

## Format for ANSWERING REVIEWERS



November 13, 2022

Dear Editors,

On behalf of all the authors, I would like to thank you for your consideration of this paper. In the revised manuscript you will find the changes that we made in response to the Reviewers. In this response to reviewer letter, we also indicated how we have dealt with the Reviewers' comments.

Please find enclosed the edited manuscript in Word format.

**Name of Journal:** World Journal of Gastroenterology

**Manuscript Type:** Opinion review

**Irreversible electroporation (IRE) for the management of pancreatic cancer. Current data and future directions.**

Stavros Spiliopoulos, Lazaros Reppas, Dimitrios Filippiadis, Antonella Delvecchio, Conticchio Maria, Riccardo Memeo, Riccardo Inchingolo

**Invited Manuscript ID:**

**Manuscript NO:**

The manuscript has been improved according to the suggestions of reviewer and Editorial Office's comments:

**Reviewer #1:**

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? YES. 2 Abstract. Does the abstract summarize and reflect the work

described in the manuscript? YES. 3 Key words. Do the key words reflect the focus of the manuscript? Basically compliant. 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? The author described the present status of IRE study, however, not comprehensive. In line 6,86, the cell death after IRE treatment has other words, the pyroptosis and necroptosis may contribute, instead of apoptosis. 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? N/A 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The article reviewed the pre-clinical, clinical application status, and future direction, give a comprehensive review of IRE. 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? N/A 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? YES. 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? N/A 10 Units. Does the manuscript meet the requirements of use of SI units? N/A 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? YES. 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? YES. 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? N/A 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? N/A

**Specific Comments To Authors:** IRE has been used in clinical practice for the management of inoperable pancreatic cancer. The review gives a comprehensive introduction of the basic principles of IRE technology, currently available data, as well as future directions. The reader could get a whole understand of the IRE basic study and clinic use. However, as the cell death is a very important part of this review, the article need to add more information of recent study. The pyroptosis and necroptosis has been reported to contribute the IRE cell death, instead of apoptosis. These studies should be added to the review. As mentioned in the review, immunoreaction happened after IRE therapy. It's better to add immune-associated studies to the review.

A: Thank you for the consideration of this paper and for your comment. The requested changes have been done, in particular regarding alternative cell death types and immune-associated studies.

Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** There are limited options for locally advanced unresectable pancreatic cancer. The article reviews a relatively novel treatment modality of IRE. What are the contraindications to IRE - duodenal wall invasion, blood vessel involvement? Are there technical difficulties/limitations to placing the electrodes within the target lesion? How does the presence and extent of fibrosis related to the pancreatic tumor affect the results of the IRE?

A: Thank you for the consideration of this paper and for your comment. The requested changes have been done.

Reviewer #3:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** This is a well-written and well-organized review about a topic of real interest: the role of irreversible electroporation (IRE) in the management of locally-advanced, non-resectable PDAC. The paper nicely presents the mechanism of action of IRE, highlighting the potential advantages of IRE over other local therapies in PDAC. Noteworthy, the current limitations of the method are also discussed. Furthermore, pre-clinical and clinical outcomes of IRE are provided based on the available literature research. In conclusion, the paper would be of interest to journal readers. Only a few modifications should be made before potential acceptance for publication. Major ones: Please resume the current indications of IRE in PDAC. Minor ones: In line 150, replace IRA with IRE. The references' citations in the text should follow the journal's requirements.

A: Thank you for the consideration of this paper and for your comment. The requested changes have been done, in particular a new table has been added.

Reviewer #4:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The possibility of IRE for locally advanced pancreatic

cancer is suggested, but the synergistic effect of combined chemotherapy needs to be investigated. You should also mention the difference in clinical outcomes from heavy ion therapy and proton therapy.

A: Thank you for the consideration of this paper and for your comment. The requested changes have been done.

Revision reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** No additional comments.

A: The authors would like to thank the reviewer for his positive review.

Revision reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** Please correct a few editing errors such as: "Brock et al (add ref from your mail)" "Regarding large vessels close to the tumor, a minimum safety distance of 2 mm is recommended to avoid the risk of burn damage. In cases of locally advanced pancreatic cancer with involvement of the mesenteric artery/vein, placing the needles parallel to the vessels has been proven effective. (ref 44 from current version)" "The results of IRE in animals' model for the pancreatic cancer treatment showed the ability to ablate the pancreas cells preserving the collagen architecture of vascular, biliary, or neuronal structures [28] 33]."

A: Thank you for the consideration of this paper and for your comment. The requested changes have been done.

**(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)

A: Thank you for the consideration of this paper and for your comment.

**(2) Company editor-in-chief:**

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, 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. Before final acceptance, 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. 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/>.

A: Thank you for the consideration of this paper and for your comment.

Finally, we wish to thank the Editors and the Reviewers for their comments that helped us to increase the value of our paper.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Stavros Spilipoulos