

Our Response to Reviewers' Comments:

We sincerely thank the reviewers for their time, comments, and valuable feedback that helped us further improve the manuscript. Please refer to our detailed responses below. Our responses to the reviewer's comments are in italics and bold; new additions to the manuscript are shown here in red and highlighted in yellow in the manuscript file.

Reviewer #1:

Scientific Quality: Grade C (Good)

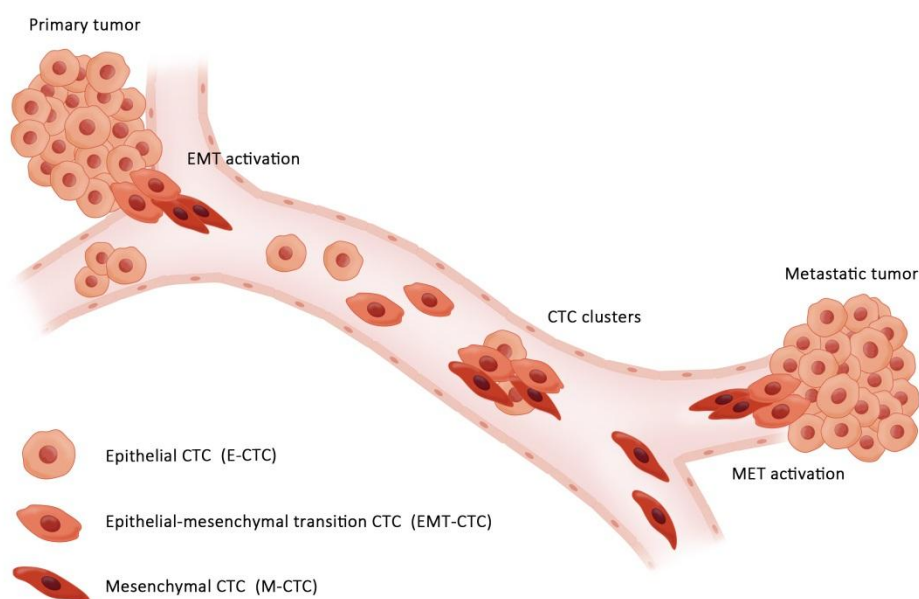
Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors demonstrated the clinical significance of portal venous circulating tumor cells (CTCs) in patients with pancreatic cancer. There are some queries and comments.

Comment 1. Epithelial CTCs, mesenchymal CTCs, and epithelial-mesenchymal transition CTCs should be explained as Figure.

Response: Thank you for your great suggestion. As suggested, we added Figure 2, explaining the various phenotypes of CTCs and their blood dissemination.



“Figure 2. Characteristic stages of CTCs during metastasis. Cells from the primary tumor undergo epithelial–mesenchymal transition, which enables them to disseminate to blood vessels. Cancer cells travel as various phenotypes of CTCs and extravasate the vascular system after undergoing mesenchymal-epithelial transition. This reverse process allows CTCs to escape from blood vessels into distant organs to form a metastatic tumor. CTC: circulating tumor cell; EMT: epithelial–mesenchymal transition; MET: mesenchymal–epithelial transition.”

Comment 2. Please confirm (Page 5, lines 5; po CTCs).

Response: Thank you for pointing out our mistake. We revised the sentence on page 5 as follows:

“The aim of this review was to describe the clinical implications and perspectives of portal venous CTCs in patients with PC.”

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a very interesting and well written review. Very nice. Please add the thickness of the needle used in EUS-FNA and the amount of sample required for measurement.

Response: Thank you for your compliments. As suggested, we added an explanation of EUS-needle sizes and sample amounts on page 7, as follows:

“It is recommended to use a wide bore needle, such as a 19-G needle, for EUS-guided portal venous sampling to prevent blood clotting and CTC damage. The amount of blood required for CTC isolation and identification is generally between 5 and 10 mL.”

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript of Sung Woo Ko and Seung Bae Yoon provides an overview of the importance of portal circulating tumour cells (CTCs) as a

biomarker in pancreatic cancer. This is a very interesting aspect, considering the oncological challenge on the treatment of this kind of tumour. Even though the overall structure of the manuscript is good, a very important part is missing and regards the contribution of CTCs in radioresistance as Yu et al. 2021 and Yang X. et al. 2022 have described. This aspect is crucial, since the better understanding of CTCs in this mechanism could significantly improve radiotherapy outcomes and personalized treatment options.

Response: Thank you for your great suggestion. We have expanded the text on page 5 to mention the prognostic roles of CTCs in cancer patients receiving chemoradiotherapy.

“Detecting CTCs in cancerous diseases allows for the identification of high-risk patients who may require more intensive surveillance and treatment. Specifically, CTCs could be a potential prognostic indicator of chemoradiotherapy in gastrointestinal malignancies^[17,18].”

- 17 Su K, Guo L, He K, Rao M, Zhang J, Yang X, Huang W, Gu T, Xu K, Liu Y, Wang J, Chen J, Wu Z, Hu L, Zeng H, Li H, Tong J, Li X, Yang Y, Liu H, Xu Y, Tan Z, Tang X, Feng X, Chen S, Yang B, Jin H, Zhu L, Li B, Han Y. PD-L1 expression on circulating tumor cells can be a predictive biomarker to PD-1 inhibitors combined with radiotherapy and antiangiogenic therapy in advanced hepatocellular carcinoma. *Front Oncol* 2022; **12**: 873830 [PMID: 35982979 DOI: 10.3389/fonc.2022.873830]
- 18 Yu E, Allan AL, Sanatani M, Lewis D, Warner A, Dar AR, Yaremko BP, Lowes LE, Palma DA, Raphael J, Vincent MD, Rodrigues GB, Fortin D, Inculet RI, Frechette E, Bierer J, Law J, Younus J, Malthaner RA. Circulating tumor cells detected in follow-up predict survival outcomes in tri-modality management of advanced non-metastatic esophageal cancer: a secondary analysis of the QUINTETT randomized trial. *BMC Cancer* 2022; **22**: 746 [PMID: 35804307 DOI: 10.1186/s12885-022-09846-0]

Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

Response: We appreciate the editor's consideration of our study as a MINI REVIEW.

Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary

citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: Thank you for your suggestions. We revised our paper according to the reviewers' points, and received additional language editing from Editage (<https://www.editage.com>), which the Baishideng Publishing Group strongly recommends. We will be happy to provide the English Language Certificate prior to publication.

We appreciate the suggestion to use RCA as a reference database to identify cutting-edge research results; in fact, we already utilized this tool in the preparation of the manuscript. We have edited our figure and table captions to reflect uniform presentation and required formatting, as suggested. Additionally, according to the instructions, our decomposable figures have been organized into a single PPT file, with added copyright information.

We look forward to hearing from you and would be happy to make further changes, if required.