January 26, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13888-review.doc).

Title: Management of recurrent hepatocellular carcinoma after liver transplant

Author: Kenneth Siu Ho Chok

Name of Journal: World Journal of Hepatology

ESPS Manuscript NO: 13888

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 reviewers:

Reviewer number: 2860795

(1) In the abstract, you mention "bonus point system" for HCC. This is not an accurate statement. It is a MELD exception system.

Answer: Amendment has been made accordingly.

(2) I would be very cautious about recommending PET scan so strongly (page 5). The data has had mixed reviews about its utility in HCC patients, especially pre-OLT. It is not standard of care, so it should not be written as such.

Answer: The text has been modified and addition has been made: "PET using the radiotracer ^{18}F-FDG *seems* effective in detecting ^{18}F-FDG-avid lesions and thus can be used *as an adjunct* to detect microvascular invasion. *Nonetheless, such use is still at its infancy and more large-scale trials are needed for its validation*."

(3) On page 6, you discuss LDLT, and inferior oncologic outcomes. There may also be an element of increased recurrence with LDLT because of the shorter wait time. Several studies have come out recently that a wait time of less than 6 months is associated with a much higher risk of recurrence. A longer wait time probably selects out the tumors with more favorable biology.

Answer: This is certainly true. In actual practice, however, both donors and recipients are keen for salvage transplantation despite a relatively higher recurrence rate; so we are bound to accept that. The following text has been added: "*In Hong Kong, the policy of "6-month-wait" before salvage transplantation does not apply to LDLT, since both donors and recipients willingly accept the relatively higher recurrence rate with the realization that LDLT is their only option*."

(4) On page 7, in your discussion of multidisciplinary teams, you leave out hepatologists and radiation oncologists, who are two critical members of the team.

Answer: Addition has been made accordingly.

(5) On page 11, you should spend much more time on discussion of mTOR use, of which there is much more data than you reviewed. You also should discuss more information about the use of sorafenib post transplant.

Answer: Four additional studies (references 53, 57, 58, 59) are discussed on pages 12 & 13 respectively.

(6) Overall this is a good review, but much of the manuscript is spent on pre-transplant treatment with locoregional therapies, and very little of the manuscript actually discusses management of post transplant HCC recurrence. If you really want to have the title be about treatment of recurrence, then the manuscript should be edited to reflect that.

Answer: Data on this topic is scarce, and thus this review was initiated. I believe some pre-LT treatments are applicable to post-LT HCC recurrence, although not without special problems (e.g. much more technically demanding liver resection, much more difficult intervention with post-LT hepatic arteries, etc.). In the review the problems were discussed. A thorough literature search has been done and it seems that all available case series and reports have been discussed in the review.

Reviewer number 4882

(1) In this paper, it is described that PET is effective for evaluating micro-vascular invasion. This is important for deciding indication of liver transplantation. The authors should describe how PET is useful for evaluating micro-vascular invasion.

Answer: I agree that more concrete evidence is needed before a strong claim can be made. The text on this has been modified: "PET using the radiotracer ^{18}F-FDG *seems* effective in detecting ^{18}F-FDG-avid lesions and thus can be used *as an adjunct* to detect microvascular invasion. *Nonetheless, such use is still at its infancy and more large-scale trials are needed for its validation*."

3. References and typesetting were corrected.

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

Sincerely yours,

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