January 25, 2022

RE: World Journal of Gastroenterology Manuscript Review of Manuscript NO: 73737

Dear Editor-in-Chief,

We are submitting our revised manuscript entitled "***Reevaluation of the expanded indications in undifferentiated early gastric cancer for endoscopic submucosal dissection"*** for consideration for publication in the *World Journal of Gastroenterology*.

We appreciate your kind consideration and valuable comments on our manuscript. Thanks to your comments, we discovered several flaws in the submitted manuscript and revised it accordingly. Our point-by-point responses to the concerns and the additional changes we made to the revised manuscript are included below. The revised and/or added sentences in the manuscript are shown in red-colored text.

We hope that this revised manuscript meets the publication standards of *World Journal of Gastroenterology*, and we look forward to hearing from you soon.

Sincerely,

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Point-by-Point Responses to the Reviewers' and Editorial Office's Comments:

We appreciate your kind consideration and valuable comments on our manuscript. We revised our manuscript according to your suggestions, and the point-by-point responses are included below. The revised sentences in the manuscript are shown in red-colored text. Our responses to the Reviewers' and Editorial office's comments are as follows:

- **Reviewer #1:**

Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The author present an evaluation of ESD in EGC-UD, it is quite interesting that they found EGC-UD may have relatively higher LNM rate, which may lead to poor prognosis due to the flaws of ESD. This article is well-organized, and of great importance. However, the author needs to solve some problems, here is may concerns.

1. Only 14 patients with LNM were used in this evaluation, more patients are needed.

Response:

Thank you for your valuable comment. As we discussed in the submitted manuscript, it has been well recognized that the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Some researchers have even reported that there were no cases of LNM in patients with UD-EGC meeting the expanded indications of ESD (reference #14 in the revised manuscript). For this reason, we would like to insist that the number of patients with LNM is inevitably small. We would also like to emphasize that these 14 patients were discovered by reviewing all patients who underwent curative gastrectomy with extended lymphadenectomy for UD-EGC at the Asan Medical Center between January 2008 and February 2019. Furthermore, the Asan Medical Center is one of the largest referral hospitals in the Republic of Korea, the country with the highest incidence rates of gastric cancer (**Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 2018; 68(6): 394-424). We could not include patients before 2008 due to

the limited availability of clinical information and material. Considering the low incidence, a large-scale, prospective, multicenter study is needed to confirm these findings. In addition, being a single-center study is the major limitation of our work, so we have added further comments on this limitation to the revised manuscript.

> "Finally, this study had limitations inherent to the nature of a retrospective, single-center study. Although the number of patients with LNM was small, this is because the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Considering the low incidence, a large-scacole, prospective, multicenter study is needed to confirm our findings." (revised manuscript, page 18, lines 13–18)

2. Independent cohorts are needed for confirming the findings.

Response:

Thank you for your comment. The need for validation in independent cohorts is obvious, as we admitted in the submitted manuscript (page 18, lines 2–4). As we stated above, because of the inherently low rate of LNM in the patients that satisfy the expanded criteria for UD-EGC, the analysis of all patients operated on during the last 12 years in the largest referral hospital yielded only 14 patients with LNM. For this reason, it was impossible to establish an independent cohort within our institution. It was also difficult to seek an opportunity for a multicenter study because the revision period of this manuscript was limited. We believe that a large-scale, prospective, multicenter study will eventually be needed to confirm our findings. We are planning to establish a validation cohort based on the patients who have received ESD and satisfy the expanded criteria.

