**Response to peer-reviewers**

## Title: A Nomogram using F-18 FDG PET/CT for Preoperative Prediction of Lymph Node Metastasis in Gastric Cancer

I thank the reviewers and the editor for the helpful comments about this manuscript. I have made my best effort to address the concerns raised and have amended the manuscript according to the suggestions. I sincerely hope these explanations would be suitable for your considerations on publishing this manuscript in "*World Journal of Gastrointestinal Oncology*". My point-by-point responses to the comments and corrections are provided as below in blue.

**Reviewers comments:**

**Reviewer #1:**

**Comment 1)** The author should refer to the strength of accurate preoperative prediction of LN in GC. How to use this nomogram in real practice?

**Answer 1)** The present study successfully developed an effective nomogram to predict LN metastasis in GC using T_SUVmax, N_SUVmax, serum albumin, and CA 19-9. And these parameters are preoperative factors which are a non-invasive diagnostic tool for assessment of LN metastasis status in patients with GC. Therefore, the nomogram is a reliable and non-invasive tool for preoperative prediction of LN status and can be used to optimize the current treatment strategy for patients with GC patients. The accurate preoperative prediction of LN can support clinicians in classifying patients who could receive minimal surgery or may derive

greater clinical benefit from more extensive treatment. I have revised my manuscript. Thank you for your comments.

**Comment 2)** This study included only the development of the prediction model. The author had better to validate this model in another data set.

**Answer 2)** Since this study is a retrospective study, it could not be externally validated. Instead, I have divided this cohort into the train set and test set, developing the prediction model from the train set and internally validating it in the test set. Consequently, the maximum standardized uptake value (SUVmax) of the primary tumor (T_SUVmax), and SUVmax of LN (N_SUVmax) were independent predictive factors for LN metastasis in the test set as well as the train set. And stepwise backward elimination method revealed that the combination of T_SUVmax, N_SUVmax, serum albumin, and CA 19-9 showed the best LN metastasis prediction model in the train set. Finally, this model yielded an area under the curve (AUC) of 0.733 (95% CI, 0.683–0.784, $P = 0.025$) in the training cohort and AUC of 0.756 (95% CI, 0.678–0.833, $P < 0.001$) in the test cohort. The new study design and results have been added in the Abstract, MATERIALS AND METHODS, and RESULTS. External validation could not be performed in this study, but considering the results of LN metastasis prediction performance in internal validation was good, the LN metastasis prediction model could facilitate the preoperative individualized prediction of LN status in patients with gastric cancer. In addition, I have added about the limitation of this study that has not been externally validated.

**Comment 3)** The positive rate of LN differs by T stage. Predictive power of the model depends on the T stage percentage, so the author should analyze by T stage. In addition, the clinical significance of preoperative prediction of LN also depends on T stage.

**Answer 3)** I totally agree with your comments. However, the endpoint of this study is the development of the preoperative LN metastasis prediction model. Therefore, despite the positive rate of LN differing by T stage, T stage can not be considered as a predictive parameter in this study. Of course,

there are several studies for the precise diagnosis of T stage using endoscopic ultrasonography (EUS), the accuracy of EUS for T stage ranged between <50 and >90% (1–4). I also believe that the clinical significance of the preoperative prediction of LN differs depends on T stage. However, precise and detailed staging prior to treatment is not easy. Although my answers would not be perfect, I tried to explain the rationale of doing this study at my best. I have added these discussions in the DISCUSSION section. Thank you for your kind comments.

**Comment 4)** Please mention how to select the predictive factors in detail. The author chose 4 factors as factors of nomogram in page 9, this description was not enough.

**Answer 4)** Multiple logistic analysis was performed with stepwise backward elimination. First, all variables with $P < 0.05$ in the univariate logistic analysis were selected for multivariate logistic analysis in the training cohort. All the independent variables are entered into the LN metastasis prediction model equation first, and deleting the variable whose loss gives the most statistically insignificant deterioration of the prediction model fit. And repeating this process until no further variables can be deleted without a statistically significant loss of fit. Lastly, four predictive factors were selected for the nomogram. I have added the following sentences in the Statistical Analysis section.

