Peer Review File

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Review Comments:

Reviewer A:

This paper aims to examine whether variability in multimodal treatment among centers affects survival in patients with nmGC. I have the followings comments:

- my main concern is about the term "curative surgery". Once used, it is implied that a gastrectomy with lymphadenectomy was performed, with negative margins and at least 16 lymph nodes retrieved. 35% of the patients had less than 15 lymph nodes and 9% positive margins. They did not receive curative gastrectomy and should not be compared with others.

Reply: as we had stated in our first manuscript submission, our study cohort included nmGC patients who underwent gastrectomy with an intent to cure. One of the motivations of this study was to recognize the variability in how the surgical treatment of gastric adenocarcinoma is conducted within a single institution and across different institutions. The variations in margin status and lymph node recovery presented in this paper represent what is currently occurring in clinical practice. Another goal of this study was to determine whether this variability in surgical practices truly affected the overall outcomes of multimodality treatment. Therefore, we feel that it is important to keep these patients in our analysis. Please see the revised Methods sections on page #3 (abstract) and page #6 (main text).

- 23 patients had 0 (zero) lymph nodes retrieved, 90 had less than 16, and 15 were NA. This fact draws attention once we compare the number of retrieved lymph nodes from other institutions from different continents. Several aspects may explain (High patient BMI? lack of communication between surgeon and pathologist? surgeon did not dissect nodal individually before sending to the pathology? a low number of gastrectomies/year?)

Reply: we have included a sentence in the discussion alluding to the potential causes for inadequate lymph node retrieval. However, we acknowledge that due to the retrospective nature of this study, we cannot ascertain the reasons for inadequate lymph node retrieval. Please see the revised Discussion section on page #15.

- patients were classified according to which guideline? AJCC 8th edition? This should be described.

Reply: the AJCC 7th edition was used to stage tumors. This information has been added to the revised Methods section on page #7.

- any particular reason for T1a patients not receiving endoscopic treatment?

Reply: Patients receiving endoscopic surgery were not included in this study because endoscopic therapy for early gastric adenocarcinoma was limited in frequency at the

study institutions and often reserved for very early tumors (Tis) or for patients unable to undergo formal resection. This information has been added to the revised Methods section on page #6.

-table 1: "Number of recovered lymph nodes (%)": results are not in the same line.
Reply: the numbers appear to be properly lined up in the submission version as we see it on our end. It could be that the version the editors sent to the reviewers was accidentally reformatted, causing this error. We will work with the editors to fix this error.

- table 3: what was considered for choosing the variables? Why group smoking and alcohol consumption in the same group? I don't think that previous history of cancer is a prognostic factor in any other publication. Tumor´s sizes (large/medium/small) were based on which guideline?
Reply: Although no literature had indicated these variables as prognostic factors for cancer treatment, we considered and presented these variables as our own exploratory investigation. Unfortunately in our study design, we combined smoking and alcohol consumption when we extracted this information from medical charts; so we were not able to separate them apart in the analysis. The cut-offs presented in the manuscript were chosen as they were mentioned in literature guidelines for lymph node dissections. Please see these clarifications in the revised Methods section on pages #7.

-Classical prognostic factors for nmGC such as nodal status and T should be evaluated separately rather than localized vs loco-regional. it is more interesting for readers.
Reply: when we compared overall survival by individual T and N stages, we found that survival decreased as T and N stages increased (please see Figures 1-2 below), which was consistent with other reports in the literature. However, when we compared survival among the subgroups of patients receiving different treatment modalities stratified by individual T and N stages, the sample size in each subgroup was too small to demonstrate statistical significance. Therefore, we decided to combine T and N stages into two categories (T1-3, N0) versus (T4, N1+) to increase the sample sizes of the comparison groups; and we defined (T1-3, N0) tumors as localized disease and (T4, N1+) tumors as loco-regional disease. Interestingly, we found that a demonstrable increase in survival due to higher lymph node recovery was most profound among patients with localized tumors while an increase in survival due to chemotherapy was most profound among patients with loco-regional tumors (please see Figure 3 below). These information has been added to the Supplemental Data section and mentioned in the revised Results section on pages #11-12.

