

Peer Review File

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Reviewer A

This is an interesting study but the conclusions do not give us much scope for change of practice or further studies. I do not think the paper adds to the literature in its current format but it may be informative and publishable if the authors are able to publish some data on the actual treatments and regimens the patients received and how that may have impacted survival. It would also benefit from being proof read and grammatically edited by an author whose first language is English.

Reply: Thank you for your kind suggestions. Some clinical data have been added in the manuscript, and we have tried our best to polish language in the revised manuscript.

Changes in the text: Here we did not list the changes but marked in different colour in the revised paper.

Reviewer B

Pan et al present an analysis of the differential outcomes of advanced stage esophageal adenocarcinoma compared with squamous cell carcinoma. Esophageal cancer typically presents at an advanced stage and its treatment is evolving.

1. Line 17, although the incidence of esophageal cancer is rising and it is the 8th most common cancer worldwide, the incidence in the SEER database would be much less. Consider revising or eliminating the opening phrase.

a. Consider: "Esophageal cancer is the sixth leading cause of cancer death and 50% of cases..."

Reply 1: Thank you, we agree and have deleted that sentence. In addition, we added this part in the introduction.

Changes in the text: It was rectified at Page 1 line 17 and Page 3 lines 65-66.

2. This manuscript should undergo English language editing, there are several grammatical errors that do not obscure the meaning but interrupt the process of the reader.

Reply 2: Thanks for your suggestion. We have tried our best to polish language in the revised manuscript.

Changes in the text: Here we did not list the changes but marked in different colour in the revised paper.

3. Lines 55-57, more recent data about EC incidence and mortality are available. For example in 2020 there were 604,000 EC diagnosed (<https://www.wcrf.org/cancer-trends/worldwide-cancer-data/>).

Reply 3: We were really sorry for our mistakes. Thank you for your reminder.
Changes in the text: We have re-written this part according to the Reviewer's suggestion. (see Page 3-4, lines 66-67)

4. Lines 60-61, is to not clear that the morbidity of EAC is increasing. The reference provided does not clearly substantiate the authors' statement. This sentence may not be necessary for the message of manuscript since it well accepted that EC is increasing in incidence.

Reply 4: Thanks a lot for reminding us of this important point.

Changes in the text: We have made some corrections on Page 4, lines 70-72.

5. Line 63, consider changing "pay back" to "carry"

Reply 5: It was indeed our mistake.

Changes in the text: We have revised it on Page 4, line 74.

6. Lines 84-85, please include information on which of edition of the AJCC staging system was used.

Reply 6: We thank the reviewer for pointing out this issue.

Changes in the text: It was rectified at Page 5, line 97.

7. Lines 113-114, this sentence is unclear. Do the authors mean the most prevalent primary site of ESSC was the middle of 1/3 of the esophagus and that of EAC was the lower 1/3 of the esophagus? That would be consistent with the wording of table 1 and the most likely intended meaning.

Reply 7: Thanks, we agree and have revised.

Changes in the text: Please see page 6 of the revised manuscript, lines 128-129.

8. Lina 114-115, instead of "low grade" consider reporting it as grades II and III or moderately and poorly differentiated, typically low grade means well differentiated which is grade I. While most patients were either grade II or III.

a. Line 145 grades II and III are the most common which should mean moderate or poorly differentiated.

b. Also in lines 164-167

Reply 8: We have made the changed.

Changes in the text: we have modified our text as advised (see Page 6 line 130, Page 9 line 191, Page 10 line 209).

9. Figure 1, in the excluded box, change "AJCC stage is black" to AJCC stage is blank.

Reply 9: We are very sorry for our careless mistake.

Changes in the text: It was rectified in Figure 1.

