

April 29, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: The Grey Zone in the BCLC Classification for Hepatocellular Carcinoma: Surgeons' Perspective

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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

(1) **Reviewer #1 (No.3259435):** *The authors focus on a relevant issue of interest regarding the classification and treatment algorithms of HCC. They point out the limits of the BCLC staging system. This staging system has been compared and validated in comparison to other staging systems for non-resectable HCC (e.g. Op den Winkel et al., PLoSOne 2012;7(10)). The authors could discuss other staging systems and suggest concrete prognostic factors that should be included in classification and treatment algorithms.*

Response:

We have added on page 7-8 in the revised manuscript the following sentences:

The lack of a consensus on an HCC staging system is mostly in part related to the heterogeneity in treatment modalities at diagnosis[34]. Therefore, as we think, it is necessary to establish specific HCC staging systems to assess prognosis, directed toward different treatment modalities, for example, for those patients with resectable or non-resectable HCC[35, 36]. Considering the most complexities of HCC treatment among all malignancies, it was inadvisable and impractical to try conducting a specific or sole treatment modality for all HCCs by using a seemingly simple but uniform treatment algorithm just like the current BCLC guideline, which may well do more than good in the real life. Therefore, this should be the major intrinsic limitation of the BCLC classification, since this so-called “authoritative guidance” attempts generalize all probabilities of

the treatment for patients with HCC.

[34] Chen CH, Hu FC, Huang GT, et al. Applicability of staging systems for patients with hepatocellular carcinoma is dependent on treatment method--analysis of 2010 Taiwanese patients. Eur J Cancer. 2009. 45(9): 1630-9.

[35] Yang T, Zhang J, Lu JH, et al. A new staging system for resectable hepatocellular carcinoma: comparison with six existing staging systems in a large Chinese cohort. J Cancer Res Clin Oncol. 2011. 137(5): 739-50.

[36] den Winkel M o, Nagel D, Sappl J, et al. Prognosis of patients with hepatocellular carcinoma. Validation and ranking of established staging-systems in a large western HCC-cohort. PLoS One. 2012. 7(10): e45066.

(2) Reviewer #2 (No. 1852833): *I am very approving of the ideas that the authors demonstrate. The authors considered the shortages of BCLC classification from the surgeons perspective, however, as the part of the comprehensive treatment, TCM also uses in HCC treatment, and play important roles (Eg, PMID 25074882, 24666672 by Prof. Ling, and PMID 15339547 by Prof. Wu,) in patients in Stage C and D, also in prevent the metastasis and recurrence after surgery (PMID 23506690). So, I suggest the authors would include the this point in this MS.*

Response:

We thank Reviewer #2 for the favorable comments. The following sentences have been added in the revised paper.

In addition, it should be noted that only surgery, radiofrequency ablation, TACE, oral sorafenib, and symptomatic treatment were recommended in the BCLC guideline, but many other effective or promising treatment modalities for HCC have never been mentioned by the BCLC treatment schedule, such as radiotherapy, Yttrium(90) radioembolization, cryotherapy, microwave coagulation therapy, laser therapy, traditional Chinese medicine, immunotherapy, and so on^[37-41]. Therefore, it should be considered as biased and insufficient for the BCLC treatment guideline, which may also need to be further modified by the BCLC conductors in the future.

It's worth mentioning that nowadays the majority of patients who are not considered ideal candidates based on the BCLC guideline still agree to undergo hepatic resection all around the world^[8, 42, 43]. An international multicenter study by Roayaie *et al*^[1] which reported a 5-year

overall survival rate of > 30% in the candidates based on the current guidelines for HCC. This group of patients accounted for nearly 70% of all the patients who underwent hepatic resection during the study period. These figures tell us currently there are many hepatic surgeons who do not follow the guidelines for HCC according to the BCLC recommendation^[44-46]. Are these surgeons irresponsible? Or have patients been misled by these surgeons to make a wrong decision?

[37] Poon RT, Fan ST, Tsang FH, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon's perspective. Ann Surg. 2002. 235(4): 466-86.

[38] Poon D, Anderson BO, Chen LT, et al. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009. 10(11): 1111-8.

[39] Wu MC. [Traditional Chinese medicine in prevention and treatment of liver cancer: function, status and existed problems]. Zhong Xi Yi Jie He Xue Bao. 2003. 1(3): 163-4.

[40] Zhai XF, Chen Z, Li B, et al. Traditional herbal medicine in preventing recurrence after resection of small hepatocellular carcinoma: a multicenter randomized controlled trial. J Integr Med. 2013. 11(2): 90-100.

[41] Greten TF, Wang XW, Korangy F. Current concepts of immune based treatments for patients with HCC: from basic science to novel treatment approaches. Gut. 2015. 64(5): 842-848.

[42] Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 2015 .

[43] Vitale A, Burra P, Frigo AC, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol. 2015. 62(3): 617-24.

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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