3. Why choose 1:4 ratio?

Response:

Thank you for your comment. The relatively small numbers of LNM cases meeting the expanded criteria for ESD in UD-EGC patients observed in this study may not be sufficient to analyze the risk factors. Thus, we performed case-control matching analysis to improve the statistical power of the study. The 1:4 ratio matching was chosen by Dr. HJ Kim from the Department of Clinical Epidemiology and Biostatistics in our center, for whom we consulted

for the design of the case-control study. Generally, the statistical power to detect significant interaction in case-control studies increases as the number of controls per case increases, and saturates when the number of controls reaches 4 (**Cologne JB**, Sharp GB, Neriishi K, Verkasalo PK, Land CE, Nakachi K. Improving the efficiency of nested case-control studies of interaction by selecting controls using counter matching on exposure. *Int J Epidemiol* 2004; **33**: 485-492 [PMID: 15105408 DOI: 10.1093/ije/dyh097]). At the same time, limitations in time and budget prevented us from choosing a higher number of controls per case. Therefore, the 1:4 ratio was chosen to maximize the statistical power in the most efficient way. We hope this explanation suffices.

4. Besides Blurring of MM, there are some markers for doctors to identify EGC-UD with potential LNM in ESD process?

Response:

As we discussed in the submitted manuscript, tumor size, invasion depth, and lymphovascular invasion have been consistently recognized as major risk factors of LNM of UD-EGC. For this reason, the current expanded indication criteria for UD-EGC consists of the three markers. The purpose of our study was to explore additional risk factors. To identify the risk of EGC-UD with potential LNM in the ESD process, we investigated some endoscopic features, including tumor location, the lesion's macroscopic type, the endoscopic presence of ulcers, converging folds, exudates, and tumor island. In contrast to our initial expectation, these variables were not significant in increasing the risk. Additionally, with the idea that the degree of fibrosis is involved in the risk in the ESD process, we specifically focused on fibrosis. We performed special staining and analyzed the slides visually and computationally to investigate the degree, extent, and pattern of peritumoral fibrosis. However, the degree of peritumoral fibrosis did not show a statistically significant association with the risk of LNM. In our study, besides blurring of MM, we discovered marginal statistical significance of mixed histology, which is consistent with some previous studies (references #18 and #19 in the revised manuscript). Further studies are needed to discover more clinically feasible risk factors.

- **Reviewer #2:**

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

1. Please specify which version of the guidance is used for the current expanded criteria.

Response:

Thank you for your comment. We used the 2018 Korean Practice Guideline for Gastric Cancer and the 2014 Japanese gastric cancer treatment guideline (ver. 4). Per your suggestion, we attached the appropriate reference in the previously submitted manuscript and added a new reference (#3) with the following reference in the revised manuscript:

> "we included those meeting all of the following criteria for the expanded indication of ESD: 1) confinement to the mucosal layer (pT1a), 2) size ≤ 2 cm, 3) absence of ulcer, and 4) absence of LVI.[3],[4]" (revised manuscript, page 6, line 23)

References

> "3. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; **20**: 1-19 [PMID: 27342689 DOI: 10.1007/s10120-016-0622-4]"
>
> "4. Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach. *J Gastric Cancer* 2019; **19**: 1-48 [PMID: 30944757 DOI: 10.5230/jgc.2019.19.e8]"

2. Detailed clinical information of the 14 patients with LNM should include the total number of dissected lymph node.

Response:

Thank you for your comment. We identified the total number of dissected lymph nodes in 14 patients with LNM. The results are expressed in the revised Table 2.

Case No.	Age (years)	Sex	Type	Size (cm)	Location	Histology	Depth of invasion	Total number of dissected LNs	Number of metastatic LNs
1	59	Female	IIb	1.5	Middle	PD with SRC	LP	31	3
2	41	Female	IIc	1.3	Lower	PD with SRC	LP	18	3
3	57	Male	IIc	1.3	Lower	SRC	LP	21	1
4	47	Female	IIc	1.8	Middle	PD with SRC	LP	21	3
5	46	Female	IIb	2.0	Lower	PD with SRC	LP	25	6
6	37	Female	IIc	1.5	Lower	PD with SRC	MM	31	3
7	48	Female	IIc	1.5	Lower	PD with SRC	LP	37	1
8	35	Male	IIc	0.9	Lower	PD with SRC	LP	38	1
9	35	Female	IIc	1.5	Lower	PD with SRC	LP	27	1
10	52	Female	IIb	0.7	Lower	PD with SRC	LP	29	1
11	60	Male	III	0.6	Lower	PD with SRC	MM	30	1
12	39	Female	IIc	2.0	Lower	PD with SRC	LP	37	1
13	37	Female	IIb	1.8	Lower	PD with SRC	LP	42	1
14	33	Male	IIc	2.0	Lower	PD with SRC	LP	48	3

