Date:	August 15th, 2023
To:	editorialoffice@wjgnet.com
From:	"Gong Li" chicoco2023@163.com
Subject:	No.86183 Revisions & Response

Dear Editors and Reviewers:

I wish to resubmit our revised manuscript for publication in *World Journal of Clinical Cases*. The manuscript NO is 86183.

We thank you and the reviewers for your thoughtful suggestions and insights, and constructive comments. We carefully read all comments and suggestions, and have revised our manuscript accordingly.

The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in *World Journal of Clinical Cases*.

The manuscript has been re-checked and the necessary changes have been made in accordance with the reviewers' suggestions. The point-by-point responses to all comments have been prepared and attached herewith. The revised portions are highlighted in the manuscript.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
Gong Li, MD

Response to Reviewer 1:

Thanks for your comments.

I believe that many hepatologists have already experienced similar cases. Unless there are other case reports of CR without recurrence, this manuscript would merit publication in your Journal. The authors' experience of multidiciplinary treatments of far advanced HCC was very informative and gave valuable suggestions to hepatologists in clinical settings.

Response： Thank you for this invaluable comment.

Response to Reviewer 2:

Thank you for your comments on our paper. We have revised our paper in accordance with the suggestions you made.

1. *Firstly, there is a concern about the accuracy of the first sentence in the introduction, which states, "The incidence of hepatocellular carcinoma (HCC) among patients with portal vein tumor thrombus (PVTT) has been reported to be 44-62.2%." It should be verified whether the correct statement is, "The incidence of PVTT among patients with HCC has been reported to be 44-62.2%."*

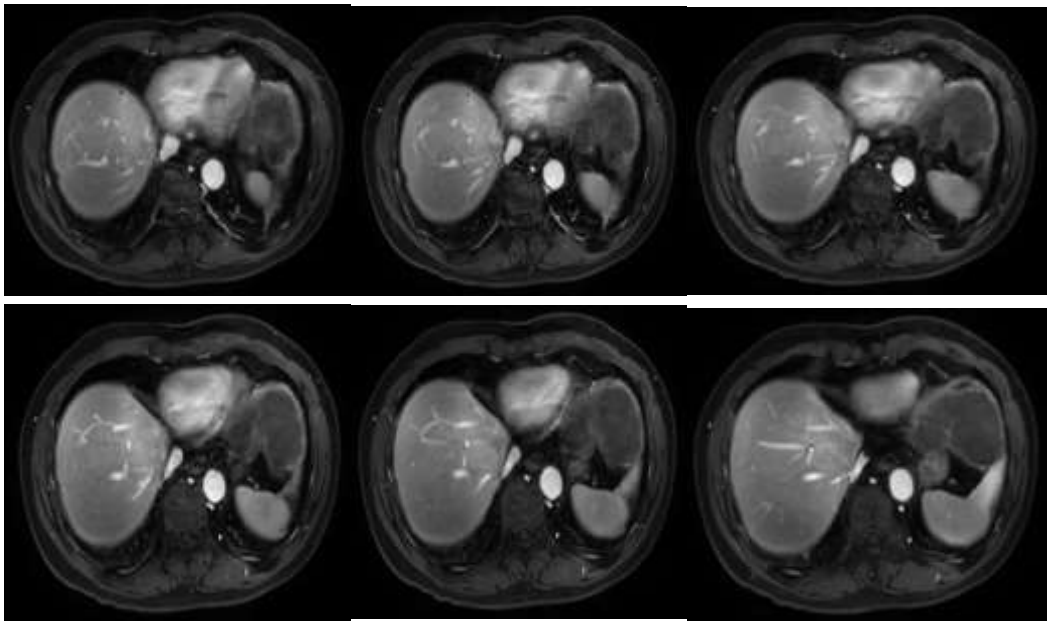
Response: Thank you very much for your reminding, and we apologize for our poor English expression. We have modified this corresponding part on page 2, lines 15-18 in the revised manuscript to make the expression more accurate and clearer. The underlined part is the added content: “The incidence of portal vein tumor thrombus (PVTT) among patients with hepatocellular carcinoma (HCC) has been reported to be 44-62.2%”.

