ANSWERING REVIEWERS

January 14, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7482-edited.doc).

Title: Hepatocellular Carcinoma: Surgical Perspectives beyond the Barcelona Clinic Liver Cancer (BCLC) Recommendations

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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:
Q1) Hepatitis B virus (HBV) infection is the main risk factor for HCC in Eastern Asia and Africa，however, in Western countries and Japan, hepatitis C virus (HCV) infection is the main risk factor. HBV and HCV differ in their mechanisms of carcinogenesis, they even differ in their way of responding to treatment. Therefore, even if many studies in Western countries have validated the usefulness of BCLC staging system, this classification is still under criticism due to some drawbacks. What's more, it does not necessarily mean that BCLC staging system is applicable in Asia and Africa. The risk factors vary significantly from region to region, which requires any staging system would need to be validated in both western and Asia-Pacific patients. To date, however, no such globally validated classification exists, and BCLC staging system is no exception. Having been repeatedly revised, BCLC staging system still has other drawbacks.
In summary, compared with BCLC staging system, the most important thing in the treatment of HCC is to tailor treatment to each patient's needs.
In my opinion, the above topics should be reflected in the manuscript.

A1) we agree with the comment of the reviewer. The BCLC staging system has been validated in Western and Eastern studies demonstrating its prognostic value compared to other staging systems [1]. It has been approved as treatment algorithm in Western country guidelines. In Eastern countries other treatment algorithms were proposed and applied in clinical practice. The BLCL system is not globally accepted as treatment algorithm because it excludes many patients from potentially curative surgical treatment. The aim of our manuscripts was to underline the limits of BCLC and to report the results of surgery in patients belonging to BCLC classes in which surgical resection should not be recommended. In the conclusion we underlined that the treatment strategy should be tailored on the single patient, based on literature data.

The text has been modified as follow:

... , but not by the main Asian associations for the study of liver diseases...

... Nowadays, no other HCC classification proposed has been approved worldwide and the treatment strategy should be tailored on the single patient, based on literature data...

1 Kim BK, Kim SU, Park JY, Kim do Y, Ahn SH, Park MS, Kim EH, Seong J, Lee do Y, Han KH. Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naive patients with hepatocellular carcinoma. *Liver Int* 2012; **32**(7): 1120-1127 [PMID: 22524688 DOI: 10.1111/j.1478-3231.2012.02811.x]

Q2) In the paragraph "BCLC B Large HCC (recommended TACE) ",

Although tumor size is not an absolute contraindication to liver resection, the risk of vascular invasion and dissemination increases with tumor size growth; thus, TACE might be a better initial treatment in patients with large HCCs. Before doing surgical resection for those patients with large HCCs, it is imperative to conduct a thorough evaluation in order to ensure that the lesion is well circumscribed.

I hope that the authors should pay attention to these questions in this paragraph.

A2) The reviewer suggest a correct comment. Since the introduction of advanced imaging modalities such as contrast-enhanced computed tomography (CE-CT) and magnetic resonance imaging (MRI) with hepatocyte-specific contrast, the diagnostic role of transarterial angiography and post-TACE CE-CT is decreased. However, in some limited cases, TACE can be proposed before surgical resection in patients with large HCC in which macroscopic vascular invasion and the presence of multiple satellite are frequent. Unfortunately the data of the literature failed to demonstrate a survival benefit for patients submitted to TACE + surgery compared to surgery alone in patients with resectable large HCC [2, 3].

The text has been modified as follow:

... In patients with large HCC, in which the presence of negative prognostic factors is frequent, the indication for preoperative TACE should improve the results of surgical resection. However, recent data did not show a survival benefit in the use of the combined approach preoperative TACE + surgery compared to surgery alone in patients with resectable large HCC…

2 Zhou WP, Lai EC, Li AJ, Fu SY, Zhou JP, Pan ZY, Lau WY, Wu MC. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. *Ann Surg* 2009; **249**(2): 195-202 [PMID: 19212170 DOI: 10.1097/SLA.0b013e3181961c16 00000658-200902000-00004 [pii]]

3 Chua TC, Liauw W, Saxena A, Chu F, Glenn D, Chai A, Morris DL. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. *Liver Int* 2010; **30**(2): 166-174 [PMID: 19912531 DOI: LIV2166 [pii]10.1111/j.1478-3231.2009.02166.x]

Reviewer 2:
Q1) The gene expression profiles in HCC from different manuscripts published are vastly different. How to transform this information into practice needs to be analyzed.

A1) we totally agree with the reviewer. Currently, a widely accepted molecular classification system for HCC is still not available. Future perspectives should include the identification of molecular panel able to classify different patients according to their expected survival. This molecular classification could suggest the tailored type of treatment including new target therapies.

The text has been modified as follow:
... Currently, a widely accepted molecular classification system for HCC is still not available. Future perspectives should include the identification of molecular panel able to classify different patients according to their expected survival. This molecular classification could suggest the tailored type of treatment including new target therapies...

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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