Editor-in-Chief of *World Journal of Gastroenterology*

July 5th, 2017

Dear Sir:

Thank you very much for the decision letter of June 23rd, 2017 with respect to our manuscript (34785 “Novel predictors for lymph node metastasis in submucosal invasive colorectal carcinoma”) together with comments. We have made the necessary corrections and clarifications in the manuscript after going over the reviewers’ comments. The corrected portions in the revised manuscript were marked in red. Below we specify what we have done in response to each of your points. In addition, this manuscript has been read and corrected for clarity, grammar and spelling by a language specialist.

We hope the revised manuscript will now meet the requirements of your journal for publication. We thank the editor and the referees of *World Journal of Gastroenterology* once again for the constructive review of our paper.

Sincerely,

Sung Hak Lee, M.D., Ph.D. (Corresponding author)
Department of Hospital Pathology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea
Tel: 82-2-2258-1617
Fax: 82-2-2258-1627
E-mail: hakjjang@catholic.ac.kr

Comments to Reviewers

Reviewer 1 (Reviewer's code: 00035901)

The authors demonstrated the predicting factor for LN metastasis in CRC. They showed 4 predicting factors including lymphatic invasion (difference AUC=0.204), the presence or absence of tumor budding (difference AUC=0.190), presence of PDCs (difference AUC=0.172) and tumor budding graded by the Ueno method (difference AUC=0.128). The present study was well investigated and will give us an important information especially in the field of clinical gastroenterology. To improve the quality of this paper, they should revise it according to the following suggestions;

1) These AUC scores of 4 predictors were very low. The authors should perform the multiple logistic regression analysis of these factors to detect the best combination of 4 factors to predict LN metastasis.

Our response: We share the reviewer' concern about this point. Unfortunately, we could not perform the multiple logistic regression analysis as the reviewers suggested.

We have performed the statistical analysis of this study with the help of statisticians. They suggested that for the number of event per variable (EPV) of 10 or greater, no major problems occurred, however, for low EPV (values less than 10), the regression coefficients were biased in both positive and negative directions. (J Clin Epidemiol Vol. 49, No. 12, pp. 1373-1379, 1996)

Thus, they recommended that we could perform multiple logistic regression analysis including 'Tumor type' and 'Desmoplasia' parameters (Table 3).

2) As shown in Table 1, the depth of sm invasion determined by JSCCR or by Ueno significantly affect the incidence of LN metastasis. However, the authors did not indicate the conclusion. Please explain the significance of sm invasion.

Our response: We agree with the reviewer about that. We have added these details in the Discussion section (page 11, line 25) and Conclusion section (page 14, line 25).

In addition, we have explained the details about the depth of sm invasion in result part (page 11, line 1) and discussion part (page 12, line 10).

The depth of submucosal invasion has long been identified as a predictor of LNM. However, we have revealed that the width of the submucosal invasion was more accurate for predicting LNM than the depth of invasion and the depth multiplied by width was even more powerful than the depth of invasion or width of invasion alone in the present study.

Reviewer 2 (Reviewer's code: 02445408)

To the authors Orthographic page 5 line 10 ≥1000 mm it should be 1000 μm

Our response: We have corrected the manuscript as the reviewers suggested (page 6, line 14).

Reviewer 3 (Reviewer's code: 02445450)

This is a well-written manuscript showing predictive factors for lymph node metastasis of SICRC. If pathological definition of lymphatic invasion and venous invasion become clearer that the discussion would become more precise. How did the authors distinguish lymphatic invasion from venous invasion only by HE stain? Did they use IHC analysis, such as D2-40 and CD34, for differentiation? Once it is classified as lymphatic invasion, what level of invasion was considered as positive? Thank you.

Our response: We have added these details in the MATERIALS AND METHODS section (page 8, line 19).

Immunohistochemical staining for D2-40, CD31 and CD34 were performed on several cases in which it was difficult to judge the presence or absence of lymphovascular invasion (page 8, line 30).

In order to assess the level of lymphatic invasion, we evaluated mainly peritumoral areas, and only peritumoral lymphatic invasion were counted as lymphatic invasion. In many cases such as tumors with micropapillary pattern, intratumoral lymphatic invasion can be misinterpreted as retraction artifact. Thus, intratumoral lymphatic invasion was not counted in this study.