Peer Review File

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Reviewer A

Comment 1: In the introduction section the authors say - "Most research supported that worse survival was witnessed in patients with metastatic H-PC compared with metastatic BT-PC 3-6" - this is not true and actually the exact opposite. Evidently, the references that the authors bring (3-6), support the notion that the opposite is true - BT-PC has worse outcome compared with H-PC. this notion is well known to anyone in the field - probably due to early detection of H-PC due to jaundice. Hence, the data the authors show regarding the worse outcome of BT-PC is well known and not new.

Reply 1: Thanks for your comments! We have modified our text as advised (see Page 2, line 46-48). Thanks again for reminding us of such an important problem!

Changes in the text: “For all patients with PC, most research supports that better survival is witnessed in patients with H-PC compared with BT-PC.(3-6) And it may be attributed to the early onset of jaundice of H-PC, while BT-PC is usually detected late due to lack of early specific symptoms.

Comment 2: It would be interesting to see if the metastatic load is different between the groups, not only the number of metastatic sites, but also the load of the disease within the site. This could provide some interesting data - but this information is not available. I would presume that those with BT-PC have higher disease load (again due to later discovery of the disease). Additional data such as time from symptoms to diagnosis, metabolic statues at diagnosis, and even simple laboratory indices as well as tumor markers (CA19-9, CEA) are not even mentioned.

Reply 2: Thanks for your comments! The factors you mentioned are indeed crucial and we would like to collect those data, but they are not available in the SEER database, and we have mentioned it as a limitation of this article(see Page 9, line 233-235). But the merit of SEER database is the large samples we can utilize. We have read some relevant references and found that most research pay more attention to the number and size of metastatic lesions, treatment possibility and metastatic organs regarding the metastases, while CA19-9, CEA, metabolic status are almost still blank fields.[1] The factors you mentioned are indeed important, we would like to collect and analyze these data in our own clinical trials in the future to explore the specific roles they play in metastases. Thanks for such a significative suggestion, and we will collect these data in the future!

1. Leonhardt CS, Stamm T, Hank T, Prager G, Strobel O. Defining oligometastatic pancreatic cancer: a systematic review and critical synthesis of consensus. ESMO Open. 2023 Dec;8(6):102067. doi: 10.1016/j.esmoop.2023.102067. Epub 2023 Nov 20. PMID: 37988953; PMCID: PMC10774968.

Changes in the text: “Some other data relating to metastases such as metastatic load, tumor markers and metabolic status were not available in the database.”

Comment 3:Regarding the OS survival data in figure 2 - the blue and red plots in figure 2a and 2b look exactly the same. I find it surprising that the P was 0.001 or lower when the graphs look exactly the same (and it's impossible to say in which one the survival is better according to

these plots) - I would recombed the authors to validate the results, if this was not already done.
Reply 3: Thanks for your comments! Although the red and blue lines in Figures 2a and 2b appear almost identical, they are indeed genuine and have been validated by us. We have attached the original SPSS file. The reason for this similarity may be attributed to the large sample sizes (Figure 2a is based on 14,406 patients, while 2b is based on 7,813 observers) and the high number of deaths (as all included patients have metastatic pancreatic cancer, resulting in a high mortality rate), thereby causing the survival curves of the two groups to appear indistinguishable. Additionally, the hazard ratios for these two figures are only 1.094 and 1.109, respectively, which may also contribute to the almost overlapping red and blue lines in both graphs.
Thanks again for your meaningful advice!
Changes in the text: None.

Comment 4: The language and grammar need to be improved. for example:
In the conclusion - "worse OS and increased possible to suffer..."
Discussion - "tumor grade of too much patients was absence..."
Reply 4: Thanks for your kind comments! We have modified some grammar and language mistakes according to the editorial comments.
Changes in the text: For details, please see the part of response to editorial comments.

Reviewer B

Comment 1: First, the authors need to revise the current title to denote the focus of OS and its associations with primary locations and sites of metastatistics, as well as the clinical research design of this study, i.e., a prospective cohort study.
Reply 1: Thanks for your kind comments! We have modified our title as advised (see Page 1, line 1-2).
Changes in the text: The title was revised to “Increased Risk of Multiple Metastases and Worse Overall Survival of Metastatic Pancreatic Body and Tail Cancer: A Retrospective Cohort Study”.

