

Dear Editors and Reviewers,

We appreciate all of your careful review and constructive suggestions with regard to the manuscript "Laparoscopic versus open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: a propensity score matching analysis." (NO.: 69879). Those comments are professional and helpful to improve our paper, as well as having the extensive guiding significance to our researches. We have studied these comments carefully and updated the manuscript.

Our responses to the reviewer's comments are as follows and you can see the highlighted main corrections in the manuscript as a file named "69879-Manuscript File-Revised" in "Supplementary Material", where the correction lines were highlighted in orange, and to-be-deleted lines were highlighted in red.

Reviewer #1(Number ID: 05301514):

Comment 1-1: "American Society of Anesthesiologist (ASA)" is the name of the society. The authors should revise to "American Society of Anesthesiologists physical status classification (ASA)" or "American Society of Anesthesiologists physical status classification (ASA-PS)"

Response 1-1: We agreed the reviewer's comments and this has been modified in the text.

Comment 1-2: The authors chose ypT, ypN, and ypTNM as variables for calculating propensity score using logistic regression analysis. However, strictly speaking, the authors should choose Clinical T, Clinical N, and Clinical TNM because at the time of choice between LTG and OTG, the surgeon does not know the pathological result. The variable for calculating propensity score must be a factor that has already been determined at a point in time (or at the same time) prior to the assignment of LTG or OTG. However, since ypT, ypN, ypTNM and Clinical T, Clinical N, Clinical TNM are often similar variables, I allow the authors to choose ypT, ypN, and ypTNM as variables. Please check the following paper: Long-term Outcomes of Laparoscopic Versus Open Surgery for Clinical Stage I Gastric Cancer: The LOC-1 Study. Honda M, Hiki N, Kinoshita T, et al. Ann Surg. 2016;264(2):214-22.

Response 1-2: We have reviewed the paper that you recommended before. At the beginning, we considered to choose Clinical T, Clinical N, Clinical TNM as variables, however, due to the small gap between the two series of variables, and ypTNM staging was more accurate, we finally chose ypT, ypN, and ypTNM as variables. Thank you for your understanding our data.

Comment 1-3: Which did the authors use, the log-rank test or the generalized Wilcoxon test, to compare the survival curves? Please specify.

Response 1-3: Thanks for pointing out the omission. We used the log-rank test to compare the survival curves and added this in the revised manuscript.

Comment 2. RESULTS - Clinicopathologic Characteristics of Patients Comment: The second line of this paragraph, "...before PSM (n=185) and after PSM (n=138). There was a significant difference between the two groups..." Please add "Before PSM," between "(n=138)" and "There was"

Response 2: Sorry for this omission. We have corrected accordingly.

Comment 3: “metastasis (P=0103)” is a typo and should be revised to “metastasis (P=0.103)”

Response 3: Sorry for this omission. We have corrected accordingly.

Comment 4-1: Page 12, “By using a multivariate Cox regression analysis, we further found that pathological T stage and N stage were independent risk factors for OS and that the type of total gastrectomy did not influence the prognosis.” Please revise “multivariate” to “univariate and multivariate” because hazard ratio of LTG vs OTG was calculated using univariate Cox regression analysis, and LTG vs OTG was not put into multivariate Cox regression analysis.

Response 4-1: We agreed your comments and have modified the text accordingly.

Comment 4-2: In this study, cases with missing data were excluded and multiple imputation was not performed. The authors should describe it as a limitation.

Response 4-2: Thank you for your advice. We have noticed this limitation and improved the manuscript accordingly. The modified paragraph is as followed. [page 13 in " 69879-Manuscript File-Revised."]

“In our study, we excluded the missing data instead of multiple imputation, which may bring less statistical power and bias.”

Comment 5: Table 1 Comment: “Pathological T satge” and “Pathological N satge” are typos. “stage” is correct.

Response 5: Sorry for this omission. We have corrected accordingly.

Reviewer #2(Number ID: 05194798):

Comment 1: In neoadjuvant therapy for advanced gastric cancer, chemotherapy is common than chemoradiotherapy. I recommend that the authors focus on the patients who underwent neoadjuvant chemotherapy.

Response 1: We agreed that chemotherapy is more widely used in advanced gastric cancer than chemoradiotherapy. However, in our study some patients who underwent total gastrectomy were diagnosed as carcinoma of the gastroesophageal junction (GEJ). According to current cancer treatment guidelines, neoadjuvant concurrent chemoradiation therapy (nCRT) followed by surgery is a standard treatment for patients with locoregionally advanced, resectable GEJ. Besides, in our study patients who underwent chemoradiotherapy accounted for less than 10 percent of all patients, and for LTG and OTG group, the number was close. Thank you for your understanding our data.

Comment 2: (Table 1) I think the patients with distant metastasis belong to IVB in the pathological TNM stage.

Response 2: According to the 8th AJCC/UICC edition staging system in gastric cancer, for clinical staging, T4b, N any and M0 belongs to IVA, T any, N any and M1 belongs to IVB; for pathological staging, T any, N any and M1 belongs to IV. IVA and IVB did not mention in the 8th AJCC/UICC pathological staging system. Thanks for your notice. We now correct the “IVA” to “IV” (Pathological TNM stage, Table 1).

