Peer review file
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Comment 1: There are many general syntax/grammatical errors which detract from the potential impact of this paper. This manuscript would benefit greatly from a thorough editing by a scientific writer, and this must be undertaken prior to acceptance. This applies to all sections of the manuscript. Consider utilizing the word "histologic" in place of "pathologic/pathological" throughout the manuscript – this is not the correct term for what you are describing.
Reply 1: Thank you for your opinion and suggestions. We overlooked this question and we have revised the "histologic" to "pathologic/pathological" in the manuscript. At the same time, we have polished the manuscript (see Page 5, line 87).
Changes in the text: Independent variables were selected into the propensity model, including age, gender, pathological type, marital status, race, grade and tumor location.

Comment 2: This manuscript was submitted to a palliative medicine journal, but at no point are patient symptoms/QoL between different treatment combinations addressed. If the information is available, this would be highly important to comment on. This may be an inherent limitation of utilizing SEER data, but then a palliative medicine journal may not be the best place for this manuscript.
Reply 2: Thank you for your opinion and suggestions. Indeed, patient symptoms/QoL is important for the study of advanced tumors. Unfortunately, there is no data about patient symptoms/QoL in SEER database. This is one of limitation of our research. We have pointed out the limitation in the discussion section. But we still believe that this manuscript is appropriate for publication by the APM. The purpose of treatment is to reduce the cancer-related symptoms and prolong the survival period. Our article focuses on the treatment of metastatic esophageal cancer. We wished to develop individualized treatment strategies for inoperable metastatic esophageal cancer.

Comment 3: Was information available about patterns of recurrence, for example local/locoregional v. distant metastatic progression? This would be particularly informative if it could be compared between different tumor histologies.
Reply 3: Unfortunately, there is no recurrence-related data in this database. But the opinion is meaningful for recurrent esophageal cancer.

Comment 4: There are a number of studies recently published regarding the role of immunotherapy, specifically checkpoint inhibitors, in the management of advanced and metastatic esophageal cancers. This warrants discussion, particularly as patients in this manuscript were treated in 2016 or earlier (the

reason for this is unclear) and commentary on these studies and how their results compare to survival outcomes discussed in the manuscript.

Reply 4: Indeed, immunotherapy has been widely studied in advanced esophageal cancer, and it can improve the prognosis of esophageal cancer. However, SEER database does not contain immunotherapy information. Besides, there may be not many patients receiving immunotherapy before 2016. In addition, our concern is chemotherapy and radiotherapy. Therefore, we did not discuss the role of immunotherapy in advanced esophageal cancer.

Comment 5: Although the points that the authors are trying to make are well-intended, this reviewer does not feel that enough data is presented to support the conclusions that have been stated. Additionally, there is a lack of relationship between the results seen on subgroup analyses and on MVA that should be further explained.

Reply 5: 1) We thank the reviewer for the comment, but feel sorry again that we could not fully agree with this. Both Kaplan-Meier curves and subgroup analysis based on multivariable Cox regression support our conclusions. Interaction tests showed that OS and CSS of CT group and CRT group significantly varied across different pathological types ($P_{intercation\ for\ OS}$ and $P_{intercation\ for\ CSS}$ <0.001, Figure 3)(see Page 7, line 133). In addition, in order to show our results more clearly, we changed Table 3 into Figure 3. To clearly state the relationship between subgroup and MVA, we have changed the sentence (see Page 5, line 92) .

Changes in the text: We performed multivariable Cox proportional hazards regression analysis to account for potential confounders and screen prognosis-related factors, which were expressed as the adjusted hazard ratios (HR) and 95% confidence interval (CI). Independent prognostic factors were included in subgroup analysis. Moreover, interaction tests were performed to explore whether any survival benefit conferred by treatment varied across subgroups.

Abstract:

There are many studies looking at systemic therapy in metastatic esophageal cancer patients, including a recent wave investigating immunotherapy. To say that there are "few" studies focusing on this population is incorrect.

Reply: Thanks very much for your careful and patient comments. We have revised the Abstract section (see Page 2, line 15).

Changes in the text: The aim of this study was to explore the impact of chemotherapy (CT) and chemoradiotherapy (CRT) on prognosis in metastatic esophageal cancer (mEC) patients.

Introduction:

Page 3 Lines 12-14 do not make sense, why would you give chemoradiotherapy for a CR to other chemoradiotherapy?

Reply: Sorry, we did not express it clearly. This part has been revised (see Page 8, line 154).

Changes in the text: According to the treatment guidelines in the west, chemoradiotherapy is an acceptable treatment for unresectable mEC.

Methods:

Please elaborate more on any specific aspects of radiation necessary for inclusion (was there a minimum dose required? Was RT delivered to the primary tumor in all cases? What was the intent of RT? How was RT delivered?). If this information was not available, this must also be acknowledged.

Reply: Radiotherapy in the test concludes beam radiation, radioactive implants and radioisotopes. Radiotherapy was delivered to the primary tumor in all cases. But information on the minimum dose of radiotherapy is missing in the database

Results:

Comment 1: Page 6 Lines 23-25, Page 7 lines 1-4 – This section is very confusing to interpret, for example the statement "did not demonstrate a significant survival disadvantage in the OS" could be reworded in a better way. I cannot understand the main point the authors are trying to make out of this paragraph. Is the intended statement that including radiation did not make survival worse in these patients? If so, statistics for a non-inferiority design will need to be considered.