Comment 2: Second, the abstract needs further revisions. The research purpose needs to be correctly described and explain the clinical needs for this focus in the introduction. The materials and methods need to describe the inclusion of subjects, how they were followed up, the data collection of clinical factors, and measurement of OS. The results need to describe the baseline clinical characteristics of the study sample.
Reply 2: Thanks for your kind comments! We have clarified the aim and clinical need of this article: “explore the differences in prognosis and patterns of metastasis among metastatic pancreatic cancer originating from different primary sites, as well as investigating the prognostic differences among metastatic pancreatic cancer at different metastatic sites” (Page 1, line 4-14). We have added inclusion and exclusion criteria of subjects, data collection of clinical factors and measurement of OS (Page 1, line15-20). Although we would like to collect, the details of follow-up are not available on SEER database. Besides, we have added baseline characteristics in the results part (Page 1, line 24-25).
Changes in the text:

Comment 3: Third, in the introduction of the main text, please clarify what did the authors mean by “It indicated that the H-PC and BT-PC should be regarded as different categories”. In this part, the authors need to review what has been known on the factors associated with the prognosis in metastatic pancreatic cancer, in particular its association with primary locations and sites of metastatistics, analyze the knowledge gaps and limitations of prior studies, and what the potential clinical significance of this study is. The major issue of this part is the unclear focus of this study.

Reply 3: Thanks for your comments! We have modified this sentence as advised(see Page 2, line 48-51). Besides, we added a review of factors associated with the prognosis in metastatic pancreatic cancer(see Page 3, line 60-66), and analyze the knowledge gaps and limitations of prior studies(see Page 3, line 66-68). The potential clinical significance of this study the clinical significance of this study lies in exploring the differences in prognosis and patterns of metastasis among metastatic pancreatic cancer originating from different primary sites, as well as investigating the prognostic differences among metastatic pancreatic cancer at different metastatic sites. The different prognosis may indicate different primary locations and metastatic sites may require different therapy and follow-up strategy. It is hoped that these findings will lay the groundwork for future guideline updates and related research.(Page 3, line 73-78) Moreover, we clarified the focus of this study(see Page 3, line 69-73).

Thanks again!

Changes in the text: “Considerable research has investigated the survival of different primary tumor location and metastatic sites in patients with PC. However, there has been a dearth of studies specifically focusing on metastatic PC. Existing research has primarily examined prognostic factors associated with metastatic PC, with a limited number of studies shedding light on this aspect. For instance, Xiao et al. identified elevated serum Gamma-glutamyltransferase as a potential predictor of poorer OS (12) And another study showed that increased circulating NPTX2 methylation levels were associated with poor prognosis.(13) Despite these findings, there remains a gap in the field regarding OS across different primary tumor locations and metastatic sites, as well as the metastatic patterns associated with various primary tumor locations in patients with metastatic PC. Thus, our study aims to address this gap by analyzing data from a large population sourced from the Surveillance, Epidemiology, and End Results database. Currently, the NCCN guidelines have incorporated the impact of primary site on treatment decisions for colon cancer.(14) While the NCCN guidelines for pancreatic head and body/tail cancers are currently the same, as mentioned earlier, their prognoses differ significantly. Therefore, the clinical significance of this study lies in exploring the differences in prognosis and patterns of metastasis among metastatic pancreatic cancer originating from different primary sites, as well as investigating the prognostic differences among metastatic pancreatic cancer at different metastatic sites. The different prognosis may indicate that different primary locations and metastatic sites may require different therapy and follow-up strategy. It is hoped that these findings will lay the groundwork for future guideline updates and related research.”

Comment 4: Fourth, in the methodology of the main text, please describe how the subjects were followed up and details of the ascertainment of primary locations and sites of metastasis. In

statistics, the authors need to provide more details of the Cox regression analysis for assessing OS's relationships with primary locations and sites of metastatistics. Please ensure P<0.05 is two-sided.

Reply 4: Thanks for your comments! It is really a problem, but due to the limitation of SEER database, it is not available to describe how the subjects were followed up, as well as the details of ascertainment of primary locations and sites of metastasis. We search patients by using pathology codes (See page 3-4, line 87-92). We have added details of the Cox regression analysis (Page 4, line 100-111). We have added "P values less than 0.05 (bilateral)" in text (Page 4, line 116). Thanks again for your helpful comments!

Changes in the text: "Univariate and multivariate Cox regression analyses were performed on all variables to determine independent prognostic factors, hazard ratios (HRs) with 95% CI were used to present the results." "P values less than 0.05 (bilateral)"