

May 14, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2671-review.doc).

Title: Proposal of new classification for hepatocellular carcinoma patients based on tumor characteristics

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Name of Journal: World Journal of Gastroenterology

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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

Reviewer: 1

The grammar and English need to be corrected. Examples: The first sentence of the introduction is a fragment and should be corrected. In the introduction the word "malignancy" should read "malignant".

Response: Thank you very much for your valuable suggestion. We have carefully read them and made revisions accordingly. The grammar and English had been corrected. The major revisions have been highlighted with blue color in the manuscript.

(2)Two hundred and eighty-eight in patient section. A full editing is required.

Response: Thank you very much for your valuable suggestion. We have carefully read them and made revisions accordingly.

Reviewer: 2

(1)The definition of the invasive growth such as satellite nodules (including perforation of the tumor encapsulation) and nodules fusion (including diffuse growth lack tumor encapsulation) is not concrete. It is recommended to demonstrate clearly with representative figures.

Response: I'm very grateful to you for your constructive suggestions. We have

complemented a figure to demonstrated tumor's growth characteristics, such as single tumor, multiple tumors, satellite nodules and nodules fusion, in the modified manuscript.

(2)As to the disseminative growth, the definition of vascular involvement is not concrete, either. It should be delineated what size of vessels are involved

Response: Thank you very much for your valuable suggestion. In our study, the vascular involvement is that Hepatic vein or branch of Hepatic vein. This status was identified based on the CT, MRI or PET-CT.

(3)To facilitate for readers to understanding the new staging system, stage I to IV is summarized with proper cartoons. Minor points.

Response: I really appreciate your constructive suggestion. I have added table 3 to summarize stage I to IV in the modified manuscript.

(4) For the title, "tumor growth characterics" is more suitable for the content.

Response: Thank you very much for your valuable suggestion. We have made revisions accordingly.

Reviewer: 3

data are insufficient to support the conclusions. In the paper, the classification of HCC was just according to the survival analysis, other characters should be added like pathomorphological classification, molecular features, the character of gene expression and so on. The analysis did not remove the influences of these factors and treatment strategies on patients' prognosis. Moreover, the Expansive - Invasive - Disseminative growth staging classification is not different from early - medium - late stages, and is impossible to be superior to TNM classification in diagnosis of HCC.

Response: Firstly, the aim of all of the cancer classifications is determining the survival of patients, other than pathomorphological classification, molecular features, the character of gene expression, and so on.

Secondly, many researches about classification of HCC just include 100 - 500 patients. CLIP investigators externally validated the CLIP score in 196

patients with cirrhosis and HCC [The Cancer of the Liver Italian Program (CLIP) investigators. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology*. 2000;31: 840-845]. In addition, modified TNM that Izumi published in 1994 have only 104 patients [Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Hepatology*. 1994 Mar;106(3):720-7]. Thirdly, none of the classifications, such as TNM, CLIP score, Chinese University Prognostic Index, Japan Integrated Staging score and BCLC staging classification, include the molecular features, such as the character of gene expression.

Finally, the early - medium - late stages of HCC just based on tumor's size and been discard many years ago. TNM staging system, which is designed for all of HCC patients, based on some character of tumor, such as tumor size, vascular invasion, regional lymph node metastasis and extrahepatic spread. In our study, we explore an appropriate staging system for resectable patients with HCC based on tumor's growth characteristics (such as expansive growth, invasive growth and disseminative growth).

Reviewer: 4

(1)The title should be revised according to this study. Proposal of new classification for postoperative patients with HCC based on tumor characteristics may be suitable

Response: Thank you very much for your valuable suggestion. We have made revisions accordingly.

(2)The abstract on this article, particularly in RESULTS and CONCLUSIONS, is poor. It should be carefully revised.

Response: Thank you very much for your valuable suggestion. We have made revisions accordingly.

(3)EID stage (I II III IV) characteristics such as age, gender, HBV or HCV infection or antivirus, AFP level and tumor size also should be present

respectively, in addition to all HCC patients and tumor characteristics(n = 288) was present in this study.

Response: Thank you very much for your constructive suggestion. I have added table 4 to summarize the characteristics stage of EID stage (I/II/III/IV) in the modified manuscript.

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

Sincerely yours,

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