

## Format for ANSWERING REVIEWERS



October 26, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12990-Review.doc).

**Title:** Role of hepatectomy for recurrent or initially unresectable hepatocellular carcinoma

**Author:** Yoji Kishi, Kazuaki Shimada, Satoshi Nara, Minoru Esaki, Tomoo Kosuge

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 12990

The manuscript has been improved according to the suggestions of reviewers. All revision were made in red font in the revised manuscript:

1 Format has been updated

According to the editor's comment, we added the header in Table 2.

2 Revision has been made according to the suggestions of the reviewers.

We appreciate the all reviewers' comments to enhance the quality of the manuscript. One of the three reviewer almost fully accepted our manuscript and suggested no revisions. The other two reviewers critically gave us the comments for revising the paper and we responded to this reviewer's comment in a point by point manner as the follows.

1. Response to Reviewer 00054255's comments

The reviewer commented that our comments on the issue that survival outcomes were different among the studies presented in Table 1.

**Response:** Five-year overall survival rate after repeat hepatectomy ranged from 20 to 80%. It was difficult to precisely analyze the difference according to the studies due to the insufficient data, but would probably have been influenced by the difference in the background liver damage, types of recurrence, and tumoral factors such as size, number, and vascular invasions. This description was added in page

2. Response to Reviewer 000504405's comments

(1) The reviewer commented that the aim of the study was not specified in the abstract.

**Response:** The aim of this study was to evaluate the role of hepatectomy for recurrent or initially unresectable hepatocellular carcinoma as was suggested by the title. This is a review article but not an original article, and the instruction for the authors do not provided specific format for the abstract to present the aim or background of the study. We made clear the aim of this review in the introduction section by revising the last sentence (page 4), but we did not revise the abstract.

- (2) The reviewer commented that the definitions of recurrent/refractory/down-staged HCC for initially unresectable are not specified in the manuscript.

**Response:** As the reviewer described, the definition of especially “unresectable” vary according to the surgeons and it is difficult to present a clear unanimous definition especially in a review article. We did not think further explanation of the term “recurrent” was necessary, but explanation for the term “refractory” and “unresectability” was added in page 7 and 12, respectively.

- (3) The reviewer commented that only limited information are presented in Table 1.

**Response:** As the reviewer pointed out, the Table 1 showed only limited representative data from the studies on hepatectomy for recurrent HCC. It was possible to present other variables including prognosis after first hepatectomy or prognostic predictors, which were not reported in all of the studies. However, the aim of presenting this Table was to simply show the repeat hepatectomy rate and prognosis after repeat hepatectomy. Addition of other variables would only make the table complicated with little effect to summarize the information. Therefore, we did not revise the Table 1.

- (4) The reviewer commented that the role of hepatic resection was never analyzed according to the quality of liver parenchyma or aetiology of liver disease.

**Response:** As the reviewer commented, patients with HCC are heterogeneous in terms of the background liver disease etiology and the degree of liver function. However, treatment strategy including indication does not change according to the etiology of the liver in any kind of treatment. The different oncological behavior according to the background liver disease was beyond the theme of this review. We added the words “irrespective of the etiology of the liver disease” in page 4 to suggest that the indication of hepatectomy is regulated by liver function but not the types of disease.

- (5) The reviewer commented that the role of hepatectomy was never balanced against that of liver transplantation.

**Response:** We have mentioned that liver transplantation was the most promising treatment, but we also cited studies showing hepatectomy showed comparable outcomes in patients with Child-Pugh class A liver cirrhosis. Further, liver transplantation is applied in very limited situation due to the issues including donor organ shortage, patients’ age, and high medical expenses. However, it was critical that the comparison of hepatectomy with liver transplantation was absent in this review, so we added description on the salvage liver transplantation in page 6-7.

- (6) The reviewer commented that in the talking about the prognostic factors, only tumoral factors were mentioned and underlying liver disease was not assessed.

**Response:** Prognostic predictors shown in the studied for repeat hepatectomy included not only tumor factors but also the degree of background liver disease or cirrhosis as assessed by Child-Pugh status, ICG retention rate, or platelet count. We added this description in page 5.

- (7) The reviewer commented that the term "differentiation" used with the meaning of "distinction" was confusing because it might suggest "tumor differentiation".

**Response:** The term "differentiation" was replaced with "distinction" in page 5-6.

- (8) The reviewer commented that the description on the respective role of hepatectomy and radiofrequency ablation (RFA) as first-intent treatment, which was out of the subject, and that our description suggesting hepatectomy than RFA should be less peremptory.

**Response:** Comparison of hepatectomy with RFA was necessary in this context, but as the reviewer's comment, the referenced we cited were basically based on the evaluation of the treatment for primary HCC rather than recurrent HCC. We added the explanation in page 9. Regarding the comparison of hepatectomy with RFA, most studies showed better results after hepatectomy and comparable outcomes were shown in the selected subsets of patients with small size and numbers of HCCs. However, this issue is still in debate and we revised the description in page 8.

3 References and typesetting were corrected

Because we newly added references #26-31 for the response to the reviewer's comment of (5) in the above, reference list was updated.

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

Sincerely yours,



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