

February 20, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 7079-edited1.docx).

Title: Laparoscopic versus open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis

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Name of Journal: *World Journal of Gastroenterology*

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We would like to thank all the reviewers for taking their time to read through our manuscript and provide constructive criticism for us. 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 02860530 –

1) *"In introduction section (second para), authors state that "approximately 90% of patients with such chronic liver disease develop HCC". The inference is that 90% of cirrhotic patients develop HCC. Isn't that a very high and odd figure? Authors need to recheck the reference and look for other related references on natural history of cirrhosis."*

- Thank you for this comment. The statement was incorrectly worded and has been corrected after re-assessing the reference used and now states "Approximately 80% of patients with HCC develop the tumour from such chronic liver diseases (Llovet et al). The incidence of HCC in cirrhotic patients varies from between 0.2% to 8% per year depending on the cause of (Bruix et al)". (2nd paragraph of the introduction, page 5 of the document)

2) *"In the same para, authors mention that HCC is the foremost cause of death in such patients. The inference is that HCC is most common cause of death. Again, authors need to recheck and add more reference supporting this."*

- The article previously stated 'HCC is the foremost cause of death in such patients'. This was changed to highlighting that HCC is a major cause of death. We have also reworded to the statement to show that HCC was a major cause of death in deaths attributable to a liver disease. References were added and helped to quote direct figures according to European Cohort studies to show exact figures of HCC as a cause of death in deaths directly related to liver disease. The article now states 'The mortality rate of HCC associated with liver cirrhosis is rising in developed countries with HCC now being a major cause of death in patients with compensated cirrhosis. European cohort studies have suggested that HCC is responsible for 54% to 70% of deaths in patients who died of a liver related cause with compensated cirrhosis.' (2nd paragraph of introduction, page 5 of document)

3) *"In third para of introduction section, authors state that esophageal varices are limitation or contraindication for liver transplantation. Need to recheck on this and quote more references."*

- Thank you for this comment – this statement is incorrect, as the reviewer has correctly pointed out, it has been deleted from the article.
(3rd paragraph of introduction, page 5 of document)

4) *"In the fourth para of discussion, authors state that 'The results of this meta-analysis have shown that surgeons performing laparoscopic procedures returned wider histological tumour margins following resection when compared to the open approach.' Authors need to give a suitable explanation for this difference in LR vs OR."*

Though the studies assessed offer no inferences on this, one possible explanation could be the use of high definition magnification used in laparoscopic procedures, which may provide easier assessment of affected tissue and aid the surgeon to resect a tumour-free wide margin. This can further be aided through the routine use of laparoscopic ultrasound during laparoscopic resection. (Paragraph 5 of discussion, page 12 of document)

5) *"Language errors need to rectified"* - The language errors have been rectified

6) *"Similar meta-analysis have been done and published already with same conclusions."*

- The reviewer states that similar meta-analysis have been done with the same conclusions. Although we agree that meta-analysis have been done highlighting laparoscopic vs open hepatic resection in HCC, no previous systematic review or meta-analysis has been performed looking at patients with known cirrhosis specifically - an important factor given the challenges associated with cirrhotic patients as highlighted in the introduction.

Reviewer 02540479 –

"There was no new information to the reader. In addition, similar studies and meta-analysis were done and published on the same topic and with the same conclusions."

Thank you for this comment, however, as mentioned above, although we agree that meta-analysis have been done highlighting laparoscopic vs open hepatic resection in HCC, no previous systematic review or meta-analysis has been performed looking at patients with known cirrhosis specifically, as such we believe that this new review has potential to add significantly to the body of literature in this area.

Reviewer 00503536 –

1) *"There is no description on the comparative analysis for postoperative complications"*

- Comparative analysis of morbidity rates and specific complications, where reported by included studies, was performed as described in the methods and results. Pooled meta-analysis of complications suggested postoperatively the OR cohort significantly suffered from higher morbidity rates compared to the LR cohort (as shown in Figure 6). The overall RR of suffering from postoperative morbidity is 0.25 in favour of the OR cohort (95% CI 0.17, 0.37), $p < 0.001$, with moderate heterogeneity (I-squared 41.1%, $p = 0.165$). (As discussed in the Results section under postoperative outcomes and survival, Page 10 of document).

2) *"The location of the tumor might greatly affect the suitable operative approach as briefly stated in the results section, but how the indication of the operative procedure according to the location of the tumor might affected the present analysis is unclear"*

- We thank the reviewer for this comment. We have further expanded upon this issue with further comment in the discussion section now, which now reads; The fact that all included studies were cohort studies, rather than randomised trials, incurs a risk of selection bias. It is possible that certain factors, such as a tumour's anatomic location, may have influenced the choice of procedure. However, this was not commented upon by any of the included studies, which also controlled for other tumour-related factors such as size and staging to reduce bias risk. (Paragraph 6 of discussion, page 13 of document)

3) *“The reasons for less intraoperative blood loss and wider resection margins in laparoscopic approach than in open surgery are unclear, and they should be discussed”*

- The explanation for wider tumour margins has been provided above. However, the reduced blood loss may possibly be related to the laparoscopic surgery allowing for smaller incisions to perform the operation, as well as the development of high-definition laparoscopic devices which allow magnification, enable the surgeons to obtain a decent view for performing haemostasis. (Discussion paragraphs 4 and 5, pages 11 and 12 of document).

4) *“In the Core Tip, “This review suggests that not only is laparoscopic surgery for patients with hepatocellular carcinoma and known cirrhosis safe” needs to be revised”*

The sentence in the core tip was corrected and now reads; This review suggests that not only is laparoscopic surgery for patients with HCC and known cirrhosis safe, it may have improved outcomes compared to the open technique.

3 References and typesetting were corrected

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

Sincerely yours,

Ahmed Twaij