

Peer Review File

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Response to Reviewer A's Comments

Comment 1: Regarding upper gastric cancer without invasion to the greater curvature, Sano *et al.* demonstrated that non-No.10 LND was not inferior to No.10 LND in the pivotal Japanese trial, which is cited in this manuscript. Thus, just whether surgeons should dissect No.10 lymph nodes for upper gastric cancer with invasion to the greater curvature is controversial. In this study, the authors do not consider such evidence and unmet needs.

Response 1: Thank you for your positive and encouraging comments on our manuscript. In the second sub-section of the Discussion section of this manuscript, we cited the literature of Sano *et al.* to demonstrate that, for the treatment of proximal advanced gastric cancer, splenectomy has no survival benefit compared to spleen-preservation surgery (without intentional No. 10 dissection). However, as you have mentioned, the cited study (Sano *et al.*) is limited to patients with upper gastric cancer without invasion to the greater curvature. The information related to whether a survival benefit of splenectomy exists for upper gastric cancer with invasion to the greater curvature is missing in our previous manuscript. Thus, **we added the information of this portion and updated the related references to dispel the ambiguity and insufficiency of the provided evidence in our newly revised manuscript (see Pages 13-14, lines 258-267; Page 26, lines 521-523)**. With respect to whether surgeons should dissect No. 10 lymph nodes with spleen preservation for upper gastric cancer with invasion to the greater curvature, we had discussed this topic at the end of the third sub-section of the Discussion section (see Page 16, lines 305-319).

Changes in the text: We added some information related to whether a survival benefit of splenectomy exists for upper gastric cancer with invasion to the greater

curvature and updated the related references in our newly revised manuscript (see Page 13-14, lines 258-267; Page 26, lines 521-523).

Comment 2: The findings that OS and DFS of the No. 10 LND group was significantly better than the non-No.10 LND group are surely associated with the stage migration. In retrospective studies, investigators should take much care of such phenomena. Some past studies revealed that survival outcomes of D2+paraaortic LND for advanced gastric cancer were better than those of D2 alone. However, the pivotal Japanese study demonstrated that D2+paraaortic LND did not improve survival outcomes. The same can be said regarding No.10 LND. In the present study, patients who underwent total gastrectomy without No.10 LND were underestimated in No.10 lymph node metastasis and staging. The results of survival outcomes in this study may be just affected by comparison between No.10 LN-underestimated and proper-estimated groups. They may differ from the truth.

Response 2: In the current study, our pooled result led to the conclusion that the No. 10 LND can improve the survival outcomes of patients with gastric cancer and/or Siewert type II / III AEG who underwent total gastrectomy. However, as you have mentioned, the results of patients who underwent total gastrectomy without No. 10 LND might have been underestimated in No. 10 LN metastasis and staging. Therefore, we further evaluated the effect of No. 10 LN metastasis and staging on the results of this study. The results revealed that the metastatic rate of No. 10 LNs ranges from 7.3% to 18.3% in previous reports (1-8). However, the abovementioned data are almost limited to patients who underwent total gastrectomy with No. 10 LND. Although we have thoroughly searched the literature, we found no results regarding No. 10 LN metastasis and staging for patients who underwent total gastrectomy without No. 10 LND. We speculate that the reason may be that for patients who underwent total gastrectomy without No. 10 LND, the No. 10 LN would not be dissected by the surgeons intraoperatively nor further identified to be either positive or negative. Meanwhile, for surgeons, detecting LN metastasis and staging intraoperatively is a difficult task that may be easily omitted. Thus, it is difficult to

analyze and draw a conclusion regarding the No. 10 LN metastasis and staging without No. 10 LND (see Page 19, lines 368-371).

Nevertheless, we have searched the literature to evaluate the extent of the effect of No. 10 LN metastasis and staging on our results. We found that tumor size, cT stage, and cN stage are considered as independent risk factors for the metastasis of No. 10 LN (9), along with advanced gastric cancer with greater curvature invasion (10,11). Therefore, we compared and analyzed these factors between two groups of each included study, and our results showed no significant difference between the two groups in terms of the basic lines of the abovementioned factors. Thus, according to the results, we can determine whether we can conclude that there exists a negligible difference in the No. 10 LN metastasis and staging between the No. 10 LND and the non-No. 10 LND groups indirectly and if the effect of No. 10 LN metastasis and staging on the results of our study is limited.

Based on such information, the improved comprehensive approach of imaging diagnosis, intraoperative diagnosis, and experimental design methods on LN metastasis and staging can be expected (see Page 19, lines 371-373; Page 28, lines 563-565) (12).

References:

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- (2) Shin SH, Jung H, Choi SH, et al. Clinical significance of splenic hilar lymph node metastasis in proximal gastric cancer. Ann Surg Oncol 2009;16:1304-9.
- (3) Sasada S, Ninomiya M, Nishizaki M, et al. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. Anticancer Res 2009;29:3347-51.
- (4) Nashimoto A, Yabusaki H, Matsuki A. The significance of splenectomy for advanced proximal gastric cancer. Int J Surg Oncol 2012;2012:301530.
- (5) Kunisaki C, Makino H, Suwa H, et al. Impact of splenectomy in patients with gastric adenocarcinoma of the cardia. J Gastrointest Surg 2007;11:1039-44.

