Editorial Commentary

Proton beam therapy for downstaging hepatocellular carcinoma with lobar portal vein tumor thrombosis to living donor liver transplantation

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Introduction

Liver transplantation (LT) is considered as the definitive standard treatment for hepatocellular carcinoma (HCC) with the advantage of addressing both malignancy and the underlying cirrhosis, thus, providing the best overall and recurrence-free survival. Unfortunately, only 20–25% of patients meet the eligibility criteria for LT. Hence, there have been constant efforts from transplant communities to expand the conventional acceptance criteria to expand the pool of patients that can potentially have an acceptable survival benefit from LT (1-5).

Portal vein tumor thrombosis (PVTT), occurring in 10–40% of patients with HCC, has been considered as an absolute contraindication to LT due to exceedingly high recurrence rates (3,6-8). These patients have extremely limited therapeutic options with a median survival time ranging from 2–4 months if without treatment (3,6,7,9). The most recent Barcelona Clinic Liver Cancer (BCLC) strategy [2022] recommends the combination of atezolizumab with bevacizumab as the first-line treatment since this has shown improved outcomes compared to sorafenib—median progression-free survival of 6.8 *vs.* 4.3 months (10,11). With the rapidly evolving treatment landscape, current data have demonstrated that acceptable outcomes can be achieved more specifically among patients with segmental PVTT (second-order PV branch), with a 5-year overall survival rate of 50.3% but this is reduced to a dismal 14.3% for lobar PVTT (first-order PV branch). Due to persistently inferior outcomes, lobar PVTT is still recommended as a contraindication to LT (2,9,12).

Recent reports have shown the expanding role of radiation therapy (RT) in the management of locally advanced HCC particularly in patients who are deemed unsuitable for other treatment modalities—making the previously untransplantable patients, transplantable with survival rates closely approximating their within criteria counterparts (1,13). Among the available RT modalities, proton beam therapy (PBT) offers a dosimetric superiority and a lower toxicity profile, hence, its increasing applicability in locally advanced HCC is being explored (1,5,14). The details of the planning, preparation, and the proton irradiation procedure have been described in a previous report on PBT for locally advanced HCC (1).

Ultimately, the choice of therapeutic strategy should be individualized as demonstrated in the cases presented here. By using a combination of potentially more powerful

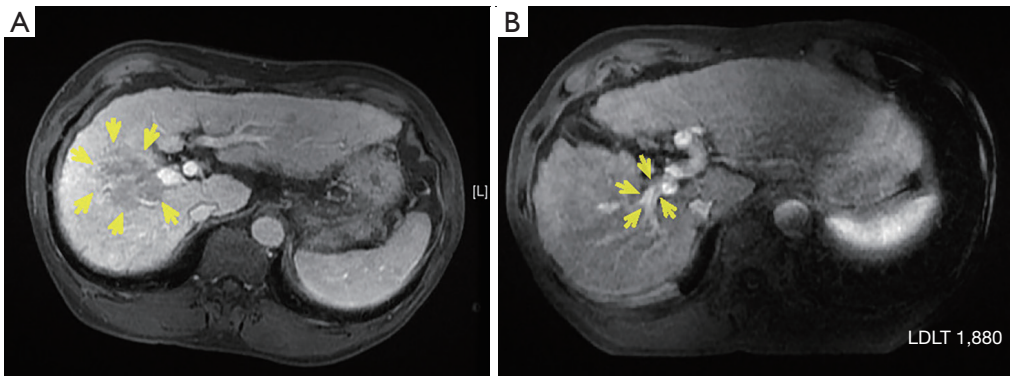

Figure 1 MRI pre- and post-PBT of case 1. (A) MRI with enhancement (case 1) showing 6.2 cm HCC in S8 with right PV invasion and PVTT (arrows). (B) MRI status post-PBT showing no tumor enhancement with recanalization of PV without residual PVTT (arrows). MRI, magnetic resonance imaging; PBT, proton beam therapy; HCC, hepatocellular carcinoma; PV, portal vein; PVTT, portal vein tumor thrombosis.

