

Answering Reviewers

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "The comparison of the short and long-term outcomes between laparoscopic and open total gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy" (No.72688). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1.

The present study well analyzed the surgical outcomes after OTG and LTG following NACT. However, the present study was retrospective and single institutional study. Therefore, the authors should analyze historical bias. Major comments.

1. Introduction. Line 3, Page 5. The authors mentioned that neoadjuvant chemotherapy (NACT) reduced surgical risk. The authors should cite appropriate references about this. Postoperative complication rate after NAC may be equivalent to that of surgery-first therapy.

Response to reviewers: Many thanks to your valuable comments. It's our misunderstanding that NACT reduce surgical risk. Just as the reviewer's comment, it's correct to describe the advantages of NACT like postoperative complication rate after NACT may be equivalent to that of surgery-first therapy. Thus, we rectify this part in the introduction section and add appropriate reference to prove our demonstration.

chemotherapy prior to surgery which bring advantages as follows: (1) More possibility of reducing tumor stage and increasing R0 resection rate^[3]; (2) Better tolerance to chemotherapy before surgery; (3) Identical surgical safety compared with surgery-first therapy^[4,5]; (4) Guarantee higher complete rate of total chemotherapy; (5) Potential survival benefit compared with other interventional treatment. After MAGIC study^[6] firstly proved the surgical

2. Material and methods. Patients. Since when have the authors perform LTG following NACT? If the authors performed LTG after NACT since 2012, how did the authors select LTG patients? The authors mentioned the present study was retrospective. Did not the present study include historical factor? This means the present study contained improvement of surgical technique of LTG between 2012 and 2019. The authors should number of patients undergoing LTG from 2012 to 2015, and that from 2016 to 2019 in Table 1.

Response to reviewers: Many thanks for your professional comments for our manuscript. It's indispensable to analyze the impact of the historical factors and improvement of surgical technique because of the limitation of retrospective study and longer duration of the enrolled patients. In our medical center, we firstly performed LTG in 2006 and conducted LTG after NACT in 2011. Because there was no unified standard for indication of LTG after NACT, the enrolled criteria of patients in LTG and OTG group in our study is identical. To avoid the bias of historical factor as the reviewer's recommendation, we have collected the number of patients undergoing LTG and OTG from 2012 to 2015, and that from 2016 to 2019 and found no significant difference between two groups($P=0.088$) which illustrated in Table 1.

3. Results. The authors should perform multivariate analyses of OS and DFS including historical factor (i.e., from 2012 to 2015 vs. from 2016 to 2019).

Response to reviewers: Thank you for your effort to improve the quality of our manuscript. As the reviewer said, we conducted uni- and multivariate cox analysis of OS and DFS. The results showed that BMI and pTNM stage were independent risk factors of OS while vascular invasion and pTNM stage were independent risk factors of DFS ($P < 0.05$). Historical factor was not significantly associated with OS ($P=0.861$) and DFS ($P=0.691$), showed in **Table 7 and Table 8**.

4. Result & Conclusion. The abbreviations of pCR, ORR, AGC should be fully spelled when first appeared.

Response to reviewers: We truly appreciate the reviewer for the kind reminders. We have carefully revised our manuscript according to the comments, and added the complete spelling of abbreviations when first appeared.

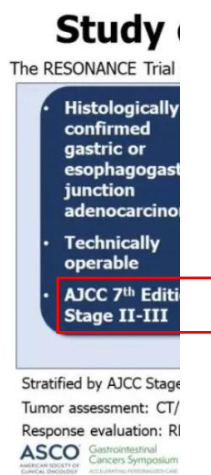
Reviewer #2.

There are many articles reporting that NACT have an advantage in advanced gastric cancer. Recent results from the RESOLVE study showed that Perioperative SOX has a better survival than adjuvant SOX which suggest the benefit of NACT. On the other hand, there are several articles showing that LTG has a same oncological outcomes as OTG. However, there are no phase III RCT trial showing that LTG is inferior to OTG in advanced gastric cancer. In this study, authors showed that the operative outcomes were similar between treatment groups which provides new aspect to this field.

1. In general, NACT is administered to locally unresectable nonmetastatic gastric cancer or patients who are at a high risk of developing distant metastasis. In this study, it seems that there are several patients who does not have a indication for NACT, although there is no clear indication for NACT. It might be better to limit the sample to those with general indications for NACT.

Response to reviewers: We truly appreciate the reviewer for your knowledgeable background and professional advice. Just like the reviewer's comment, there is still no clear indication for NACT. FLOT4 study conducted by Europe regarded cT2-4N0/+M0 patients as the indication for NACT. JCOG-0501 study conducted by Japan regarded Borrmann IV or large III(≥ 8 cm), N0-2M0 as the indication for NACT. PRODIGY study conducted by South Korea regarded cT2-3N+M0,

T4NanyM0 as the indication for NACT. RESOLVE study conducted by China regarded cT4aN+M0/cT4bNxM0 as the indication for NACT. In our study, clinical tumor stage ranges from II~III (including Bulky N or Borrmann large type III~ IV) were enrolled into our study which was in accordance with the RESONANCE trial led by our medical center and was basically in line with international RCT studies. The aim of our study is to figure out the short and long-term outcomes between LTG and OTG after NACT for the patients under our indications so that we could provide clinical reference for further studies. We have rechecked the criteria of enrollment so that all patients included in our study are in accordance with the stipulation.



The design of RESONANCE trial

2. Several patients used S-1 alone as a NACT. However, S-1 is usually combined with other chemotherapy. Therefore, I recommend excluding patients treated with S-1 alone for NACT.

Response to reviewers: Many thanks for your reminder. We have deleted the information of patients who accepted S-1 alone as a NACT. All the data mentioned in our study has been updated after rescreening the appropriate patients.

