September 30, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 21978-review.doc).

Title: Clinical Impact of Atypical Endoscopic Features in Rectal Neuroendocrine Tumors

Author: Jong Hee Hyun, M.D., Seong Dae Lee, M.D., Eui Gon Youk, M.D., Jae Bum Lee, M.D., Eun Jung Lee, M.D., Hee Jin Chang, M.D., Dae Kyung Sohn, M.D.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 21978

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

1. Before submitting, we were corrected English. Thus, we attached invoice.

2. As you recommended, abstract has been corrected.

3. Format has been updated

3. References and typesetting were corrected

Response to Reviewer's Comments.

Reviewer #1

1. The authors explored the association between atypical features and immunohistochemical staining, though I wonder whether it would also be valuable to analyze the association between endoscopic appearance and other factors such as mitotic rate (Ki-67) which also provides prognostic information, if these tests were obtained.

➔ **Response:** We thank the reviewer for this comment. We did not performed evaluation of mitotic rate routinely in our institution. Thus, we could not analyze the association between endoscopic appearance and Ki-67 index. We will be conducted analysis between endoscopic appearance and other factors in

further study.

2. The authors should comment on the role of endoscopic features in determining treatment of lesions 11-19 mm in diameter, in light of data from Gleeson et al (Gastrointest Endosc 2014) indicating that these lesions behave similarly to >20 mm lesions and their suggestion that any lesion of 11 mm or more should be further staged by EUS to help determine nodal status and depth of invasion.

➔ **Response:** We thank the reviewer for insightful comment. We have added the assessment and treatment strategy for rectal NETs 11mm -19mm in diameter.

- Page 11 Lines 11-13. The following revision was made

We suggest that rectal NTEs 11-19mm in diameter, which showed atypical features in endoscopic findings, should be performed the CT or EUS to evaluate the lymph node metastasis.

3. The atypical features are shown in Figure 2 and described in Table 3, but are not explicitly described in the text of the manuscript. Adding these descriptions may be helpful for the reader, as well as a mention in the conclusions which endoscopic features are most important to consider when examining a known carcinoid (depression, etc).

➔ **Response:** We thank the reviewer for insightful comment. We were adding description of the atypical features in legends of Figure 2.

- Page 17 Legends of Figure 2. The following revision was made

A) Semipedunculated type with hyperemia B) Semipedunculated type with erosio n and hyperemia, C) Sessile type with hyperemia D) An ulcerofungating types mi micking rectal cancer.

Reviewer #2

1. In the present study, the authors defined LNM as nodes > 3mm in diameter in the perirectal area or nodes > 1cm in diameter in the pelvis. As this criteria is not common, the authors should describe sensitivity and specificity of this criteria for LNM. Further, the authors should discuss about this criteria with limitation of this study.

➔ **Response:** We thank the reviewer for insightful comment. we have been using this criteria referenced by Rifkin et al. " Staging of rectal carcinoma: prospective comparison of endorectal US and CT. *Radiology* 1989" and Balthazar et al. "Carcinoma of the colon: detection and preoperative staging by CT. *AJR* 1988". This criteria showed about a sensitivity of 73% and a specificity of 58%.

- Page 12 Lines 8-12. The following revision was made

To evaluate the lymph node status, we were using criteria that distinguished positive

node which showed >3mm in diameter in perirectal area or >1cm in diameter in the pelvis[11,12]. These criteria showed about a sensitivity of 73% and a specificity of 58% in previous reports. Thus, we have to consider a difference between CT finding and pathology.

- Reference No.11-12 was revised

11 **Rifkin MD**, Ehrlich SM, Marks G. Staging of rectal carcinoma: prospective comparison of endorectal US and CT. *Radiology* 1989; **170**(2): 319-322 [PMID: 2643135 DOI: 10.1148/radiology.170.2.2643135]

12 **Balthazar EJ**, Megibow AJ, Hulnick D, Naidich DP. Carcinoma of the colon: detection and preoperative staging by CT. *AJR American journal of roentgenology* 1988; **150**(2): 301-306 [PMID: 3257314 DOI: 10.2214/ajr.150.2.301]

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

Sincerely yours,

Dae Kyung Sohn
Center for Colorectal Cancer, Research Institute and Hospital,
National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do
410-769, South Korea
E-mail: gsgsbal@ncc.re.kr
Tel: +82-31-920-1636, Fax: +82-31-920-1289