Peer Review File

Article Information: http://dx.doi.org/10.21037/jgo-20-374

Reviewer A

This an observational study evaluating patients enrolled in a single institution undergoing total gastrectomy for gastric cancer following neoadjuvant chemotherapy. The authors should clarify that this is a retrospective analysis of perhaps a prospectively maintained database.
A: The clarification has been made. Many thanks for pointing out this important issue.
Changes in the text: Pg 3 Line 22

The authors should be able to answer these questions.
1) what is the protocol in determining stage? Were these patients subjected to endoscopy, endoscopic ultrasound, CT scan? The yP staging in table 1 shows a total of 10 patients with stage 0 disease. Yet, the RECIST criteria does not list any complete responders. Is this a function of overstaging these patients? Similarly, the same question applies to those with yP stage 1 disease.
A: The clinical stage was done by CT scan, although most of our patients also had endoscopic ultrasound record. Radiological or ultrasound evaluation is not the gold standard for staging, nor it is accurate. One of the key factors is that the CT scan may reveal the "tumor bed" but not the actual tumor lesion area after neoadjuvant treatment. Thus, CT scan or ultrasound is suitable for evaluating the primary tumor but for evaluating the yp stage may not reflect. Also, based on our previous experience, the RECIST criteria has limited value in the use of response evaluation of gastric cancer to neoadjuvant chemotherapy (Tang L, Li ZY, Zhang XP. RECIST criteria in the response evaluation of gastric cancer to neoadjuvant chemotherapy: Achilles' heel? Transl Gastrointest Cancer 2013;2(S1):AB16. doi: 10.3978/j.issn.2224-4778.2013.s016). Although we presented the evaluation based on RECIST criteria, we believe it would be more accurate to use thickness of gastric wall to measure the response instead of "longest diameter". In this manuscript, the response was measured according to the "longest diameter" referring to RECIST v1.1 criteria. And, we hardly give out "CR" evaluation for post-treatment effect in locally advanced gastric cancer before pathological results.
Changes in the text: Pg 3 Line 29

2)There are many chemotherapy regimens included in this observation. Why are so many different regimens utilized? Why include patients who received < 2 cycles of chemotherapy? And what was the reason these patients could not complete the recommended course of neoadjuvant chemotherapy? How many cycles is typically recommended?
A: We are very sorry for the poor presentation of our data and many thanks for reviewers to point it out. Because this work and manuscript was done one and a half year, we have taken time to re-investigate our dataset and correct several points of our work. For this part of the questions, the answer was separately listed below:
Why are so many different regimens utilized?
A: Most of our patient used 5-Fu based doublet drugs, and oxaliplatin/S-1 or oxaliplatin/ capecitabine were the major regimens. For patients who are suspected of NET tumor or have major NET components, etoposide/cisplatin or docetaxel/carboplatin should be recommended. As a research institution, there is a

small fraction of patients underwent different preoperative regimens for clinical cohorts after obtaining informed consent, e.g., POS, FOLFIRI/XELIRI, and especially for some triplet-drug therapy. As our current topic limited to the postoperative safety after NACT rather than patients survival, we believe it is acceptable to enlarge the sample size without limiting the treatment protocols, plus its retrospective nature.

Changes in the text: Pg 4 Line9, Table S1

Why include patients who received < 2 cycles of chemotherapy? And what was the reason these patients could not complete the recommended course of neoadjuvant chemotherapy?

A: We are very sorry for this ambiguity. The initial target of our study plan was to include patients who are well tolerated to NACT and should be at least two rounds of NACT. After correcting our data, the two patients in LTG and OTG groups received two and three cycles respectively. But their records of NACT was only one cycle in our institution (they have NACT record at other institution). In fact, as NACT for LAGC is widely adopted in our center, there are some patients (not only two) who are strongly against the preoperative treatment after first cycle for various reasons. These patients were not initially included in our current dataset. Because of this problem the reviewers proposed, we then took time to retrieve the data that were relevant to NACT and made a minor correction. We also modified the methods in calculating the numbers of cycles because there are two-week and three-week protocols that should not be equalized. All have been revised in our Methods part. Also, the PSM was reconducted and was presented in a formal, statistical way.

