Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1881

Reviewer A

Comment 1: The title is somewhat difficult to comprehend and probably poorly phrased - "Recommendations for Enhancing Inclusion and Management of Esophagus Cancer Clinical Trials: ...". I do not understand the meanings of "enhancing inclusion and management" of a certain disease "clinical trials". There is not a single clinical trial mentioned or referenced in the entire paper. How do you "enhance inclusion of clinical trials" and how do you "enhance management of clinical trials" when in your introduction you do not mention anything about Esophagus-2 patients being excluded from clinical trials on esophageal cancer? The title only made some sense to me after reading the Highlight box.

Reply 1: I am sorry to confuse you on the meaning of the title. We changed the title slightly and explained the current situation of esophagus cancer clinical trials and why we aimed to broadening eligibility criteria.

Changes in the text: We changed the title. (see Page 1, line 1-3) and explained the current situation of esophagus cancer clinical trials and why we aimed to broadening eligibility criteria in the part of *Introduction.* (see Page 5, line 10-20)

Comment 2: The methodology involves trawling through large amount of SEER data on mortality after the diagnosis of esophageal cancer, whether it is a first or second primary malignancy, over a vast period of 45 years. The statistical report that is generated and presented in the article lacks real practical or clinical value to any clinician, because full staging of the disease (TNM staging), treatment details (curative vs palliative), remission rate and duration, disease-free survival, time to recurrence from Esophagus-1 and Esophagus-2 have not been fully available and analysed separately. Rather, a summary figure is presented for some of the categories mentioned. No presentation on the status of the first malignancy (i.e. localised/metastatic, treated/untreated, in remission, recurrent, etc.) in Esophagus-2 group makes it difficult to make sense of all the survival results presented on Esophagus-2.

Reply 2: We don’t agree that the statistical report that is generated and presented in the article lacks real practical or clinical value to any clinician. First, although we lack data on TNM staging, treatment details (curative vs palliative), remission rate and duration, disease-free survival and time to recurrence, we separately analyzed the seer stage to replace TNM staging, because the TNM staging system varies every few years and can’t adapt for pan-cancer (first malignancy of esophagus-2) analyses. We also analyzed subgroups of chemotherapy and radiation therapy to somewhat reveal the treatment details. Second, we had presentation on the status of the first malignancy (cancer type, tumor stage, time relapse from

prior cancer to esophagus-2, radiation therapy and chemotherapy) in Table 2-4, while we presented on the status of esophagus in Table S4-S6.

Changes in the text: We think the reason why you think our study lacks real practical or clinical value to any clinician is that we lack detailed discussion on how the mortality disparity analyses impact on the inclusion of esophagus-2 into clinical trails. Aiming at this problem, we add 2 paragraphs of discussion. (see Page 15, line 8-29)

Comment 3: You have presented data on esophageal cancer specific mortality and non-cancer related mortality but very importantly you have left out mortality caused by the first (non-esophageal) cancer in Esophagus-2 patients. I think the status of the first malignancy has very high impact on the prognosis of Esophagus-2 patients and will influence the decision for aggressive treatment for the second primary esophageal cancer.

Reply 3: I agree that the status of the first malignancy has very high impact on the prognosis of Esophagus-2 patients and will influence the decision for aggressive treatment for the second primary esophageal cancer. Thus, we analyzed the mortality among patients with second primary esophagus cancer stratified by tumor and clinical characteristics of first malignancy (**Table 2-4**) and esophagus cancer (**Table S4-S6**). The study aims to contrast different causes of mortality between esophagus-2 versus esophagus-1. However, no previous malignancy occurred for esophagus-1 patients. Thus, we can't compare the mortality caused by the first (non-esophageal) cancer between esophagus-2 and esophagus-1 patients. And the impact of the first malignancy has been reflected on the overall mortality. Nevertheless, we estimated any-cancer related mortality (esophagus cancer specific and previous cancer related mortality) between esophagus-2 and esophagus-1 (**Fig. S1**) and the overall mortality among second primary esophagus cancer patients with different sites of first malignancy (**Fig. S2**).