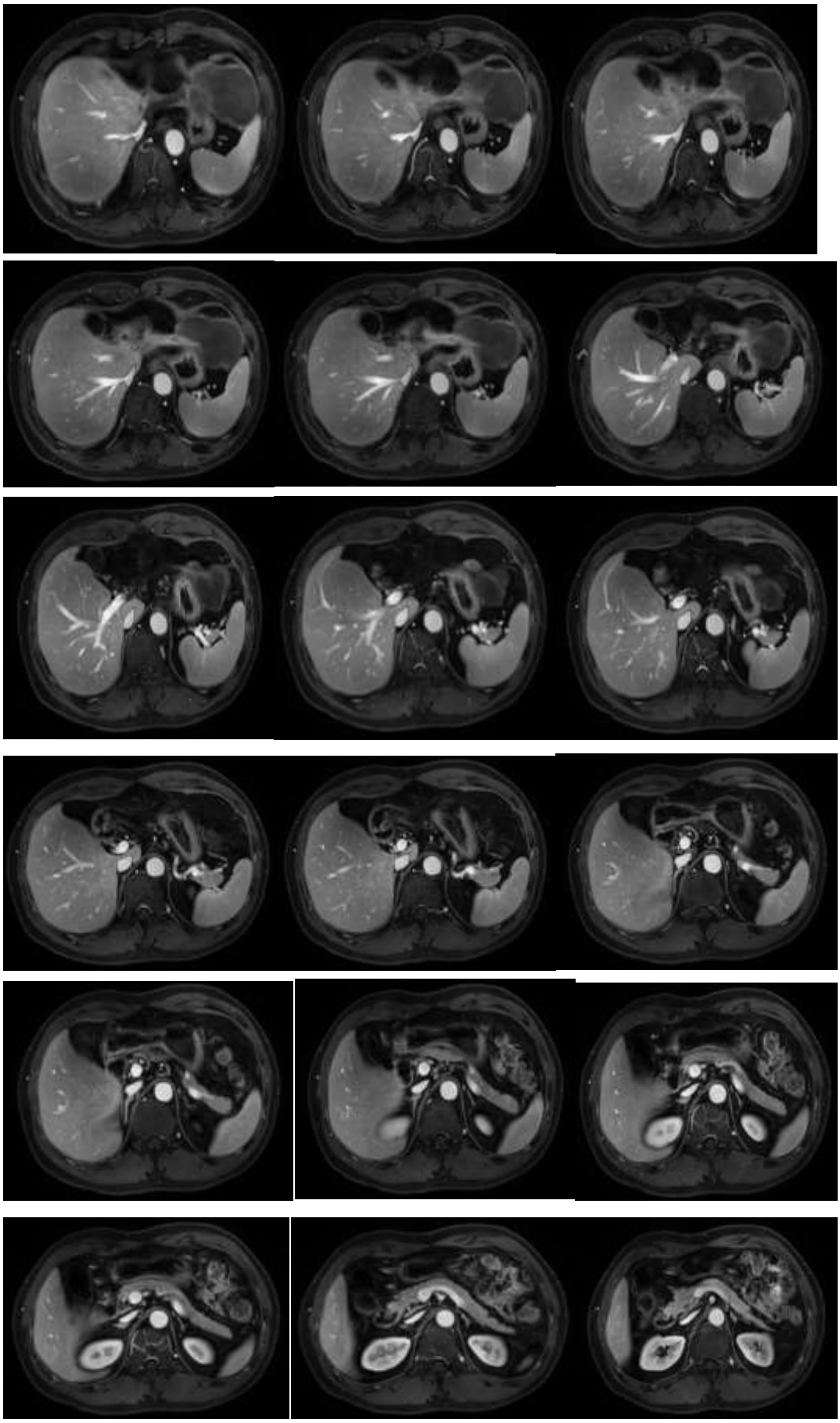
2. *In the subsection "History of present illness," it is suggested to revise the phrase "a 10.6x8.3 cm nodule" to "a 10.6x8.3 cm mass."*

Response: Thank you for your suggestion. We have modified this phrase on page 3, lines 25-26 in the revised manuscript; the underlined part is the added content: “a 10.6x8.3 cm mass”.

3. *In Figure 1 G-H-I, it appears that surgical resection was performed on the left lobe of the liver, but this information was not mentioned in the manuscript. It is recommended to clarify this discrepancy.*

Response: Thank you for your question. The patient actually did not have underwent surgery. Knife-cut sign in the left margin of the liver was the change due to liver atrophy after radiotherapy. The word document cannot insert moving pictures, so the screenshots for most image levels of 36 months after radiotherapy were listed below.





