

Peer Review File

Article information: <http://dx.doi.org/10.21037/tcr-20-3421>

Reviewer A

Comment 1: Generally, life expectancies in female are longer than those in male. Therefore, OS in female should be better when the patients will not be relapsed disease, even if the age of female at the diagnosis was higher than male. There is no discussion about this issue.

Reply 1: We added some discussion about this issue.

Changes in the text: We added some discussion (see Page 9, line 258).

Reviewer B

Comment 1: Please carefully edit for grammatical and textual errors.

Reply 1: We had revised the manuscript according to your comments.

Changes in the text: Please check the revised manuscript.

Comment 2: Much of the text can be edited down and better summarized.

Reply 2: We had revised the manuscript according to your comments.

Changes in the text: Please check the revised manuscript.

Comment 3: Gender should not be used. Please make sure that 'sex' is used.

Reply 3: We had revised the manuscript according to your comments.

Changes in the text: Please check the revised manuscript.

Comment 4: As this is an association study, all language used in the interpretation of the results needs to reflect that.

Reply 4: We had revised the manuscript according to your comments.

Changes in the text: Please check the revised manuscript.

Comment 5: There is a significant lack of references in the Discussion.

Reply 5: We had revised the manuscript according to your comments.

Changes in the text: Please check the revised manuscript.

Comment 6: Please define 'early stage' in the Methods.

Reply 6: Our previous definition of early stage is not accurate, and now it has been changed to localized stage. The localized stage is defined as a T1-4N0M0 in the Methods.

Changes in the text: We had modified our text as advised (see Page 5, line 117).

Comment 7: In the Results, include the stages evaluated when presenting advances pT

stage.

Reply 7: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 2, line 45).

Comment 8: Line 48 – Change language from proven to shown, as this is an association study.

Reply 8: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 2, line 50).

Comment 9: Line 53 – Add reference to 2020 case estimates.

Reply 9: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 3, line 76).

Comment 10: Much of the first paragraph of the Introduction can be summarized more succinctly.

Reply 10: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 3, line 63).

Comment 11: Line 73 – Add a reference for the sentence speculating that differences in male/female morbidity and prognosis is why cancer statistics are separated. This claim needs to be backed up.

Reply 11: We are just guessing that it's the reason cancer statistics are separated. We had changed language from "is" to "may be".

Changes in the text: We had modified our text as advised (see Page 3, line 79).

Comment 12: Line 77 – Change to 'be diagnosed with CRC'.

Reply 12: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 3, line 84).

Comment 13: Lines 77-78 – Please clarify this sentence ('their risk equivalent...').

Reply 13: We had revised this sentence.

Changes in the text: We had modified our text as advised (see Page 3, line 85).

Comment 14: Line 80 – Delete 'hormones may be one reason'.

Reply 14: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 4, line 90).

Comment 15: Lines 82-83 – Clarify this sentence (expand) ("the link between...").

Reply 15: We had revised this sentence.

Changes in the text: We had modified our text as advised (see Page 4, line 93).

Comment 16: Line 83 – Provide additional detail to potential biological features that differ between sexes, rather than vaguely mentioning.

Reply 16: We want to express clinicopathologic features rather than biological

features. We had changed language from “biological” to “clinicopathologic”.
Changes in the text: We had modified our text as advised (see Page 4, line 95).

Comment 17: Line 89 – The first sentence of this paragraph doesn’t make any sense.

Reply 17: We had deleted first sentence of this paragraph.

Changes in the text: We had modified our text as advised (see Page 4, line 100).

Comment 18: Line 90 – What is the rationale for the choice of age 60 and older? Additionally, T3 and T4 are not early-stage tumors, however are localized. If the authors want to focus on early stage, they should analyze T1 and T2, or refer to the cases as localized.

Reply 18: Because of the limitations of the database, only patients over 60 years of age were selected. A small number of CRC under 60 years of age are available in the database, and most of them combine underlying diseases. Our previous definition of early stage is not accurate, and now it has been changed to localized stage. The localized stage is defined as a T1-4N0M0 in the Methods.

Changes in the text: We had modified our text as advised (see Page 5, line 117).

Comment 19: The authors need to better set up their argument for removing/reducing confounding factors, as well as make clear that it is impossible to completely remove confounders.

Reply 19: We had made clear that it is impossible to completely remove confounders. We had changed language from “removal” to “reduce”.

Changes in the text: We had modified our text as advised (see Page 4, line 104).

Comment 20: - Line 103 – Change language from ‘had other cancers before’ to history or previous cancer.

Reply 20: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 4, line 114).

Comment 21: - Which SEER build did the authors use? Please include this in the Methods.

