

ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in word format (file name: 27300-edited).

Title: Local ablative treatments for hepatocellular carcinoma: An updated review

Author: Antonio Facciorusso, Gaetano Serviddio, Nicola Muscatiello

Name of Journal: *World Journal of Gastrointestinal pharmacology and therapeutics*

ESPS Manuscript NO: 27300

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

Reviewer 1:

Excellent, comprehensive review of the mechanisms and clinical evidence supporting thermal ablation for hepatocellular carcinoma. The authors also appropriately discuss complementary topics including pharmacologic and intra-arterial combination therapies. Minor comments are as follows:

1. Introduction: Please remove the temperature ranges for the definitions of hyperthermic and hypothermic, since some modalities, i.e. microwave, routinely achieve temperatures > 100C.

RE: Temperature ranges have been removed as per reviewer's suggestion.

2. I do not necessarily consider ascites as an absolute contraindication to thermal ablation, though certainly these patients typically have severely compromised liver function.

RE: In fact, table 1 reports liver decompensation as a contraindication. Ascites is usually a feature of liver decompensation but it does not represent a contraindication by itself.

3. The authors mention that 1cm margins should be achieved, but this is not necessarily the case for all HCC. Recommend a brief discussion (1-2 sentences) on this topic, with reference to other reviews, for example Wells, S. A. et al. Liver Ablation: Best Practice. Radiol Clin North Am 53, 933-971 (2015).

RE: One cm of margin has been shown to represent a gold standard in radiofrequency ablation of HCC and liver metastases.

4. Recommend a brief section on the mechanism and (theoretical) role of irreversible electroporation.

RE: Irreversible electroporation is not standardized yet, hence we prefer to omit a discussion about this topic.

5. Add the following references: a. Role of RFA in liver transplant, mentioned in Introduction: Sheth, R. A. et al. Role of Locoregional Therapy and Predictors for Dropout in Patients with Hepatocellular Carcinoma Listed for Liver Transplantation. J Vasc Interv Radiol 26, 1761-1768 (2015). b. Margins for ablation: Wells, S. A. et al. Liver Ablation: Best Practice. Radiol Clin North Am 53, 933-971 (2015). c. Laser ablation (primarily metastases but also includes HCC): Vogl, T.

J., Straub, R., Eichler, K., Woitaschek, D. & Mack, M. G. Malignant Liver Tumors Treated with MR Imaging-guided Laser-induced Thermoablation: Experience with Complications in 899 Patients (2,520 lesions) 1. *Radiology* 225, 367-377 (2002).

RE: We think our work has references enough. We consider references suggested by the reviewer as redundant.

Reviewer 2:

The presentation reflects the present state of knowledge and the data are attained from a large amount of literature and author's group supported by the line of reasoning. The description in the text is very clear and easy to follow. The graphical presentation is truthful and easy to understand. The table present data is also clear and truthful. I recommend to consideration for the publication of this article. However it requires some minor revisions prior to its publication, for details see below. (1) Mechanism of action and equipment of radiofrequency ablation-suggest to delete , it is overlong. (2) Adverse events of RFA- This part is too simple which can't introduce some common complications including decreased heart rate and local pain etc. it is benefit to clinical doctor.

RE: The chapter "Mechanism of action and equipment of radiofrequency ablation" has been considerably shortened, as per reviewer's suggestion.

Reviewer 3:

This is a well written manuscript illustrating in detail the local ablative therapies for early HCC with a focus on RFA in comparison with other thermal techniques. I see that this review is very illustrative and collected many previous studies concerning the issue. However, what is the difference between this review and others published in the same topic like (PMCID: PMC4284241)? I think that the authors should highlight the major new points that will add to the field.

RE: The difference is in the up-to-date overview we provide on this topic. Previous studies and reviews, such as that cited by the referee, needed to be updated in light of several novel results and studies published in the last year.

This concept is well-described in the manuscript.

We hope to have adequately addressed the point raised by the reviewer.

Thank you again for considering our manuscript for publication in the *World Journal of Gastrointestinal Pharmacology and Therapeutics*.

Sincerely yours,

Facciorusso Antonio

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