

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting review about a hot topic. The introduction is well contextualized, the review itself covers the most relevant issues about the possible utility of exosomes in PDAC. Table and figures are clear and appropriate and references are updated. The main limitation of the manuscript is that the main studies are presented superficially: the authors jump to the conclusions without showing supporting data. This makes it difficult for the reader to understand what this kind of liquid biopsy may offer over alternative techniques such as DNACf, CTCs, or even Ca19.9.

Response: All information depicting all relevant information comparing each is given as table

Additional comments: - Core Tip: "Exosomes are released by the tumor during cancer and their release may correlate with cancer outcome". This sentence seems to be incomplete. - Only data from exosomes are shown when talking about the meta-analysis (ref 47), but data from CTC and DNACf should also be shown. -

Response: done and included in text

Authors should show data supporting their statement "Melo et al described that Glyptican-1 identifies cancer exosomes and detects early pancreatic cancer": sensitivity, specificity and number of patients, for instance. - Page 7, first paragraph:

Response: changes made in text

The study about a miRNA expression profile based on exosomes refers to prognosis, so it should be located in the next section, not in the section of early diagnosis. -

Response: changes made in text

The sentence "A study by evaluated serum...." Is difficult to understand. A reference should be added. -

Response: changes made in text and reference shown

Table 1, in the section of CTCs: "indicated a sensitivity of 75%, specificity of 96%, and 100%, AUC of 0.87...". What is this 100% referred to?

Response: changes made in table 1 as

the presence of CTCs in 54/72 patients with confirmed PDAC (sensitivity=75.0%, specificity=96.4%, area under the curve (AUROC)=0.867, 95% CI=0.798-0.935, and $P<0.001$). [12]

- a cut-off of ≥ 3 CTCs in 4 ml blood could differentiate between local/regional and metastatic disease (AUROC=0.885; 95% CI=0.800-0.969; and $P<0.001$)

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Thank you for inviting me to evaluate the minireviews titled "Clinical Application of Exosomes in Pancreatic Cancer". It is an interesting paper which summarizes that exosomes in liquid biopsies can be used as non-invasive biomarkers for early detection, diagnosis, monitoring as well as therapeutic drug delivery vehicles for cancer therapy. The information in this review is helpful to clinical communities. The paper is well arranged and the logic is clear, and the provided figure and tables are well composed and understandable. The quality of language of the manuscript is quite acceptable for me. So, I recommend that this manuscript may be accepted after minor revision.

There are some advices for the authors: 1) Can exosomes be used for monitoring anti-tumor efficacy, and how will they be implemented?

Response: Optimization of miRNA-based assessment of tumour using exosome miRNAs as a biomarker for monitoring both clinical and treatment outcomes represent a key step toward a correct and efficient clinical application of exosomes.

2) The paper lacks the latest references.

Response: Latest references included

Makler A, Asghar W. Exosomal biomarkers for cancer diagnosis and patient monitoring. *Expert Rev Mol Diagn.* 2020 Apr;20(4):387-400. doi: 10.1080/14737159.2020.1731308. Epub 2020 Feb 20. PMID: 32067543; PMCID: PMC7071954.

Raufi AG, May MS, Hadfield MJ, Seyhan AA, El-Deiry WS. Advances in Liquid Biopsy Technology and Implications for Pancreatic Cancer. *International Journal of Molecular Sciences.* 2023; 24(4):4238. <https://doi.org/10.3390/ijms24044238>

Heredia-Soto V, Rodríguez-Salas N, Feliu J. Liquid Biopsy in Pancreatic Cancer: Are We Ready to Apply It in the Clinical Practice? *Cancers.* 2021; 13(8):1986. <https://doi.org/10.3390/cancers13081986>

Reviewer #3:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Rejection

Specific Comments to Authors: Manuscript ID: 84619 Title: Precision medicine in pancreatic ductal adenocarcinoma: the impact of target therapies on survival in patients harboring actionable mutations

1. In the manuscript, exosomes can be used as non-invasive biomarkers for the early detection, diagnosis and monitoring of pancreatic cancer, as well as therapeutic drug delivery vectors for cancer therapy.

Response: yes, given in text

2. In "Different methods to isolate exosomes", the authors should compare the advantages and disadvantages of different separation methods in detail in order to provide readers with the optimal separation method for the analysis of exosomes.

Response: yes, compared the advantages and disadvantages of different separation methods in detail in order to provide readers with the optimal separation method for the analysis of exosomes and given as a table

3. In "Exosomes as diagnostic biomarker in pancreatic cancer", the authors should increase the biogenic relationship between exosomes and the genesis, development, and metastasis of pancreatic cancer. In order to better understand why exosomes can be used as biomarkers for pancreatic cancer diagnosis.

Response: yes, included in text

4. In "Exosomes as diagnostic biomarker in pancreatic cancer", the authors only describe the MicroRNAs involved in exosomes. In fact, there are some specific proteins in exosomes. The author should analyze and discuss it in detail.

Response: yes, included in text

5. For "pancreatic cancer related miRNAs (miR-21, miR-155, miR-17-5p and miR-196a)", the authors should discuss the relationship between each specific MicroRNA and pancreatic cancer development, development and metastasis.

Response: yes, discussed the relationship between each specific MicroRNA and pancreatic cancer development, development and metastasis and included in text

6. The authors should increase the prospects of exosomes in the diagnosis, treatment, and monitoring of the occurrence, progression, and metastasis of pancreatic cancer. According to the related research results reported in the literature, it is expected to explore the future development of exosomes in the diagnosis, treatment and monitoring of pancreatic cancer.

Response: yes, included in text

Round 2

Response to comments

1. Specific Comments to Authors: Manuscript ID: 84619 Title: Clinical Application of Exosomes in Pancreatic Cancer The author has made a comprehensive revision and improvement to the content of the manuscript, basically has met the requirements. However, with regard to the title "Clinical Application of Exosomes in Pancreatic Cancer", the authors should be revised. At present, the application of exosomes in pancreatic cancer is still limited to clinical studies or application studies, and exosomes have not been comprehensively used in pancreatic cancer diagnosis. Therefore, the original title "Clinical Application of Exosomes in Pancreatic Cancer" is poor, and the authors should revise the title.

Answer: The title revised as follows;

Title: – Evolving utility of Exosomes in Pancreatic Cancer Management

2. Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes. -----

Answer: done

3. Your manuscript has been checked by CrossCheck. Please read the attached CrossCheck report for details. Our editorial policy states the overall similarity should be less than 30%, the overlapped section should be less than 5% in single papers, including author's own work. -----Please revise in the attached file "84619_Auto_edited" and reply within seven days, thank you! Only one file is available in F6publishing system, please upload all files with zip format, or send to me by email (y.l.chen@wjgnet.com).

Answer: done