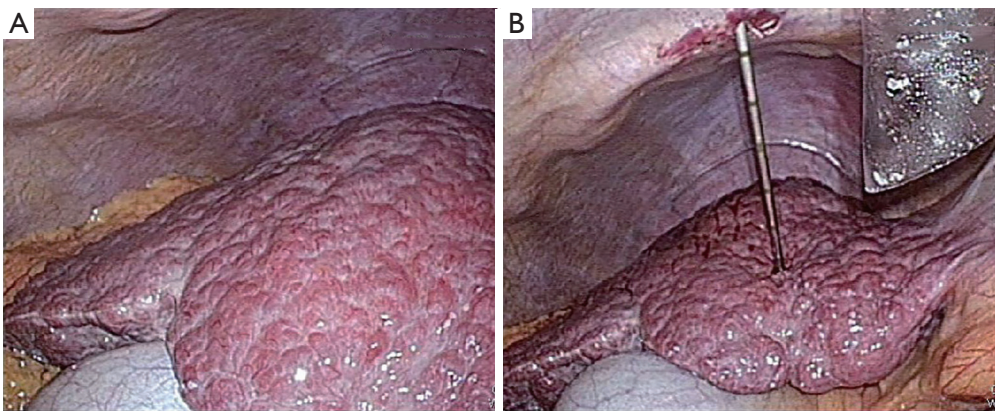

Figure 2 Laparoscopic exploration of case 1. (A) Intraoperative findings showed moderately advanced liver cirrhosis precluding a right lobectomy with PV tumor thrombectomy; (B) needle biopsy confirmed the diagnosis of HCC. PV, portal vein; HCC, hepatocellular carcinoma.

locoregional and systemic therapies, namely PBT, targeted and immunotherapy, favorable outcomes are now achievable for these patients who had otherwise a dismal prognosis. 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 LT (LDLT) with satisfactory outcomes.

Case presentation

Case 1 (Figures 1-4)

The first case was a 60-year-old male with an Eastern Cooperative Oncology Group (ECOG) score of 0 who had a history of hepatitis B virus (HBV) infection which resolved without antiviral treatment. On initial work-up, the patient presented with a model for end-stage liver disease (MELD) of 8, Child-Turcotte-Pugh (CTP) 5, hepatitis B surface antigen (HBsAg) (–), hepatitis B core antibody (HBcAb) (+), hepatitis B surface antibody (HBsAb) 827 IU/L, HBV DNA (–), alpha-fetoprotein (AFP) 3.9 ng/mL. Magnetic resonance imaging (MRI) with enhancement revealed 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 portal vein (PV) (*Figure 1A*). Laparoscopic exploration revealed moderately advanced liver cirrhosis precluding a right lobectomy with PV tumor thrombectomy. Ultrasound-guided needle biopsy confirmed the diagnosis of HCC (*Figure 2*).

PBT was delivered to the HCC and PVTT at a dose

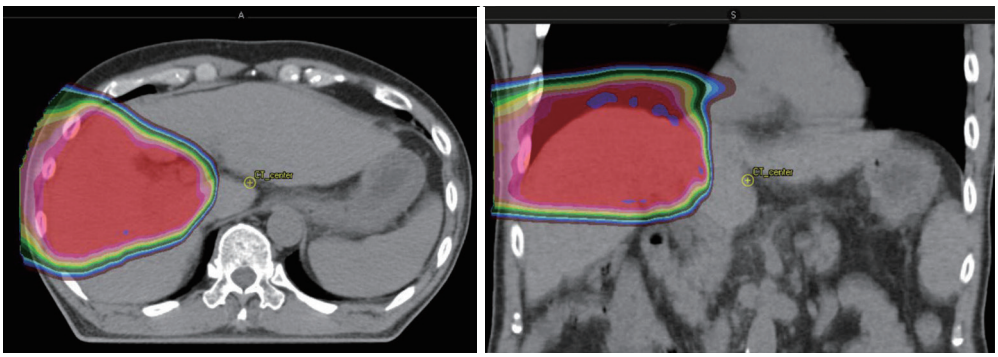

Figure 3 PBT of case 1. PBT was delivered to the HCC and PVTT at a dose of 72.6 Gy (RBE) in 22 fractions as shown by the color-washed areas. PBT, proton beam therapy; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; RBE, relative biological effectiveness.