LNM: lymph node metastasis; PD: poorly differentiated carcinoma; SRC: signet ring cell; SRCC: signet ring cell carcinoma; LP: lamina propria,

3. Please specify the criteria for inclusion of indicators in the multivariate analysis

Response:

All variables with < 0.2 in the univariate analysis (mixed histology, background stomach, the presence of *H. pylori*, TIL abundance, and MM blurring) were included. We additionally added invasion depth because some previous studies have reported that tumors invading the MM are more likely to metastasize into regional lymph nodes than those limited to the lamina propria (Reference #28 in the revised manuscript, and "**Kim YI**, Lee JH, Kook MC, Lee JY, Kim CG, Ryu KW, Kim YW, Choi IJ. Lymph node metastasis risk according to the depth of invasion in early gastric cancers confined to the mucosal layer. *Gastric Cancer* 2016; **19**: 860-868 [DOI: 10.1007/s10120-015-0535-7]"). Fibrosis score was also added to assess the effect of fibrosis.

4. The author points out that mixed histology (tumors consisting of 10–90% of signet ring cells) had a marginally significant association (P = 0.059) with the risk of LNM. Can the proportion of signet ring cells be divided in more detail, such as 10-50%, 50-90%, >90%?

Response:

Thank you for your kind comment. As you mentioned, we performed further analysis. The results are expressed in the revised Table 3.

Table 3. Histologic features of the tumors and background stomach according to the presence of lymph node metastasis

Variables	LNM- (n = 73)	LNM+ (n = 14)	*P* value
Depth of invasion			0.503
LP	53 (72.6)	12 (85.7)	
MM	20 (27.4)	2 (14.3)	
Size, cm	1.5 (1.2–1.7)	1.5 (1.3–1.8)	0.642
% of SRCs			0.157
<10%	17 (23.3)	0 (0)	
≥10% and <50%	35 (47.9)	10 (71.4)	
≥50% and <90%	14 (19.2)	3 (21.4)	
≥90%	7 (9.6)	1 (7.1)	
Diagnostic category according to the proportion of SRCs			0.059
Non-mixed (SRCC and PD)	24 (32.9)	1 (7.1)	
Mixed (PD with SRC component)	49 (67.1)	13 (92.9)	
Background stomach			0.278
Mild CG	8 (11.0)	0 (0)	
Moderate CG or IM	24 (32.9)	3 (21.4)	
CAG	22 (30.1)	4 (28.6)	
CAG with visible *H. pylori*	19 (26.0)	7 (50.0)	
***H. pylori* abundance, n/total n**			0.263
0	23/71 (32.4)	2/14 (14.3)	
1+	14/71 (19.7)	3/14 (21.4)	
2+	14/71 (19.7)	6/14 (42.9)	
3+	20/71 (28.2)	3/14 (21.4)	
TP53 expression, n/total			> 0.999
Loss (0)	3/70 (4.3)	0/14 (0)	
Wildtype pattern (1+/2+)	63/70 (90.0)	13/14 (92.9)	

Overexpression (3+)	4/70 (5.7)	1/14 (7.1)

LNM: lymph node metastasis; IQR: interquartile range; LP: lamina propria; MM: muscularis mucosa; SRC: signet ring cell; SRCC: signet ring cell carcinoma; PD: poorly differentiated carcinoma encompassing adenocarcinoma and non-signet ring cell type of poorly cohesive carcinoma; CG: chronic gastritis; IM: intestinal metaplasia; CAG: chronic active gastritis.