Changes in the text: We add a paragraph to discuss the impact of first malignancy on the prognosis of esophagus-2 patients and the decision for clinical trail inclusion. (see Page 15, line 16-29)

Comment 4: With regards to the tables (Tables 1, 2, 3, 4, S3, S4 and S5), how is it possible to have IR (incidence rate per 100 person-years) be almost all greater than 100 occurring in the column "From 0 to < 1 y after diagnosis"? There must have been some errors when generating these rates, which are about 5 times of what they should be, from using simple calculation of proportion. Potential errors may also be present in the other columns if the calculations are erroneous.

Reply 4: Thanks for your careful review. The result that "the IR are almost greater than 100" is due to the inappropriate subgroup we followed. When we calculated the IR in the column "From 0 to < 1 y after diagnosis", we took the subgroup of patients from 0 to <1 y after diagnosis rather than the whole cohort after diagnosis as observed objects. Thus, we underestimated the sum of person-year. We change the way we calculated IR this time and the

IR in the column "From 0 to < 1 y after diagnosis", “From 1 to < 5 y after diagnosis" and “From 5 to < 10 y after diagnosis" are all corrected.

Changes in the text: The IRs in Table 1, 2, 3, 4, S3, S4, S5 and S6 are corrected as advised.

Comment 5: In your conclusion, you wrote "... there is no sufficient reason opting for conservative care solely based on a history of first malignancy.". However, the figures presented in Tables S1 and S2 show that the odd ratios of second primary esophageal cancer receiving surgery, chemotherapy and radiotherapy are 0.90, 0.95 and 0.94 respectively. These figures do suggest that second primary esophageal cancer are still being treated aggressively, quite contrary to your conclusion statement.

Reply 5: The figures presented in Tables S1 showed that the rates of receiving surgery, chemotherapy and radiotherapy are 21.2%, 48.5% and 51.5% in esophagus-2, lower than that of esophagus-1 (25.9%, 53.4% and 54.4%). We further calculated the odd ratios using generalized linear model in Table S2. The odd ratios of 0.90, 0.95 and 0.94 reveals that esophagus-2 patients are less likely to receive surgery, chemotherapy and radiotherapy. The evidence is apparent, and I don’t understand why you think the figures are contrary to the conclusion statement.

Changes in the text: No changes are made.

Reviewer B

Comment 1: A more detailed discussion on non-cancer-related mortality would enhance the paper. Clarifying the reasons behind observed trends and delving into the underlying mechanisms, especially concerning the high mortality rate associated with lung and bronchus malignancy, would contribute to a deeper understanding.

Reply 2: Thanks for your advice. We agree that a more detailed discussion on non-cancer-related mortality would enhance the paper and added some text to clarify the mechanisms of HR trends and heterogeneity in HRs of different types of first malignancy.

Changes in the text: We further depicted the time-varying HRs of non-cancer related mortality (see Page 10, line 12-13) and attempt to explain why esophagus-2 suffered highest non-cancer related death just after esophagus diagnosis (see Page 13, line 25-29 and Page 14, line 1-7). We think the underlying mechanisms concerning the high mortality rate associated with lung and bronchus malignancy is relevant to its its progressive nature and thus high rate of receiving chemotherapy and radiotherapy (see Page 10, line 19-20 and Page 13, line 22-24).

Comment 2: Specific Proposals for Clinical Practice: Strengthening the conclusion with more specific proposals or approaches on how the study's results could impact clinical practice

would be beneficial. Providing insights into the best approaches for each type of malignancy would further enhance the practical implications of the study.

Reply 2: We found the discrepancy in overall survival influenced by different status of first malignancy, which reminded us that exclusions based on a history of prior malignancy or presence of concurrent malignancy should be liberalized, both in terms of when the malignancy occurred and was treated and types of prior malignancies. Thus, we think the clinicians should set up different exclusion window bacause the point at which a patient may be considered “cured” of a cancer is variable.

Changes in the text: We added discussion on the association of 5-year OS rate (esophagus-2 vs. esophagus-1) and exclusion criteria of esophagus-2 (see Page 15, line 8-15). Whereafter, to replace entire exclusion criteria, we presented a new exclusion criteria (i.e., exclusion window) which is not constant and should be changed according to the cancer type, tumor stage or grade of prior cancer (see Page 15, line 16-29).