

December 13, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 13479_review1.doc). We have addressed all the comments made by the reviewers. Please find the answer to each comment below.

Title: STRATEGIES TO IMPROVE OUTCOME OF PATIENTS WITH HEPATOCELLULAR CARCINOMA RECEIVING A LIVER TRANSPLANTATION

Authors: Marta Guerrero Misas, Manuel Rodríguez-Perálvarez and Manuel de la Mata.

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13479

To the **REVIEWER 1**

We do not agree with most of the comments made. The reviewer said in his “general comments” that the manuscript is not focused, is redundant, and the language is poor. The manuscript is based in clinical studies addressing the strategies to prevent HCC recurrence after liver transplantation. The final section summarizes the recommendations to be applied into clinical practice, and also gives some clues for future clinical studies, and thus we do not agree with a lack of focus. However we agree that the manuscript is long and some messages have been repeated along the manuscript. The new version has been significantly shortened by 1,044 words without omitting any relevant information, but avoiding repetitions (the original manuscript had 6,040 words and the new version has 4,996 words).

Concerning the language the authors of the present manuscript are sufficiently skilled with the English and have a long standing experience with many papers published in international high-impact journals.

The topic addressed is mainly clinical and we think that this reviewer may not be familiar with clinical practice according to some of his comments as further discussed below. Thus we believe that the “reviewer 1” may not be an appropriate referee for the present manuscript. However the answer to each comment can be read below:

1- Original comment: "tumour" means tumor? Note misspelling of key word in abstract gives impression poor quality of the manuscript.

Answer: There should be a misunderstanding here. "Tumour" is not a misspelling as the reviewer suggested. Tumour is an accepted English word which is commonly used in the scientific literature. A quick search in pubmed of "tumour" results in 2985415 entries (at 23rd November 2014). The definition of the word tumour in English can be found elsewhere:

<http://www.collinsdictionary.com/dictionary/english/tumour?showCookiePolicy=true>

We feel that the use of the word "tumour" should not give the impression of poor quality of the manuscript as the reviewer has pointed out. We have kept this word in its present form.

2- Original comment: Give a definition of abbreviation written at first in manuscript

Answer: We have included the list of abbreviations the abstract page as required.

3- Original comment: P3; HCC is 2-4 fold increased in male. Is it means only male patient increase? Hard to understand.

Answer: This sentence means that HCC is more frequent in men as compared to women. We have changed the expression to avoid misunderstanding.

4- Original comment: P3; unresectable HCC; Is it for anatomical reason?

Answer: Liver resection is preferred for small HCC in absence of portal hypertension and with preserved liver function. Patients with a more advanced HCC (but within Milan criteria) or either with impaired liver function or portal hypertension may benefit from liver transplantation (see BCLC algorithm elsewhere). The use of liver transplantation instead of resection does not depend on anatomical reasons but on the stage of HCC and on the underlying liver disease. We have not included this information in the manuscript because it is out of the topic.

5- Original comment: P3 line 24; LT offer; Can you show survival rate?

Answer: Liver transplantation offers the best long term survival for selected patients with HCC since it is the only therapy able to treat both, the tumour and the underlying cirrhosis. The 5 year survival rates are 70% for HCC transplanted patients. We have included this information in the manuscript.

6- Original comment: P4 line 5; Waiting is better than resection?

Answer: In patients with HCC not candidates to liver resection, liver transplantation is the best option whenever possible, even when the patient has to wait. See answer to comments 4 and 5.

7- Original comment: P4, line 12; Any change survival rate of small HCC with or without cirrhosis?

Answer: More than 90% of patients with HCC have underlying cirrhosis. The whole manuscript refers to cirrhotic population. The treatment and prognosis of HCC without underlying cirrhosis is out of the topic.

8- Original comment: P5, need to describe definition of OLT

Answer: We apologize. This was a typo. We meant "LT". We have corrected this.

9- Original comment: P5, line 6, survival rate. 3 years? 5 years?

Answer: Survival rates shown are at 5 years. We have included this information.