Comment 3: (Results) Please provide a breakdown of distant metastasis.

Response 3: We have noticed this limitation and added a breakdown of distant metastasis. The manuscript accordingly. The modified paragraph is as followed. [page 8 in " 69879-Manuscript File-Revised."]

“5 of distant metastasis occurred in the peritoneum and 1 occurred in liver in LTG group, and 4 occurred in the peritoneum and 1 occurred in liver in OTG group.”

Comment 4: (Results) The authors should provide data regarding the past history of abdominal surgical treatment, which can influence the outcomes.

Response 4: We have added the relevant data in Table 1 (The history of abdominal surgery). Our analysis showed that the difference between LTG and OTG groups was not significant ($P=0.362$). Therefore, we did not add this variable in PSM analysis.

Comment 5: (P10L4) Please insert a decimal point in “ $P=0.103$ ”.

Response 5: Sorry for this omission. We have corrected accordingly.

Comment 6: (P12L20-) I feel this paragraph seems somewhat sudden and little coherence. I understand the importance of staging laparoscopy; however, it seems to get off the main topic in this study.

Response 6: In our study, there were 11 patients who did not find evidence of metastasis before surgery were diagnosed as M1 finally. Besides our study, the STOMACH trial also found a similar situation, which 10 patients were found peritoneal metastasis. Therefore, we further discuss this situation and staging laparoscopy may be an effective method to avoid this. However, this may make people feel digress. So we decided to delete this paragraph. Thanks for your advice.

Reviewer #3(Number ID:05225448):

Comment 1: The authors described a high-dose opioid with more than 120mg/day of oral morphine. They need to state this rationale.

Response 1: We guess the Reviewer is referring to Line 8-9, Page6, “S-1 was administered orally twice daily when receiving radiotherapy.” It seems that the abbreviation caused misunderstanding. S-1 is one kind of chemotherapy drugs which is widely used in the advanced gastric cancer. Its main ingredients are tegafur, gimeracil and oteracil. To avoid misunderstanding, we have corrected accordingly.

Comment 2: The authors compared LTG and OTG retrospectively. Were there selection biases? Why the authors choice the LDG without the safety data of LTG?

Response 2: In our study, we focused on the he long- and short-term outcomes between LTG and OTG. As for the selection biases, we enrolled all the patients who received total gastrectomy with neoadjuvant therapy in the Cancer Hospital of the Chinese Academy of Medical Sciences from April 2011 to May 2018, and then excluded cases according to the exclusion criteria, which includes the missing data. We have noticed this limitation and improved the manuscript accordingly. The modified paragraph is as followed. [page 13 in " 69879-Manuscript File-Revised."]

“In our study, we excluded the missing data instead of multiple imputation, which may bring less

statistical power and bias.”

Since our study was a retrospective study, we performed propensity score matching (PSM) to minimize bias between the baseline of the two groups.

Although LTG has not recommended in guidelines, LTG has been confirmed to have better short-term outcomes and prognosis than OTG in early gastric cancer in trial JCOG0912 and CLASS02. And some retrospective studies and meta-analyses have shown that LTG has advantages in short-term outcomes than OTG. In our study, we further discuss the safety and prognosis for patients underwent LTG compared to OTG following neoadjuvant therapy, and hope to share our experience with other research teams so that they may learn from and build upon our work.

Comment 3: Reference 15 reported the long-term outcomes of LTG following NAT. The authors need to describe the difference from this report.

Response 3: Reference 15, Fujisaki M et al, Short- and long-term outcomes of laparoscopic versus open gastrectomy for locally advanced gastric cancer following neoadjuvant chemotherapy. This study enrolled two types of gastrectomy, distal and total, instead of specially focusing on the comparison between LTG and OTG. Besides, this study was a small sample retrospective study. The number of total patients is 49 and only 9 patients received LTG. In our study, we have more sample size (185 in total), and we also performed PSM analysis to minimize potential bias.

Comment 4: In discussion, it was unnecessary “To the best of our knowledge” twice.

Response 4: Thanks for your notice. We have deleted the unnecessary sentence (Page12 Line 16).

Science editor:

Comment: This manuscript is a retrospective study that for advanced gastric cancer following neoadjuvant therapy. I find it a well-structured interesting study. Nevertheless, there are a number points that may deserve some revisions. It is unacceptable to have more than 3 references from the same journal. Self Citation Count is four, The self-referencing rate should be less than 3%. The authors should keep reasonable self-citations. The article needs a great deal of language polishing, such as metastasis (P=0103). The results may have been biased, the number of patients was small and there was only one central study.

Response: Thanks for your advice. We have removed unnecessary citations to meet your requirement and corner label numbers have corrected in the text. Also, we made further language polishing. We sincerely hope that we have been able to satisfy these revisions.

Thank you again for your warm work and illuminating comments which help us to think more deeply about our interested area.