ANSWERING REVIEWERS

February 2, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: XXXX)

Title: Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: Where do we stand?

Author: Masato Fujiki, Federico Aucejo, Minsig Choi and Richard Kim

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5818-edited

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

1. Format has been updated.
2. Two senior authors are US trained and major revision was done to improve the quality of the paper in terms of language.
3. Revision has been made according to the suggestions of the reviewers.

(1) **Re: Comment from Reviewer 1. (Reviewer code: 00053659):**
"The text needs to be focus on the neo-adjuvant therapy."
In the section of EMERGING LRT; DEB-TACE, TARE, AND EBRT, we deleted several sentences or totally removef the context of some of the studies on non-transplant settings.

(2) **Re: Suggestion to add tables from Reviewer 1 and 3. (Reviewer code: 00053659, 00004157)**
We added Tables 1, 2 and 3 to summarize section for EBRT, down-staging and bridging therapy, respectively to help readers to understand better.

(3) **Re: Comment from Reviewer 4. (Reviewer code: 00007472)**
"In the last part of the Introduction section it is stated that the reportedly

increased post-transplant recurrence rate in the case of living donor liver transplantation could be due "to the less frequency of neoadjuvant therapy". Since there is no sound scientific evidence that neoadjuvant therapy reduces recurrence rate this statement can be misleading"

To avoid misleading, the sentences in the introduction that the Reviewer pointed out were deleted. Accordingly, we revised the corresponding part in LDLT section and emphasized that the fast tracking course in LDLT may have the role in the increase in posttransplant HCC recurrence.

(4) **Re: Comment from Reviewer 4. (Reviewer code: 00007472)**
"I suggest to make it clear from the beginning and precise that according to Zurich consensus conference "Bridging strategies might be appropriate for patients with UNOS T2 lesions (one nodule 2–5 cm or three or fewer nodules each ≤3 cm) who are likely to wait 6 months or longer" but not for smaller or larger tumors or shorter waiting lists."
"Regarding down-staging, again the lack of adequate evidence should be highlighted upfront and the recommendation from the consensus may be stressed in particular those related to the aim (achieving a 5-year survival comparable to that of HCC patients who meet the criteria for liver transplantation without requiring downstaging) and the fact that based on existing evidence, no recommendation can be made for preferring a specific locoregional therapy for downstaging over others."

Thank you for detailed comments and suggestions.
We included the comment from consensus conference in the introduction of the original manuscript in page 6, followed by sentences "However, there is no evidence that bridging therapies are of any benefit in patients with United Network for Organ Sharing (UNOS) T1 (one nodule < 2 cm) or shorter waiting time."
In the revised manuscript, we have mentioned that most of studies on down-staging are uncontrolled observation studies indicating the evidence level is low. We put this comment in later part of manuscript because we would like to discuss previous studies first before reaching that conclusion.
We also quoted the comment from the consensus conference "no

recommendation can be made for preferring any type of LRT to others, in patients listed for LT or in those entering a down-staging protocol" in page 10.

(5) **Re: Comment from Reviewer 4. (Reviewer code: 00007472)**
"In the TARE section, resin microspheres should be considered too, since they are approved in most countries worldwide (including Europe, Asia Pacific and Australia) with the exception of the United States. References should be updated accordingly. When considering the role of TARE as compared with conventional TACE, authors should amend the text since patients with PVT are by definition in the advanced and not in the intermediate stage. And the last sentence arguing for the need of a RCT comparing TARE vs. cTACE or DEB-TACE should probably be tuned down due to the lack of evidence for cTACE or DEB-TACE themselves. More probably a 3 arm would be needed (best supportive care, TACE and TARE) no matter how feasible this RCT may be."
In the revised manuscript, we mentioned resin microspheres and added the study using resin microsphere for down-staging. References are also updated.
In original paper, we meant PVT as non-malignant PVT. To avoid confusion, we clarified in the revised manuscript that PVT could be bland or malignant and tumor thrombus should be ruled out before the patient is considered for liver transplantation.
At last, we decided to remove the sentence arguing for the need of a RCT based on the comment.

(6) **Re: Comment from Reviewer 4. (Reviewer code: 00007472)**
"The granularity provided for EBRT is in contrast with the other therapeutic options, and the low level of evidence is not discussed."
We mentioned twice in the revised manuscript that its clinical experience is limited in contrast to other LRT.

4. References and typesetting were corrected.

We hope that with these modifications, our manuscript will be considered suitable for publication in *World Journal of Gastroenterology*.

Sincerely yours,

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