- (6) Kinoshita T, Okayama T. Is splenic hilar lymph node dissection necessary for proximal gastric cancer surgery? *Ann Gastroenterol Surg* 2021;5:173-82.
- (7) Jeong O, Jung MR, Ryu SY. Clinicopathological features and prognostic impact of splenic hilar lymph node metastasis in proximal gastric carcinoma. *Eur J Surg Oncol* 2019;45:432-8.
- (8) Huang CM, Zhang JR, Zheng CH, et al. A 346 case analysis for laparoscopic spleen-preserving no.10 lymph node dissection for proximal gastric cancer: a single center study. *PLoS One* 2014;9:e108480.
- (9) Guner A, Hyung WJ. Advantages of Splenic Hilar Lymph Node Dissection in Proximal Gastric Cancer Surgery. *J Gastric Cancer* 2020;20:19-28.
- (10) Kinoshita T. Splenic hilar dissection in the treatment of proximal advanced gastric cancer: what is an adequate strategy? *Transl Gastroenterol Hepatol* 2016;1:72.
- (11) Yura M, Yoshikawa T, Otsuki S, et al. The Therapeutic Survival Benefit of Splenic Hilar Nodal Dissection for Advanced Proximal Gastric Cancer Invading the Greater Curvature. *Ann Surg Oncol* 2019;26:829-35.
- (12) Lee S, Song JH, Choi S, et al. Fluorescent lymphography during minimally invasive total gastrectomy for gastric cancer: an effective technique for splenic hilar lymph node dissection. *Surg Endosc* 2022;36:2914-24.

Changes in the text: We have added the discussion of this topic at the sixth sub-section of the Discussion section as advised (see Page 19, lines 368-373; Page 28, lines 563-565).

Comment 3: Considering the descriptions above, the reviewer would say that the manuscript has little value to be published in the international scientific journal.

Response 3: Currently, whether the No. 10 LN should be dissected in total gastrectomy remains controversial. This work focused on the controversy about whether the No. 10 LND with spleen preservation has survival benefit for patients with gastric cancer and/or Siewert type II/III AEG who underwent the total gastrectomy. We expect this study could provide important evidence concerning the

beneficial effect of No. 10 LND with spleen preservation for patients who have undergone total gastrectomy.

Changes in the text: No change in the text.

Once again, thank you for your valuable comments.

Response to Reviewer B's Comments

Comment 1 (major comment): According to the authors' inclusion and exclusion criteria, total eight studies were included for the study. However, five studies overlapped in terms of institution and operation year in which the patients underwent total gastrectomy. Three studies were conducted at Fujian Medical University Union Hospital in 2007-2014, 2007-2012, and 2008-2014, and two at West China Hospital, Sichuan University in 2006-2011 and 2006-2015. Therefore, there may be duplicate patients and the authors should address this issue.

Response 1: Thank you for your careful review and constructive suggestions on our manuscript. As you have mentioned, there may be duplicate patients due to several overlaps in terms of institution and operation year, in which the patients underwent total gastrectomy. Thus, we tried to explore the issue by tracing the trials, asking for the authors of the trials, and further analyzing the included studies. Several results were obtained after performing this process. (1) The included study by Lv *et al.*, which aimed to identify the value of No. 10 LND for patients with Siewert type II / III AEG who underwent total gastrectomy, has little possibility of overlapped patients with the other two studies that included patients with proximal gastric cancer who underwent total gastrectomy, as performed in one institution (Fujian Medical University Union Hospital). (2) Two studies conducted at Fujian Medical University Union Hospital (Huang 2017, Lin 2021), and two at West China Hospital, Sichuan University (Yang 2014, Liu 2021) included duplicate patients. Nevertheless, the scale is small due to the fact that the ranges of the operation years of the patients are not overlapped entirely. However, we failed to eliminate the duplicate data because of the insufficient reported information in the included studies. Therefore, we conducted

sensitivity analyses of the studies that may have contained duplicate patients to verify the stability of the results. The analysis results indicated that the survival outcomes in this study are slightly influenced by potential duplicate patients. **We have added this discussion to explain this issue in our newly revised manuscript (see Pages 18-19, lines 361-368).** We hope the revised manuscript could meet with approval.

Changes in the text: We have added the discussion of this topic at the sixth sub-section of the Discussion section as advised (see Pages 18-19, lines 361-368).

Comment 2 (major comment): Survival curves demonstrated in the Reference 29 (J Gastrointest Surg 2016;20:1295-304.) looks different from the forest plot shown in the figure by the authors. For example, the 1-year survival of patients without No. 10 LND was superior to those with No. 10 LND in contrast to the survival curves in Figure 2 of this study. It is necessary to check the correctness of this data.

Response 2: We are sorry for a mistake has been made in extracting this data. **We have corrected the wrong data after extracting information again, and have revised the text accordingly (see Page 3, lines 50-53; Pages 10-11, lines 184-188, lines 193-198, lines 205-207).**

Changes in the text: We have modified our text as advised (see Page 3, lines 50-53; Pages 10-11, lines 184-188, lines 193-198, lines 205-207).

Comment 3 (minor comment): This paper is a study to analyze the efficacy of No. 10 LND in spleen-preserving total gastrectomy patients. However, spleen-preserving was not emphasized in the abstract.

Response 3: We have improved this content as advised.

Changes in the text: (see Page 3, line 39; Page 4, line 57; Page 5, line 88; Page 13, line 245; Page 19, line 380)

Comment 4 (minor comment): Contents not related to this study, such as tumor size and stages, are described in the discussion section. It is better to delete unnecessary sentences to maintain the flow of the thesis.

Response 4: We have deleted this sub-section in our text as advised.

Changes in the text: (see Page 16, line 319)