

Dear Editors and Reviewers,

Thank you very much for your instructions and the reviewer's insightful comments on our manuscript entitled " Anatomical versus nonanatomical liver resection for solitary hepatocellular carcinoma: A systematic review and meta-analysis (Manuscript NO: 62664)". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction according to the comments. The revision has been marked with red signs in the revised paper.

All changes in the text are as follows. The relevant reviewers' comments and our responses are presented below.

We hope that the revised manuscript is now acceptable for publication in your journal. If there is any question on our paper, please notify us and we will try our best to revise it.

Thank you once again for your comments and suggestions. We look forward to hearing from you.

Yours sincerely,

Corresponding author:

Wu Hong, MD, PhD.

**Reviewer #1: The text is concise and well-written and the results match the objectives of the study. Statistical analysis is solid and the weaknesses of the study are well described in the discussion part.**

**Response:** We very much appreciate this reviewer's positive comments on our work.

**Q1: Studies by Dong 2016, Hwang 2015, Yamazaki 2010, Ahn 2013 and Fan 2013 have different objectives, however, they offer comparable data that could be used in this manuscript. Studies by Wakai 2007 and Sasaki 2013 reached similar conclusions with the current meta-analysis but they have not been included in the tables, although they appear in the references. Ziparo 2002, Regimbeau 2002 are non-Asian studies which could have been included to enhance diversity. Conversely, studies by Kobayashi 2008, Nanashima 2008, Eltawil 2010, Yamashita 2014 did not show superiority of AR over NAR.**

**Response:** Thank you for your constructive advice for improving our study. The reasons why those studies were excluded are as follows:

Dong 2016, Regimbeau 2002. Some patients who received preoperative TACE were included in the study, which did not meet our inclusion criteria.

Hwang 2015. This article didn't divided patients with solitary hepatocellular carcinoma into anatomical and non-anatomical hepatectomy group.

Yamazaki 2010, Wakai 2007, Sasaki 2013 and Nanashima 2008. These four studies were from Japan, and they were carried out on patients with HCC who underwent a curative liver resection between January 1994 and January 2007, January 1990 and December 2004, January 1990 and December 2010, and January 1994 and August 2005 respectively. After reading them carefully, we think included patients of them may partly overlap with Eguchi 2008 which is a Japanese nationwide cohort between 1994 and 2001. Finally, we deleted these four studies and included the largest cohort the Eguchi 2008.

Ahn 2013, Ziparo 2002. These two articles included some patients with multiple tumors.

Fan 2013. The full-text article cannot be found.

Kobayashi 2008. As is described in the text "some patients had undergone TACE preoperatively at other hospitals." It did not meet our inclusion criteria.

Eltawil 2010. This article didn't report the long-term outcomes.

Yamashita 2014. This article included patients with solitary recurrent HCC, not primary HCC.

**Q2: Impaired liver function at baseline is associated with worse prognosis, thus this may act as a confounding factor. The authors might want to include this in the discussion part.**

**Response:** We very much appreciate the insightful comments on our work. Patients with impaired liver function always have the background of hepatitis, liver fibrosis or cirrhosis. First, in order to avoid postoperative liver dysfunction, patients with impaired liver function are more likely to receive NAR. Furthermore, in these patients, the degree of fibrosis or cirrhosis of liver parenchyma would be a significant risk factor of recurrence of HCC after hepatectomy and lead to a worse prognosis.

According to your suggestion, we have added the this in the discussion part.

Discussion part (Page 11): Unlike other tumors, underlying liver function plays an important role in patients' prognosis after initial liver resection.<sup>[47, 48]</sup> **“As is known to us, impaired liver function is associated with worse prognosis. Because of the superiority of AR and the preference of surgeons, AR is always conducted in patients with better liver function compared to NAR, our synthetic results proved it. Although part of included studies used PSM to decrease confounders as much as possible, liver function is still a potential confounder which can't be bypassed, and we need take it into consideration when interpreting the result”.** Less remnant liver volume, more intraoperative loss and longer operating time were related to AR, which theoretically increased the risk of postoperative complications such as liver failure.

**Reviewer #2: Well written manuscript I have no further suggestions**

**Response:** We very much appreciate this reviewer's positive comments on our work.

## **EDITORIAL OFFICE'S COMMENTS**

**Science editor:**

**(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).**

**Response:** Thanks for the kind suggestion. We have uploaded funding agency copy of approval documents accordingly.

**(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.**

**Response:** Thanks for the kind suggestion. We have provided the original figure documents accordingly.

**(3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.**

**Response:** Thanks for the kind suggestion. We have added the “Article Highlights” section at the end of the main text accordingly.

#### Research background

Patients diagnosed with solitary hepatocellular carcinoma always received liver resection. More and more patients are undergoing anatomical hepatectomy which aimed to eradicate tumor. Accumulating studies had been developed to compare these two kinds of surgical technology. However, it is still not yet whether anatomical hepatectomy is superior to non-anatomical hepatectomy.

#### Research motivation

Clarifying the survival benefits of anatomical and non-anatomical hepatectomy is of vital importance for patients with solitary hepatocellular carcinoma. Furthermore, it will be instructive for doctor to choose better surgical method.

#### Research objectives

To perform a systematic review and meta-analysis on short- and long-term results of anatomical and non-anatomical hepatectomy in patients with solitary hepatocellular carcinoma.

#### Research methods

PubMed, Medline (Ovid), Embase (Ovid) and Cochrane Library were searched for articles from the inception of each database to 2020 according to the designed extraction scheme, and perform the Statistical analysis using Cochrane Collaboration’s Revman Manager 5.3 software. The quality of included papers was assessed with the modified Newcastle–Ottawa Scale. The main results of this study included overall survival (OS) and disease-free survival (DFS).

## Research results

Fourteen studies (9444 patients) comparing anatomical and non-anatomical hepatectomy were included for final analysis with 4260 AR and 5184 NAR. Anatomical hepatectomy has higher 5-year OS [odds ratio (OR):1.10, 95% Confidence interval (CI): 1.08–1.30] and DFS (OR: 1.26,95% CI: 1.15–1.39).

AR was associated with longer operating time [mean difference (MD): 47.08;  $P < 0.001$ ], more blood loss (MD: 169.29;  $P = 0.001$ ) and wider surgical margin (MD = 1.35;  $P = 0.04$ ) compared to NAR. There was no obvious difference in blood transfusion ratio (OR: 1.16;  $P = 0.65$ ) and postoperative complications (OR: 1.24,  $P = 0.18$ ).

## Research conclusions

This meta-analysis confirmed that AR is superior to NAR in terms of long-term outcomes. Thus, AR can be recommended as a reasonable surgical approach in patients with solitary HCC.

## Research perspectives

There are some limitations that should take into consideration when interpreting the results. The most vital limitation is that the included studies are non-randomized controlled trial and retrospective. Future studies with large-scale and well-designed RCT are needed to further verify the benefits of anatomical hepatectomy for patients with solitary hepatocellular carcinoma.