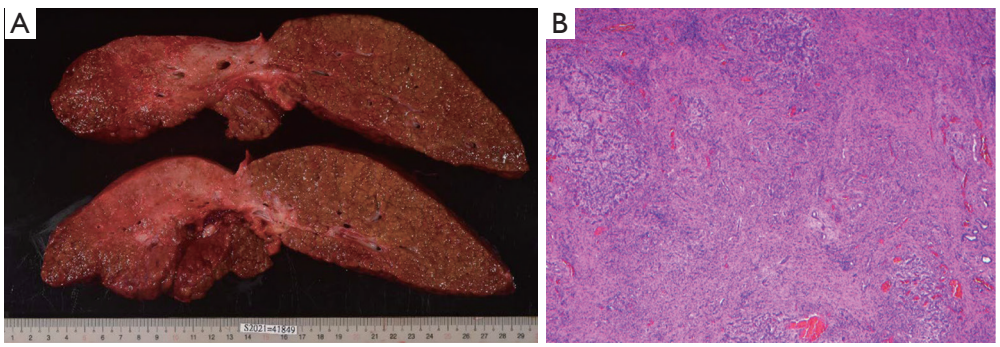

Figure 4 Explant pathology of case 1. (A) Gross pathology showing an 8.5 cm poorly demarcated nodular fibrosis with patent PV. (B) Histopathology showing marked fibrosis with myxoid degeneration, fibroblast and vascular proliferation without residual PVTT or viable HCC (H&E stain, ×40 magnification). PV, portal vein; PVTT, portal vein tumor thrombosis; HCC, hepatocellular carcinoma; H&E, hematoxylin and eosin.

of 72.6 Gy [relative biological effectiveness (RBE)] in 22 fractions (*Figure 3*) and was given concurrently with lenvatinib, a tyrosine kinase inhibitor (TKI). Follow-up computed tomography (CT) at 8 months after PBT showed complete regression of the HCC without enhancement and with no residual PVTT (*Figure 1B*). Moreover, positron emission tomography (PET)-CT scan revealed no fluorodeoxyglucose (FDG) uptake. Therefore, the patient subsequently underwent LDLT with a right liver graft from his donor son. The final histopathology revealed an 8.5 cm poorly demarcated nodular fibrosis without residual PVTT or viable HCC (*Figure 4*).

Post-transplant, the patient was maintained on dual-drug immunosuppression that included a calcineurin inhibitor (CNI) and a mammalian target of rapamycin (mTOR) inhibitor, concurrently taken with lenvatinib. The patient has since been well without recurrent disease 24 months after LDLT.

Case 2 (Figures 5-8)

The second case was a 61-year-old male with an ECOG score of 1 who had a history of hepatitis C virus (HCV) without prior anti-viral treatment. On initial work-up, the patient presented with a MELD of 13, CTP 8, AFP 479 ng/mL, carcinoembryonic antigen (CEA) 2.17 ng/mL, and carbohydrate antigen 19-9 (CA19-9) <2 U/mL. CT with enhancement triphasic scan and MRI with enhancement revealed a 12 cm HCC in segments 7 and 8 that was contiguous with the RHV and MHV. There was extensive PVTT in the right anterior PV and left PV and another 1.5 cm satellite nodule in segment 4 (*Figure 5A-5C*).

Lenvatinib was initiated followed by PBT that was delivered to the HCC and PVTT at a dose of 66 Gy (RBE) in 20 fractions. The main tumor decreased to 7.9 cm with remarkable regression of the PVTT (*Figure 5D-5F*).

