

Dear Editor-in-Chief of World Journal of Gastroenterology:

Thank you for helpful comments on the manuscript titled ‘Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis?’ (Manuscript NO.: 72788). We have revised our manuscript, including 2nd English editing by Editage on revised version, as suggested by the reviewers and agree to the points the reviewers have indicated. They are as follows:

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is an excellently written review from a well-known Korean team addressing the issue of external beam radiotherapy, surgery, and the combination for treating hepatocellular carcinoma with portal vein thrombosis. This topic is worth reviewing because of the advance of radiotherapy in recent years, and the new and only randomized controlled trial has been published to demonstrate a survival benefit for neoadjuvant radiotherapy in the population. Specific comment: 1. Paragraph “Palliating portal invasion with external radiotherapy”: compared with photon radiotherapy, proton beam radiotherapy has been demonstrated to improve overall survival by lowering liver toxicity. (PMID 32605627; 30684667). Moreover, there are some retrospective reports that demonstrate clinical outcomes by proton beam radiotherapy (for example, PMID 31772968). It would be great if the outcome and technique could be mentioned. 2. About the surgery and radiotherapy as a combination treatment, there is data exploring the possibility of liver transplant for the patient well down-staged by external beam radiotherapy and demonstrated impressive outcome albeit with an only limited case number. (PMID 32032291) I would recommend including this potential treatment option as a future perspective.

Revision answer: We appreciate your valuable comments. We are very glad to know that proton therapy achieved such a promising results; therefore we added a section at *page 8 1st paragraph* also including the reference studies you have suggested. It is also noteworthy that, albeit LT has been contraindicated for HCC with PVT, downstaging including SBRT and sequential LT yielded comparable outcome to those without PVT but underwent LT. Therefore we added a sentence referencing study by Soin et al. (*Page 11 1st paragraph*) Thank you again for all your thoughtful comment.

Add: In addition, particle therapy (e.g. proton or heavy ion therapy) can provide additional benefits compared to conventional EBRT using X-ray in treating locally advanced HCC. Particle therapy is mostly similar as conventional EBRT in terms of the overall principle of causing cancer cell death, but dose escalation and complication reduction could be achieved based on the physical characteristic called Bragg -peak (e.g, the phenomenon that energy deposits almost disappear after radiation passes through the body and progresses to a certain depth) [36]. Sanford et al. reported benefit of proton therapy as compared to conventional EBRT for 133 unresectable HCC patients regarding survival (median OS; 31 vs. 14 months, HR=0.47, p=0.008) and liver

toxicities (odds ratio: 0.26, $p=0.03$) [37]. Cheng et al [38]. also reported benefit of proton therapy as compared to conventional EBRT in survival (HR 0.56, $p=0.032$) and radiation induced liver disease (11.8% vs. 36.4%, $p=0.004$), using a propensity matched cohort. The current hurdle of particle therapy is its accessibility; currently, there are about 110 particle therapy centers in operation around the world, but most of them are in major developed countries such as US, Japan, and Germany [39]. The financial burden of treatment due to the high cost of equipment is also a problem to be resolved. However, the efficiency of EBRT could be greatly improved once these difficulties are gradually resolved.

Add: Sooin et al [48]. reported encouraging results that comparable survival was achieved from HCC patient with PVT after down-staging including SBRT and liver transplantation, to those without PVT but underwent transplantation (5-year OS 57% vs. 65%, $p=0.06$).

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: no

Revision answer: We appreciate your considerate and kind review.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: Portal invasion of hepatocellular carcinoma (HCC) is associated with poor clinical prognosis. Since it characterized the advanced stages of HCC, it is a common cause of inoperability and systemic therapy is currently the standard treatment for HCC in the Barcelona Clinic of Liver Cancer guidelines. However, the median survival of the Asian population was only ~6 months, and the tumor response rate was less than moderate (<5%). Various locoregional modalities were performed, including external beam radiotherapy (EBRT), transarterial chemoembolization, hepatic arterial infusion chemotherapy, and surgery, alone or in combination. Among them, EBRT is a noninvasive method and can safely treat tumors involving the major vessels. Palliative EBRT has been commonly performed, especially in East Asian countries, where locally invasive HCC is highly prevalent. Although surgery is not commonly indicated, pioneering studies have demonstrated encouraging results in recent decades. Furthermore, the combination of neo- or adjuvant EBRT and surgery has been recently used and has significantly improved the outcomes of HCC patients, as reported in a few randomized studies. Regarding