Reply 21: This study population was assembled from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program. SEER data include cancer cases from different locations and sources across the United States. I got permission and downloaded the data from <https://seer.cancer.gov/>. SEER*Stat software version 8.3.6 was used to gather the main data.

Comment 22: - How was survival time calculated? Additional details of the variables and calculations used in the analysis are needed to better understand the analysis.

Reply 22: Additional details of the variables including survival time are provided by the SEER. For specific information, see https://seer.cancer.gov/manuals/2021/SPCSM_2021_MainDoc.pdf.

Comment 23: - Line 126–Include any variables that were used in the logistic regression models.

Reply 23: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 5, line 138).

Comment 24: - Please provide mean/median survival times between males and females, as one of the primary arguments the authors are trying to make is differences in survival between sexes.

Reply 24: We had added median survival times between males and females in Results.

Changes in the text: We had added some texts in Results (see Page 6, line 156).

Comment 25: - Figure 1 – Change the title on the y-axis, removing rate. What is presented is not a rate.

Reply 25: We had revised the Figure 1 according to your comments.

Changes in the text: We had modified Figure 1 as advised.

Comment 26: - Figure 1 – Please include life tables with the Kaplan-Meier curves.

Reply 26: We had revised the Figure 1 according to your comments.

Changes in the text: We had modified Figure 1 as advised.

Comment 27: - Table 2 – HRs and 95% CIs could be rounded to two digits.

Reply 27: We had revised the manuscript according to your comments.

Changes in the text: We had modified Table 2 as advised.

Comment 28: - Table 2 – Include a description of the model used for the multivariate analysis

Reply 28: We had revised the manuscript according to your comments.

Changes in the text: We had modified Table 2 as advised.

Comment 29: - Lines 145-147 – The authors define sex as an independent prognostic factor, however all variables presented are independent prognostic factors. This needs to be addressed in the Results.

Reply 29: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 165).

Comment 30: - Line 148 – Change ‘gender’ to ‘sex’. Be consistent in the terminology.

Reply 30: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 168).

Comment 31: - Lines 149-150 – add ‘s’ to differences, and remove CRC, as the authors are discussing colon cancer.

Reply 31: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 171).

Comment 32: - Figure 2 – To allow for better viewing of the Kaplan Meier curves, please adjust the y-axes with the lower limit of 0.5.

Reply 32: We had revised Figure 2 according to your comments.

Changes in the text: We had modified Figure 2 as advised.

Comment 33: - Figure 3 – What is the reference category? I believe that it is males, but please make this clearer.

Reply 33: This reference category is males. We had added a footnote in Figure 3.

Changes in the text: We had modified Figure 3 as advised.

Comment 34: - Figure 3 – Please clean up the figure, removing the axis beneath the HR table.

Reply 34: We had revised Figure 3 according to your comments.

Changes in the text: We had modified Figure 3 as advised.

Comment 35: - Figure 3 – Though there were not survival differences by Kaplan Meier for T4, that information should still be included in the figure. Please add the regression analysis for T4 (HRs, 95% CIs) in Figure 3.

Reply 35: We added this information in Figure 3.

Changes in the text: We added some information in Figure 3.

Comment 36: - Lines 155-156 – Revise this sentence (“We also saw...”).

Reply 36: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 176).

Comment 37: - Line 156 – Change language from ‘proven’ to associated, or something of the like.

Reply 37: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 177).

Comment 38: - Lines 149-174 – This information can be substantially summarized.

Reply 38: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 6, line 170-203).

Comment 39: - Line 175, 177 – Please use ‘sex’ instead of ‘gender’.

Reply 39: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 7, line 204, 206).

Comment 40: - Supplemental Table 4 – The text describes associations of sex, but the table doesn’t include sex. Please clarify/check the analysis and text.

Reply 40: Research direction of the text is the influence of sex on survival. But at the same time, we are afraid to ignore the impact of these factors on survival, so Age, Race and Histology were used in this univariate analysis.

Comment 41: - Line 199 – Change this sentence; as written, it is exactly the same as the introduction

Reply 41: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 8, line 229).

Comment 42: - Line 200-205 – Include references.

Reply 42: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 8, line 231-234).

Comment 43: - Line 256-258 – There is no way to know that the authors accounted for ALL known confounding factors. For example, they did not account for diet, alcohol consumption, physical activity, family history, etc. This language, in the Introduction and Discussion, required revision to represent the analysis more accurately.

Reply 43: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 10, line 289).

Comment 44: - Lines 264-265 – Please revise this sentence; it is currently a sentence fragment.

Reply 44: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page xx, line xx).

Comment 45: - Line 289 – Change ‘proven’ to shown or associated with. Again, this is an association study.

Reply 45: We had revised the manuscript according to your comments.

Changes in the text: We had modified our text as advised (see Page 10, line 294).