

Feb 16th, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format

**Title: Central Hepatectomy for centrally located malignant liver tumors: A systematic review**

**Author:** Ser Yee, LEE

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 7886

The manuscript has been improved according to the suggestions of reviewers:

We would like to express our thanks and appreciation for the time and efforts of the reviewers in reviewing this paper, and have detailed our response to the reviewers' comments as below.

**Reviewer 1**

This is a very interesting and well written systematic review about central hepatectomy outcomes. I have only some minor comments: 1)Page 8; "Study characteristics and operative deaths": please add the total number of patients by indication 2)Page 9; "Mortality and morbidity": how the 19.8% bile leakage morbidity was computed? (if data are pooled together please specify how you did it in the methods section) In addition, if available, please add the same proportions for the other complications. 3)Page 10; the same observation made in point 9 can be done when reporting mortality in this paragraph 4)Page 14; in comparison to the work of Stratopoulos what is new in the present review? (I believe that the present review encompasses more recent articles, so please add this information) 5) Page 16; please remove "demonstrated" from conclusion section 6) Tables: please add in the legend, how pooled proportions and pooled means were calculated. It was used a meta-analytic approach (i.e. random effect DerSimonian approach) or it was a simple weighted pooling? This point is the most important of my comments.

1. We have updated the breakdown of operative diagnosis/indication in the text.
2. We have included how the overall bile leakage morbidity was calculated in the methods section. Also the proportions of the other complications are also shown in a new table, Table 3.
3. The method of calculating mortality is also described in the Methods section
4. We have included that this review includes more recent studies (page 13).
5. We have removed 'demonstrated' from the conclusion section.
6. We have included the legend with the table: weighted means were calculated when outcomes were expressed as means.

### **Reviewer 2**

A nice topic and a well written review about central hepatectomy outcomes. I just think the Abstract is too long.

Thank you for your input. We have shortened the abstract as suggested.

### **Reviewer 3**

This is a well written thorough review of the technique and outcomes of this surgical procedure. It should be published. There are a number of grammatical errors; fixing those is my only suggestion. I would also shorten the abstract.

We have corrected the grammar and shortened the abstract as suggested.

### **Reviewer 4**

In the present manuscript the authors performed a meta-analysis to evaluate the implication of central hepatectomy (CH) for the management of central hepatic malignancies and to compare the perioperative, short and long term results of CH to lobar/extended hemihepatectomy. The authors concluded that CH is a promising option for anatomical parenchymal preserving procedure in patients with centrally located liver malignancies; it is safe and comparable in both perioperative, early and long term outcomes when compared to patients undergoing hemi-/extended hepatectomy. 1) Authors searches MEDLINE (PubMed) from January 1993 to June 2013 for studies. There were 21 relevant studies were found with a total of 895 subjects included into this meta-analysis. The number of acquired papers would be enough for the review. However, further high-quality studies based on larger sample sizes are still needed to confirm the conclusion. 2) The authors did not assess the publication bias by visual examination of funnel plot and statistical tests. Furthermore, whether there were significant heterogeneities between studies were unknown. These would be important limitations of the review. The authors did not mention these point in the limitations of their meta-analysis.

Thank you for your detailed comments. This was a systematic review of studies that looked at central hepatectomy, rather than a meta-analysis of as there are very few trials or studies that compared central hepatectomy versus other extended/hemihpatectomies. In addition, as highlighted in the limitations, there is definitely selection and some degree of publication bias as these are retrospective series and experiences; there are no prospective studies for this procedure and there is no intervention per se. As such, a funnel plot would not be necessary or indicated strictly. In our understanding, funnel plots have their limitations as well, as interpretations of such plots are subjective.<sup>1,2</sup> An asymmetric funnel plots may not be truly indicative of publication bias; and may be attributable to other factors instead, such as location bias, true heterogeneity between studies (intervention intensity, study population differences, risk profile), data irregularities etc.<sup>3</sup> We have included a statement on the need for further high-quality studies such as prospective studies or a randomized controlled trial with large sample sizes to confirm the utility of central hepatectomy for centrally located liver tumors.

1. Lau et al. The case of the misleading funnel plot. *BMJ* 2006 September 16; 333(7568): 597–600; Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol.* 2005 Sep;58(9):894-901.
2. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D, Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ.* 2011 Jul 22;343:d4002.
3. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315: 629-34.

Thank you again for the consideration in publishing our manuscript in the *World Journal of Hepatology*

Sincerely yours,

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