Figure 1: Comparison of overall survival among T stages

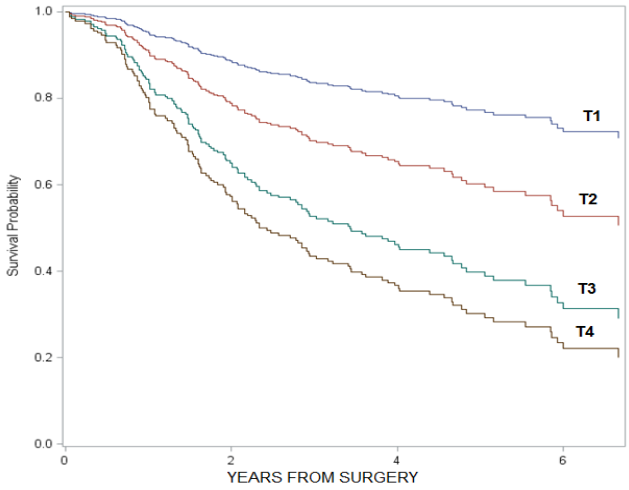


Figure 2: Comparison of overall survival among N stages

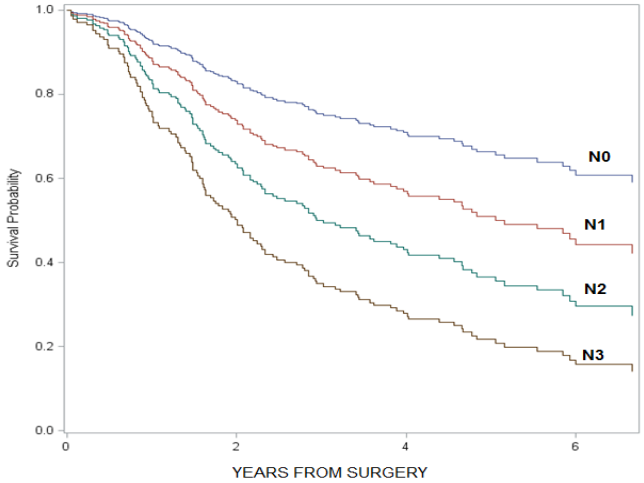
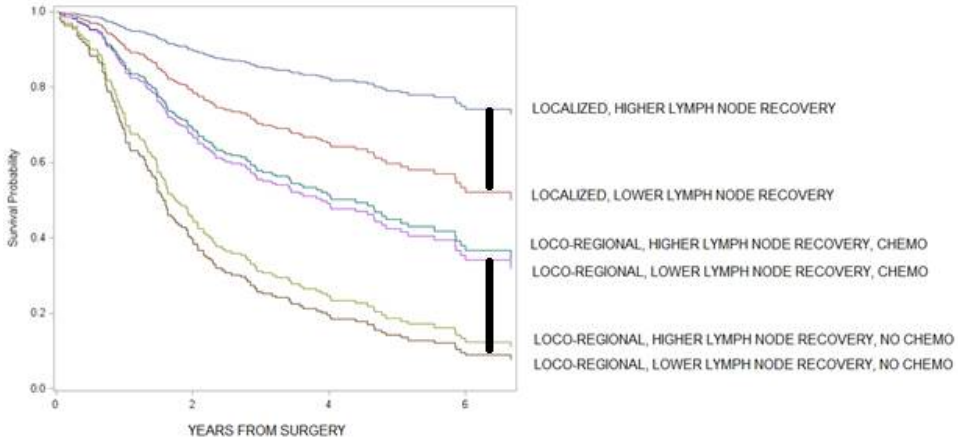


Figure 3: comparison of overall survival among treatment groups stratified by stages



-Please see the revised Results section on page #10.- page 14 / line 4: "how many lymph nodes an individual surgeon decided to remove" - this phrase should be reviewed.

Reply: we have rephrased the sentence as follows, “when we examined the number of

recovered lymph nodes at the provider level, we found no correlation between the number of recovered lymph nodes and tumor extent. However, in aggregation across all providers, we found that the higher the tumor stage, the higher the median number of recovered lymph nodes." Please see the revised Discussion section on page #13.

- page 14 / line 9: "use of laparoscopic technique might have constrained surgeons' visibility" - actually one of the main benefits of the laparoscopy is better visualization of structures, including vessels and lymph node station

Reply: The dissection around the major vessels such as the celiac axis, anterior common hepatic, and proximal splenic arteries is delicate to avoid vessel injury. Standard laparoscopic scopes and camera systems (2D) can be challenged particularly in visualizing the areas named above. Conversely, robotic 3D cameras do have a higher resolution and ability to visualize these same areas. Further, there is a definite "learning curve" to using standard laparoscopic techniques for delicate peri-vascular dissections. It is likely that not all of the surgery providers included in this study may have pursued an aggressive effort for lymph node recovery when performing a laparoscopic resection. However, given that these considerations cannot be demonstrated in this study, we would like to remove this sentence from the manuscript. Please see the revised Discussion section on page #14.