4. *The authors need to include the reason why only the left part of the tumor was irradiated. Additionally, the percentage of the tumor volume that was irradiated should be provided.*

Response: Thank you for your comment. The obvious tumor volume was 781cc and the liver volume was 1479cc (781/1479=52.8%), moreover, multiple metastases were found in the right lobe of the liver. **First**, considering the dose constraints of normal liver and neighboring organs at risk (especially stomach and duodenum), we had only partial irradiation. **Secondly**, as PVTT can cause HCC cells to be disseminated, RT plan was used to target the whole PVTT lesion. And the rate of bleeding risk and liver dysfunction would reduce if portal vein recanalization occurred. **Thirdly**, when RT given in combination with immunotherapy, enables the destruction of tumors at anatomical locations far outside of the radiation field owing to local activation of systemic antitumor immunity, otherwise known as the abscopal effect. However, the current lack of positive data, suggest that adding irradiation of a single lesion to ICI does not substantially increase the response rate — requires radiotherapy to be delivered to as much of the tumor burden as can be safely irradiated, rather than limiting radiotherapy to a single lesion (Brooks ED, Chang JY. Nat Rev Clin Oncol. 2019;16(2):123-135). Huang, A. C. et al also found reducing disease burden to the greatest possible extent could help to optimize responses to ICI (Huang, A. C. et al. Nature. 2017; 545, 60–65). Thus in order to reduce the tumor burden to a greater extent, we not only irradiated PVTT, but also the adjacent left part of the tumor. **Finally**, RT with volumetric modulated arc therapy (VMAT) treatment plans were used to target the whole PVTT and adjacent left part of tumor (409cc/781cc =52.4%).

5. *Was the PVTT lesion irradiated? The manuscript should explicitly state whether the PVTT lesion received irradiation or not.*

Response: Thank you for your question. The PVTT lesion was irradiated. According to your advice, we have added the phrase “whole PVTT” on page 5, lines 27 in the revised manuscript.

6. *The methods of radiotherapy used in this patient should be described in detail. It should be mentioned whether Intensity-Modulated Radiation Therapy was utilized and how respiratory movement of the tumor was managed during irradiation.*

Response: Thank you for your comment, we have modified this corresponding part on page 5, lines 10-26 in the revised manuscript. The underlined part is the added content: “The patient underwent four-dimensional computed tomography (4DCT) simulations. The respiratory cycle was divided into 0%-90% respiratory phase images based on the respiratory signal, which were reconstructed by the system (Elekat, Sweden) for treatment planning. Thermoplastic shell was used as custom immobilization device in the simulation. RT was delivered to lesion using the volumetric modulated arc therapy (VMAT) technique. Cone-beam CT images matching the target volume were used for daily imaging guidance. The gross tumor volume (GTV) of liver lesion was defined as a visible tumor on fusion images of CT with MRI. The internal target volume (ITV) was the envelope of all GTVs from the ten respiratory phases. The clinical tumour volume (CTV) of the primary tumour was generated by adding 5 mm to the ITV in all directions. The PTV of the primary tumour was expanded to include a 5mm margin from the CTV. At least 95% of the PTV was covered by the prescribed dose, which was prescribed to the periphery of the PTV. As PVTT can cause HCC cells to be disseminated, and considering the dose constraints of normal liver and neighboring organs at risk, meanwhile reducing disease burden to the greatest possible extent for helping to optimize responses to ICI, we had partial irradiation. RT, which irradiated only on the whole PVTT and left part of the tumor”.