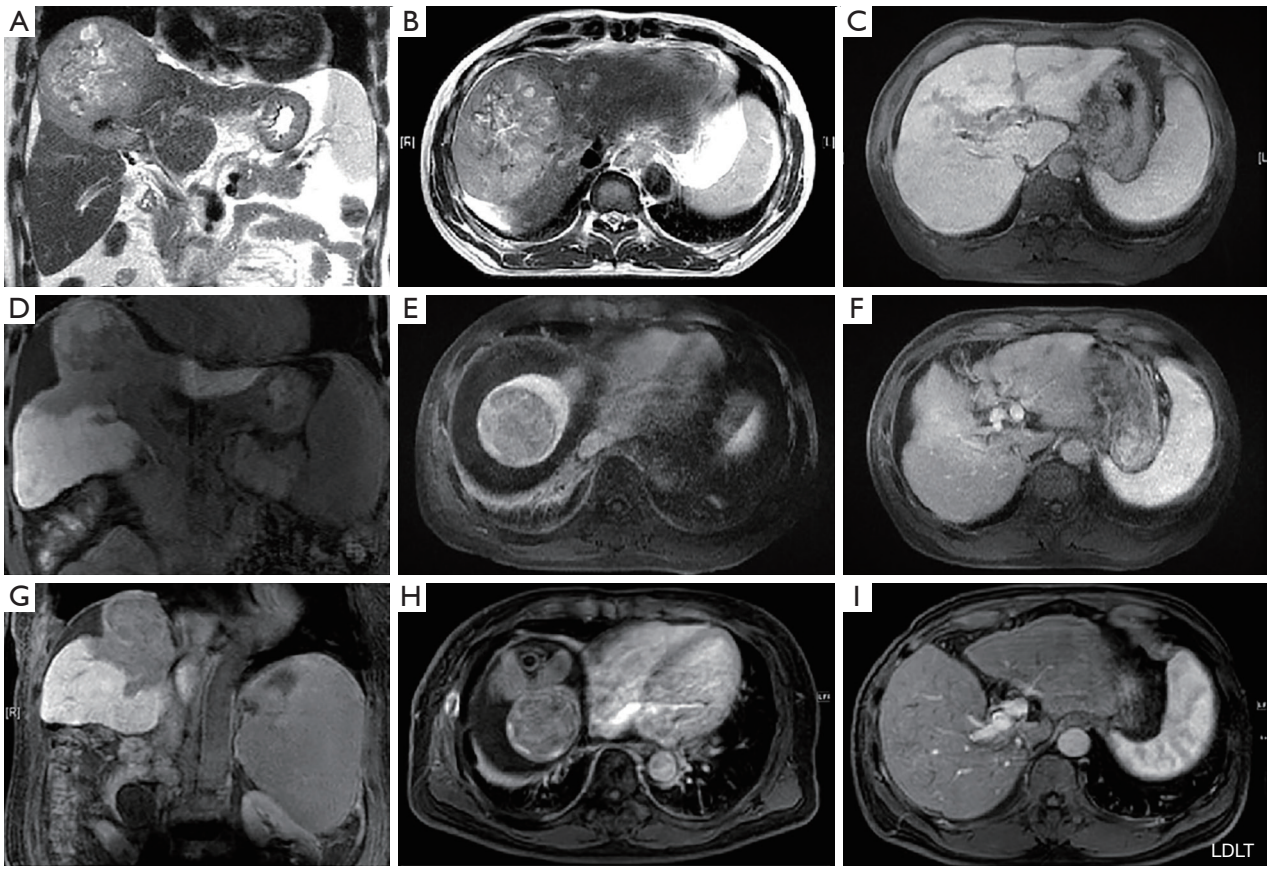

Figure 5 MRI pre- and post-therapy of case 2. (A,B) MRI with enhancement coronal and axial views revealing a 12 cm HCC in segments 7 and 8 contiguous with the RHV and MHV and another 1.5 cm satellite nodule in segment 4. (C) There was extensive PVTT in right anterior PV and left PV. (D-F) Status post lenvatinib and PBT, the main HCC decreased to 7.9 cm with regression of PVTT. (G-I) Status post immunotherapy, the main HCC decreased to 6 cm without enhancement, with further regression of PVTT. LDLT, living donor liver transplantation; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; RHV, right hepatic vein; MHV, middle hepatic vein; PVTT, portal vein tumor thrombosis; PV, portal vein; PBT, proton beam therapy.