Changes in the text: Pg 3 Line 28, Pg 4 Line 4, Pg4 Line 9, Pg 6 Line 12, Table 1, Table S2, Figure 1-2

How many cycles is typically recommended?

A: The timing of surgery was determined by MDT discussion based on patients preference after completion of at least two cycles of treatment. We have rewritten a scrutinized treatment protocol (Table S1).

Changes in the text: Pg 3 Line 29

3) There was no statistically significant observed difference in morbidity between the laparoscopic and open groups. However, esophagojejunal leak is one of the most concerning complications. Was this leak rate similar between the two? Is the incidence of toxic shock syndrome related to anastomotic leak?

A: We thank the reviewer for this great suggestion. We, too, believe the specific types of complications, rather than single Clavien-dindo grade, should be cautioned including anastomotic leak, abdominal infection, pulmonary infection, hemorrhage and so on. We have done this and added into our results as well as discussion in our newly revised manuscript. The TSS, on the other hand, was linked to the severe abdominal infection which at last lead to systemic shock. In these two cases, one experienced anastomotic leak while the other was not. The reason for TSS was related in our revision.

Changes in the text: Pg 7 Line 26, Table 3

Reviewer B

The authors compared perioperative outcomes between LTG and OTG for advanced gastric cancer after neoadjuvant chemotherapy, showing no significant difference in complications and less pain in LTG

group. There were several concerns in the study.

Major:

λ Please use standardized difference to compare the baseline characteristics. P -value had little meaning to compare the groups with small sample size. Absolute value of standardized difference <0.1 is usually considered nonsignificant imbalance.

Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083-107.

A: We are very sorry for our poor performance in methods presenting. For the PSM methods, we previously referred to -psmatch2- command in Stata. However, the seed of our previous log cannot be retrieved as the -psmatch2- generated different matched results each time making it impossible to replicate. After summarizing all the reviewers comments we have re-investigated our previous dataset, recategorized the baseline factors, as well as made a minor correction on our previous baseline information on NACT cycles. After these major revisions, there is nothing better than reran the PSM. At this time, however, the 1:3 is not suitable for the dataset but 1:2 using R package "MatchIt" (Ver. 3.6.2). The caliper was changed to 0.15. The output of this package was fixed. A detailed narrative of methodology has been revised. The SMD was used to compare the baseline characteristics following your valuable suggestions. A flow chart of PSM conduction was also presented. We added distribution figures (before vs after PSM) to fortify the reasons for this method. Also the SMD for per-match and post-match for each covariates were visualized.

Changes in the text: Pg 3 Line 28, Figure 1-2, table S2, table 1

λ Please eliminate Stage IV from ypTMN stage category

A: We thank the reviewer for this suggestion. The yp stage has been recategorized.

Changes in the text: Table 1

λ Most of the numbers of NACT regimen in LGT group were 0. It is inappropriate to make category having the group with no patient. Please group into SOX, CapeOX and the others.

A: Our previous version in presenting the baseline covariates is out-of-focus and has been pointed out by so many reviewers. We feel very sorry for making our work looks unprofessional. A great deal of this part has been revised. NACT protocols have been recategorized as platin-based, Taxol-based and others. During our practice, CapeOX and SOX has nearly the same treatment efficacy.

Changes in the text: Table 1, Table S2

Minor:

λ Please add c-statistics and distribution figures of propensity score.

A: We are pleased to present this part of the information. However, we are fearing that c-statistics may not be available as "MatchIt" does not have this function part if you mean the AUC that reveal the PS's discriminatory power (higher means better). The post-match AUC based on logistic regression was 0.531 which means a good distribution.

Changes in the text: Figure 2

λ In the discussion, “Although the rate of morbidity was higher in LTG than OTG which might require further investigations, the result showed no statistical significance.” The authors did not compare the

total morbidity rate between the groups. Please add the result comparing total morbidity rate including CD I/II and III/IV.

A: We are pleased to present this part of the information. Also, we decided to make a little more discussion on this topic, although the complications rate did not differ statistically

Changes in the text: Table 3, Pg 7 Line 24

Reviewer C

Thank you to give me the opportunity to read and to review this manuscript.

It addresses an important issue about laparoscopic total gastrectomy.

This study is well written and is focused only on total gastrectomy. Indeed, most manuscript about safetyness of laparoscopic approach during gastrectomy involves mostly partial gastrectomy. Hence, this study is original on that part.