5. The number of patients with LNM in only 14, and he conclusions of this paper need to be verified by larger sample data.

Response:

Thank you for your valuable comment. As we discussed in the submitted manuscript, it has been well recognized that the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Some researchers have even reported that there were no cases of LNM in patients with UD-EGC meeting the expanded indications of ESD (reference #14 in the revised manuscript). For this reason, we would like to insist that the number of patients with LNM is inevitably small. We would also like to emphasize that these 14 patients were discovered by reviewing all patients who underwent curative gastrectomy with extended lymphadenectomy for UD-EGC at the Asan Medical Center between January 2008 and February 2019. Furthermore, the Asan Medical Center is one of the largest referral hospitals in the Republic of Korea, the country with the highest incidence rates of gastric cancer (**Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 2018; 68(6): 394-424). We could not include patients before 2008 due to the limited availability of clinical information and material. Considering the low incidence, a large-scale, prospective. multicenter study is needed to confirm these findings. In addition, being a single-center study is the major limitation of our work, so we have added further comments on this limitation to the revised manuscript.

> "Finally, this study had limitations inherent to the nature of a retrospective, single-center study. Although the number of patients with LNM was small, this is because the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Considering the low incidence, a large-scale, prospective, multicenter study is needed to confirm our findings." (revised manuscript, page 18, lines 13–18)

- **Editorial Office's comments:**

1) Science editor

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Specific Comments to Authors: The manuscript elaborated a study of re-evaluation of indications for endoscopic submucosal dissection to expand undifferentiated early gastric cancer. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario. Nevertheless, there are a number points that may deserve some revisions.

1. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Response:

As per your guidance on proper citation, we deleted eight references (#3, #5, #6, #18, #20, #21, #25, and #32 in the original submitted manuscript). Because some of the deleted references were crucial and irreplaceable, some descriptions in the manuscript had to be revised to compensate the losses.

We replaced #3, #5, and #18 with the following reference in the revised manuscript.

> "Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; **20**: 1-19 [PMID: 27342689 DOI: 10.1007/s10120-016-0622-4]"

We replaced #6 with the following reference in the revised manuscript.

> "**Kang HJ**, Kim DH, Jeon TY, Lee SH, Shin N, Chae SH, Kim GH, Song GA, Kim DH, Srivastava A, Park DY, Lauwers GY. Lymph node metastasis from intestinal-type early gastric cancer: Experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. *Gastrointest Endosc* 2010; 72: 508-515 [PMID: 20554277 DOI: 10.1016/j.gie.2010.03.1077]"

We replaced #20 and #21 with the following references in the revised manuscript.

"**Huh CW**, Jung DH, Kim JH, Lee YC, Kim H, Kim H, Yoon SO, Youn YH, Park H, Lee SI, Choi SH, Cheong JH, Noh SH. Signet ring cell mixed histology may show more aggressive behavior than other histologies in early gastric cancer. *J Surg Oncol* 2013; 107: 124-129 [PMID: 22991272 DOI: 10.1002/jso.23261]"

"**Seo HS**, Lee GE, Kang MG, Han KH, Jung ES, Song KY. Mixed histology is a risk factor for lymph node metastasis in early gastric cancer. *J Surg Res* 2019; 236: 271-277 [PMID: 30694766 DOI: 10.1016/j.jss.2018.11.055]"

As we deleted references #20 and #21, we replaced the following sentences in the submitted original manuscript with the red-colored sentence below:

"In a previous study on 410 cases of intramucosal GC, tumors with predominantly undifferentiated components (e.g., poorly differentiated adenocarcinoma, SRCC, and mucinous carcinoma) and minorly differentiated components were significantly associated with a higher rate of LNM than those with purely undifferentiated components.[20] Also, another study showed that mixed histology (consisting of < 50% SRCs) is an independent risk factor for LNM in EGC. [21]"

"This is consistent with previous studies suggesting more aggressive histology of EGC by using mixed histology rather than pure adenocarcinoma and SRCC.[18,19]" (revised manuscript, page 16, lines 14–16)

As we deleted reference #32, we revised a sentence in the submitted original manuscript as follows:

"Indeed, it has been reported that tumors invading the MM are more likely to metastasize into regional lymph nodes than those limited to the lamina propria.[28]" (revised manuscript, page 17, line 10)

Accordingly, our final version of the manuscript has a total of 30 references. We hope that this revision satisfies the guidelines of the journal.