Additional immunotherapy with atezolizumab (1,200 mg) and bevacizumab (100 mg) was given for 9 cycles. The main tumor decreased to 6 cm without enhancement and further regression of PVTT was noted (*Figure 5G-5I*). Over a surveillance period of 3 months, there was no recurrence on primovist MRI, no FDG uptake on PET scan, and AFP 7.6 g/mL. Therefore, the patient subsequently underwent LDLT with a right liver graft from his donor son.

A Roux-en-Y hepaticojejunostomy biliary reconstruction was performed due to the proximity of the extensive PVTT in the right anterior PV and left PV to the hepatic hilum. The final histopathology of the explanted liver revealed a 5.9 cm tumor with 100% necrosis and total regression of the PVTT (*Figure 6A-6D*). Post-transplant, the patient was maintained on dual-drug immunosuppression that included a CNI and a mTOR inhibitor, concurrently taken with lenvatinib. The patient experienced an episode of mild acute cellular rejection 16 weeks after LDLT which was reversed readily by increased immunosuppression.

Subsequently, he complained of epigastric pain for which an MRI was done, revealing a 3 cm pancreatic head tumor with proximal PV narrowing and pancreatic duct dilatation (*Figure 7A,7B*). PET scan disclosed an increased FDG uptake with maximum standard unit value (SUVmax) of 5.1 and tumor to non-tumor liver uptake ratio (TNR) of 2.1. His tumor markers remained normal (CEA 1.09 ng/L, CA19-9 2.76 U/mL, AFP <2 ng/mL). Endoscopic ultrasound (EUS)-guided fine needle biopsy confirmed adenocarcinoma.

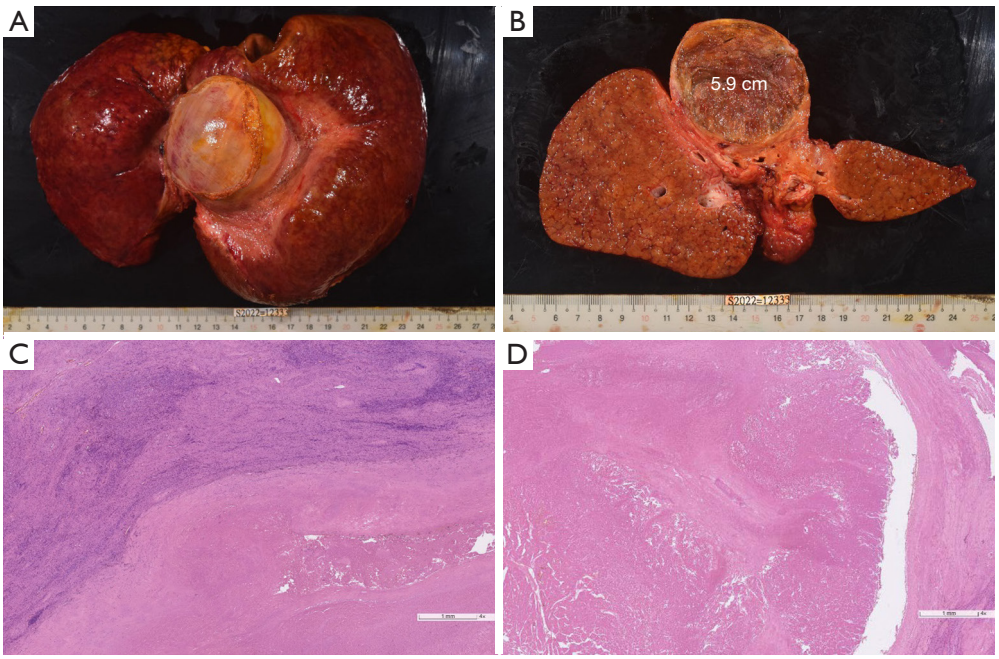

Figure 6 Explant pathology of case 2. Gross liver explant showing a 5.9 cm well demarcated tumor with extensive fibrosis (A,B), histopathology showing 100% tumor necrosis without PVTT (C,D) (H&E stain, ×40 magnification). PVTT, portal vein tumor thrombosis; H&E, hematoxylin and eosin.

