

Peer Review File

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Reviewer A

Comment 1: In the first case, the authors have stated that the PVTT inside the right anterior PV and right PV. The author needs to present MRI pictures more accurately pre- and post-treatment, especially the right anterior PV and right PV.

Reply 1: The MR images clearly demonstrated tumor invasion with occlusion of the right PV. After proton beam therapy, MRI showed patent right PV and the explant histopathology confirmed no residual tumor thrombus inside the portal vein. We also removed “right anterior PV and” in the text.

Changes in the text: a 6.2 cm HCC in segment 8 which was contiguous with the right hepatic vein (RHV) and middle hepatic vein (MHV) with PVTT inside [the right PV](#) (Figure 1A). (Page 4, Line 84)

Comments 2&3: In the second case, the authors have stated that the PVTT inside right anterior PV and left PV. The author needs to present MRI pictures more accurately pre- and post-treatment , especially right anterior PV and left PV. In Figure 5B, the authors should present MRI picture of portal phase rather than T2 phase.

Reply 2&3: The previous T2W1 image in figure 5C was replaced by MRI with portal phase image. It can be clearly seen in this image that the right anterior PV and left PV are occluded by the tumor thrombus. After combination of proton, targeted and immunotherapy, the portal vein is patent without filling defect (Figure 5I)

Comment 4: The authors have stated “HCC in segments 7 and 8” in Line 89 and Figure 5, this is ambiguous the authors stated that “A roux-en-Y hepatico-jejunostomy biliary reconstruction was performed due to the proximity of the main tumor to the hepatic hilum” in Line 102-103.

Reply 4: Thank you for the insightful comment. To make it clearer, we changed the “main tumor” to “extensive PVTT in the right anterior PV and left PV”.

Changes in the text: “A roux-en-Y hepatico-jejunostomy biliary reconstruction was performed due to the proximity of the [extensive PVTT in the right anterior PV and left PV](#) to the hepatic hilum” (Page 5, Line 128)

Reviewer B

Comment 1: the submitted paper by Chen et al can be published as such in your journal. The Chen paper is very well written, very well documented and addresses novel developments in the field of oncologic transplantation. I would only propose that the authors omit as much as possible the wording "we..." This can be replaced many times without problems.

Reply 1: Thank you for the reviewer's kind words and insightful comment. The authors have rephrased the sentences with "we" and "our".

Changes in the text:

- The details of the planning, preparation, and the proton irradiation procedure have been described in [a](#) previous report on PBT for locally advanced HCC. (Page 3, Line 61)
- To the best of [the authors'](#) knowledge, this is the first report on PBT combined with targeted and/or immunotherapy for downstaging lobar and extensive PVTT to living donor liver transplantation (LDLT) with satisfactory outcomes. (Page 3, Line 69)
- [The authors](#) have previously published [their](#) findings regarding high FDG-PET avidity as a predictor of inferior outcomes after transplant. Based on this, it has become mandatory at [their](#) center to acquire a tissue diagnosis for patients with high FDG-PET avidity or atypical tumors on imaging to exclude unfavorable histopathology. (Page 7, Line 180)
- For more than two decades, [the authors'](#) center has been downstaging HCC with locoregional therapies to fit criteria as mandated by the Taiwan citizens' health insurance policy—Milan Criteria from 1999 to 2006 and University of California San Francisco (UCSF) criteria from 2006 up to the present. (Page 8, Line 196)
- But apart from compliance with the insurance mandate, [they](#) have increasingly employed downstaging for patients beyond criteria because [their](#) initial experience with downstaging have demonstrated an excellent 5-year survival rate of 90%. (Page 8, Line 200 and 201)

- Furthermore, **the authors** have also reported the positive impact of complete pathologic response after downstaging on patient outcomes—1.2% vs 12.6% recurrence rate for those with complete vs incomplete response. (Page 8, Line 203)
- With this in mind, **their** multidisciplinary treatment protocol for locally advanced HCC (Page, Line 206)
- Two other patients with locally advanced HCC (non-PVTT) treated with PBT prior to LDLT have been previously reported. (Page 9, Line 231)
- The promising outcomes achieved for the aforementioned cases have led **the authors** to further expand the role of PBT for locally advanced HCC in these 2 patients with lobar PVTT presented in this report. (Page 9, Line 238)
- There were no PBT-related complications observed in **the** patients presented here. (Page 11, Line 275)
- **These** cases have demonstrated that PBT in combination with targeted and/or immunotherapy appears to be a powerful neoadjuvant downstaging strategy for HCC with lobar PVTT. (Page 11, Line 279)
- **This** experience has shown that favorable outcomes are achievable even in lobar PVTT which has been shown to have dismal outcomes despite significant downstaging. (Page 11, Line 281)

Comment 2: I would also suggest that the authors add in the reference list the paper written by Lerut J et al. because addressing very well addressing the ongoing extension of inclusion criteria of HCC pats for LT in one single paper: Hepatocellular cancer selection systems and liver transplantation: from the tower of Babel to an ideal comprehensive score
J.LERUT,M.FOGUENNE, Q.LAI. Updates in Surgery , 2021 ;73;1599-1614

Reply 2: We have incorporated the reference as suggested.