Format for ANSWERING REVIEWERS

October 3, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13158-review.doc).

Title: Outcome of transarterial chemoembolization-based multi-modal treatment in patients with unresectable 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

Review 1 (No. 32933)

This retrospective study collected consecutive series of 146 treatment naive cases with HCC greater than 10 cm. Diagnosis and Treatment of each case was reviewed and decided by HCC tumor board team. In general multi-modal treatment could be applied to these cases if suitable. They found that 17 cases were down staged and received surgical resection. This group showed the best survival while those not received any treatment showed the worst outcome.

Comments:

1. Abstract: case number was miscounted.

Response: We corrected the error.

2. How many patients really refused treatment rather than unable to treat decided by HCC tumor board.

Response: All patients in the conservative treatment group were those who refused the treatment. We added "All patients who met the inclusion criteria were recommended to receive the treatment that had been determined by the tumor board".

3. Were there any different pretreatment factors between surgical and non-surgical treatment groups?

Response: In response to this comment, we added the new table (Table 6), and subgroup analysis of baseline characteristics in the treatment group. There were no statistically significant differences between two groups. However, surgical treatment group tended to have more favorable prognostic factors, such as well demarcated tumor, no PVT, and lower tumor stage (P = 0.051, P = 0.094, and P = 0.071, respectively).

4. Both DBE and sorafenib were not used in this study. The paragraph in discussion section about these therapies may be delated. Please add a brief discussion about severe complication, such as liver abscess development, after TACE for giant HCC.

Response: In response to this comment, we added "Although TACE procedure has the risk of severe complication such as hepatic arterial occlusion, liver abscess, and spontaneous rupture of tumor, there were no serious complication in this study' to the discussion.

5. Table 3: Please add case number to each treatment group. Please also add p-value to this table.

Response: We added the case number to each treatment group, and P-values were also added in this table.

6. Table 6 may be delated and described in the text.

Response: In response to this comment, we deleted the table 6 because the all adverse effects are described in the text.

Reviewer 2 (No. 35938)

General comments: Song and coworkers present an important, retrospective study on the outcome of TACE in 146 patients with large HCC, defined as >10 cm tumour diameter. Most patients underwent multimodal treatment, a small subgroup could be downstaged to receive salvage surgery or transplantation. The data are well presented and the discussion is balanced. The statistic methods are appropriate. A few numbers need to be corrected.

Minor comments:

1. The numbers in the abstract do not add up. 146 patients were included, but 149 underwent TACE and 27 conservative management. Please clarify.

Response: In response to this comment, we correct the error.

2. Please state very clearly the characteristic of the conservative group: The conservative group included only patients refusing TACE, not patients with poor performance status who were unfit for any treatment?

Response: We added "All patients who met the inclusion criteria were recommended to receive the treatment that had been determined by tumor board". The patients with poor performance status were excluded by inclusion criteria.

3. Please also state in the methods that the conservative group did not receive surafenib.

Response: We added "Sorafenib could not be administered to treatment group and conservative group because it was not available during the study period' to the Method.

4. What were the criteria used for liver transplantation?

Response: We added "Liver transplantations were performed in the patients who met the University of California, San Francisco (UCSF) criteria".

5. The title is slightly misleading as the article focuses on the general TACE outcome in large HCC and only 20 (15+5) patients underwent resection or transplantation after downsizing as stated under treatment response. However, in figure 1 only 17 patients are mentioned undergoing resection or transplantation.

Response: In response to this comment, we corrected the number of resection and transplant in the Results, and changed the title to 'Outcome of transarterial chemoembolization-based multi-modal treatment in patients with unresectable hepatocellular carcinoma'.

6. Why is the survival curve for the conservative group different in A and B despite the same scale of the

Response: In response to this comment, we changed the figure 2.

Reviewer 3 (No. 57695)

This retrospective study looks at the efficacy and safety of transarterial chemoembolization (TACE)–based multimodal treatment in 146 patients with huge (>10 cm) hepatocellular carcinoma (HCC). The manuscript is within the scope of the journal. It is well-written, clear, concise and well referenced. I have the following comments:

1. Abstract, Results section: why the number of patients became 149?! Also instead of "the remaining 27 patients received conservative management", rephrase to 'another 27 patients received …'. This makes the total number of the studied patients with large HCC 173. Hence, this should be changed throughout the text.

Response: In response to this comment, we corrected the error in the abstract.

2. Page 7, under Therapeutic Modalities: change 'radiologic oncologist' to 'radiation oncologist' or 'radiation therapist'. Why medical oncologist was not involved?

Response: In response to this comment, we changed 'radiologic oncologist' to 'radiation oncologist'. In addition, we added the 'medical oncologist' because medical oncologists were also members of our tumor board team.

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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