ID (00537002)

Name of journal: World Journal of Hepatology
Manuscript NO.: 36482
Column: Review
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Authors: TOSHIYA Kamiyama, Tatsuhiko Kakisaka, Tatsuya Orimo and Kenji Wakayama

Dear Jin-Xin Kong
Science Editor, Editorial Office
Baishideng Publishing Group Inc

We are most grateful to you and the reviewers for providing helpful and insightful comments on the original version of our manuscript. We have taken all of these concerns and suggestions into consideration when revising our manuscript which we enclose as a resubmission. Our point-to-point responses to each of these concerns are included in the attachment to this letter.

We hope that this revised version of our manuscript is now suitable for publication in World Journal of Hepatology and we look forward to hearing from you at your earliest convenience.

Sincerely,

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 00182114
Reviewer's country: Japan
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-03
Review time: 8 Hours

COMMENTS TO AUTHORS

1. Radiation is good effective for PVT with HCC. Radiation-induced liver disease (RILD), which typically presents as anicteric hepatomegaly and ascites 2-3 mo after RT. The pathology of radiation-induced liver damage shows changes similar to veno-occlusive disease, including endothelial swelling, terminal venule occlusion and sinusoidal congestion. RILD is a major concern in liver RT, because there is no established treatment and some patients will die of liver failure, although a few patients may recover. Therefore, please comment RILD for preoperative radiation on the PVTT. 2. Another important obstacle to RT application in HCC is the radiation susceptibility of the bowel, including the stomach and duodenum. The positive correlation between the incidence of symptomatic bowel toxicity and RT dose/bowel volume has been confirmed in several studies. Please comment bowel toxicity of stomach and intestine

We thank the reviewer for this comment. We agree with this comment and have added the following sentence.Page 14, Line 1-9

RT for HCC has been limited to palliative treatment because of the low tolerance of the liver for RT [32, 33]. However, the effects of a high dose of local RT have been investigated for the treatment of HCC [13, 31]. Kamiyama et al described that no apparent late radiation-induced complications were noted in any patients and radiation hepatitis did not occur in any of our patients. External RT targeting the PVTT, not the whole tumor, was indicated in the PVTT patients prior to the surgery. Their method of irradiation minimized the irradiation in the normal liver tissue and

facilitated an increase in the RT dose without significantly increasing toxicity.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 00053888
Reviewer's country: United Kingdom
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-03
Review time: 18 Hours

COMMENTS TO AUTHORS
The authors have presented an interesting review of papers reporting liver resection in the presence of PV invasion. This is interesting but the data have not undergone meta-analysis, presumably because of the mixed bag of additional therapies given to the patients. What is demonstrated is that in these patients the surgery has been carried out safely. The authors have not mentioned the prevalence of HBV infection among these patients. There is no doubt that this will have made a significant difference to surgical outcome. Tumours in patients with HBV infection occur at an early stage in the progression of parenchymal liver disease than in other aetiological causes of cirrhosis. This means that surgery can be carried out in a greater proportion of patients and more safely. The authors do need to stress this in their conclusions. The manuscript is interesting and worthy of publication but there are a number of typographical & grammatical errors that need correction. In addition I think the authors should consider bringing the manuscript together with a discussion rather than discussing each section.

We thank the reviewer for this comment. We agree with this comment and have added the following sentence.

Page18, Line 8-10.
The estimated cause was that the majority of patients described in this review

paper had a Child-Pugh score of A and were infected with HBV (Table 1) and thus had a good liver function reserve.
Page20, Line 11-14.
Most of the patients described in the studies we reviewed had a Child-Pugh score of A and were infected HBV (Table 1). This status might be a requirement for adaptation to hepatectomy to prevent postoperative hepatic decompensation.

Since the contents of each section are diverse, I discussed in each section. However, I performed short discussion as below in conclusion section.

Hepatectomy might prolong the survival of patients with HCC with PVTT when the liver function reserve is preserved, such as in Child-Pugh score A cases. Effective multidisciplinary treatments may improve the prognosis and prevent recurrence due to disseminated cancer cells in these patients. Moreover, hepatectomy may be a feasible adjunct treatment for HCC with PVTT due to the current mortality rates after hepatectomy being quite low.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 00058381
Reviewer's country: Austria
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-06
Review time: 3 Days

COMMENTS TO AUTHORS
This is a review article on an important topic; however, the sources/references that were used must be thoroughly reviewed; e.g., page 18: "Moreover, Kokudo T. reported from the data of nationwide surveys of patients with primary liver cancer performed by the Liver Cancer Study Group of Japan that the survival benefit of liver resection was statistically significant only in patients with PVTT invading the

main trunk or contralateral branch (44)": Kokudo et al. reported exactly the opposite in the paper cited here. Please check the correct writing of the names (page 24/table 2): "Capssottis (2004)" -> Capussotti) and clarify statements like "On the other hand, there have been reports of long-term survival after hepatectomy in patients with macroscopic portal invasion, but this treatment is optimal for patients with major PVTT remains controversial" (page 6/7; this sentence is grammatically unclear (although the authors provided a certificate of a language editing service), and for the reports mentioned here references would be required). A limitation of this review is that it mainly pertains to the findings in Eastern Asian countries (as stated by the authors at the end of the manuscript).

We thank the reviewer for this comment. We agree with this comment.

Kokudo T in reference 54 is different from Kokudo N in reference 17.

I corrected the name of Capssottis to Capussotti.

Page 7, Line 1-2.
I changed "this treatment is optimal for patients with major PVTT remains controversial." to "whether this treatment is optimal for patients with major PVTT remains controversial."

