

Format for ANSWERING REVIEWERS



July 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3652-Review.doc).

Title: Magnifying endoscopy for diagnosis of specialized intestinal metaplasia in short-segment Barrett's esophagus

Author: Nam Seok Ham, Jae Young Jang, Sung Woo Ryu, Ji Hye Kim, Eui Joo Park, Woong Cheul Lee, Kwang Yeun Shim, Soung Won Jeong, Hyun Gun Kim, Tae Hee Lee, Sung Ran Jeon, Jun Hyung Cho, Joo Young Cho, So Young Jin, Ji Sung Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3652

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

(1) No distinction is made between low-grade dysplasia and high-grade dysplasia as far as progression to adenocarcinoma is concerned i.e. it is not "rapid" in both.

>> I added below text and reference.

The latent period of transition to high grade dysplasia (HGD)/EAC is significantly shorter for patients with low grade dysplasia (LGD) (median of 2.75 years) than for patients without LGD (median of 9.88 years).

Reference) G. S. Dulai, P. G. Shekelle, D. M. Jensen, B. M. Spiegel, J. Chen, D. Oh and K. L. Kahn, "Dysplasia and risk of further neoplastic progression in a regional Veterans Administration Barrett's cohort." Am. J. Gastroenterol., vol. 100, pp. 775-783, Apr, 2005.

(2) Areas of dysplasia do not cause symptoms to my knowledge (Ref 10 - 12) - remove "symptomless".

>> I checked and removed "symptomless" as you had advised.

(3) What make of endoscopes were used?

>> Olympus GIF-Q240Z was used. It can be possible to extend up to eightyfold.

(4) And what was the magnification obtained?

>> The magnified images were obtained and analyzed with respect to pit patterns, which were simultaneously classified in five epithelial types (I. Small round, II. Straight, III. Long oval, IV. Tubular,

V. Villous) by Endo's classification.

(5) What was the concentration of MB used (typically 0.5%)?

>> 0.5% solution of methylene blue was sprayed over columnar mucosa. The excess of dye was flushed away with 50 ml of water after 2 min.

(6) How was reflux diagnosed?

>> It was histological diagnosis.

(7) If it is histological, then it should be 11/26.

>> As you had advised, I corrected number.

(8) The patients without RE – did they have a history of GERD?

>> The patients without RE did not have a history of GERD.

(9) A positive predictive value of 60% is probably too low to equate a type V epithelial pattern "might be characteristic". It is rather "compatible" with SIM.

>> As you had advised, I corrected.

(10) The fact that a combination of ME and MB staining may improve the diagnostic yield is not addressed.

>> I added below text and reference.

Sharma *et al.* reported that high magnification chromoendoscopy might be a useful clinical tool for the increased detection of patients with intestinal metaplasia. Statistically, there is no doubt that the results are improved when magnifying endoscopy performed with MB staining simultaneously, if both they are characteristics of SIM. In our study, MB-positive staining cannot be considered characteristic of SIM. So, we did not try to demonstrate that the simultaneous performance of ME and MB staining for improving the results.

Reference) Sharma P, Weston AP, Topalovski M, Cherian R, Bhattacharyya A, Sampliner RE. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. *Gut* 2003; 52(1): 24-27

(11) The time period mentioned in manuscript is 2002, I hope that is correctly mentioned. If yes, I am wondering what took authors so long to send this manuscript for publication?

>> The cause of long interval between the study and manuscript is just author's laziness, therefore we apologize these problem.

(12) The information authors give on types of pit patterns they saw in their cohort is appreciated.

>> The magnified images were obtained and analyzed with respect to pit patterns, which were simultaneously classified in five epithelial types (I. Small round, II. Straight, III. Long oval, IV. Tubular, V. Villous) by Endo's classification.

(13) I appreciate the link authors are trying to establish between pit pattern and intestinal metaplasia, however the numbers are too small in the present study (3 out of 5 patients with type V pit pattern).

May be the authors can enrol more patients to establish the link more strongly?

>> We agree with your comments. However, this study was very difficult to enroll the patients because of too many refusal of patients and its quite rare prevalence in Korea.

(14) Authors make a comment regarding a study by Dave et al that MB staining was associated with prolongation of endoscopy. I believe the same is true for even magnification endoscopy to look for pit pattern, which will also prolong the endoscopy. Authors need to probably justify this and also add a paragraph regarding advantages and disadvantages they foresee in use of this technology.

>> As your comments, both methods were time consuming and caused patient's discomfort. These are disadvantage of the study. I added below text

In summary, we found the usefulness of magnifying endoscopy for the diagnosis of SIM in patients with short-segment BE as preceding studies. But, we could not show the usefulness of MB chromoendoscopy. Because of we did not count the total number of biopsies, we could not confirm that both endoscopic examinations might decrease the number of biopsies, costs, and inspection time. We though both methods were time consuming and caused patient's discomfort. These are disadvantage of the studies.

(15) I am wondering why long segment patients were excluded? It would be a good information to have - pit pattern in long segment salmon colored mucosa and also pit-pattern correlation with histological diagnosis of BE. A statement regarding this choice must be included in the manuscript.

> The risk of progression to malignancy appears to increase significantly with increasing lengths of BE. However, there is conflicting evidence in the literature. Both short-segment and long-segment BE are biologically identical and have significant if not equivalent malignant potential. In addition, the patients with long-segment BE are very rare in Korea. So, we focused on short-segment BE in this study.

Reference)

A.P.Weston,P.Sharma,S.Mathur,S.Banerjee,A.K.Jafri,R.Churian,D.McGregor,R.S.Hassanein and M.Hall, "Risk stratification of Barrett's esophagus : updated prospective multivariate analysis." Am.J.Gastroenterol.,vol.99,pp.1657-1666,Sep,2004.

J.Martinek,M.Benes,P.Brandtl,T.Hucl,M.Vasicek,L.Voska,V.Lanska,V.NosekandJ.Spacak.(2008,Sep).

Low incidence of adenocarcinoma and high-grade intraepithelial neoplasia in patients with Barrett's esophagus : A prospective cohort study.

R.E.Rudolph,T.L.Vaughan,B.E.Storer,R.C.Haggitt,P.S.Rabinovitch,D.S.LevineandB.J.Reid,"Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus." Ann.Intern.Med.,vol.132,pp.612-620,Apr18,2000.

(16) Authors mention regarding a manuscript by Horwhat and mention that as Ref 13, however, I donot see that in the bibliography. I would urge the authors to please check their bibliography.

>> I'm terribly sorry. I checked and corrected bibliography.

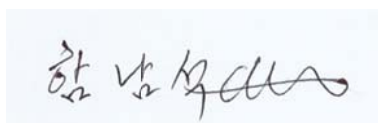
(17) Minor : Background section, second paragraph last line, there is word 'is' repeated, please correct.

>> As you had advised, I corrected.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink on a light blue background. The signature is written in Korean characters, appearing to be '한석남' (Ham Seok Nam), followed by a stylized flourish.

Nam Seok Ham, MD

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