

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72788

Title: Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis?

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05127202

Position: Peer Reviewer

Academic degree: PhD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: South Korea

Manuscript submission date: 2021-10-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-28 08:30

Reviewer performed review: 2021-10-28 09:21

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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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.

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Peer-review model: Single blind

Reviewer's code: 00028182

Position: Peer Reviewer

Academic degree: MD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: South Korea

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Reviewer accepted review: 2021-10-28 15:44

Reviewer performed review: 2021-10-28 21:11

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Scientific quality	[<input checked="" type="radio"/>] Grade A: Excellent [<input type="radio"/>] Grade B: Very good [<input type="radio"/>] Grade C: Good [<input type="radio"/>] Grade D: Fair [<input type="radio"/>] Grade E: Do not publish
Language quality	[<input checked="" type="radio"/>] Grade A: Priority publishing [<input type="radio"/>] Grade B: Minor language polishing [<input type="radio"/>] Grade C: A great deal of language polishing [<input type="radio"/>] Grade D: Rejection
Conclusion	[<input type="radio"/>] Accept (High priority) [<input type="radio"/>] Accept (General priority) [<input checked="" type="radio"/>] Minor revision [<input type="radio"/>] Major revision [<input type="radio"/>] Rejection
Re-review	[<input checked="" type="radio"/>] Yes [<input type="radio"/>] No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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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



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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.).

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Peer-review model: Single blind

Reviewer's code: 05665137

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: South Korea

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Reviewer performed review: 2021-10-29 03:26

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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**Peer-reviewer
statements**

Peer-Review: ☒ Anonymous ☐ Onymous

Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

no

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Peer-review model: Single blind

Reviewer's code: 06170143

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: South Korea

Manuscript submission date: 2021-10-28

Reviewer chosen by: AI Technique

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Reviewer performed review: 2021-11-01 00:19

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Scientific quality	[<input checked="" type="radio"/>] Grade A: Excellent [<input type="radio"/>] Grade B: Very good [<input type="radio"/>] Grade C: Good [<input type="radio"/>] Grade D: Fair [<input type="radio"/>] Grade E: Do not publish
Language quality	[<input checked="" type="radio"/>] Grade A: Priority publishing [<input type="radio"/>] Grade B: Minor language polishing [<input type="radio"/>] Grade C: A great deal of language polishing [<input type="radio"/>] Grade D: Rejection
Conclusion	[<input checked="" type="radio"/>] Accept (High priority) [<input type="radio"/>] Accept (General priority) [<input type="radio"/>] Minor revision [<input type="radio"/>] Major revision [<input type="radio"/>] Rejection
Re-review	[<input checked="" type="radio"/>] Yes [<input type="radio"/>] No

Peer-reviewer statements	Peer-Review: [<input type="checkbox"/>] Anonymous [<input checked="" type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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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.