ANSWERING REVIEWERS

September 27, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4925-Review.doc).

Title: The clinical significance of white gastric crypt openings via magnifying endoscopy

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4925

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

1 Format has been updated

We improved English grammar in the entire manuscript according to the English language editing company (American journal Experts), and got a recommendation letter.

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

Reviewer comment (#00001114)

(1) I am not sure the difference between this classification of COs whiteness and A-B classification by Dr. Yagi (Stomach and Intestine (Tokyo) Vol.42 No.5 (2007.04) P.697-704). It looks like that "white-edged dark spot" type is similar to B-0 type, "white" type is similar to B-1 type, and "DWP" type is similar to B-3 by Dr. Yagi. Please clarify the difference and where is a new finding.

Response: Yagi *et al*. described A-B classification. This classification is modified their former classification (Z-classification), and based on the combination of microsurface and microvascular patterns. (Type B-0 consists of pinhole pits, the network of true capillaries, and the regular arrangement of collecting venules; Type B-1 consists of round pits and a network of capillaries; Type B-2 consists of white pits and sulci; and Type B-3 consists of dilated white pits with surrounding microvessels.) Although this classification was considered useful, we often observed other combinations of microstructure and microvessel changes than those described in the A-B classification (e.g., pinhole pits without capillaries). The current study classified our observations into three types of ME findings based on the color of the gastric pits and found strong correlations with histological HP-induced inflammation and activity. Our classification is advantageous because it is simple and easy to understand and does not include variations in the combination of microstructure and microvessels.

We described in Discussion part 2nd paragraph.

(2) In this study, a round pit pattern was not detectable in 104/350 areas examined. I speculate that it is difficult to detect a round pit pattern in case of severe atrophy. So I wonder this classification is not enough for patients with H.pylori infection because about 30% areas were not detectable. Please discuss this point.

Response: As pointed by reviewer, the microsurface pattern changes a round pit pattern to vertical long pits, tubular and granular patterns with continuous HP inflammation. Thus, in the case of severe endoscopic atrophy, tubular and granular patterns (but not pit patterns) were often observed via ME. Given the difficulty of assessing histological inflammation (which differs from histological glandular atrophy) under endoscopic observations, our results suggest that ME is a useful method for predicting HP inflammation in detail. However, our ME classification might not be acceptable in cases with severe atrophy.

We described this limitation in Discussion part 6th paragraph.

(3) I was wondering if patients with H.pylori infection were clearly divided into one of the three type of COs whiteness. Because the authors described that COs whiteness correlated with histological inflammation. If so, it seems that COs pattern is various and it seems not to be a homogenous distribution, in other word, it seems to be possible that the same patient has various type of COs. Please explain if COs whiteness pattern

is homogenous or heterogeneous. If COs whiteness is heterogeneous, please show the way to decide the type of COs whiteness.

Respond: Several reports have described that the prevalence, distribution, and grade of HP-induced gastritis varies among individuals. We previously reported that the ME findings of the gastric mucosa in HP-infected patients are also heterogeneous in the stomach[15]. The present study investigated each case at two sites (the greater and lesser curvature of the upper corpus) because a multipoint evaluation of gastritis is important for assessing its status. Our results indicated that most round pit areas existed in the endoscopic non-atrophied area; furthermore, more were found in the greater curvature of the corpus. These results are in agreement with those of a previous report showing that gastric atrophy starts at the lower portion of the lesser curvature in the corpus, then extends to the upper portion and laterally involves the greater curvature[24]. The diagnosis for the CO whiteness grade seemed to be homogenous under magnified observations (see the figures). We diagnosed using maximum magnification at all sites; therefore, the CO whiteness types were recognized as a homogenous pattern using these narrow fields of view (approximately 2-mm squares).

We described in Discussion part 3th paragraph.

(4) Is an area examined by ME the same as one biopsied?

Respond: The microsurface structures of the non-cancerous areas in the greater and lesser curvatures of the upper gastric corpus were evaluated for the presence of patterns such as round pit, long pit, tubular, or granular. If areas with round pit microstructures were observed under maximum magnification, then we evaluated the whiteness of the gastric pit crypt openings (COs). Then, the specific area that had just been magnified was biopsied under magnification.

We added this sentence in Endoscopic procedure.

(5) Please comment if this method is reproducible or not in case of a different endoscopist performed this examination.

Respond: We thought it is reproducible study because we classified simply based on the whiteness of CO

without variations in the combination of microstructure and microvessels.

However, assessments of the inter- and intra-observer variability with regard to the classification of CO whiteness are required to generalize the diagnostic ability of our findings.

We described in limitation part.

(6) About the paragraph about gastric cancer in discussion, it seems to be too much speculation to consider the relationship between gastric cancer and COs whiteness pattern from this results.

Respond: We shorten the Discussion part and conclusion about diagnosis for *H. pylori* infection and gastric cancer, because the paragraph seems to be too speculation as reviewer's suggestion.

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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