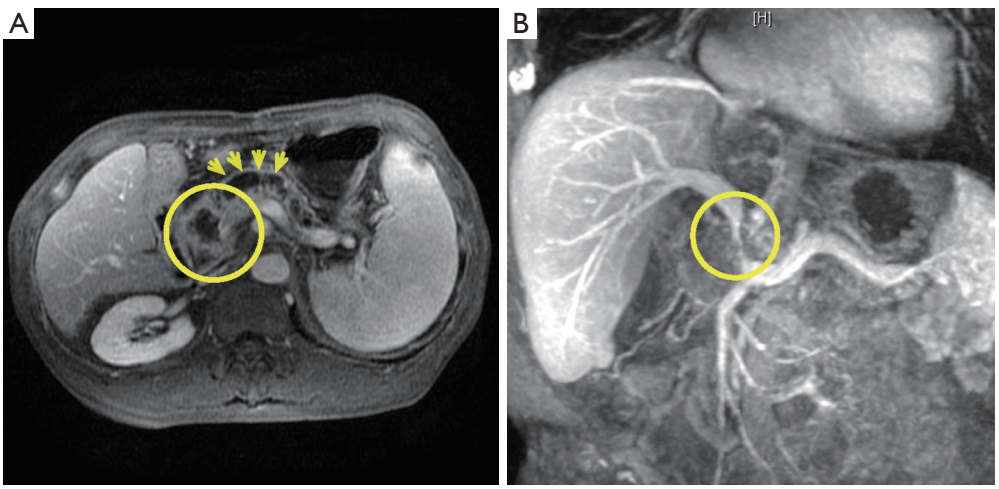

Figure 7 MRI of case 2 at 7 months after LDLT. (A) MRI axial view showing 3 cm tumor in pancreatic head (circle) with pancreatic duct dilatation (arrows); (B) coronal view showing proximal PV narrowing (circle). MRI, magnetic resonance imaging; LDLT, living donor liver transplantation; PV, portal vein.

Under the diagnosis of borderline resectable pancreatic head adenocarcinoma, neoadjuvant chemotherapy with gemcitabine (1,400 mg) and abraxane (150 mg) was given for 6 cycles. Repeat PET scan showed decreased FDG uptake to SUVmax 2.5 and TNR 1.7. Whipple's pylorus-preserving pancreaticoduodenectomy was performed 7 months after LDLT. The PV segment encroached by the tumor was resected and reconstructed with GoreTex®

