

7th -November-2021

Dear Editor-in-Chief:

**RE: “Sex-Based Differences in Histology, Staging, and Prognosis among
2,983 Gastric Cancer Surgery Patients”**

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Young Hoon Kim

Thank you very much for giving us an opportunity to revise our manuscript. Three sets of
comments by the reviewers provided extremely useful opinions in rewriting this paper. The
revisions are based on the reviewers’ comments and here we respond to them point by point.
We hope that these changes now make this paper acceptable and appropriate for publication.
The changes are in **yellow** in the text, in the revised manuscript and tables to avoid any
confusion.

Thank you for your attention and kind reply to our manuscript.

Sincerely,
Nayoung Kim, M.D., Ph.D.

Reviewers' comments:

Reviewer #1:

1. The “Conclusions” part in Abstract should be more detailed. And “These differences may originate from hormonal factors.” is not really proper in this study because hormonal factors were not mentioned.

Answers: Thank you for pointing out the important point. We have modified the conclusions part in abstract as below.

Page 3, line 1 - 2:

"Sex-based differences of gastric cancer were observed in the clinicopathological features including age of diagnosis, tumor location, histologic type, survival rate, and comorbidities."

2. Results: “Overall survival rate was significantly higher in females ($P < 0.001$), but this difference disappeared for GC-specific survival ($P = 0.168$).” Core tip: “There was a significant predominance in the GC-specific survival rate in advanced-stage cancer in males”. It is better to show both significant result in “Results” section of Abstract.

Answers: Thank you for the comment. We agree that it would be better to express it more in detail. So we revised the description as follows.

Page 2, line 17-19:

"Overall survival rate was significantly higher in females ($P < 0.001$). However, this difference disappeared for GC-specific survival ($P = 0.168$) except poor GC-specific survival rate in advanced-stage cancer (stage III or above) in females ($P = 0.045$)."

3. In the first paragraph of "Discussion" section, is it proper to conclude that tumor location and differences in histology could result in significant predominance in the GC-specific survival rate in advanced-stage cancer in males?

Answers: Thank you for the crucial comment. In this study, we observed the relationship between tumor location and histologic type, which has also been confirmed in several previous studies, as mentioned in the text. As the reviewer mentioned this may not completely explain the difference in prognosis between males and females. However, it is well known that diffuse type GC has a worse prognosis, and typically, Chen et al. reported a lower 5-year survival rate, higher prevalence in young ages and females, tendency of occurring frequently in the body of stomach, and infiltrative behavior (deeper invasion and frequent lymphovascular invasion) in diffuse type GC compared to intestinal type GC, that Lauren's histologic classification as an independent prognostic factor^[1]. These characteristics could make it difficult to diagnosis of GC in the females in the early stage.

Although this study enrolled patients who received surgical treatment for GC thus could not show much difference. However, we found that younger diagnostic age, higher N stage, and poor GC-specific survival rate in advanced-stage cancer in females ($P = 0.045$). It could be explained by Lauren's histologic classification. That is, there were more diffuse type GCs in females, especially in young females before menopause. Our results remind the Korean

gastroenterologists that although GC is common in aged males but this is reverse in young females thus diagnostic endoscopy should be performed vigilantly in females before menopause. .

We revised the content as follows, so that the conclusion is not too conclusive.

Page 9, line 4-8:

"In addition, the correlation between higher proportion of diffuse-type and gastric body cancer in females and intestinal-type and antral cancer in males could be the reasons of higher N stage and poor GC-specific survival in females (stage III or above, $P = 0.045$). Furthermore, there was also a difference in comorbidities including causes of death other than GC between males and females."

4. The figure should be better.

Answers: Thank you for your comment. We also think that original figures were too much condensed to understand. Following the reviewer's comment the figures were revised and we made a Figure 4 as following:

FIGURE 4. Gastric cancer-specific survival in (A) stage I, (B) stage II, and (C) stage above III. There were no significant differences between males and females in stages I and II, but a statistically significant male predominance was observed in advanced-stage cancer (stage III or above, $P = 0.045$). P values were calculated using the log-rank test.

The authors really appreciated the reviewer's kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.

Reviewer #2:

In this manuscript, the authors revealed the clinicopathological features and prognosis of GC were related to the gender, which is significant for the treatment of GC. And in the discussion section, the authors compared their results and previous study in details, which fully clarified the higher proportion of diffuse-type histology, mortality, and comorbidities may originate from hormonal factors. However, none figure was found in the manuscript.

Answers: We are very sorry for the omission. There was a technical error during the uploading process, and the figures and tables were added later. Now the revised figures are available. Sorry for the inconvenience again.

The authors really appreciated the reviewer's kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.

References:

1. **Chen YC**, Fang WL, Wang RF, Liu CA, Yang MH, Lo SS, Wu CW, Li AF, Shyr YM, Huang KH. Clinicopathological variation of Lauren classification in gastric cancer. *Pathol Oncol Res* 2016; **22**: 197–202 [PMID: 26502923 DOI: 10.1007/s12253-015-9996-6]