

Peer Review File

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**Reviewer A**

I have reviewed your article "Metastasis patterns and prognosis in patients with gastric cancer: A Surveillance, Epidemiology, and End Results-based analysis".

Please see the several comments.

I look forward to better submissions in the future.

1. Lines 66-68: "Due to the absence of specific symptoms in the early stages, the majority of patients with gastric cancer are diagnosed at an advanced stage, leading to limited treatment options and poor prognosis<sup>2</sup>." Reference 2 is a paper on early-stage gastric cancer and does not provide details on treatment options in advanced gastric cancer.

**Reply1:** Thank you for raising this point. We replaced this reference with another one related to advanced gastric cancer.

**Changes in the text:** Page 9, line 279-280.

2. Lines 82-83: "However, the association between metastatic patterns and survival outcomes in patients with advanced gastric cancer has not been fully explored." Reference 8 and references 11, 12, and 17 describe the association between metastasis and prognosis of gastric cancer. Please describe the novelty in more detail.

**Reply 2:** Thank you for your comment. In reference 8, only data on signet-ring cell carcinoma of gastric cancer were included in the analysis. In reference 11, the medical records of only 2,975 patients with gastric cancer were included, while we included medical records from 10,262 patients. In reference 12, the evaluation mainly focused on young gastric cancer patients. In reference 17, the differences in prognosis between patients with single-site metastasis and multisite metastasis were not compared.

**Changes in the text:** None.

3. Lines 100-101: "All medical records of patients who were diagnosed with stage IV gastric cancer between 2010 and 2015 were reviewed." These data are from the era before immune checkpoint inhibitors and are far removed from current gastric cancer treatment and prognosis. Data from a more recent era should be included in the analysis.

**Reply 3:** Thank you for raising this relevant question. The inclusion of data from 2010 to 2015 was to ensure a sufficiently large sample size for robust statistical analysis, as well as to allow for long-term follow-up.

**Changes in the text:** None.

4. Lines 224-226: “Second, this study was based on information from the SEER database, and some metastatic sites were not recorded, such as peritoneal metastasis and lymph node metastasis.” It is unclear whether patients classified as having single-site metastases had truly single-site metastases since no mention of peritoneal dissemination or lymph node metastases is indicated.

**Reply 4:** Thank you for highlighting this limitation. We acknowledge that the SEER database does not capture some metastatic sites, such as peritoneal and lymph node metastases. This limitation may lead to the misclassification of some patients who were recorded as having single-site metastases when, in fact, they could have had additional metastatic involvement in sites not documented in the database. We have addressed this issue in the limitations section of the manuscript and will further emphasize it in the revised version. Unfortunately, due to the nature of the SEER data, we cannot obtain more detailed information regarding the metastatic spread beyond what is available in the dataset. We emphasized this point in the limitation section.

**Changes in the text:** Page 8, line 239-240.

## **Reviewer B**

I am grateful for your efforts. This study is a large population study, but it cannot provide new findings or knowledge because there are many previous studies that reported the prognosis of patients with stage 4 gastric cancer. In addition, this study has several methodological weaknesses. The diagnosis process for stage 4 patients did not specify a clear method or tool to identify the location of metastasis. In this study, there were no reports of patients whose cancer spread to the peritoneum and paraaortic lymph nodes, which are the locations where gastric cancer often spreads. In terms of treatment, some patients may not receive any treatment, but the prognosis was not described and compared in this study. For surgical treatment, the details of the surgery, the type of gastrectomy, including lymph node dissection should be described. The type of systemic chemotherapy, and the compliance of treatments should be specified, because it is well known that these factors affect the patient's prognosis. The graphs are quite small and cannot clearly show the differences. The presentation of data in tables, especially Tables 3 and 4, should be improved to be more concise and understandable.

**Reply:** Thank you for your comments. We acknowledge that this study has certain methodological limitations due to the nature of the SEER database. The SEER database

does not provide detailed information regarding the methods used to diagnose metastasis, nor does it specify the exact locations of metastases such as the peritoneum or paraaortic lymph nodes, which are common metastatic sites in gastric cancer. As a result, it is challenging to capture all relevant metastatic information, potentially leading to underreporting or misclassification of metastatic sites. Nevertheless, our analysis aimed to provide a broader understanding of the prognosis of stage IV gastric cancer patients based on a large population dataset, while acknowledging the constraints inherent in using SEER data. While we acknowledge that larger graphs may enhance visibility, we opted to maintain the current size to ensure clarity in the overall layout of the manuscript. For table 3 and table 4, our aim was to provide a comprehensive overview of the data while maintaining the necessary details for thorough analysis and we believe the current format allows for clear comparison and context.

**Changes in the text:** None.

### **Reviewer C**

This paper presents a statistical analysis of gastric cancer metastasis and prognosis. The number of cases is very large, and the identification of factors affecting prognosis is worthwhile. However, the current treatment of gastric cancer is based on the genetic form of the cancer. Some patients with multiple metastases have a good prognosis when molecular-targeted therapies are successful. If you have any data on the correlation between the site of metastasis and genetic analysis of gastric cancer, please present them. This would make this paper more valuable.

**Reply:** Thank you for this insightful comment. We agree that the genetic characteristics of gastric cancer play a significant role in determining treatment outcomes and that integrating genetic information with the analysis of metastatic sites could provide valuable insights. However, the SEER database does not include genetic or molecular data on the tumors, which limits our ability to analyze the correlation between metastatic sites and genetic characteristics

**Changes in the text:** None.

### **Reviewer D**

This study is a clinical investigation focusing on patients with stage IV gastric cancer. The authors, using the SEER database, analyzed metastasis patterns and the associated prognosis in these patients. However, SEER data makes it challenging to capture information on peritoneal metastasis, which is the most common form of distant metastasis in gastric cancer. Indeed, there is no mention of peritoneal metastasis in this

manuscript. Consequently, the authors' analysis is based on incomplete data, which risks leading to incorrect treatment decisions in gastric cancer and lacks scientific rationale.

**Reply:** Thank you for pointing out the limitations associated with the use of the SEER database. We have already acknowledged the absence of peritoneal metastasis data as a limitation in the manuscript. We believe that while this limitation is significant, our study still provides valuable insights into the prognosis associated with other documented metastatic sites. Our findings can serve as a foundation for further research that includes more detailed metastatic data.

**Changes in the text:** None.