Format for ANSWERING REVIEWERS

September 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:4773-review.doc).

Title: Transarterial Chemoembolization in Barcelona Clinic Liver Cancer Stage 0~A Hepatocellular Carcinoma

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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
3. We made use of a copyediting service provided by professional English language editing companies.(American Journal Experts)

We marked all correction with red color in 4773-Edited file

First of all, we appreciate the Reviewers' thoughtful and helpful comments. Also, we are pleased to have an opportunity to make this paper to be an even better one and to be accepted with revision, because the Reviewers provided additional important points that we have not realized before.

1. Point-to-point responses to comments by the Reviewer 1

   The authors wish to thank the Reviewer for offering careful and helpful comments.

Comment 1: my major concern is that most research contents are discussing the risk factors of mortality and clinical characteristics to influence the survival of HCC with TACE treatment, which is unrelated with the study goal. Therefore, the title is unrelated to the contents; the goal of study need modified if you keep the contents; the results are unrelated with the goal; and finally it is inappropriate to derive the conclusion that "the efficacy of TACE for BCLC stage 0 and stage A HCC might be comparable with that of other curative therapies", if only analyzing HCC underwent TACE, no other therapies involved in comparisons, such as resection, transplantation, or ablation therapy. Overall, the inconsistence in contents and goal make the novelty and innovation of the research significantly reduced.

Response 1: The reviewer makes a very good point. As the reviewer pointed out, we modified the goal of study and conclusion.

'Aim: **:** To evaluate the clinical characteristics of patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 and A hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE).

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'Conclusion: TACE may be used as curative-intent therapy in patients with BCLC stage 0 and stage A HCC. The Child-Pugh score, arterio-venous shunt, amount of lipiodol used, and sex were related to mortality after TACE.

Comment 2: The overall description of the manuscript is clear and understandable. This study has received a priori approval by the institutional review board for human research of hospitals, so no ethnic concern. One minor comment on page 11: why the factors of age, gender, and plausible risk factors from univariate analysis with $p<0.50$ (not $p<0.05$) were used in the Cox regression analysis?

Response 2: For the reliable data, in the statistics, we inserted the plausible variables ($p<0.50$) were in the multivariate analysis. Because this study was retrospective study, some statistical bias could affect the results. We consulted a statist, and he suggested this method to reduce the bias.

2. Point-to-point responses to comments by the Reviewer 2

Comment 1: The authors should provide additional data from their Center comparing the PFS and OS times for patients treated other than TACE in this Setting to Show equality or superiority of their Treatment. Some minor changes (spellings e.g. Frans instead of France) and not to use the word "gender" when speaking of "sex" are recommended.

Response 1: We appreciate the reviewer's thoughtful comment. We did not compare the TACE and other modalities. However, we concluded that efficacy of TACE was comparable to other modalities. We changed the conclusion.

'Conclusion: TACE may be used as curative-intent therapy in patients with BCLC stage 0 and stage A HCC. The Child-Pugh score, arterio-venous shunt, amount of lipiodol used, and sex were related to mortality after TACE.

In addition, we changed gender to sex and Frans to France)

3. Point-to-point responses to comments by the Reviewer 3

Comment 1: In general, for small tumors, RFA is considered superior to TACE (especially for tumors <3 cm). The authors should discuss differences with literature in detail in the Discussion section.

Response1: We totally agree with Author's opinion. We discussed the differences with literature in detail in the discussion section.

'In general, resection, transplantation, and ablation have been considered superior to TACE for very early-/early-stage of HCC. However, few studies comparing TACE and other curative therapies in patients with early-stage HCC are available. Therefore, prospective studies comparing the efficacy of TACE, surgery, and ablation are needed in the future.'

Comment 2: Although predictive factors for mortality are identified, potential predictive factors for radiological response (according to modified resist or easl criteria) are not explored. The authors should do this in a revised version. Especially, the effect of tumour diameter on response.