10. Combining stages III and IV dilutes the message of this manuscript. Regarding stage IV disease, the number and location of metastasis can help with prognosis and therapeutic decisions. The treatment strategy and decision making for stage

III disease is markedly different, where there is a curative intent.

a. The time course for identifying and characterizing metastatic disease is inherently different between stage III and IV

b. Most patients with stage III disease would have received some form of treatment, especially systemic therapy. Which may skew the number and location of metastatic deposits.

c. Radiation strategy for stage III disease is quite different than radiation for stage IV disease. Stage IV radiation would typically for palliation of pain either at the primary site or in bone metastasis. Lumping them together is not a fair evaluation of the efficacy of radiation therapy. There are reports of local therapy such as SBRT to oligometastatic liver and lung metastasis

d. Similarly what type of surgery and when was it performed. Resection would be rare in stage IV disease. While esophagectomy is common for stage III disease and patient may present later with metastatic disease. Are those patients included in the survival analysis?

i. Lies 188-189 and 193, it could be postulated that the rationale for radiotherapy in patients with bone metastasis was for palliation of pain and not a greater radiosensitivity of bone metastasis.

e. The poor survival of stage IV patients may dominate the results.

Reply 10: Thank you for your precious comments. We have changed our research population stage III-IV EC to stage IV EC, and performed statistical analysis again. The purpose of radiotherapy for patients with stage IV ESCC and EAC is not only to treat the primary disease, but also to reduce the pain of primary or metastatic lesions. We agree with the reviewer and have made corresponding changes in the original article.

Changes in the text: We have modified the title(Page 1 line2), abstract(Page 1 line18, Page 2 line 26, line 40), introduction(Page 4 line 73), highlight box(Page 3 line 58), materials and methods(Page 5 line 97), results(Page 6 lines 127), discussion(Page 9 line 189, Page 10 line 203, 205, 217, 219,), conclusion (Page 13 lines 268) and some figures and tables.

11. Line 116 and table 1 report 3707 distant metastasis. Line 121 and table 2 report 2717 metastasis. Can the authors clarify the difference.

a. Table 1 reports patient numbers, the M row has $920+2787= 3707$

b. Line 121 states: "There 2717 patients present metastasis."

Reply 11: We deeply appreciate the reviewer's suggestion. According to the reviewer's comment, we have provided more details to describe the reasons. 3,707 patients in table 1 present all distant metastases. There were only four organs metastases including bone, lung, liver and brain reported in SEER database. Therefore, 2,717 patients in table 3 present four organs metastases including bone, lung, liver and brain.

Changes in the text: We have modified this expression on Page 7, lines 145-150.

12. Figures 2&3, consider adding the number of patients at risk below the x-axis.

Reply 12: We think this is an excellent suggestion. We have added the number of patients at risk below the x-axis.

Changes in the text: It was rectified in Figure 2-4.

13. Lines 129-130, consider reporting the median survival. Although there is a statistical difference shown in Figure 2, it may not be clinically significant. Another option would be to report the restricted median survival. (Ben-Aharon O, Magnezi R, Leshno M, Goldstein DA. Median Survival or Mean Survival: Which Measure Is the Most Appropriate for Patients, Physicians, and Policymakers? *Oncologist*. 2019 Nov;24(11):1469-1478. doi: 10.1634/theoncologist.2019-0175. Epub 2019 Jul 18. PMID: 31320502; PMCID: PMC6853128.)

Reply 13: Thank you for underlining this deficiency. This section has been revised according to the suggestion by the reviewer.

Changes in the text: We have made correction in Page 8, lines 166-167.

14. Lines 157-158, this manuscript is focused on stage III/IV disease. The data presented do not include patients with stages I/II. This statement is not supported by the data presented.

Reply 14: Sorry, it's our mistake. That sentence has been deleted.

Changes in the text: We have modified on Page 10, line 102.

15. Lines 161-163, the authors should provide a reference supporting the statements regarding male hormones promoting EC growth and that in esophageal cancer patients there is a gender difference in alcohol and tobacco use.

Reply 15: Thanks for your suggestion. We have added the reference required as explained above.

Changes in the text: Please see the Page 10, lines 206-207.

16. Lines 202-211 do not directly relate to body of the manuscript. They should not be included in the discussion.

Reply 16: Thank you for your comment, and we have deleted that paragraph.

Changes in the text: Please see the Page 12, line 259.

17. Line 51-52, there is little data presented regarding surgery. Surgery has been the mainstay of stage III therapy. It is not clear from the data presented that surgery has no role in stage III disease.

Reply 17: We are grateful for the suggestion, and we have modified this expression.

Changes in the text: Please see the Page 3, lines 61-63.