Format for ANSWERING REVIEWERS

Dec 04, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14897-review.doc).

Title: A comparison of hepatic resection and transarterial chemoembolization for solitary hepatocellular carcinoma

Author: Dong-Zhi Zhang, Xiao-Dong Wei, Xiao-Peng Wang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14897

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer 1

1. **Response to comment**: (Indeed the Barcelona Clinic Liver Cancer (BCLC) system is also used to guide treatment, it is used to stage hepatocellular carcinoma. Because it is a staging system, the prognosis of the group with solitary HCC more than 6cm should be compared with BCLC stage A or stage B in order to change the staging criteria. I think it is hard to advocate changing the staging system itself according to the results of this study. I suggest reorganizing the manuscript to propose that solitary HCC more than 6cm is suitable to be treated by TACE rather than to be treated by surgery among the cases of BCLC A stage)

Response: It is really true as reviewer suggested that: t is hard to advocate changing the staging system itself, however, as we know, The BCLC staging classification is primarily based on the prognostic analysis of several small cohorts of predominantly HCV-infected patients (no more than 50 cases) with early HCC who were treated via resection, transplantation, or percutaneous ethanol injection. Meanwhile, according to the

BCLC staging system, all solitary HCC should be graded as BCLC stage A and radical therapies LT, resection, RFA should be recommended, and there is a obvious shortcoming in this system, and I have send E-mail to Pro. Llovet JM last year, and get affirmation from him, and this study was under Pro. Llovet JM's guidance. Meanwhile, multiple center analysis is been performing, we are looking forward the results.

2. **Response to comment**: (Specific comments In the Patients and Methods section, TACE protocol: Sponzel is usually injected after administering mixture of doxorubicin and Lipiodol. Did the authors use sponzel during the TACE procedures?)

Response: Yes, we use sponzel during the TACE procedures in the past but not now.

3. **Response to comment**: (In the Patients and Methods section, Follow-up assessments: When the HCC recurred during the follow up, how did the authors treat the recurrent HCCs? Did they perform re-resection or TACE for the recurrent HCCs ? The authors should describe the treatments for the recurrent HCCs.)

Response: Considering the reviewer's suggestion, we have added the treatments for the recurrent HCCs in the patients and methods section: The treatment protocol for HCC recurrence was implemented according to the tumor location and size and the liver function of the patient. Re-resection, RFA, repeated TACE, and sorafenib were administered for most recurrence cases. When lung metastasis was found, γ knife was the primary recommended treatment.

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

1. **Response to comment**: (The main concern of the study is the selection bias that may have resulted from the comparison of these non-randomized groups and the retrospective analysis. I would be interesting to know who decided the indication for surgery or TACE and what were the factors evaluated when deciding the treatment.)

Response: As Reviewer stated that the present study is a non-randomized and the retrospective analysis. However, based on our result, we are performing a multiple center, perspective study, and we are looking forward the results. The choice of treatment protocol for solitary HCC was mainly based on the liver function, tumor diameter, tumor location and ECOG score. And we have added this information in our revised paper.

2. **Response to comment**: (Patients in the group of TACE. How many procedures were performed in each patient?. This data should be mentioned in the text or Table 1)

Response: The mean TACE times was 2.3±1.2 for the TACE group patients, and we have added the information.

3. **Response to comment**: (Discussion section. "Therefore, RFA should be adopted and replaced by liver

resection or liver transplantation when the diameter is large than 5 cm" I don't agree with this sentence. The local recurrence rate of tumours larger than 3 cm is too high to be recommended as a radical treatment. On the other hand indications for LT are based on Milan criteria (solitary tumour < 5 cm) and liver resection is only applicable in patients with excellent liver function and solitary tumours peripherally located. Please correct.)

Response: According to reviewer's suggestion, we have corrected this sentence: Therefore, RFA should be adopted when the tumor diameter was larger than 5cm

4. **Response to comment**: (The discussion is too long, should be shortened: With respect to discussion I would suggest to rewrite this section considerably, starting with major findings. Also give more attention to patient selection and bias.)

Response: we have shorted the discussion, and made changes according to the suggestion.

5. **Response to comment**: (Overall in text: It is recommended to spell out the numbers one through nine and use figures thereafter)

Response: we have made changes according to the authors' suggestion.

3 References and typesetting were corrected

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

Sincerely yours,

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Jan 04, 2015

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Revision has been made according to the suggestions of the Editor:

1. **Response to comment**: (There are some misconceptions about BCLC A stage in this study. The BCLC A stage is a solitary tumor, Child-Pugh A-B, and perforamnce status 0. Performance status 1-2 is not BCLC A stage. So, please do not emphasize that this study results suggested that the cutoff criteria for BCLC A and B stage should be 6 cm. Actually, the surgical indication in BCLC staging system was determined whether the 5-year survival after resection is similar to that after liver transplantation (60-70% or higher). It was not determined whether the survival is superior to that of TACE. In this regard, the cutoff size of 6 cm in this study can be reasonable because of the comparable survival rate after LT. Therefore, in the discussion session, please insert the paragraph that the survival in patients with single HCC of <6 cm was comparable with that after LT in patients with Milan criteria. And also, please insert the paragraph that this study included some BCLC C (performace status 1-2) patients in the discussion session (limitation).)

Response: It is really true as reviewer suggested, we have edited this paper according to the editor's suggestion.

2. **Response to comment**: (The response to number three comment from reviewer 2 is not adequate. The reviewer 2 suggested that tumors larger than 3 cm is not adequate for RFA. Personally, I do agree with the reviewer 2's opinion. But some centers perform RFA in tumors upto 5 cm or more. Therefore, the sentence

should be corrected as follows: Therefore, RFA can (not should) be adopted when the tumor diameter was smaller (not larger) than 5 cm)

Response: We have corrected this sentence according to the Editor's suggestion.

3. **Response to comment**: (There are still some errors in English.)

Response: We have had our paper been re-edited in English by American Journal Experts.

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

Sincerely yours,

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