Response 2: We appreciate the reviewer's thoughtful comment. We initially tried to insert the responsiveness to the analysis. However, data of many patients showed variability in the result (ex: Responsiveness was changed according to TACE number. The results were different according to the kind of variables (RECIST and EASL). Moreover, in some period, numbers of some variables are not sufficient for analysis. So, we consulted a statist about the insertion of response in the cox regression. After the consultation, we deleted the responsiveness of tumor because Initial diameter was inserted in the analysis.

Comment 3: Time to tumor progression should be given.

Response 3: We appreciate the reviewer's thoughtful comment. We commented about time to progression in the Table 4.

Comment 4: No data are given on side effects of the TACE procedures. As mentioned in the results section: 18

patients were observed with arterio-venous shunt. Could TACE be performed successfully in these patients or was this considered as contraindication to proceed with the procedure? Were these patients excluded from the analysis? Currently, DEB tace (with drug eluting beads) rather than Tace is generally used.

Response 4: This article was retrospective CHART REVIEW data. So, we could not perfectly collect the side effects of the TACE. In the A-V shunt, in the chart, TACE was performed in patients with AV shunt. So, we included these patients in the analysis. In addition, we included patients treated with only TACE.

4. Point-to-point responses to comments by the Reviewer 4

Comment 1: The authors conclude that the efficacy of TACE for BCLC stage 0 and stage A might be comparable with that of other curative therapies. However, no studies were performed in this study between TACE and other curative therapies.

Response 1: The reviewer makes a very good point. We did not compare the TACE and other modalities. However, we concluded that efficacy of TACE was comparable to other modalities. We changed the conclusion.

'Conclusion: TACE may be used as curative-intent therapy in patients with BCLC stage 0 and stage A HCC. The Child-Pugh score, arterio-venous shunt, amount of lipiodol used, and sex were related to mortality after TACE.'

Comment 2: In this study, no information about treatment about recurrent HCCs. I think that overall survival outcome was quite different by recurrent treatment.

Response 2: We appreciate the reviewer's thoughtful comment. We included patients who were treated with only TACE. As we described in the Figure 1, most excluded patients (78 patients, 33 patients, and 22 patients) were treated with other treatment after recurrence.

Comment 3: This was not a randomized trial, but the patients were assigned to either a TAI or a TACE group. How were the patients assigned to these treatment group? I think that in this study, dosage of doxorubicin and iodized oil were unclear. In the methods, the authors explain the dosage of doxorubicine/lipiodol ratio was 10mg / 2ml. However, in Table 3, hazard ratio of doxorubicine and lipiodol were different.

Response 3: We included patients who were treated with TACE not TAI.

As the reviewer pointed out, we made mistakes. We apologize the mistake. As we described in the methods, the dose of anticancer agent and lipiodol used for TACE was determined by the radiologist based on the size, number and blood supply of the target tumors. Another sentence [The doxorubicine /lipiodol ratio was calculated according to the tumor size (10 mg of doxorubicin and 2 mL lipiodol per centimeter of tumor diameter)] can make misunderstanding. So, we deleted the sentence.

Comment 4: I cannot understand the sentence of 'time to recurrence was defined as time from randomization to recurrence' When randomization was performed in this study?

Response 4: As the reviewer pointed out, we made mistakes. We apologize the mistake. We changed the sentence.

Randomization -> treatment

Comment 5: There were no studies about recurrence or survival between RECIST, EASL, and mRECIST. Why the authors recommend EASL and mRECIST. The authors used Cox-regression analysis for mortality. Odds ratio should describe Hazard ratio.

Response 4: As reviewer recommended, there were no studies about recurrence or survival between RECIST, EASL, and mRECIST. We want to see and evaluate the survival of Stage 0-1 HCC after TACE. Other methods were not validated as a marker for survival. In addition, we described that 'Definition of recurrence and progression was based on the mRECIST amendments.'

We changed OR -> HR

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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