RESPONSES TO REVIEWERS AND EDITORS

December 2nd, 2014

Title: Current Management of Hepatocellular Carcinoma: an Eastern Perspective

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13407

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13407-review.doc).

We are re-submitting our manuscript entitled "Current management of hepatocellular carcinoma; an Eastern perspective" for publication in World Journal of Gastroenterology as a review article. We appreciate the opportunity to revise and improve our manuscript and to resubmit to the journal. We also thank the reviewers for the constructive comments. The manuscript has been improved according to the suggestions of reviewers and editorial office as follows:

1 Title has been modified as "Current Management of Hepatocellular Carcinoma: an Eastern Perspective".

2 Format has been updated in compliance with the guidance from the Editorial Office.

3 Revision has been made according to the suggestions of the reviewer. The point by point responses and the revised sentences are described on the followings. **Revisions in response to comments are higlighted on the manuscript.**

Reviewer's Comment 1.

- **If possible, both targeting drug delivery system and molecular targeted therapy of hepatocellular carcinoma should be involved in the part of emerging combination of HCC treatment strategies.**

  Responses: Thank you for the important comment. We have added detailed descriptions for targeting drug delivery system (p.10) and suggested a combination with target therapy (p.11). In addition, drug eluting beads (DEB), which is one of drug delivery system in use, was exemplified for treating HCC in combination with sorafenib.(p.15)

  Revisions:

  p.10-11
  Currently, several target delivery systems has been exploited for the treatment of HCC. New formulations including polymetric nanoparticles, nanocapsules,

liposomes, nanoemulsions, microsphere, and polymeric micelles have been reported[117,118]. Novel drug delivery systems are expected to improve treatment efficacy and to decrease toxicity by drug targeting to the specific site of action[118]. For example, the asialoglycoprotein (ASPG) receptor is expressed on hepatocyte, and a synthetic ligand, lactosylated liposomes can be used for effective delivery vehicles of doxorubicin in HCC therapy[119]. In a previous report, lactosylated liposomes encapsulating doxorubicin showed stronger anti-tumor response than the non-targeted liposomal doxorubicin and free doxorubicin. A galactose ligand with chitosan modifications, galactosylated chitosan, is also a promising carrier of chemotherapeutic agent, such as 5-fluorouracil, to the ASPG receptor, and its in vitro and in vivo efficacy was well described[120]. It is thought that efficacy of anticancer therapy utilizing target delivery system will be more synergized by combination of molecular target therapy. Further studies are warrantied.

p.15
A phase II study which combined DEB-TACE with sorafenib showed objective response rate of 58% and disease control rate of 100% in advanced HCC patients[152]. The combination is a promising HCC treatment strategy considering the current data, but its benefits compared with monotherapy needs to be confirmed in a future phase III trial.

- **In addition, there are still some problems about language and editing to be improved and perfected**

Responses: We appreciate your recommendation. We requested English editing services to "Editage (www.editage.com)", which is a world-leading English editing group, and received full correction of our manuscript. The certificate is submitted to the editorial office. Thank you for your considerate comment.

Reviewer's Comment 2

- **Please put an additional topic on the new Hong Kong Liver Cancer Staging System, with comments on comparison with the Barcelona Clinic Liver Cancer Staging System. It will enhance this article further**

Responses: Thank you very much for the important suggestion. We added a new topic titled "Need of updated staging system" on the last part of main body (p.17). Then, we introduced Hong Kong Liver Cancer classification and described its benefits over BCLC. Thank you very much again.

Revisions:

p.17
Need of updated staging system
With the advancement of therapeutic modalities and aggressive treatment by either mono- or combination therapy as reviewed so far, the prognosis of HCC has improved remarkably; survival benefits are better observed in more advanced stage diseases. In this regard, reevaluation of preexisting staging systems and refinement of the best-fit models have been performed in Korea, Japan, Taiwan, and China. Most recently, a newer staging system was pronounced from a single center in Hong Kong, reflecting recent improved survival outcomes in subsets of

intermediate and advanced stage patients with more radical therapies[172]. In addition, the Hong Kong Liver Cancer staging was better than BCLC staging in stratifying HCC patients with different prognostic groups. Although further validation may be needed in non-Asian patients, the system will be helpful for identifying patients who are suitable for more aggressive treatments than what BCLC staging system recommends.

4 References and typesetting were corrected.

5 A figure covering the main idea of the current article has been added.

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

Sincerely yours,

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