

October 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13731-review.doc).



Title: Tolerability of magnifying narrow band imaging endoscopy for esophageal cancer screening

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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.

Please check the below response letter.

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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Response letter

We would like to thank you for allowing us to resubmit our manuscript (WJG-13731). The comments of the reviewers have been helpful in allowing us to revise our manuscript. We have been revised according to the reviewer's comments, and provided a point-by-point reply to each comment. As you can see, we agreed with most of the reviewer's comments and modified the original manuscript accordingly.

Thank you for your consideration of the revised version. Please consider this manuscript for the publication in *World Journal of Gastroenterology*.

Reviewer1.

This study aimed to compare the tolerability of magnifying NBI and lugol chromoendoscopy in the screening of esophageal cancer. The authors found the magnifying NBI had less adverse symptoms, less affecting HR and shorter procedure time. However, before reaching these conclusions, several issues needed to be considered and further clarified.

1. The reviewer commented "Procedure time, which includes the time spent on biopsy of the suspected lesions, may be affected by the total biopsy numbers. Since more biopsy procedures were done in the Lugol group, a longer total procedure time is anticipated." To answer the reviewer's comment, we evaluated procedure time in 44 patients without biopsy and added sentences in discussion. The added sentences are "To remove an effect of biopsy, we evaluated the adverse symptoms and esophageal observation time in 44 patients without biopsy. Twenty-four patients in the NBI group and 20 patients in the Lugol group were compared. The median esophageal observation time in the NBI group was 39 ± 14 seconds, and that in the Lugol group was 122 ± 134 seconds ($P < 0.001$)." in page 11 line 19.
2. The reviewer commented "Biopsy per se also may cause symptoms such as chest pain and more biopsy procedures performed in the lugol group may also cause more discomfort." To answer the reviewer's comment, we added sentences in discussion. The added sentences are "In the same way, the VAS scores for heartburn in the NBI group were significantly better than those in the Lugol group ($P=0.021$, ANOVA for repeated measures). There were no differences in the VAS scores for retrosternal pain between the two groups ($P=0.074$, ANOVA for repeated measures). These results enhanced the reliability of our conclusion (data not shown)." in page 11 line 24.
3. The reviewer suggested to show more clearly the biopsy criteria. To answer the reviewer's comment, we added sentences in materials and methods. The added sentences are "Biopsy specimens were obtained using disposable forceps from well demarcated brownish areas with abnormal IPCL and brownish color change, or from LVL greater than 5mm in diameter." in page 7 line 18.
4. The reviewer commented "in my personal experience, for patients undergoing magnified endoscopy, some patients may complain of throat pain and sometimes minor mucosa abrasion and bleeding due to large diameter of the magnifying endoscope. These adverse symptoms have not been evaluated in the present study." We totally agreed with the comment. In our study, magnifying endoscopes (GIF-H260Z, Olympus Optical, Tokyo, Japan) was used in all procedures to compare the difference of tolerability between the magnifying NBI endoscopy and the lugol chromoendoscopy. Thus, complain of throat pain and minor mucosa adhesion and bleeding were equal in both NBI group and Lugol group.
5. The reviewer commented "two endoscopists took part in the study. How about their endoscopy experiences and interobserver concordance?" To answer the reviewer's comment, we added sentences

in materials and methods. The added sentences are "Y.Y and R.T, with more than 5 years' experience with conventional endoscopy. They had experienced more than 2,000 esophagogastroduodenoscopies, and had more than 4 year of experience with NBI. R.T had specialist qualifications from the Japan Gastroenterological Endoscopy Society." in page 6 line 20. In addition, we added sentences in results "There was no significant difference between the two endoscopists with respect to the mean VAS scores for heartburn, retrosternal pain and dyspnea after the examinations, procedure time and change of vital signs in each group." in page 10 line 9.

6. The reviewer commented "In addition to the tolerability, the diagnostic yield/accuracy should also be considered. In the magnifying group, the esophageal observation time was reported as short as 25 sec, which may hamper the diagnostic yield." To answer the reviewer's comment, we added sentences in discussion. "It was reported that NBI is easily applied with a modicum of experience^[22]. A little training makes it possible to detect brownish areas in magnifying NBI. In this study, NBI endoscopy was performed with a mean time of 39 seconds enough to observe the entire esophagus if there was no well demarcated brownish area." in page 12 line 9.

7. The reviewer commented "The diagnostic performance, in terms of sensitivity and specificity, is also important in the comparison of different screening methods. What is the gold standard in the screening of the esophageal cancer? " As commented by the reviewer, the diagnostic performance is important in the screening. We previously reported that magnifying endoscopy with NBI has comparable sensitivity, superior specificity, and superior accuracy, compared with Lugol chromoendoscopy, in detecting esophageal cancer(ref 11). Furthermore, in this study, we demonstrated that magnifying NBI endoscopy reduced the adverse symptoms compared with lugol chromoendoscopy. We have described in discussion, "Although lugol chromoendoscopy is the current gold standard for screening for esophageal cancer, NBI endoscopy might be the first-choice endoscopy for screening in the future. NBI endoscopy is useful for screening because this modality is less likely to cause adverse symptoms and requires a short time to observe the esophagus." in page 12 line 4. We also described in discussion "for the initial endoscopy for esophageal screening of patients at high risk for esophageal cancer, lugol chromoendoscopy is recommended as best suited to predict the risk for esophageal cancer and to determine the intervals for surveillance and screening endoscopy. Then, from the second endoscopy on, we recommend that NBI endoscopy should be periodically performed as a painless screening procedure." in page 12 line 21.

8. The reviewer commented "The sample size was relatively small." As we have described in materials and methods, we conducted a preliminary pilot study and calculated sample size.

9. The reviewer commented "The title should be more specific." To answer the reviewer's comment, we changed the title. The title is "Tolerability of magnifying narrow band imaging endoscopy for esophageal cancer screening."

Reviewer2

I have the opportunity to review the manuscript entitled "Comparison of tolerability of the narrow band imaging endoscopy with lugo chromoendoscopy". The authors have demonstrated with 51 patients that NBI is better than lugol chromoendoscopy for esophageal cancer screening. I have any comment to do.

Thank you for your review.

Editor

A2. Thank you for your comments.

We added relevant data, but we did not show relevant data of ANOVA for repeated measures because there is no

relevant data.