Reviewer B:

The authors have performed a multi-institutional retrospective cohort study to identify survival predictors among gastric cancer patients treated with curative intent. Their results confirm different impacts of the extent of lymph node dissection and multimodality therapies among patients who had localized or loco-regional disease. It is a good-sized cohort for an American study and the study population is somewhat homogeneous in the fact that they are from the same state treated at different university hospitals. Some significant issues would have to be addressed:

1 - The manuscript should be reviewed and restructured. Several results were obtained through unadjusted survival analyses and some subgroups were divided in a non-appropriate way (e.g. a pT3N0 tumor would not be considered to be localized disease; neoadjuvant chemotherapy is essentially a part of perioperative chemotherapy regimens - they should not be analyzed separately unless different treatment protocols are used in the institution). The main idea should still be focused on the impact of the extent of lymphadenectomy and multimodality treatment on survival. All analyses should be directed to this study question. Tables and figures should be less and focused on the study aim.

Reply:

- When we compared overall survival by individual T and N stages, we found that survival decreased as T and N stages increased (please see Figures 1-2 below), which was consistent with other reports in the literature. However, when we compared survival among the subgroups of patients receiving different treatment modalities stratified by individual T and N stages, the sample size in each subgroup was too small to demonstrate statistical significance. Therefore, we

decided to combine T and N stages into two categories (T1-3, N0) versus (T4, N1+) to increase the sample sizes of the comparison groups; and we defined (T1-3, N0) tumors as localized disease and (T4, N1+) tumors as loco-regional disease. Interestingly, we found that a demonstrable increase in survival due to higher lymph node recovery was most profound among patients with localized tumors while an increase in survival due to chemotherapy was most profound among patients with loco-regional tumors (please see Figure 3 below). These information has been added to the Supplemental Data section and mentioned in the revised Results section on pages #11-12.

- We have added a clarification that neoadjuvant chemotherapy indicated pre-surgical chemotherapy alone; adjuvant chemotherapy indicated post-surgical chemotherapy alone; and perioperative chemotherapy indicated chemotherapies before and after surgery. Please see the revised Methods and Results sections on pages #3, 7, and 11 and Table 1.
- We have added a clarification that all results were obtained through multivariable regression analyses, adjusted for the patient demographic, clinical, and tumor variables that were found significantly associated with survival. Please see the revised Methods section on pages #8-9.
- To reduce the number of tables and figures, we have moved some tables and figures to Supplemental Data section.