2. Small sample size.

Response:

Thank you for your valuable comment. As we discussed in the submitted manuscript, it has been well recognized that the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Some researchers have even reported that there were no cases of LNM in patients with UD-EGC meeting the expanded indications of ESD (reference #14 in the manuscript). For this reason, we would like to insist that the number of patients with LNM is inevitably small. We would also like to emphasize that these 14 patients were discovered by reviewing all patients who underwent curative gastrectomy with extended lymphadenectomy for UD-EGC at the Asan Medical Center between January 2008 and February 2019. Furthermore, the Asan Medical Center is one of the largest referral hospitals in the Republic of Korea, the country with the highest incidence rates of gastric cancer (reference #1 in the manuscript). We could not include patients before 2008 due to the limited availability of clinical information and material. Considering the low incidence, a large-scale, prospective multicenter study is needed to confirm these findings. In addition, being a single-center study is the major limitation of our work, so we have added further comments on this limitation to the revised manuscript.

> "Finally, this study had limitations inherent to the nature of a retrospective, single-center study. Although the number of patients with LNM was small, this is because the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Considering the low incidence, a large-scale, prospective, multicenter study is needed to confirm our findings." (revised manuscript, page 18, lines 13–18)

3. Is there any other data center validation?

Response:

Thank you for your comment. The need for validation in independent cohorts is obvious, as we admitted in the submitted manuscript (page 18, lines 2–4). As we stated above, because of the inherently low rate of LNM in the patients that satisfy the expanded criteria for UD-EGC, the analysis of all patients operated on during the last 12 years in the largest referral hospital yielded only 14 patients with LNM. For this reason, it was impossible to establish an independent cohort within our institution. It was also difficult to seek an opportunity for a multicenter study because the revision period of this manuscript was limited. We believe that a large-scale, prospective, multicenter study will eventually be needed to confirm our findings. We are planning to establish a validation cohort based on the patients who have

received ESD and satisfy the expanded criteria.

2) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

1. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Response:

Per your guidance, we have re-checked the figures. We will submit the figures in the style required.

2. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Response:

Per your guidance, we will submit decomposable figures.

3. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response:

We have read and checked the tables. We found errors in Supplementary Table 2. Per your

guidance, we have edited the table (revised supplementary material). We hope that this revision satisfies the guidelines of the journal. We will submit the tables in the style required.

4. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response:

We have checked and confirmed whether the figures are original. Per your guidance, we have added copyright information to the bottom right-hand side of the picture in PowerPoint.

5. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Response:

We have checked and confirmed whether the figures are original. Our figures have not been published elsewhere.

** Dear Editor,

We have read and checked the revised manuscript, and we found that TIL abundance appeared in Tables 3 and 4. We thus eliminated it from Table 3.

Lastly, per the journal's guidance (A short running title of no more than 6 words should be provided), we have revised "Risk factors of LNM of UD-EGC meeting the expanded criteria" to "Risk factors of LNM of UD-EGC".

Best regards

March 02, 2022

RE: World Journal of Gastroenterology Manuscript review of Manuscript NO: 73737

Dear Editor-in-Chief,

We are submitting our revised manuscript entitled "***Reevaluation of the expanded indications in undifferentiated early gastric cancer for endoscopic submucosal dissection"*** for consideration of publication in the *World Journal of Gastroenterology*.

We appreciate your kind consideration and valuable comments on our manuscript. Our point-by-point responses to the concerns made to the revised manuscript are included below.

