

Format for ANSWERING REVIEWERS

June 15, 2019



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.

Title: Locoregional treatments for hepatocellular carcinoma: current evidence and future directions

Running title: percutaneous approach to hepatocellular carcinoma

Authors List: Riccardo Inchingolo, Alessandro Posa, Martin Mariappan, Stavros Spiliopoulos

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 48752

The manuscript has been improved according to the suggestions of reviewers:

Reviewer # 1

This is a well written detailed review on locoregional therapies in HCC.

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

Few comments.

Q: Include tables comparing different locoregional therapies.

A: A new table has been added.

Q: Include table/information to comment on imaging response guidelines for HCC (Response Evaluation Criteria in Solid Tumors - RECIST, modified-RECIST).

A: Despite we agree that this is a important topic, we do not find it relevant in our review, that is focused on treatment and not on imaging. Moreover discussing this topic, would make the manuscript even more lengthy.

Q: Include information on IRE (irreversible electroporation)

A: A new paragraph has been added.

Q: Recommend using or introducing TARE (transarterial radioembolization) terminology for Yttrium-90

A: The new terminology has been added

Reviewer # 2

Dear authors: The review is very complete, objective and precise.

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

However, some big issues have to be written again:

Q: 1-Focus on primary end-points and design of each trial that was comment on this review: e.g if overall survival was a secondary end-point, please do not conclude that the trial demonstrated a better overall survival as a main outcome (Page 6).

A: Thank you for your suggestion; however, we thoroughly re-read the work by Liu et al. and the primary end-point of their study was the comparison of Overall Survival among the three treatment groups, which was significantly higher in the multi-drug TACE group than in the doxorubicin-alone group.

Q: 2-Page 12: TARE vs sorafenib: the paragraph should be written again considering what I have mentioned in point 1 and my comment supported in the word format (attached).

A: The authors have revised the paragraph according to the reviewer's comments.

Q: 3-Cautious with recommendations based on non robust evidence: combination therapies.

A: We re-wrote the first paragraph of the combined therapies section according to your suggestion, as the great majority of studies comparing efficacy of combined treatments against RFA or TACE alone

are retrospective, and thus do not represent a robust evidence.

Q: 4-TACE + sorafenib: please review again SPACE and TACTICS trials.

A: we reviewed the above mentioned trials and modified the manuscript focusing on their primary end-points. We also reviewed and included the BRISK-TA trial (Brivanib plus TACE).

Reviewer # 3

This paper is an up-to-date review on the current status of locoregional treatment for HCC that will guide the future direction.

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

Reviewer # 4

Congratulations on your extensive review.

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

My suggestions are as follows: -

Q: Please include a section about laser ablation in HCC- it has shown promising results and in can be considered curative in small tumors.

A: A new short section has been added

Q: - Regarding TACE, current debates are aimed at comparing efficiency between various TACE methods (which you have discussed) and at establishing the optimal time period between procedures.

This need further discussion in you review.

A: we added a paragraph explaining the trends on number and time-interval of multiple TACE sessions.

Q: A table including indications, advantages and disadvantages of each therapeutic option

A: A new table has been added

Q: - There are minor English grammar errors that need correction.

A: A further language revision has been done

Reviewer # 5

Comments for ESPS Manuscript NO 48752 This is a review about the current status of loregional treatment for HCC. Text is well written, there are no major and few minor concerns.

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

Regarding the latter:

Q: 1.I strongly suggest supporting the text with additional table. This table should include advantages and disadvantages of each loregional treatment mentioned in this review, which will help to better understand the text.

A: A new table has been added

Q: 2.Minor language polishing is needed.

A: A further language revision has been done

Reviewer # 6

Drs. Inchingolo et al., provide a review paper focusing on the technical aspect of locoregional treatment options for Hepatocellular carcinoma (HCC), involving current evidence and future perspective. The work searched recent literature and compared various RCT trials, and try to present latest advance in HCC treatment. Numerous efforts have been made to provide better treatment options for HCC patients especially when they are in late stage and inoperable, therefore further works in these area will be a welcome. This work is therefore interesting with merit.

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

Q: The manuscript appears well oriented and wrote, but is also very lengthy. Adding a few subtitle, charts or cartoons may strengthen the overall quality of work, and that might be a better form of presentation for readers to understand these technical advent of available options for HCC treatment. It is also advised that authors avoid lengthy paragraphs and sentences, and try to make it concise and up-to-date.

A: new table has been added.

Q: Minor typos and grammatical errors are found throughout the text, and so are various formats of reference, which deserve authors' attention.

A: A further language revision has been done

Q: The work may require revision and summarize research directions for each treatment option in order to guide future efforts in the field. Authors are encouraged to revise and make the manuscript more concise and attractive.

A: The authors have added a relative paragraph in order to summarize research direction and suggest future efforts as suggested by the reviewer.

Specific comment for the Editor: We've checked all the references adding PMID and DOI, when available. We have listed all the authors for almost all the ref, but in few cases, usually RCT, the names were exceptionally numerous (>15); only in those cases we left "et al". Anyway, if you need, we can add them.

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

Sincerely yours,

Riccardo Inchingolo, MD, EBIR

Radiologia Diagnostica ed Interventistica

Ospedale Madonna delle Grazie

Matera