

Format for ANSWERING REVIEWERS

March 12, 2021



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 (file name: -Manuscript_edited.doc).

Name of Journal: *World Journal of Gastroenterology*

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

Radiofrequency ablation versus surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria

Maria Conticchio, Riccardo Inchingolo, Antonella Delvecchio, Letizia Laera, Francesca Ratti, Maximiliano Gelli, Ferdinando Massimiliano Anelli, Alexis Laurent, Giulio Cesare Vitali, Paolo Magistri, Giacomo Assirati, Emanuele Felli¹, Taiga Wakabayashi¹, Patrick Pessaux, Tullio Piardi, Fabrizio Di Benedetto, Nicola de'Angelis, Delgado Francisco Javier Briceno, Antonio Gaetano Rampoldi, Renè Adam, Daniel Cherqui, Luca Aldrighetti, Riccardo Memeo.

Invited Manuscript ID: 03358964

Manuscript NO.: 63629

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 A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this study, the authors compared the short and long

term outcome between radiofrequency ablation (RFA) versus surgical resection in elderly patients (>70 years) with hepatocellular carcinoma (HCC) in Milan criteria. This is an interesting multicenter retrospective study, some critical issues remain to be clarified in this manuscript.

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

1. As we know, the recurrence of HCC after RFA is associated closely with incomplete ablation. Therefore, the authors should describe how to tell whether the nodules were ablated completely or not. If incompletely, how to re-treat the nodules?

Answer: in all cases, at the end of the procedure, the nodule were ablated completely.

2. In this study, the RFA postoperative course was burdened by a lower rate of serious complications (Clavien Dindo III-IV) than the LR group ($p=0.001$). Previous reports demonstrated that laparoscopic liver resection had a fewer complications than open liver resection. Therefore, is it possible to compare laparoscopic or open RFA with laparoscopic or open liver resection (laparoscopic RFA vs laparoscopic liver resection, open RFA vs open liver resection), respectively? Or, compare RFA with laparoscopic or open surgery, respectively.

Answer: this is a good point and it's matter of another ongoing study we are working on.

3. If postoperative histopathology found microscopic vascular invasion (MVI), did the authors had other postoperative treatments? Because MVI is associated closely with recurrence after surgery.

Answer: we don't have histopathological informations about MVI for all patients, so we couldn't analyze this aspect. A new sentence has been added in the limitations of the study.

4. Because we can't tell whether the HCC patients receiving RFA had MVI which is an important recurrence risk factor, in the discussion section, the authors should discuss it.

Answer: a new sentence has been added.

5. The range of age of the elderly patients should be provided.

Answer: the range of age is 70-90 years.

Reviewer 2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The study evaluated the safety and efficacy of surgical resection and radiofrequency ablation on elderly HCC patients in Milan criteria managed in 10 European centers. The results has a certain clinical value for the clinical treatment of HCC.

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

1. There were similar reports about surgical resection and radiofrequency ablation on HCC patients in Milan criteria in the PubMed, what is the novel idea in the paper?

Answer: the novel idea is to evaluate short and long terms results in a portion of population, elderly (>70y), which is progressively growing in our era.

2.Fig1a-Fig1d in the result description corresponds to the Fig1-Fig4 actually, please revise that.

Answer: done.

3.The incidence of AEs in surgical resection group is high, How to treat for AEs?

Answer: we are sorry, but we do not understand what AEs stand for.

4.The surgical resection group were included patients who underwent laparoscopic and open liver resection, How to handle with the issue?

Answer: our intention was to focus on differences between surgery and RFA, for this reason we didn't explore two subgroups in surgery, which is an interesting point and can be matter of another paper.

5.The age of patients included in this study was ≥ 70 years, but in Table 1, 69.5 years and 69.8 years were found in the age(yr) column in the surgery group.

Answer: sorry for that. It was typesetting error.

6.The previous treatment before surgical resection or radiofrequency ablation has a great impact on the prognosis of patients, it is recommended to supply the specific treatment in Table 1.

Answer: we didn't have all informations about previous treatment, for this reason we couldn't analyze this aspect. A new sentence has been added in the limitations of the study.

Reviewer 3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Comments: Dear Authors: In general, this is a meaningful work to a certain degree. Here is my assessment from three angles, including language, content, and originality. Language The language of this article is very well, but there are still several sentences that can be adjusted.

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

1. in abstract part, "Statystical analysis was performed using the Kaplan-Meier method before and after propensity score matching(PSM)" should change into "Statistical analysis was performed using the Kaplan-Meier method before and after propensity score matching (PSM)".

Answer: done

2. "Evaluation of short and long term outcome in elderly patients(>70 years)" there should be a space between "patients" and ">70 years)". Please check the whole manuscript for there are some other similar omissions.

Answer:Done

Content 1. Question: In “MATERIALS AND METHODS”, the author should give more detail of Inclusion and exclusion criteria. And as they mentioned “non-invasive findings”, they should also describe it.

Answer:Done

2. Question: In this study, the author applied a PSM method to reduce bias of two groups. Although the intention of propensity score matching of baseline variables was to reduce differences between groups, a decreased sample size will appear when increasing matched variables. So the author should explain why choose “co-morbidities, ASA score, Child and MELD scores, number of lesions, and tumor size” as matching variables.

Answer: done

3. Suggestion: The author only did a univariate and multivariate analysis once in the study. I thought that they could conduct a univariate and multivariate analysis both before matching and after matching to obtain a more scientific result. Originality This work emerges a high degree of innovation, especially in the field of interdisciplinary clinical diagnosis and treatment of early stage HCC.

Answer: PSM attempts to reduce the bias due to confounding variables that could have an effect on the results obtained by comparing the two treatments. Since we are interested in the statistical evaluation of the causality between the two treatments, we believe it is more meaningful for this work to evaluate the correlation between the variables after PSM in univariate and multivariate analysis.

Science Editor:

1 Scientific quality: The manuscript describes a retrospective study of the radiofrequency ablation versus surgical resection in elderly patients with hepatocellular carcinoma in Milan criteria. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade C and Grade B; (2) Summary of the Peer-Review Report: The authors reported an interesting multicenter retrospective study. The results has a certain clinical value for the clinical treatment of HCC. However, the questions raised by the reviewers should be answered; and (3) Format: There are 4 tables and 4 figures. (4) References: A total of 31 references are cited, including 2 references published in the last 3 years; (5) Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B, Grade A and Grade A. 3 Academic norms and rules: The authors provided Biostatistics Review Certificate. The authors need to provide the official Institutional Review Board Approval Form and written informed consent. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not

provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.
6 Recommendation: Conditional acceptance.

A: Thank you for the consideration of this paper and for your comment. A new file with .ppt extension has been added, including original figures. As well, need Institutional Review board form has been added.

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 its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

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

Finally, we wish to thank the Editor and the Reviewer 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,

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