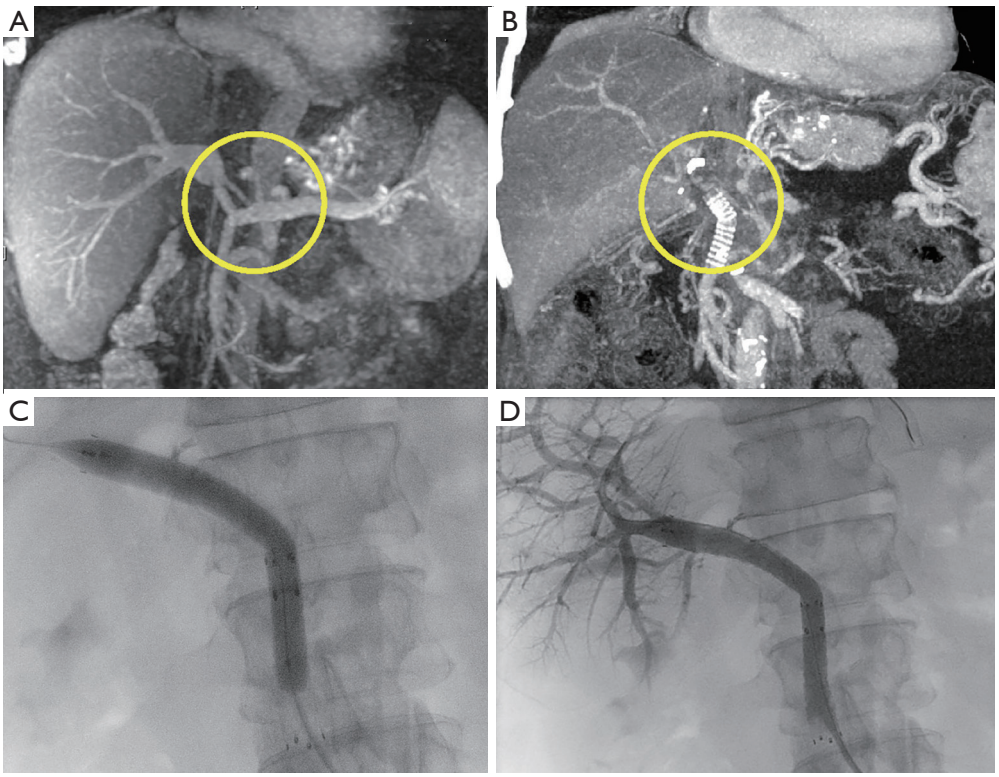

Figure 8 Post-total pancreatectomy imaging studies of case 2. MRI showing PV reconstructed with GoreTex® ePTFE ringed vascular graft and the splenic vein implanted end-to-side to the reconstructed vascular graft (circle) (A). Pharmacomechanical thrombectomy with urokinase infusion and Angiojet™ via jejunal vein catheter (circle) (B), angioplasty with a 10 mm Mustang® balloon at 14 atm (C) and deployment of two self-expandable metal E-Luminexx® stents (D). MRI, magnetic resonance imaging; PV, portal vein; ePTFE, expanded polytetrafluoroethylene.

expanded polytetrafluoroethylene (ePTFE) ringed vascular graft. However, frozen section of the resected margin of the pancreatic body disclosed adenocarcinoma, therefore, a total pancreatectomy with preservation of the spleen was performed, and the splenic vein was implanted in an end-to-side fashion to the reconstructed synthetic vascular graft (*Figure 8A*). Adjuvant oral chemotherapy with tegafur/gimeracil/oteracil (TS-1®) was given after total pancreatectomy.

Despite suffering from insulin-dependent diabetic mellitus, his post-operative recovery was otherwise uneventful until 15 months after LDLT, when he presented with hypoalbuminemia, ascites, and *Escherichia coli* (*E. coli*) bacteremia. After stabilization, CT angiography showed occlusion of the PV and the vascular graft (*Figure 8B*). Pharmacomechanical thrombectomy of the PV was conducted using the Angiojet™ system, along with urokinase infusion (600,000 IU) through catheterization of the jejunal vein. Subsequently, the remaining PV stenosis was managed by performing angioplasty with a 10 mm Mustang® balloon at 14 atm (*Figure 8C*) followed by deploying two self-expandable bare metal stents: E-Luminexx® 10 mm × 60 mm and 10 mm × 40 mm (*Figure 8D*).

At 18 months after LDLT, his tumor markers remain within normal limits and latest CT scan, MRI, and PET scan have shown no evidence of recurrence despite the incidental finding of a small solitary mesenteric nodule during the pharmacomechanical thrombectomy procedure which revealed adenocarcinoma on histopathology.

Discussion

The management for locally advanced or histopathologically unfavorable HCC is continuously evolving and there has been greater emphasis on incorporating additional preoperative parameters to predict post-transplant tumor

recurrence and survival more accurately. 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 (15,16). Over the last 3 years, with the availability of more powerful downstaging treatment modalities such as the PBT and the newer targeted and immunotherapies, some of these patients have shown acceptable outcomes after LDLT. Furthermore, studies have consistently demonstrated that the response to downstaging is an effective prognostic tool among patients who are initially beyond criteria (1,17).

Bridging or downstaging patients to convert eligibility for curative resection whether in the form of liver resection or transplant has been associated with improved outcomes compared to upfront surgery (13,17-19). 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. 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% (20). 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 (21). With this in mind, their multidisciplinary treatment protocol for locally advanced HCC employs aggressive downstaging strategies aimed at achieving maximal pathologic response, with a minimum surveillance period of 3 months to ensure disease stability prior to LDLT to provide optimal recurrence-free survival rates for these patients.