3. According to Table 5, surgery costs were higher and hospitalization costs were lower in LTG group compared with OTG group. However, total costs seems to be similar. Please provide the data for total costs.

Response to reviewers: Thank you for your comments. Our results showed that even

though LTG group spent more surgical cost than OTG (5419.99±1315.39 *Dollar* vs. 4162.36±791.93 *Dollar*, $P < 0.001$), LTG seemed more economical compared with OTG in terms of total hospitalized cost [13105.92 (11713.18-14640.53) *Dollar* vs. 14873.96 (13501.66-17131.31) *Dollar*, $P < 0.001$]. The raw data of total costs between LTG and OTG group is performed as follows.

Group (n=61)	Total costs(Dollar)	Group (n=75)	Total costs(Dollar)
LTG	10923.16	OTG	14516.80
LTG	13755.82	OTG	15750.11
LTG	12842.49	OTG	15959.77
LTG	12209.64	OTG	13001.05
LTG	10095.38	OTG	14012.84
LTG	15759.12	OTG	18485.87
LTG	14411.33	OTG	15815.33
LTG	11003.74	OTG	12666.53
LTG	11019.29	OTG	11828.38
LTG	15923.43	OTG	12515.06
LTG	14697.52	OTG	16049.35
LTG	16588.47	OTG	14873.96
LTG	15114.99	OTG	14779.82
LTG	13636.46	OTG	14852.85
LTG	16899.36	OTG	17292.54
LTG	11849.16	OTG	17429.63
LTG	14583.53	OTG	15889.45
LTG	14278.74	OTG	16264.76
LTG	12521.15	OTG	13566.91
LTG	20394.52	OTG	12155.97
LTG	12687.30	OTG	13555.03

LTG	11651.10	OTG	14108.15
LTG	15520.91	OTG	13384.00
LTG	12514.33	OTG	15384.80
LTG	12975.49	OTG	13501.66
LTG	12947.59	OTG	14032.87
LTG	10743.66	OTG	16049.35
LTG	13105.92	OTG	12104.93
LTG	11668.88	OTG	17795.78
LTG	11757.47	OTG	13770.95
LTG	11000.66	OTG	18014.34
LTG	21650.86	OTG	14200.86
LTG	9561.80	OTG	19468.58
LTG	14441.61	OTG	19814.87
LTG	16330.99	OTG	18073.03
LTG	13099.21	OTG	16072.02
LTG	12766.88	OTG	18784.96
LTG	15560.85	OTG	14643.07
LTG	10522.71	OTG	9726.83
LTG	15700.83	OTG	10802.11
LTG	12164.50	OTG	18219.09
LTG	22029.56	OTG	17131.31
LTG	13956.64	OTG	13162.85
LTG	17836.75	OTG	15830.52
LTG	12739.72	OTG	19599.33
LTG	13131.01	OTG	22197.51
LTG	10874.39	OTG	17856.90
LTG	11654.43	OTG	19295.16
LTG	12970.62	OTG	14424.33
LTG	10648.94	OTG	12960.37

LTG	13268.95	OTG	11631.75
LTG	15041.07	OTG	11207.67
LTG	12548.29	OTG	15956.32
LTG	13945.28	OTG	14007.91
LTG	13131.01	OTG	9794.53
LTG	13634.40	OTG	12742.29
LTG	13948.83	OTG	16255.89
LTG	13497.96	OTG	14047.63
LTG	13249.09	OTG	13865.39
LTG	11552.64	OTG	15203.50
LTG	11076.16	OTG	16304.15
		OTG	19159.60
		OTG	16342.11
		OTG	18256.35
		OTG	17143.02
		OTG	12111.07
		OTG	13840.64
		OTG	20133.56
		OTG	10640.83
		OTG	10450.87
		OTG	16075.28
		OTG	17105.31
		OTG	14372.62
		OTG	15263.28
		OTG	13505.70

Reviewer #3.

The manuscript is well written and interesting. No important edits are needed in my opinion.

Response to reviewers: We are very grateful to acquire your approval and encouragement. We will do our best to improve this manuscript's quality so that we hope our results can provide basic reference for clinical application. Thank you for your effort and help.

Scientific editor

The manuscript elaborated a study of the comparison of outcomes between laparoscopic and open total gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy. 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 of points that may deserve some revisions.

1. The picture is not very clear, please improve the picture quality.

Response to the editor: Many thanks for your kind reminder. We have updated the figure and summarized all clear figures into document named "72688-Image file.pptx". We will appreciate to provide any original pictures if you need further.

2. The author's study is a single-center study with a small sample size.

Response to the editor: Many thanks for your valuable comment. The main concern of the editor is the research design as a mono-institutional retrospective study which has declared in limitation section of this article, it is crucial for the manuscript's influence and authority. With the broader application of laparoscopic gastrectomy and neoadjuvant chemotherapy before surgery, it is necessary to conduct this study to explore the impact of neoadjuvant chemotherapy on LTG compared with OTG after NACT.

However, to the best of our knowledge, few studies like us compared surgical safety and oncologic outcomes between NACT-OTG and NACT-LTG. We think that this study is an exploratory study and has its scientific value to present an initial result so

that further studies like multi-institutional case-cohort study even RCT study can be carried out based on the conclusion of this manuscript.

3.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 to the editor: Many thanks for your kind reminder. We have rescreened the journal of the reference mentioned in our manuscript and modified the reference in order to ensure less than 3 references from the same journal as the editor's advice.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.

We appreciate for editors and reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions

Yours sincerely,

Hao Cui (First author)

Bo Wei (Chief physician, Professor)

(On behalf of co-authors)

Department of general surgery, the Chines PLA general hospital

No.28 Fuxing Road, Haidian District, Beijing, China