Reply 1: Sorry for our confusion expression, and thank you very much for your suggestion. We have revised the Results section (see Page 6, line 124).

Changes in the text: Multivariable analyses indicated that un-partnered, male and ESCC were significantly correlated with worse OS and CSS before and after matching (all $P<0.05$, Table 2). However, in the original model, CRT group displayed no significant differences in OS (HR = 1.02; 95% CI, 0.94-1.11; P= 0.584) and CSS (HR = 1.03; 95% CI, 0.94-1.11; P= 0.542) compared with the CT group. Similar results were observed in the PSM Cox regression model. Other factors were not associated with the prognosis of mEC patients (all $P>0.05$).

Comment 2: Please state how your factors that were significant on MVA impacted survival outcomes. Were they associated with improved or worsened survival?

Reply2: We have now rephrased the sentence and described results in the multivariate

regression more carefully (see Page 6, line 124).

Changes in the text: Multivariable analyses indicated that un-partnered, male and ESCC were significantly correlated with worse OS and CSS before and after matching (all $p<0.05$, Table 2). However, in the original model, CRT group displayed no significant differences in OS (HR = 1.02; 95% CI, 0.94-1.11; $P = 0.584$) and CSS (HR = 1.03; 95% CI, 0.94-1.11; $P = 0.542$) compared with the CT group. Similar results were also observed in the PSM Cox regression model. Other factors were not associated with the prognosis of mEC patients (all $P>0.05$).

Discussion/Conclusions:

Comment 1: The entire discussion section would benefit from editing/reorganization. The first two paragraphs are written in a very disjointed way, and makes it hard to understand the overarching conclusions.

Reply 1: We have re-edited the discussion section to make it more clearly to readers (see Page 8, line 149).

Changes in the text: This study demonstrated that ESCC patients who underwent CRT had better OS and CSS compared with those receiving CT. In contrast to CRT, perioperative chemotherapy improves OS and CSS for EAC patients. Besides, we also found that un-partnered, male and ESCC are independent prognostic factors for mEC.

Although the treatment regimens for mEC have undergone drastic changes, the standard treatment is yet to be optimized. According to the treatment guidelines in the west, chemoradiotherapy is an acceptable treatment for unresectable mEC [8,9]. Tanaka et al. [5] suggested that multimodality therapy, which includes chemotherapy, radiotherapy and surgery, could improve the outcome in patients with ESCC with distant organ metastasis compared with single-modality. However, mEC is until now not generally treated with a multimodality approach. Guidelines for the National Comprehensive Cancer Network (NCCN) recommend chemotherapy as the preferred treatment for mEC patients [9]. Notably, our research showed that there were no significant differences in OS and CSS between CT and CRT groups before and after PSM.

Comment 2: This discussion would benefit from more information on why the authors think that different histologies respond differently to CRT v. CT alone.

Reply 2: We have added additional references and revised this part (see Page 8,line 161).

Changes in the text: Previous studies revealed that ESCC was more sensitive to radiotherapy [14,15], and patients with ESCC has a higher rate of pathological complete response to chemoradiotherapy [16]. Normal cells undergo DNA repair through G1/S phase arrest after radiation, and the key gene in this process is wild-type TP53 [17,18]. However, multiple studies have confirmed that the high mutation rate of TP53 in

patients with esophageal squamous cell carcinoma [19,20]. Therefore, esophageal squamous cell carcinoma is more sensitive to radiotherapy. Steins et al. [17] reported that CRT may contribute to resistant metastatic disease in EAC patients by inducing epithelial-to-mesenchymal transition. CRT may lead to more radiation-related complications, such as pneumonia, acute respiratory distress syndrome, anastomotic leakage, and cardiac complications [18-20], which could present an additional risk. In addition, previous studies had revealed that chemoradiotherapy had more costs compared with chemotherapy alone [21]. That may be important reasons why chemotherapy alone is more suitable for metastatic EAC.

Comment 3: Page 9, Lines 13-15 - "Interestingly, our study demonstrated that patients with multiple metastatic EC may not be suitable for CRT as they often have impaired organ functions and a very short life expectancy." Where is this previously discussed? I don't see this clearly delineated anywhere else in the manuscript.
Reply 3: This was an obvious oversight on our part. We have deleted this sentence.

Figures/Tables:
Comment 1: Table 1 – Title is split before and after the table itself. Please revise.
Reply 1: We have modified the mistake (see Table 1).

Comment 2: Table 2 – What does "RF" stand for and why is it being utilized?
Reply 2: "RF" means reference. We have added "RF" to the abbreviations in Table 2.

Comment 3: Figure 2 is incredibly small and of poor quality – the titles and numbers are unreadable and uninterpretable as it stands.
Reply 3: We have re-edited the figure 2 to make it clearer, and we changed Figure 2 to Supplementary Figure 1.

Comment 4: Figures 3 and 4 should be revised to make titles/numbers more clearly readable as well. In figure 4, please consider labeling individual graphs as OS or CSS. It is very challenging to keep track of which figure is describing each subgroup. This could benefit by being split into multiple figures, for instance, one figure for OS and one separate figure for CSS.
Reply 4: We have re-edited the figures. We have now split the figure 4 (now Figure 4 and 5) into two different ones to optimize readability.