However, I think authors would have to include all patients undergoing laparoscopic gastrectomy irrespective of preoperative treatment.

A: We are pleased to hear from this constructive advice. The reviewer does give a comprehensive look of our work. The reason for only including total gastrectomy, regardless of its technical difference comparing to distal, is that we have already complete a cohort study on distal issue (Li Z, Shan F, Wang Y, Ji J. Laparoscopic versus open distal gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy: safety and short-term oncologic results. Surg Endosc. 2016 Oct;30(10):4265-71. doi: 10.1007/s00464-015-4739-z. Epub 2016 Jun 10. PMID: 27287914.). We are more willing to make others see the consistency in our work.

Changes in the text: None

Introduction:

In Europe, neoadjuvant treatment before total gastrectomy is not the rule. The most generalized practice is periperative chemotherapy or preoperative chemo-radiotherapy. I think your introduction part should be changed for that point.

A: We are sorry for our unprofessional writing. We have revised the narrative related to this.

Changes in the text: Pg 3 Line 16

Methods:

Even if you aimed to limit selection bias with the use of propensity score, this is not a randomized trial. So there are necessary some bias during selection process. In routin, when did you prefer laparoscopic approach compared to open in those patients?

A: In most circumstances, the patients had their preference on whether he/she want to receive laparoscopic surgery other than conventional open surgery. For those who had previous history of abdominal surgery, the laparotomy is preferred. For those with poor physical status, or have multiple comorbidities, or extremely heavy, the laparoscopy is more recommended to patients. The truth is, the majority of our patients are more willing to receive open surgery.

Changes in the text: Pg 3 Line 29, Pg 4 Line 16

Naso gastric tube should not be used postoperatively, since it has been demonstrated to increase pulmonary complications without lesser leakage rate.

A: Many thanks for this piece of suggestions. We have deleted relevant information of this. In fact, not all patients placed Nasogastric tube after surgery. The Nasogastric tube was mainly used for jejunum nutrient. Thus, the withdrawal timing cannot reflect the patients recovery.
Changes in the text: Pg 5 Line 23

What was the delay between chemotherapy and surgery?
A: patients are regularly appointed to 30 to 45 days for reentrance after completion of NACT. The reason for delayed surgery had various reasons. But the delay did not increase the surgical difficulties as well as postoperative complications. For a detailed discussion on this topic, please follow our recent in-publishing work at: 10.3389/fonc.2020.613988.
Changes in the text: None

Could you define a lesser performance status or a weight loss after chemotherapy?
A: We recognize the reviewer's rigorous academic value and the constructive information. But we fear such information may not be available. If we defined weight loss and lesser performance status, we should present the relevant data in our manuscript. The relevant data was not currently available. Also, we believe ASA can partially represent the patients performance status. Moreover, if too many baseline characteristics were included, the PSM may also be required to include these new variables to eradicate the skewness. Too many covariates may not be suitable for currently limited size of our data. For example, in the current manuscript, after we summarizing the previous reviewers' suggestions, the baseline character were rearranged and PSM had to be reran and the analysis set was then altered.
Changes in the text: None

“Gastroparesis syndrom” should be removed, since patients underwent total gastrectomy
A: Apologies, it is a low-level mistake. We have removed the relevant topic.
Changes in the text: Pg 6 Line 2

Results:
Time of using IV-PCA was significantly longer after open approach. However, this difference does not seem to be clinically relevant (5 hours) since visual analog scale scores were not significanly different between both groups.
A: We thank the reviewer's fair remark. Indeed, the duration of using IV-PCA is only a small fraction of perioperative parameter and the minor improvement may not reflect any clinical significance. However, we may prefer to keep this result regardless of its unknown clinical significance. Two reasons listed here: 1) As this parameter is not commonly presented in most of studies when they comparing the postoperative patients quality between groups, our findings may serve as a reminder for them. And we believe the minimally-invasive technique should have some merit on postoperative analgesia in the future studies. 2) the anesthesiology department in our institution may require this relevant published result to facilitate their further investigations.
Changes in the text: None

Conclusion:
“Efficacy” should be removed since no data on survival are given. I suggest “histopathologic findings”
A: The corrections have been made. Thank you.

Changes in the text: Pg 2, Line 16. Pg 3 Line 23,