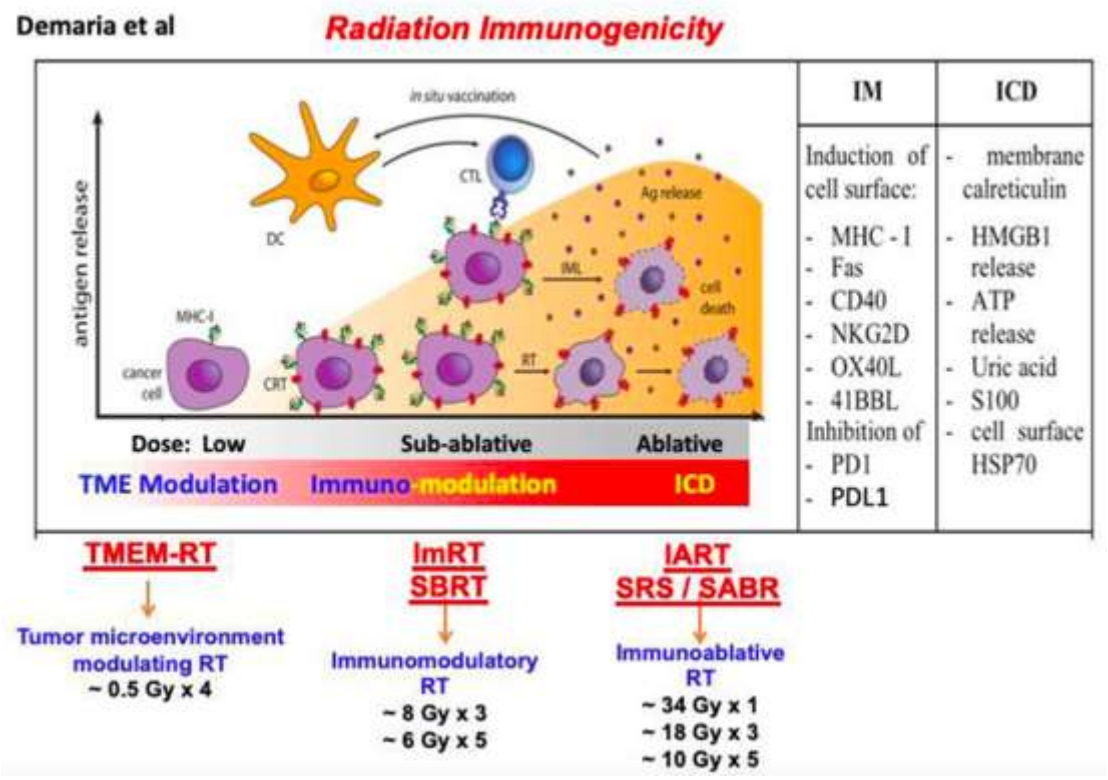
7. *The patient received a total radiation dose of 36 Gy delivered in 12 fractions. In the discussion section, it is important to address the appropriate radiation dose for the treatment of HCC or HCC with PVTT.*

Response: Thank you for your suggestion.

Multiple prospective trials and large retrospective series examining the role of EBRT for HCC, various dose and fractionation regimens, techniques, and modalities have been used. However, there are no published RCTs comparing them. The role of radiation remained controversial and lacked consensus. Kamiyama T et al compared preoperative RT to PVTT in the main trunk or first branch in patients who underwent hepatectomy with those without preoperative RT, the dose used was 30–36 Gy in 10–12 fractions, and found that preoperative RT improved the prognosis of patients, **complete necrosis of PVTT was 53.3%**, which have shown that radiotherapy is sensitive to PVTT (Kamiyama T, et al. Int J Clin Oncol. 2007;12(5):363-368).

Moderate hypofractionation is defined as EBRT with a fraction size of 300cGy to 500 cGy and typically involves between 12 and 20 fractions. For patients with HCC with macrovascular invasion, moderately hypofractionated EBRT is also conditionally recommended (ASTRO clinical practice guideline).

In the era of immunotherapy, differences in radiotherapy fractionation result in distinct immune-modulatory effects (Demaria S, et al. J Immunother Cancer. 2021;9(4):e002038). However, when combining radiotherapy with immunotherapy, there is no widely accepted radiotherapy dose and fractionation. Considering the radiation sensitivity of PVTT, the dose constraints of normal liver and neighboring organs at risk, and radiation immunogenicity, we have chosen
a total radiation dose of 36 Gy delivered in 12 fractions. We have modified this content on page 7, lines 23-27, page 8, lines 19-22 in the revised manuscript.



Demaria S, Guha C, Schoenfeld J, et al. *J Immunother Cancer*. 2021;9(4):e002038.

8. *Regarding the drug lenvatinib, it should be clarified whether it was administered solely during the 12 fractions of RT or not. The duration of lenvatinib administration before maintenance therapy should be specified.*

Response: Thank you very much for your suggestion. Lenvatinib was used not only during radiotherapy, but also continuously for 2 months after radiotherapy, and thereafter in combination with immunotherapy during the maintenance phase.
We have modified this sentence on page 6, lines 1-3 in the revised manuscript; the underlined part is the added content: “Lenvatinib was used not only during radiotherapy, but also continuously for 2 months after radiotherapy”.