ANSWERING REVIEWERS

December 5th, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format **(file name: 5940-review.doc).**

Title: ***Hepatocellular carcinoma review: current treatment, and evidence-based medicine***

Author: Ali Raza, Gagan K. Sood

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5940

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

1. Format has been updated, and we changed the font to Book Antiqua, size 10.

2 Revision has been made according to the suggestions of the reviewer

First Reviewer's Comments and Answers

(1) Because of the lengthy text, I hope the authors may use a few tables and figures to describe and compare the meanings of treatment strategy and roles of targeted molecular agents.

We have added two tables in the manuscript comparing various treatment modalities. Table 1 discusses evidence-based comparison between RFA and. surgical resection. Table 2 discusses the comparison between Sorafenib and other targeted agents (Phase III trials only)

(2) I hope the authors may describe so many therapeutic methods combined with international guidelines.

We have added the information regarding international consensus (Page # 4 and reference # 18)

(3) I also hope the authors may reduce the general introduction, and focus on the comparative analysis among different therapeutic methods by using tables and figures.

We have reduced the text slightly and added 2 tables with dense information comparing various therapeutic options

Second Reviewer's Comments and Answers

1. Liver Transplantation: for further references regarding LT for tumor exceeding Milan criteria and downstaging please read the following: Lancet Oncol. 2009 Jan;10(1):35-43; Br J Surg. 2011 Sep;98(9):1201-8. J Hepatol. 2013 Mar;58(3):609-18.
   In the section for liver transplantation, we have supplemented the information regarding LT for tumors exceeding Milan criteria and options for downstaging and have added references recommended by reviewer (Page # 4 highlighted area, and references from 14 to 20).

2. Authors stated that "Because of the shortage of available organs and an unclear impact on the survival, down staging cannot be recommended to consider eligibility for LT.". However, please check that this is true for USA areas where waiting-time for HCCs is about 3-6 months.

There are other experiences from different countries suggesting a role for bridge therapy. Please verify at Ann Surg Oncol. 2008 Apr;15(4):993-1000, . J Hepatol. 2013 Mar;58(3):609-18

We have corrected the statements regarding downstaging prior to the transplant and included both the references (Page #4 and highlighted associated references).

3. Surgical resection: please correct hepatic decomposition with decompensation (I guess it is a consequence of the automatic correction of Word).

   Corrected the word to "hepatic decompensation" (Page #5, line 8 under surgical resection)

4. In the field of surgery, portal hypertension, as contraindication for resection, is a controversial issue. This aspect should be briefly discussed. Here are some suggestions: Gastroenterology. 2008 Jun;134(7):1908-16, World J Surg. 2006 Jun;30(6):992-9, Ann Surg. 2009 Dec;250(6):922-8.

   We have discussed the surgical resection in context of portal hypertension and added additional references as suggested by the reviewer (Page # 5, 6 highlighted area in yellow and references from 24 to 30).

5. Similarly, some other important clinical references should be added when discussing about early versus late recurrence: Ann Surg. 2006 Feb;243(2):229-35.Cancer. 2000 Aug 1;89(3):500-7.Ann Surg Oncol. 2009 Feb;16(2):413-2 as well as the role of "adjuvant" therapies (Hepatology. 2006 Dec;44(6):1543-54, Ann Surg Oncol. 2010 Dec;17(12):3137-44)

   We have added the references related to early versus late recurrences (Reference number 32, 33, 34, 57, 58).

6. Regarding RFA, Authors correctly suggests that in comparison to surgery it is less expensive…and with shorter hospital stay. This statement can be supported with the following reference: J Hepatol. 2013 Aug;59(2):300-7.

   We have added the reference in section of RFA (Page # 7, and reference # 50, highlighted in yellow)

7. TACE: "Patients with compensated…with large single nodule (<5cm) or multifocal HCC.." the minus before 5cm seems incorrect, please verify.

   We have corrected it to "<5 cm" (Page #7, last paragraph)

8. TACE recommendation is compared with the best supportive cares. However, Authors should also discuss the role of hepatic resection for this tumor stage (Gastroenterology. 2008 Jun;134(7):1908-16, J Surg Oncol. 2010 Dec 1;102(7):868-76. Ann Surg. 2013 May;257(5):929-37.)

   Though the hepatic resection is not often considered as an option in patients with multiple tumors, some centers have reported optimal results with hepatic resections even in patients with multiple tumors. One recent survey from multiple eastern and western centers in Europe showed that surgical resection is widely in practice among patients with multinodular, large, and macrovascular invasive HCC, and provides acceptable short- and long-term results (Ref # 57, 58)

9. The Author statement about: "Intermediate-stage HCC includes a heterogeneous population of the patients with variable tumor burden and liver function" is correct and should be supported by recent expert opinion (Semin Liver Dis. 2012 Nov;32(4):348-59.)

We have discussed the topic with further references.

10. The section regarding HCC treatment as a bridge to transplant is insufficiently discussed. It is true that there is no high level of evidence regarding efficacy in reducing drop-out rates but there are several works that studied this issue and that are not mentioned. For an extensive review the following article should be read (J Hepatol. 2013 Mar;58(3):609-18.)
We have added this reference and we have discussed in more detail the HCC treatment as bridge to transplantation (Page # 4 highlighted area and reference # 14)

11. Literature regarding Sorafenib could be strengthened with results form clinical practice (Hepatology. 2011 Dec;54(6):2055-63.Literature has been strengthened by the addition of the table and comparing the sorafenib with other systemic agents in the Phase III clinical trials. (Table 2)

12. In the conclusion section the statement "In the early stage HCC, RFA is comparable to surgical resection in well-selected patients" is not correct, since RFA is equivalent to resection for very early HCC.
RFA is equivalent to resection for very early stage HCC; we have corrected it in conclusion section (Page # 16 highlighted area).

III. Other comments:

1. WJG reference style includes DOI. Please add this information.
DOI has been added to all the references.
2. Please check reference n°63. I have not found it in any database.
We have added new references and omitted the reference number 63.

3. References and typesetting were corrected, and we added DOI to the PMID for the references.

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

Sincerely yours,

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