

Dear Editor and Reviewers:

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "Current status of radical laparoscopy for treating hepatocellular carcinoma with portal hypertension". Those comments are all valuable and very helpful for revising and improving our paper, as well as the essential guiding significance to our researches. We have studied comments carefully and have made the correction which we hope meet with approval. The revised portion is marked in red in the paper. The main corrections in the paper and the response to the reviewer's comments are as flowing:

Comment 1

Patient selection has not been appropriately defined: which are the features of the selected population? Could these characteristics have influenced the prognosis results?

Response 1

Dear reviewers, thank you for your comments. Some hepatocellular carcinoma (HCC) with portal hypertension (PHT) patients can tolerate surgery (especially laparoscopic surgery) if their liver function is preserved. Since most surgeons remain cautious, few studies exist on the laparoscopic treatment for HCC with PHT. Therefore, the experience summary based on the existing clinical studies in this review will be affected by the original literature's screening criteria when selecting the population.

If the retrieved article indicated that all patients were subjected to HCC with PHT, this article would be included and marked as "All patients are HCC with PHT (All) "; If the retrieved article stated categorically that none of the patients suffered PHT, this article will be excluded; If all the patients in the retrieved article had to endure the misery of HCC with

cirrhosis, while only part of the patients was subjected to HCC with PHT, this article would be included and marked as "Part of the patients are HCC with PHT (Partial)"; If not all the patients in the retrieved article suffered HCC with cirrhosis, this article would also be excluded to prevent excessive heterogeneity.

Actually, we have exhibited inclusion criteria in our original manuscript—"Retrieved articles were included in the analysis if they met the following inclusion criteria; (1) explicitly indicated that the enrolled cases comprised HCC patients with PHT (all or partial); and (2) compared short- and long-term efficacy of various anti-HCC therapies for HCC with PHT, and at least one experimental group underwent radical laparoscopic treatment."

The above statement may not be precise enough, so we have made corresponding amendments.

Comment 2

Since it is not well clarified: were all the cirrhosis from a viral hepatitis or also from a NASH? Any differences in the outcome?

Response 2

Dear reviewers, thank you for your comments. We have supplemented the causes and their proportion of liver cirrhosis in Table 1. It can be found that the vast majority of patients involved in the included articles are evolved from posthepatitic liver cirrhosis. Different causes of liver cirrhosis have no significant effect on the short- and long-term prognosis, as described in Line 223-226.

Comment 3

How do you define the portal hypertension and non-portal hypertension group? The selected patients undergo an HVPG measurement or only non-invasive tests?

Response 3

Dear reviewers, thank you for your comments. We define the portal hypertension and non-portal hypertension group according to the description in the included articles. In reality, only two articles used the combination of HVPG measurement and non-invasive tests to diagnose PHT, and the majority merely used non-invasive tests, as described in Table 1 and Line 226-229.

Comment 4

“radiofrequency ablation represents a conventional palliative remedy” You report that radiofrequency ablation is a palliative treatment whereas it’s strongly demonstrated its role in curative HCC treatment. Please correct.

Response 4

Dear reviewers, thank you for your suggestions. Radiofrequency ablation (RFA) used to be a palliative remedy. With the development of imaging positioning technology, ablation morphology and regulation, RFA has achieved the radical treatment of unifocal small HCC. In deep-seated HCC patients with a tumor diameter ≤ 3 cm, RFA reportedly reveals the inconspicuous distinction in survival rate but less influence on liver function and PVP, relative to hepatectomy. It may not be clearly stated in the original manuscript

and has been revised.

Comment 5

In the process of selecting patients to undergo LLR, there is a lack of insight into what type of resection has been performed; were they mostly minor hepatectomies or not?

Response 5

Dear reviewers, thank you for your comments. We have supplemented Major Hepatectomy (≥ 3 adjacent segments) and Minor Hepatectomy (< 3 adjacent segments) in Table 2. After comparison, we can find that only G. Belli and Fabien Le Roux these two scholars included a larger number of patients undergoing major hepatectomy; almost all of the patients included by other studies went through minor hepatectomy. During major hepatectomy, Fabien Le Roux and his colleagues tend to choose LLR, while G. Belli has a disposition to OLR. But at all events, the results of these studies support the view proposed by this review that confronted with HCC with PHT, LLR is superior to OLR with regards to short-term prognosis.

Comment 6

Are available studies on laparoscopic resection for HCC developed in non-cirrhotic patients and non-cirrhotic portal hypertension? Do you think that the results you illustrated are similar for this type of patients?

Response 6

Dear reviewers, thank you for your comments. Because we concentrate on

therapeutic laparoscopy for HCC with PHT, this review does not include the related articles of non-cirrhotic patients and non-cirrhotic portal hypertension. For non-cirrhotic and non-cirrhotic portal hypertension patients, compared with OLR, LLR is the preferred treatment unless the following complex conditions are encountered. (1) Abdominal cavity infection, extensive abdominal adhesion, laparoscopic separation and exposure difficulties, or intraoperative severe hemorrhage caused by forced separation; (2) Discovery of multiple intrahepatic, intraperitoneal, and hilar lymph node metastasis after pneumoperitoneum; (3) Immense tumors affecting the exposure and dissection of the first and second hepatic portal; and (4) Uncontrollable massive bleeding (>2000 ml), as described in Line 239-246.

When encountering HCC with PHT, surgeons often hesitate in the choice of treatment strategies. This review, combined with our center and related articles' clinical experience, proposes that some patients with HCC and PHT can still tolerate surgery (especially laparoscopic surgery). HCC with PHT is not the "forbidden zone" of LLR; the premise for LLR manipulation requires that patients' preoperative liver function meet corresponding criteria, which comprises Child-Pugh grade A or B, remnant liver volume >40%, and ICG-R15 \leq 45%. We do hope that this review can provide some useful ideas for the formulation of treatment strategies.

We expect that the editorial board and the reviewers would agree on the acceptance of this study. Once again, thank you very much for your comments and suggestions!

Thank you and best regards!

Yours sincerely,

Xiao Liang

Corresponding author: Xiao Liang, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 3 East Qingchun Road, Hangzhou, Zhejiang Province, 310016, China. E-mail: srrshlx@zju.edu.cn.