment. Therefore, the final aim of our study is performing histologic diagnosis by the endoscopy without carrying out biopsies. We have revised the discussion.

(4) References: References are all before 2009 or 2010. Why? There were a few papers similar to this one published more recently that could have been mentioned.

Answer: We agree your comments. We added new references. (Ref #7, 10, 11, and 20)

7 **Tao G**, et al. Enhanced magnifying endoscopy for differential diagnosis of superficial gastric lesions identified with white-light endoscopy. *Gastric Cancer* 2014; **17**(1): 122-129

10 **Yamada S**, et al. An efficient diagnostic strategy for small, depressed early gastric cancer with magnifying narrow-band imaging: a post-hoc analysis of a prospective randomized controlled trial. *Gastrointest Endosc* 2014; **79**(1):55-63

11 **Eleftheriadis N**, et al. Acetic acid spray enhances accuracy of narrow-band imaging magnifying endoscopy for endoscopic tissue characterization of early gastric cancer. *Gastrointest Endosc* 2014; **79**(5): 712

20 **Nonaka K**, et al. Usefulness of the DL in ME with NBI for determining the expanded area of

early-stage differentiated gastric carcinoma. *World J Gastrointest Endosc* 2012; **4**(8): 362-367

(5) Tables: Tables 2, 3 and 4 are missing the total number of lesions analyzed in each of them.
Answer: We added the total number of lesions in Tables.

Reviewer 4
(1) The author should describe in detail how to judge MS pattern like the width of crypt in the materials and methods.
Answer: We classified width of crypt in EME images according to comparing with normal crypt size. We added the sentence 'The shape and regularity on EME images were classified according to the form of the mucosal surface, and the width of crypt was classified by comparison with normal crypt size.' in Materials and Methods.

(2) In the discussion, the authors should discuss more about their results.
Answer: We have revised the discussion.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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