10- Original comment: P5 line 9~; Is PIVKA II selected as a marker of micro vascular invasion, malignant type of HCC, or both? The authors should comment.

Answer: Hepatocellular carcinoma is a malignant tumour. There is no such thing as "benign" hepatocellular carcinoma. PIVKA II is a marker of poor histological differentiation and microvascular invasion, and thus has been proposed as a marker of poor prognosis in HCC. We have clarified this in the text, which can be read now as follows: "When serum PIVKA-II, which is a tumour marker related to an aggressive histological behavior of HCC, was included in the selection criteria..."

11- Original comment: P 6; in summary, elevated PIVKA II, number, and size of tumor paly role in highly malignant HCC. Is that authors want to say? If so, too redundant.

Answer: See answer to comment 10.

12- Original comment: P 7 2nd paragraph; in summary, Transplantation itself makes difficult to set control goup. Is that authors want to say? If so, too redundant.

Answer: We didn't mean that. In the referred paragraph we wanted to emphasize that, despite of all the expanded criteria published to date, none of them has been implemented in routine clinical practice because of inherent limitations. In addition we gave some clues to design further studies which may address this issue.

13- Original comment: P 7; Invasion to vessel; micro, macro, or both?

Answer: As the reviewer can read in the text this sentence refers to microvascular invasion.

14- Original comment: P 10; "with more patient transplanted" Shortage of donor is common problem in any field of transplantation. Authors should mention experimental study. Recent advance of cell culture technique can make human HCC cell.

Answer: We agree. The shortage of donors is a major problem for patient with end stage liver disease, and also for patients with hepatocellular carcinoma. The present

review is mainly clinical and it is focused on strategies to improve outcome in patients with hepatocellular carcinoma, as stated in the title. We did not describe most of the experimental studies unless they have a relevant and immediate application into clinical practice. Besides we do not understand how making human HCC cells in the laboratory would benefit patients who already have hepatocellular carcinoma. This is an exciting research field but it does not fit with the topic of the review.

15- Original comment: P 11; Hard to understand. Waiting of transplantation of malignant HCC patients should not be allowed and not be good reason for expectation to be good candidates.

Answer: The imbalance between candidates for LT and available donors is a worldwide problem. Waiting lists are not desirable but necessary in order to offer the liver transplantation to the sickest patients, and with a favorable long term survival. Patients with an aggressive HCC phenotype are expected to suffer an early tumour recurrence and to have a short life expectancy after LT. These patients should not undergo LT but to receive alternative therapies. Some authors have proposed that patients with HCC with a rapid tumour progression within waiting list should be excluded, as the rates of HCC recurrence after LT are unacceptably high. This rationale may not be shared by other authors, included ourselves, but it deserves to be kept in the manuscript, so the reader can make his/her own conclusions. For the clinical reader with experience in organ transplantation this rationale is understandable and needs no further clarification. We have changed the initial sentence of the paragraph: "A moderate delay within the waiting list would allow for a better selection of HCC candidates for LT according to some authors".

16- Original comment: P 11~; LT with/without those therapies affects prognosis? Generally not in previous studies.

Answer: There is no agreement among different studies. These therapies have shown to reduce drop-out rates when the expected time within waiting list is significant. This is extensively discussed in the text (section 2) and summarized in the conclusions of the manuscript. We feel that no further clarification is needed.

17- Original comment: P13; Sorafenib. Used final stage for HCC; Most of previous studies show bridge use of sorafenib does not improve prognosis.

Answer: The use of sorafenib in the LT setting was nicely reviewed by Castelly et al (Liver Transpl 2014, In press). The evidence is scarce and the available studies limited by their reduced sample size and the lack of randomization. We agree with the reviewer that no recommendation can be currently given, and this is what we have concluded in the manuscript: "these are very early experiences and no further recommendations should be derived until larger randomized controlled trials are performed".

18- Original comment: Page 14; difficult to set control~; Any case report LT between twins? Unnecessary immune suppression has possibility of good prognosis. Authors should study not only review papers but such a case report.