Figure 1: Comparison of overall survival among T stages

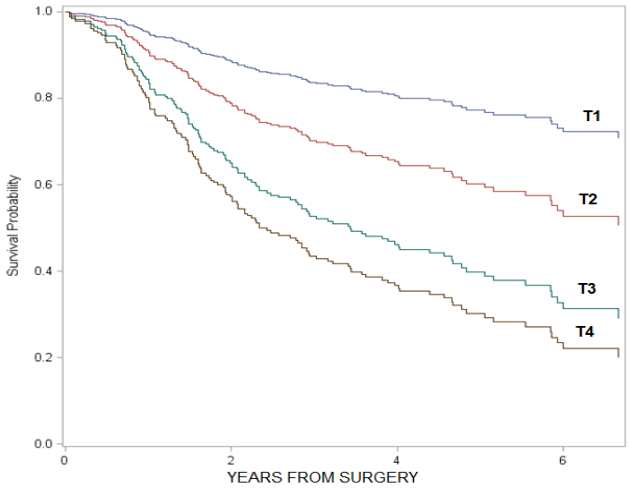


Figure 2: Comparison of overall survival among N stages

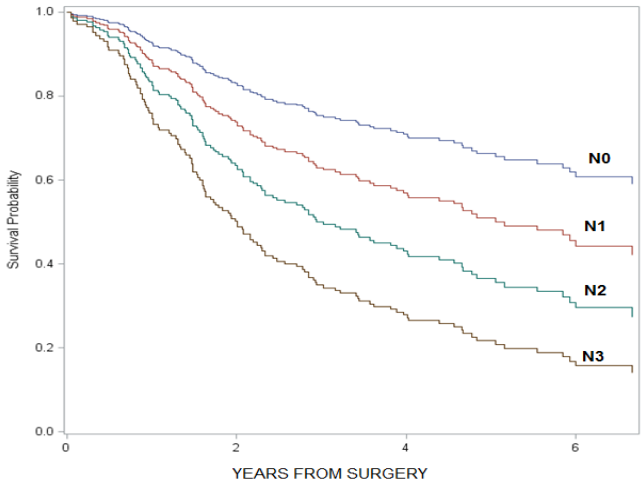
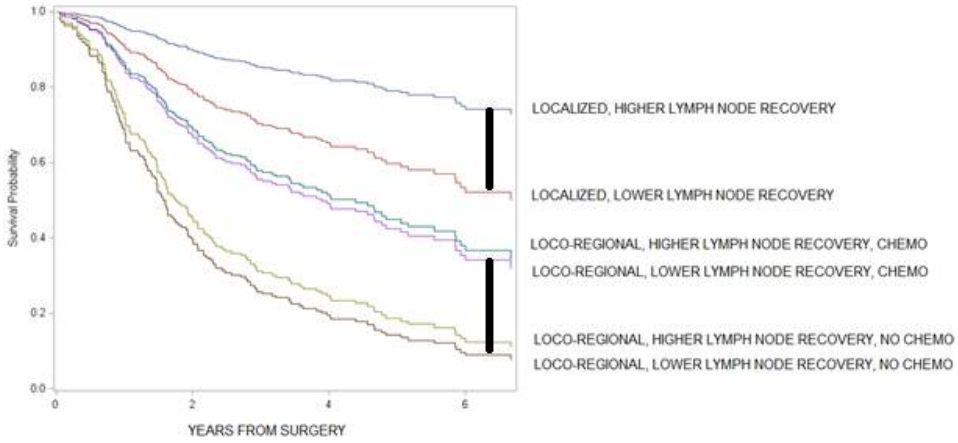


Figure 3: comparison of overall survival among treatment groups stratified by stages



2 - Statistical analyses should be reviewed also. In the methods section, t-tests and chi-square tests are described as part of descriptive statistics, which they are not. The survival event is listed as "death or recurrence" and survival is named "overall survival" in the results section. Overall survival events are generally deaths due to any cause, while recurrence events are used for progression-free or disease-free analyses. The main results obtained from regression analyses should be presented as HRs with 95% confidence intervals and they should be adjusted for all known confounders described as part of the database.

Reply:

- We revised the statistical method as follows “we summarized the demographic, clinical, tumor, and treatment characteristics of the study patients using descriptive statistics such as percentage, mean, and standard deviation. We compared these variables across the four institutions using t tests and chi-square tests whenever applicable.” Please see the revised Methods section on page #7.
- We revised the Method section to clarify that “recurrence events were used for disease-free analysis and death events due to any cause were used for overall survival analysis.” Please see the revised Methods section on page #7.
- We have added a clarification that the main results were obtained from

multivariate regression analyses, adjusted for the demographic, clinical, tumor, and treatment variables that were found significantly associated with survival. These results are now presented as hazard ratios (HRs) with 95% confidence intervals (CI) in both text and tables. Please see the revised Methods and Results sections on page #8-9, 11-12 and Table 3.

3 - National guidelines recommend that at least 15 lymph nodes are dissected. I would recommend the use of clinically relevant cut-offs for the number of lymph nodes analyses. Perhaps the use of 15 and 25 nodes as cut-offs. The latter is described in several studies as an average number of lymph nodes to be dissected in an adequate D2 dissection.

Reply: per reviewer's suggestion, we re-ran the analysis using the conventional cut-offs of 15 and 25 lymph nodes, the results were similar and the conclusion remained the same. Please see the revised Table 1 and the Discussion section on page #14.

4 - As access was granted to patients charts some relevant questions could be answered: 1 - 24% of patients recurred and 40% died. Was this difference observed because the study population included a very high number of older patients and patients with comorbidities, or was death data obtained from a different source because many patients were lost to follow-up?

Reply: recurrence events were obtained through chart reviews while death events were obtained from both chart reviews and the National Death Registry Database which is a part of the cancer registry database. The difference between death events and recurrent events were due to the fact that some patients were lost to follow-up and their deaths were not documented at the study institutions. Although we were able to obtain these death events from the National Death Registry Database, we were not able to obtain the causes of deaths. This information has been added to the revised Results section on page #10 and the Discussion on page #15.

2 - 23% of patients with locoregional disease did not receive any form of chemotherapy. Was this due to postoperative morbidity? Also, in 39% of all cases, chemotherapy information was not available. Did this affect the separation of "perioperative" and "neoadjuvant" groups?

Reply: both the cancer registry data and our chart reviews confirmed that these patients indeed did not receive any chemotherapy. Unfortunately, we could not ascertain any documented reasons for why they did not receive chemotherapy. We believed that patients who did not receive chemotherapy might have been less fit for therapy and thus more likely to have poorer survival outcomes. We had attempted to address this issue by comparing survival among patients of similar tumor stages and comorbidities. We had discussed this limitation in the Discussion section on page #15.