- ➔ Second, the LN metastasis prediction model was developed using the multivariate logistic analysis with a stepwise backward elimination method in the training cohort, and validated in the internal validation cohort. All variables with $P < 0.05$ in the univariate logistic analysis were selected for multivariate logistic analysis in the training cohort, and deleting the variable whose loss gives the most statistically insignificant deterioration of the prediction model fit.

**Comment 5)** Please state "any other treatment" in detail in page 6. Were the cases of endoscopic resection prior to surgery excluded?

**Answer 5)** Thank you for your kind comments. I have revised my manuscript. In the case of patients who received gastric endoscopic submucosal dissection without LN dissection, the status of LN

metastasis cannot be determined. Also, patients who received preoperative chemotherapy were excluded in this study, since chemotherapy before surgical resection could affect the histopathologic results, including the initial LN status. I have added the following sentences in the MATERIALS AND METHODS, Patients section. Thank you for your comments

➔ such as gastric endoscopic submucosal dissection or chemotherapy,

**Comment 6) Please correct the spelling of "preoperative" (in the middle of page 6).**

**Answer 6)** Thank you for your kind comments. I have corrected the typographic error.

[References]

1. Yoshinaga S, Oda I, Nonaka S, Kushima R, Saito Y. Endoscopic ultrasound using ultrasound probes for the diagnosis of early esophageal and gastric cancers. World J Gastrointest Endosc. 2012;4:218–226. doi: 10.4253/wjge.v4.i6.218.

2. Lee HH, Lim CH, Park JM, Cho YK, Song KY, Jeon HM, Park CH. Low accuracy of endoscopic ultrasonography for detailed T staging in gastric cancer. World J Surg Oncol. 2012;10:190. doi: 10.1186/1477-7819-10-190.

3. Kutup A, Vashist YK, Groth S, Vettorazzi E, Yekebas EF, Soehendra N, Izbicki JR. Endoscopic ultrasound staging in gastric cancer: Does it help management decisions in the era of neoadjuvant treatment? Endoscopy. 2012;44:572–576. doi: 10.1055/s-0032-1308950.

4. Jurgensen C, Brand J, Nothnagel M, Arlt A, Neser F, Habeck JO, Schreiber S, Stölzel U, Zeitz M, Hampe J. Prognostic relevance of gastric cancer staging by endoscopic ultrasound. Surg Endosc. 2013;27:1124–1129. doi: 10.1007/s00464-012-2558-z.

## Reviewer #2:

**Comment 1)** Please give a convincing and scientific explanation for the choice of only CA 19-9 and albumin for the nomogram.

**Answer 1)** Multiple logistic analysis was performed with stepwise backward elimination. First, all variables with $P < 0.05$ in the univariate logistic analysis were selected for multivariate logistic analysis in the training cohort. All the independent variables are entered into the LN metastasis prediction model equation first, and deleting the variable whose loss gives the most statistically insignificant deterioration of the prediction model fit. And repeating this process until no further variables can be deleted without a statistically significant loss of fit. Lastly, four predictive factors were selected for the nomogram. I have added the following sentences in the Statistical Analysis section.

- ➔ Second, the LN metastasis prediction model was developed using the multivariate logistic analysis with a stepwise backward elimination method in the training cohort, and validated in the internal validation cohort. All variables with $P < 0.05$ in the univariate logistic analysis were selected for multivariate logistic analysis in the training cohort, and deleting the variable whose loss gives the most statistically insignificant deterioration of the prediction model fit.

## Reviewer #3:

**Comment 1)** The description in Materials and Methods needs to be revised to explain the preoperative intervention more in detailed.

**Answer 1)** Thank you for your kind comments. I have revised my manuscript. In the case of patients who received gastric endoscopic submucosal dissection without LN dissection, the status of LN metastasis cannot be determined. Also, patients who received preoperative chemotherapy were excluded in this study, since chemotherapy before surgical resection could affect the histopathologic results,

including the initial LN status. I have added the following sentences in the MATERIALS AND METHODS, Patients section. Thank you for your comments

- ➔ such as gastric endoscopic submucosal dissection or chemotherapy,

I hope the revised manuscript will better meet the requirements of the "*World Journal of Gastrointestinal Oncology*" for publication. I thank you again for the constructive review and kind comments.

Sincerely,

Song