Answer: To our knowledge there are no studies with transplanted twins evaluating different immunosuppression protocols. Our research is focused in how a less potent immunosuppression influences long term outcome after LT, including HCC recurrence. Far from being just "case reports" as the reviewer said, these are studies with hundreds of patients, and published in high impact journals (See Rodríguez-Perálvarez et al, Am J Transplant 2012;12(10):2797-814, Rodríguez-Perálvarez et al J Hepatol 2013;59:1193-1199, Rodríguez-Perálvarez et al, J Hepatol 2013;58:262-70, among others).

To the **REVIEWER 2:**

Original comment: Very interesting review on HCC criteria for liver transplantation. Well organized and easy to read.

Answer: We thank you for your positive evaluation.

To the **REVIEWER 3:**

1- Original comment: The reading of the manuscript is hampered by redundancy. Concepts are repeated throughout the paper. Despite the intrinsic complexity of the subject, the Authors should clearly state the central message of each paragraph, avoid repetitions, condense sections which cannot be expanded in the present review (e.g. markers of aggressive tumor behaviour) and omit unnecessary details (e.g. pag 14, paragraph on immunosuppression and oncogenesis).

Answer: We agree that the manuscript is too long. The new version of the manuscript has been significantly shortened by 1,044 words without omitting any relevant information (the original manuscript had 6,040 words and the new version has 4,996 words). We have condensed the paragraph of biomarkers of microvascular invasion and also eliminated the paragraph on immunosuppression and oncogenesis as suggested.

2- Original comment: The abstract of the paper is too short. The Authors should add details of the subjects debated in the text and possibly insert data.

Answer: We have added more information to the abstract which is 196 words in the new version.

3- Original comment: Reference citations are missing in the text (e.g. pag 8 "Many studies have shown that patients with poorly differentiated tumours have increased risk of recurrence and reduced survival rates"; pag 12 "In spite of this, RFA is preferred for single tumours less than 5 cm").

Answer: These references were already cited in the text but in other locations. We have added them in the requested spots.

4- Original comment: In the section “Waiting list management” the Authors deal with the well-know problem of the waiting list management for HCC patients. However, the second part is about locoregional therapies as a bridging strategy to liver transplantation. The Author should refine the title of the section or avoid including those data.

Answer: We have grouped the strategies within the waiting list including both the prioritization and bridging. We feel that locoregional therapies are central in the waiting list management and therefore we have kept this information. We have renamed this section as suggested. The new title is as follows: “Waiting list management and bridging therapy”.

5- Original comment: The Authors should make sure that each abbreviation is expanded at first use in the text.

Answer: We have revised the text and ensured the appropriate use of abbreviations. In addition we have included a list of the abbreviations used which can be found in the abstract page.

6- Original comment: The text is a mix of British and American English. The Authors should adopt one (preferably American English) and check for consistency. Moreover, there are a number of minor grammar errors that should be revised.

Answer: We apologize but our English is mainly British as two of the authors have worked in the UK in the past. We have revised the manuscript carefully and have corrected some grammar errors.

To the **REVIEWER 4:**

Original comment: The study is a timely research. Objectives are consistent with literature review and analysis. The paper can be recommended to publish with the prior approval of the editorial board.

Answer: We appreciate your interest in our manuscript.

To the **REVIEWER 5:**

Original comment: Need to avoid repetition, give a definition of abbreviation written at first in manuscript, check spelling and grammar errors. The abstract should include the same sections as the main text in a succinct form – introduction and objective, main topics and conclusion

Answer: We appreciate your comments regarding the relevance of the topic addressed, novelty and quality of the presentation. In your comments we found a nice summary of the major topics addressed in the paper. We agree with the reviewer that there were some repetitions along the manuscript. We have significantly shortened the paper by more than 1,000 words as described above, and condensed the information as much as possible to ease the reading. In addition the abstract has been expanded to cover the most important information contained in the manuscript, although we found very difficult to keep the same sections as in the main text.

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

Sincerely yours,

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