We hope that this revised manuscript meets the publication standards of *World Journal of Gastroenterology*, and we look forward to hearing from you soon.

Sincerely,

Point-by-Point Responses to the Reviewers' comments:

We appreciate your kind consideration and valuable comments on our manuscript. The point-by-point responses are included below.

- **Reviewer #1:**

1. The author insist that 14 patients are sufficient to identify markers for EGC-UD, which is not credible for clinical practice. Furthermore, I can not find the figures and tables of the article.

Response:

Thank you for your valuable comment. As we discussed in the submitted manuscript, it has been well recognized that the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Some researchers have even reported that there were no cases of LNM in patients with UD-EGC meeting the expanded indications of ESD (reference #14 in the revised manuscript). For this reason, we would like to insist that the number of patients with LNM is inevitably small. We would also like to emphasize that these 14 patients were discovered by reviewing all patients who underwent curative gastrectomy with extended lymphadenectomy for UD-EGC at the Asan Medical Center between January 2008 and February 2019. Furthermore, the Asan Medical Center is one of the largest referral hospitals in the Republic of Korea, the country with the highest incidence rates of gastric cancer (**Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* 2018; 68(6): 394-424). We could not include patients before 2008 due to the limited availability of clinical information and material. Considering the low incidence, a large-scale, prospective, multicenter study is needed to confirm these findings. In addition, being a single-center study is the major limitation of our work, so we had further comments on this limitation to the revised manuscript.

> "Finally, this study had limitations inherent to the nature of a retrospective, single-center study. Although the number of patients with LNM was small, this is because the incidence of LNM in patients with UD-EGC meeting the expanded indications of ESD is low. Considering the low incidence, a large-scale, prospective, multicenter

study is needed to confirm our findings." (revised manuscript, page 18, lines 13–18)

Second, per guidance, we have re-checked tables & figure and we submitted decomposable figures (PPT version) and revised version (tables and supplementary materials). However, in F6 publishing system, there was no tab for additional uploading of the revised version (decomposable figures, revised tables, and revised supplementary materials). So, we attached additional files via E-mail to the Editor.

2. Besides of histology and clinical variables, there are any biomarkers for LNM identification of EGC-UD?

Response:

As we discussed in the submitted manuscript, tumor size, invasion depth, and lymphovascular invasion have been consistently recognized as major risk factors of LNM of UD-EGC. For this reason, the current expanded indication criteria for UD-EGC consists of the three markers. The purpose of our study was to explore additional risk factors. To identify the risk of EGC-UD with potential LNM in the ESD process, we investigated some endoscopic features, including tumor location, the lesion's macroscopic type, the endoscopic presence of ulcers, converging folds, exudates, and tumor island. In contrast to our initial expectation, these variables were not significant in increasing the risk. Additionally, with the idea that the degree of fibrosis is involved in the risk in the ESD process, we specifically focused on fibrosis. We performed special staining and analyzed the slides visually and computationally to investigate the degree, extent, and pattern of peritumoral fibrosis. However, the degree of peritumoral fibrosis did not show a statistically significant association with the risk of LNM. In our study, besides blurring of MM, we discovered marginal statistical significance of mixed histology, which is consistent with some previous studies (references #18 and #19 in the revised manuscript). Although a meta-analysis revealed several other risk factors for LNM in mucosal EGC such as age younger than 57 years and tumor's immunohistochemical expression of PCNA or MMP-9 (**Kwee RM**, Kwee TC. Predicting lymph node status in early gastric cancer. *Gastric Cancer* 2018; 11(3): 134–148), those markers are not currently utilized in the clinical practice. Further studies are needed to discover more clinically feasible risk factors.

3. Since all patients with LNM have signet ring cells, why the p-value is only marginal significant, what is the detail information of matched cases?