systemic modality, a combination of novel immunotherapy and VEGF inhibitor showed results superior to that of sorafenib as a first-line agent. In this interesting review the authors discuss the rationale supporting the use of combined surgery and external radiotherapy. Future clinical trials investigating the combined use of these novel agents, surgery, and EBRT are expected to improve the prognosis of HCC with portal invasion. The review is of interest, however some important topics should be discussed to further improve the clinical impact.

-The authors should first discuss current international recommendations suggesting systemic treatments for patients with advanced HCC. In particular, it would be relevant recalling the clinical benefit associated to regorafenib treatment after sorafenib failure as well described in a recent review (Experience with regorafenib in the treatment of hepatocellular carcinoma. *Therap Adv Gastroenterol.* 2021 May 28;14:17562848211016959).

-Another clinically relevant topic is treatment with impaired liver function such as patients with Child-Pugh class B who have limited therapeutic options as well described in a recent review (Non-transplant therapies for patients with hepatocellular carcinoma and Child-Pugh-Turcotte class B cirrhosis. *Lancet Oncol.* 2017 Feb;18(2):e101-e112). The authors should discuss potential treatment of such a patient category.

-Future perspective: in my opinion it would be clinically relevant discussing the impact of new emerging immunotherapies targeting tumor microenvironment, particularly targeting CD4⁺CD25⁺ regulatory T cells that have a well established immunosuppressive role in HCC microenvironment, as recently described (Hepatocellular carcinoma in viral and autoimmune liver diseases: Role of CD4⁺ CD25⁺ Foxp3⁺ regulatory T cells in the immune microenvironment. *World J Gastroenterol.* 2021 Jun 14;27(22):2994-3009.)

Revision answer: Thank you for providing us with additional important studies related to the current topic of our research. We have reviewed and included pertinent data from the suggested papers you have mentioned as shown below.

Add: (Page 4 last paragraph) In addition, it should not be overlooked that ~95% of the enrolled patients were in Child-Pugh A class in this study. Though, significant portion of the HCC patients with PVT have liver function of Child-Pugh B or C class [16]; use of sorafenib in these patients could be limited. A randomized phase 3 trial comparing sorafenib versus best supportive care alone in Child-Pugh B patients and the results are expected to provide further guidance [17]. A recent study investigated use of regorafenib for the HCC patients who have failed sorafenib; the median OS of 10.6 months was achieved in patients who received regorafenib of which was better than 7.8 months of placebo-receiving patients [18]. Although several studies on the expansion of indications for systemic and rescue therapies are in progress, but satisfactory results have not yet been obtained.

Page 4 last paragraph, 4th line: and American Association for the Study of Liver Diseases (AASLD) guidelines [15]

Add: (Page 12 1st paragraph last part) In addition, advances in understanding tumor immunity have resulted in new emerging immunotherapies. For example, CD4⁺ CD25⁺ regulatory T cells that have a well established immunosuppressive role in HCC microenvironment express various chemokine receptors and surface molecules such as PD-1, CTLA4 and others [48]. They can be potentially direct and indirect targets for newly emerging immune checkpoint inhibitors immunotherapy. Future clinical studies investigating efficacy and feasibility of novel immunotherapy and combination with EBRT are necessary

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors proposed the combination of surgery and external radiotherapy were expected to increase efficacy of treating hepatocellular carcinoma with portal invasion. In my opinion, this is a valuable viewpoint supported by relevant evidence and has certain scientific research value in the future.

Revision answer: We appreciate your considerate and kind review.

We agree the reviewers in all points and the corrections in an annotated version are the points the reviewers have indicated. Thank you and the reviewers again for considering our manuscript to be published in WJG. We look forward to receiving your answer soon.

Sincerely,

Chai Hong Rim and Jung Wan Choe, M.D., Ph.D.