Peer Review File

Reviewer A

Liu et al. present a SEER query to show that previous malignancy does not affect survival in patients with esophageal cancer.

The manuscript is very comprehensive in the data analysis with a good discussion of the findings. I have no further comments.

Reply: Thank you very much for your careful review and positive assessment of our work. We appreciate your clear summary and recognition of our work.

Reviewer B

This is an interesting paper exploring a potential relationship between prior cancer diagnosis and esophageal cancer-specific and all-cause mortality in patients diagnosed with esophageal cancer. SEER data was used for the analysis. Patients were propensity-score matched based on age, sex, race, marital status, primary site, grade, histological type, stage, as well as treatment with surgery, radiotherapy, or chemotherapy. Survival analysis was performed to compare the risk of death in those with and without prior cancer diagnosis. This is an important topic to discuss as clinical trials often struggle with external validity due to the stringent criteria for trial participation. The overall angle of this paper is strong and the methods are appropriate. Some statistical oversights are present however, which has significantly impacted the interpretation of the data. With revision, this manuscript can become much stronger.

Response to review B: Thank you very much for your recognition of our work. We appreciate your careful reading and valuable suggestions, which helped us to improve the quality of our manuscript. We have made corresponding changes in the revised manuscript.

Comments 1: The use of matching based on cancer stage and grade means that stratification of these variables in later stages of the analysis will be biased. This is shown in the data when comparing the results of subgroup analyses of cancer stage and grade for unmatched with matched data in Figures 2B, 3B, 4B, and 5B.

Reply: Thank you for your comment. We fully agree that stratification analysis of cancer stage and

grade in later stages is biased after propensity score matching based on these variables; therefore, in the revised version, we have kept the results of subgroup analysis in all-cause and esophageal cancer-specific survival before matching but removed those after matching.

Changes in the text: Page 10, lines 172–177.

Comments 2: The proportional hazards assumption appears that i may be violated in a number of survival analyses, suggesting that prior cancer has a variable effect on mortality based on the time since esophageal cancer diagnosis. Ignoring this violation has skewed the calculated hazards ratios. In Figure 6A, prior cancer history appears to be associated with increased survival between 0 and 24 months, and appears to be associated with decreased survival between 36 and 72 months. However, the HR is 0.94, with a CI of 0.772-1.145 and p-value of 0.56 because the two opposing time-varying effects have been combined. Other methods are needed for analysis if the proportional hazards assumption is violated.

Reply: Thank you for your comments. We also realized that i might be violated in a number of survival analyses, such as survival curves for subgroup of latency period of 6–12 months, which would cause incorrect conclusions. In line with your suggestions, we have added a multivariate Cox regression analysis for subgroups of latency period to confirm that prior cancer does not influence mortality, thereby avoiding interference of other factors.

Changes in the text: Page 10, lines 184–187.

Comments 3: the conclusions drawn from the results are overly broad. Importantly, there are likely subgroups of patients with prior cancer history who have increased mortality, but these patients have not been analyzed in this study. For example, patients with indolent prostate cancer or a stage I colorectal cancer that was diagnosed 10 years ago will likely have a decreased risk of death due to increased engagement with healthcare. However, someone who had been diagnosed with metastatic melanoma 2 years earlier and is on their 3rd line of treatment likely has an increased risk of death compared to someone without cancer. The author's data also suggests that the reason that prior cancer is not associated with an increased risk of death is that esophageal cancer itself has a high mortality rate and that this risk supersedes risk of death related to the prior cancer or other causes. The fact that prior cancer has an impact on esophageal cancer survival and overall survival in those with Stage 1-2 cancer, but not Stage 3-4 cancer supports this.

Reply: Thank you very much for your comments. After careful consideration, we also acknowledge that the conclusions drawn from the results were overly broad and inaccurate. Whether prior cancer has an effect on prognosis of patients with esophageal cancer is probably related to the degree of malignancy of the prior cancer, but also to the impact of the previous cancer treatment on physical health condition. However, detailed information of prior cancer clinical features, such as specific

surgical treatment options, chemotherapy, and radiotherapy regiments, is not provided by the SEER database, and the clinical characteristics of prior cancer for many patients are not available; therefore, subgroup analysis stratified by the characteristics of prior cancer is difficult to achieve. In this study, we can only conclude that prior cancer is not a definite factor affecting the prognosis of esophageal cancer. In future studies, we would like to further investigate the specific effects of previous cancer stratified according to clinical features on the prognosis in patients with esophageal cancer, so as to draw more accurate conclusions to guide clinical treatment. In line with your suggestions, the conclusions have been corrected. We have corrected the title accordingly in the revised version and have provided a detailed explanation in the discussion.

Changes in the text: Page 1, line 3; Page 4, line 53; Page 11–12, lines 209–212; Page 12, lines 224–232; Page 13, lines 251–253; Page 14, lines 257–259.

Comments 4: please show cox regression for the subgroup analyses illustrated in Figure 6.

Reply: Thank for your advice. We have added the Cox regression models for the subgroup analysis stratified by latency period to the revised version.

Changes in the text: Page 10, lines 184–187.

Comment 5: an additional subgroup analysis based on the type of initial cancer would be helpful to identify which patients with prior cancer should be excluded from trials.

Reply: We appreciate your recommendation and agree that it is a better way to make our results deeper and more comprehensive. Therefore, we have added the results of the subgroup analysis based on the type of prior cancer.

Changes in the text: Pages 10–11, lines 188–194.

Reviewer C

In this study, the authors investigated the impact of prior cancer on survival of patients with esophageal cancer by using SEER database. They showed that primary cancer did not have a significant impact on all-cause survival and esophageal cancer-specific survival before and after propensity score matching. Thus, they concluded that exclusion criteria of primary cancer history in esophageal cancer clinical trials might be reconsidered.

I think that this study is interesting and could provide a useful information on treatment for esophageal cancer. However, there are several points that need to be taken into account. I think that the impact of prior cancer history on survival of patients with esophageal cancer can be dependent on the balance of malignant potential between prior cancer and esophageal cancer. So, I think that the authors should investigate the impact of prior cancer history on survival of patients with esophageal

cancer, according to type of prior cancer and stage of prior cancer.

Response to review C: Thank you for your recognition and positive comments regarding our work. Your suggestions were valuable and helpful for revising and improving our manuscript. We have made suitable modifications as suggested.

Comments: "So, I think that the authors should investigate the impact of prior cancer history on survival of patients with esophageal cancer, according to type of prior cancer and stage of prior cancer."

Reply: We appreciate your suggestion to make our study more complete. After careful consideration, we also believe that your hypothesis might be justified, and whether prior cancer has an effect on the prognosis of esophageal cancer may be related to the degree of malignancy of the prior cancer. Therefore, after extracting the information regarding prior cancer stage, we have compared the survival function stratified by prior cancer type and stage to investigate the effect of prior cancer on the survival of patients with esophageal cancer in detail to draw a more accurate conclusion.

Changes in the text: Pages 10–11, lines 188–194.