Given the widening array of available locoregional and systemic therapeutic options for PVTT in HCC, a multidisciplinary approach is of utmost importance in determining the ideal multimodal treatment sequence for every patient (13,18). Recently, several authors have separately reported single-center retrospective studies on the survival benefits of LT in HCC patients with PVTT (2,7,9,12). These studies have employed the more commonly used locoregional therapies for downstaging such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) transarterial chemoembolization (TACE), transarterial radioembolization (TARE), conformal radiotherapy (CRT), hepatic arterial infusion chemotherapy (HAIC), concurrent chemoradiation, and stereotactic body radiotherapy (SBRT). They have reported fairly acceptable outcomes except for those with lobar PVTT in the study by Choi *et al.*: the 5-year overall survival rate was 14.3% (2). Lv *et al.* and Choi *et al.* had similar findings regarding the impact of the extent of PVTT on outcomes after LDLT and have recommended that LT should still be contraindicated for patients with lobar PVTT due to dismal outcomes (2,3).

Two other patients with locally advanced HCC (non-PVTT) treated with PBT prior to LDLT have been previously reported. One had poorly differentiated HCC with bile duct invasion while the other presented with a total tumor diameter of >12 cm (six HCC) in decompensated cirrhosis precluding other locoregional modalities (1). Both patients have remained recurrence-free for 42 and 34 months after LDLT and have returned to their premorbid work routines. 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 two patients with lobar PVTT presented in this report. They had remarkably good response as seen on post-downstaging follow-up imaging and as evidenced by complete pathologic response for both the tumor and PVTT on final liver explant histopathology. They have remained recurrence-free for 24 and 18 months after LDLT, although one of them had a more complex and challenging course due to the subsequent development of pancreatic adenocarcinoma. Further follow up is needed to evaluate the long-term outcomes for these patients with lobar PVTT.

RT is an emerging treatment modality for HCC with recent studies suggesting higher efficacy compared to other treatment modalities for unresectable HCC. It acts through direct and indirect mechanisms causing DNA damage, vascular injury, and eventually resulting in apoptosis. Similarly, it induces cell death through immunostimulatory effects and activation of antitumor cascade leading to an enhanced immune infiltration of the tumor microenvironment (5). Given this mechanism of action, radiotherapy displays a synergistic effect with immunotherapy. The addition of immunotherapy to RT could help overcome RT-induced immunosuppressive effects as well as enhance the RT-induced abscopal effect (22).

For the past two decades, technological advancements in RT for HCC had been directed towards dose escalation while minimizing radiation to organs at risk.

This fundamental aim in RT has been achieved with the introduction of PBT. The dosimetric superiority of PBT due to its ability to safely deliver a higher biologic effective dose (BED), compared to other RT modalities potentially translates to improved outcomes. This feature is particularly advantageous in certain clinical scenarios such as in the setting of larger tumors, relatively poor liver function, small liver normal reserve for those previously treated with other locoregional therapies and multifocal HCC requiring sequential treatment. Additionally, observational studies have demonstrated a lower toxicity profile of PBT which could be attributed to the ability of protons to deposit a specific dose at a precise depth without an exit dose and with minimal scatter to adjacent organs (Bragg-Peak) (5,14).

There were no PBT-related complications observed in the patients presented here. The vascular graft occlusion in the second case is more likely related to the surgical management of PV resection and reconstruction for the pancreatic cancer.

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. This experience has shown that favorable outcomes are achievable even in lobar PVTT which has been shown to have dismal outcomes despite significant downstaging.

Conclusions

The evolving treatment strategies for locally advanced HCC have broadened the eligibility criteria for LDLT. The increasing availability and utilization of newer and more potent combination of locoregional and systemic therapies for downstaging could revolutionize the current treatment consensus and optimize survival outcomes after LDLT for patients with otherwise dismal prognosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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