

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 80258

Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05226098

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor, Director

Reviewer's Country/Territory: Japan

Author's Country/Territory: Greece

Manuscript submission date: 2022-09-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-05 03:24

Reviewer performed review: 2022-10-05 03:38

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Judgment by peer reviewers	Does this manuscript meet the code of ethics standards? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important novelty? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important creativity or innovation?

	<input type="checkbox"/> [31] Yes <input type="checkbox"/> [30] No Does this manuscript use reliable research methods? <input type="checkbox"/> [41] Yes <input type="checkbox"/> [40] No Are the manuscript-accompanying data and figures authentic? <input type="checkbox"/> [51] Yes <input type="checkbox"/> [50] No Does this manuscript make scientifically significant conclusions? <input type="checkbox"/> [61] Yes <input type="checkbox"/> [60] No
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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.

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Manuscript NO: 80258

Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03998130

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Senior Lecturer, Surgeon, Surgical Oncologist, Teacher

Reviewer's Country/Territory: Romania

Author's Country/Territory: Greece

Manuscript submission date: 2022-09-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-10 12:05

Reviewer performed review: 2022-10-10 12:33

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Judgment by peer reviewers	Does this manuscript meet the code of ethics standards? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important novelty? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important creativity or innovation?

	<input type="checkbox"/> [31] Yes <input type="checkbox"/> [30] No Does this manuscript use reliable research methods? <input type="checkbox"/> [41] Yes <input type="checkbox"/> [40] No Are the manuscript-accompanying data and figures authentic? <input type="checkbox"/> [51] Yes <input type="checkbox"/> [50] No Does this manuscript make scientifically significant conclusions? <input type="checkbox"/> [61] Yes <input type="checkbox"/> [60] No
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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.

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Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06122677

Position: Editorial Board

Academic degree: FASGE, MRCP

Professional title: Assistant Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: Greece

Manuscript submission date: 2022-09-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-07 21:06

Reviewer performed review: 2022-10-12 01:37

Review time: 4 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Judgment by peer reviewers	Does this manuscript meet the code of ethics standards? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important novelty? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important creativity or innovation?

	<input type="checkbox"/> [31] Yes <input type="checkbox"/> [30] No Does this manuscript use reliable research methods? <input type="checkbox"/> [41] Yes <input type="checkbox"/> [40] No Are the manuscript-accompanying data and figures authentic? <input type="checkbox"/> [51] Yes <input type="checkbox"/> [50] No Does this manuscript make scientifically significant conclusions? <input type="checkbox"/> [61] Yes <input type="checkbox"/> [60] No
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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?

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Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05195341

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Greece

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Reviewer chosen by: AI Technique

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Reviewer performed review: 2022-10-16 10:59

Review time: 11 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Judgment by peer reviewers	Does this manuscript meet the code of ethics standards? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important novelty? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Does this manuscript have important creativity or innovation?

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Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Manuscript NO: 80258

Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05226098

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor, Director

Reviewer's Country/Territory: Japan

Author's Country/Territory: Greece

Manuscript submission date: 2022-09-28

Reviewer chosen by: Jing-Jie Wang

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Reviewer performed review: 2022-11-14 12:13

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

No additional comments.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 80258

Title: Irreversible electroporation for the management of pancreatic cancer: Current data and future directions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03998130

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Senior Lecturer, Surgeon, Surgical Oncologist, Teacher

Reviewer's Country/Territory: Romania

Author's Country/Territory: Greece

Manuscript submission date: 2022-09-28

Reviewer chosen by: Jing-Jie Wang

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Reviewer performed review: 2022-11-14 15:00

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

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]."