I referred two papers as below sentence.
Page 6, Line 17-18
On the other hand, there have been reports of long-term survival after hepatectomy in patients with macroscopic portal invasion[13, 14]

I mentioned the limitation of this review in TEXT (page 21, line 3-6) as "A limitation of this review is that most of the articles selected were published from Eastern Asian countries, and the findings may not be applicable to other regions of the world. A more comprehensive review of the global literature would be very valuable in the future."

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 01799104
Reviewer's country: Taiwan
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-10
Review time: 7 Days

COMMENTS TO AUTHORS

The authors performed the literature review and try to make important conclusion that pre- or post-surgical treatment efforts can improve the patient's outcome. Indeed, the review is not so easy because the cases are so rare and the treatment methods are so variable. I only have one minor concern that the abbreviations are using so many that in the table it is not easy to find the corresponded term in the text. The abbreviations are better also mentioned at the bottom of the table.

We thank the reviewer for this comment. We agree with this comment and have added the following abbreviations at the bottom of the table 1.

TACE: transarterial chemoembolization
PVI: portai vein infusion
HAI: hepatic arterial infusion
5-FU/IFN: 5- fluorouracil (5-FU)/interferon-alpha (IFN-α)
PIAF: cisplatin, doxorubicin and 5-FU locally administered in the portal vein with subcutaneous injection of IFN-α
PIHP: percutaneous isolated hepatic perfusion
FAIT: FU arterial infusion and interferon therapy
HAIC: hepatic arterial infusion chemotherapy
FP: cisplatin+5-FU
ADM: Adriamycin

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 02438768
Reviewer's country: China
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-11
Review time: 8 Days

COMMENTS TO AUTHORS
Comments for ESPS Manuscript NO 36482 1. General comments The review paper tackles an interesting topic. However, I have some comments regarding the paper. 2. Specific comments ⑴Major comments: ①A review paper should not be simply a summary of what others have published, but should take a critical analysis of others' findings. Obviously, it is improper to end abruptly with a short conclusion in the end of each section, but perhaps more importantly, and it should be a synthesis of the relevant findings and your comments. ②While the overall structure seems to be logical, the manuscript is full of grammatical errors, making it extremely difficult to read. It is obvious that the manuscript must undergo extensive language editing. ⑵Minor comments: The format of this manuscript should be revised according to WJH's requirement.

We thank the reviewer for this comment. We agree with this comment and have added the following sentence.We performed a synthesis of the relevant findings and our comments.

Page12, Line 18 – Page 13, Line 1.
As a curative treatment for HCC with PVTT, only hepatectomy might be insufficient, and multidisciplinary treatments must be required because portal invasion is associated with the development of metastatic nests.

Page14, Line 17 – Page 15, Line 1.
Hepatectomy for patients affected by HCC with PVTT might prolong survival in conjunction with local treatment targeting PVTT: RT or TACE.

Page 18, Line 6-11.
Major hepatectomy for HCC with macroscopic PVTT has been safely performed in many cases. The estimated cause was that the majority of patients described in this review paper had a Child-Pugh score of A and were infected with HBV (Table 1) and thus had a good liver function reserve. Therefore, we propose that the indication for hepatectomy in HCC with major PVTT should be expanded.

Page 19, Line 9-12
From these data, while HCC with PVTT located in the first or second branch of the portal vein might be a relatively good indication for hepatectomy, hepatectomy for HCC with PVTT in the main trunk or contralateral branch should be performed after careful consideration.

Page 20, Line 11 – Page 21, Line 1.
Most of the patients described in the studies we reviewed had a Child-Pugh score of A and were infected HBV (Table 1). This status might be a requirement for adaptation to hepatectomy to prevent postoperative hepatic decompensation. Moreover, increased liver function reserve might lead to a better prognosis for patients with HCC complicated by PVTT after hepatectomy due to the prevention of synchronous or metachronous tumors. Therefore, the indication of hepatectomy for HCC with macroscopic PVTT should be restricted for patients with good liver function reserve.

The manuscript underwent extensive language editing.

The format of this manuscript was revised according to WJH's requirement.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 02441161
Reviewer's country: China
Science editor: Jin-Xin Kong

Date sent for review: 2017-10-02
Date reviewed: 2017-10-13
Review time: 10 Days

COMMENTS TO AUTHORS
A good review about the role that hepatectomy.

We thank the reviewer for this comment.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
Manuscript NO: 36482
Title: Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus.
Reviewer's code: 01557574
Reviewer's country: Turkey
Science editor: Jin-Xin Kong
Date sent for review: 2017-10-02
Date reviewed: 2017-10-13
Review time: 10 Days

COMMENTS TO AUTHORS
Dear Author, This article title with 'Hepatectomy for hepatocellular carcinoma with portal vein tumor thrombus." it should be published at WJGO. It has good informations and it makes a new contribution for understanding of therapy of portal vein thrombosis. Sincerely yours.

We thank the reviewer for this comment.

Because the outcomes after hepatectomy have been greatly improved by recent advances in surgical technique and perioperative management, hepatectomy is a feasible treatment for HCC with macroscopic PVTT due to low mortality. Hepatectomy might prolong the survival of patients with HCC with macroscopic PVTT when the liver function reserve is preserved, such as in Child-Pugh score A cases. Effective multidisciplinary treatment might prevent recurrence in these patients due to disseminated cancer cells and improve the prognosis. We feel that

findings from this review will be of special interest to the readers of World Journal of Hepatology.