Response:

Thank you for your comment. In our study, the comparison was not made between tumors with and without SRCs, but between mixed (consisting of 10-90% of SRCs) and non-mixed (pure SRC carcinoma and PD carcinoma) histology. This categorization was based on some previous reports on the significance of mixed histology as a potential risk factor for LNM (reference #19 in the submitted manuscript; **Takizawa K**, Ono H, Kakushima N, et al. Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: How to manage the mixed histological type for endoscopic submucosal dissection. *Gastric Cancer* 2013;16(4):531-536). When the comparison is made between SRC-negative and SRC-positive cases, the p-value is 0.116 by Fisher's exact test. Detailed results were demonstrated in table 3.

Table 3. Histologic features of the tumors and background stomach according to the presence of lymph node metastasis

Variables	**LNM-** **(n = 73)**	**LNM+** **(n = 14)**	***P*** **value**
Depth of invasion			0.503
LP	53 (72.6)	12 (85.7)	
MM	20 (27.4)	2 (14.3)	
Size, cm	1.5 (1.2–1.7)	1.5 (1.3–1.8)	0.642
% of SRCs			0.157
<10%	17 (23.3)	0 (0)	
≥10% and <50%	35 (47.9)	10 (71.4)	
≥50% and <90%	14 (19.2)	3 (21.4)	
≥90%	7 (9.6)	1 (7.1)	
Diagnostic category according to the proportion of SRCs			0.059
Non-mixed (SRCC and PD)	24 (32.9)	1 (7.1)	
Mixed (PD with SRC component)	49 (67.1)	13 (92.9)	
Background stomach			0.278

Mild CG	8 (11.0)	0 (0)	
Moderate CG or IM	24 (32.9)	3 (21.4)	
CAG	22 (30.1)	4 (28.6)	
CAG with visible *H. pylori*	19 (26.0)	7 (50.0)	
***H. pylori* abundance, n/total n**			0.263
0	23/71 (32.4)	2/14 (14.3)	
1+	14/71 (19.7)	3/14 (21.4)	
2+	14/71 (19.7)	6/14 (42.9)	
3+	20/71 (28.2)	3/14 (21.4)	
TP53 expression, n/total			> 0.999
Loss (0)	3/70 (4.3)	0/14 (0)	
Wildtype pattern (1+/2+)	63/70 (90.0)	13/14 (92.9)	
Overexpression (3+)	4/70 (5.7)	1/14 (7.1)	

4. Since the small sample size, the author needs to perform permutation analysis by replacing the matched cases to draw reliable conclusion.

Response:

Thank you for your valuable comment. As the reviewer's suggestion, we performed permutation analysis. We have consulted Dr. HJ Kim from the Department of Clinical Epidemiology and Biostatistics in our center for permutation analysis. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). In our study, we found a significant association between diffuse MM blurring and the absence of regional LNM (P = 0.028). We also found a significant association between MM blurring and the risk of LNM in the permutation test (P = 0.034). In multivariate permutation analysis, MM blurring was the only statistically significant variable associated with the risk of LNM (P = 0.032). We hope this explanation suffices.

Variables	**Permutation test *P* value**
Depth of invasion	0.315
Diagnostic category according to % of SRCs*	
Non-mixed (SRC and PD)	

Mixed (PD with SRC component)	0.068
Background stomach	
CG	
CAG	0.147
Presence of *H. pylori*	
Absent (0)	
Present (≥1+)	0.208
TIL abundance	0.558
Fibrosis score	0.279
Blurring of MM	0.034

SRC: signet ring cell; PD: poorly differentiated carcinoma encompassing adenocarcinoma and non-signet ring cell type of poorly cohesive carcinoma; CG: chronic gastritis; CAG: chronic active gastritis; TIL: tumor-infiltrating lymphocytes; MM: muscularis mucosa.

** Dear Editor,

We have read and checked the revised manuscript, and we found that the overall *P* value for TIL abundance was accidentally omitted in table 5. There was a mistake during the editing process. Thus, we added *P* value (0.409) in table 5.

Best regards.