

Cover letter

Dear Editor and reviewers,

First, we appreciate the editor and reviewers' great comments and suggestions. We revised the manuscript (No. 80127) according to the comments. Please the following point-by-point revision. All the revised part in the manuscript was listed in the following section of reviewers' comments.

Thank you for these great suggestions.

Sincerely,

Ming Yang, PhD

Department of Surgery

University of Missouri

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: An interesting and comprehensive review on the pathogenesis, diagnosis and treatments of pancreatic cancers. I have some notes to make: - When described the combinations of ca19.9 with other markers in order to improve its sensibility and specificity, I think it should be more explored. I think that there are some works that can be cited (Coppola A, La Vaccara V, Fiore M, Farolfi T, Ramella S, Angeletti S, Coppola R, Caputo D. CA19.9 Serum Level Predicts Lymph-Nodes Status in Resectable Pancreatic Ductal Adenocarcinoma: A Retrospective Single-Center Analysis. Front Oncol. 2021 May 27; 11: 690580. Doi: 10.3389 / fonc.2021.690580. PMID: 34123859; PMCID: PMC8190389 and others more.) - In table 1, and more in general in the entire work, the Authors talk sometimes about markers in PC and sometimes about markers in PDAC. I think that this must be differentiated in order to take some conclusion. - In the treatment session and future perspectives I believe that the increasingly widespread trend of neoadjuvant therapy in resectable PDAC should be mentioned.

Response: We thank the reviewer's time and effort on these great comments. (1) The use of CA 19-9 as diagnostic markers was further explored, and the recommended study was reviewed and cited in the revised manuscript. "It has been reported that CA 19-9 serum levels are significantly associated with positive lymph nodes (N+) and positive margin status (R+) in

patients with resectable PDAC, which is important for the decision of neoadjuvant treatments[73]. In addition, the pre-operative levels of CA 19-9 are negatively associated with the overall survival, nodal involvement, and margin status positivity in resectable PC. However, some limitations impair the role of CA 19-9 in PDAC preoperative staging and management[74], including up to 50% of PDAC patients without CA 19-9 secretion.”

73 Coppola A, La Vaccara V, Fiore M, Farolfi T, Ramella S, Angeletti S, Coppola R, Caputo D. CA19.9 Serum Level Predicts Lymph-Nodes Status in Resectable Pancreatic Ductal Adenocarcinoma: A Retrospective Single-Center Analysis. *Front Oncol* 2021; 11: 690580 [PMID: 34123859 DOI: 10.3389/fonc.2021.690580]

74 Coppola A, La Vaccara V, Farolfi T, Fiore M, Cammarata R, Ramella S, Coppola R, Caputo D. Role of CA 19.9 in the Management of Resectable Pancreatic Cancer: State of the Art and Future Perspectives. *Biomedicines* 2022; 10(9) [PMID: 36140192 DOI: 10.3390/biomedicines10092091]

(2) The markers for PC and PDACs in Table 1 were separated since some studies do not further provide pancreatic cancer (PC) subtype.

(3) As the recommendation, the literature reports on neoadjuvant therapy for resectable PDAC were discussed in the section on future perspectives. Hopefully, all the revisions satisfied the suggestions.

“Neoadjuvant therapy (NAT) has been applied in clinical trials for patients with resectable PDACs, which include neoadjuvant chemotherapy, neoadjuvant radiotherapy, and neoadjuvant chemoradiotherapy[156]. The results from three randomized controlled trials with a total of 130 patients (56 receiving NAT and 74 in the control group) indicate that NAT (chemotherapy or chemoradiation + surgery followed by adjuvant therapy) increases the disease-free survival (DFS) time compared to upfront surgery followed by adjuvant therapy[157]. Another single-center long-term study also shows that PDAC patients with treatment of neoadjuvant therapy, consisting of consisted of Folfirinox, single gemcitabine or combined with cisplatin, nab-paclitaxel or capecitabine with or without radiation, have longer median disease-specific survival and DFS than those receiving treatment with upfront surgery[158]. The benefit of neoadjuvant therapy could be a stage-dependent manner. A retrospective cohort study shows that neoadjuvant therapy is positively associated with an improved survival benefit compared with conventional upfront surgery, especially in clinical stage III PC after propensity score matching within each stage[159].” Overall, it can benefit surgical treatment.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This review mainly discussed the pathogenesis, molecular signaling pathways, diagnostic markers, and potential treatments for PC. The authors provide an overview of the progress of basic research and clinical practice research in pancreatic cancer based on current research advances. The references are relatively new and meet the requirements of a review. It is logically clear and expressed in native language. I recommend the acceptance of this manuscript by World Journal of Gastroenterology after minor revision. 1. The resolution of Figure 2 is turned in low, and it is recommended to increase the image quality. 2. It is recommended to also summarize ongoing clinical trials in pancreatic cancer.

Response: We appreciate the reviewer's time and effort on these great comments. (1) Figure 2 was revised to increase the resolution. (2) Ongoing clinical trials in pancreatic cancer treatment are summarized in a new table in the revised manuscript (Table 4 Ongoing or recruiting clinical trials for pancreatic cancer treatment.). Hopefully, all the revisions satisfied the suggestions.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

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

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, 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. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. 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. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 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/>.

Response: We appreciate the editor's great comments. All the reviewers' comments were addressed in the revised manuscript. The figures and tables in the revised manuscript are original and there is no copyright issue. The tables are revised to provide the standard three lines. All the required documents for resubmission are provided when the manuscript is re-submitted.

Best regards,

Ming Yang