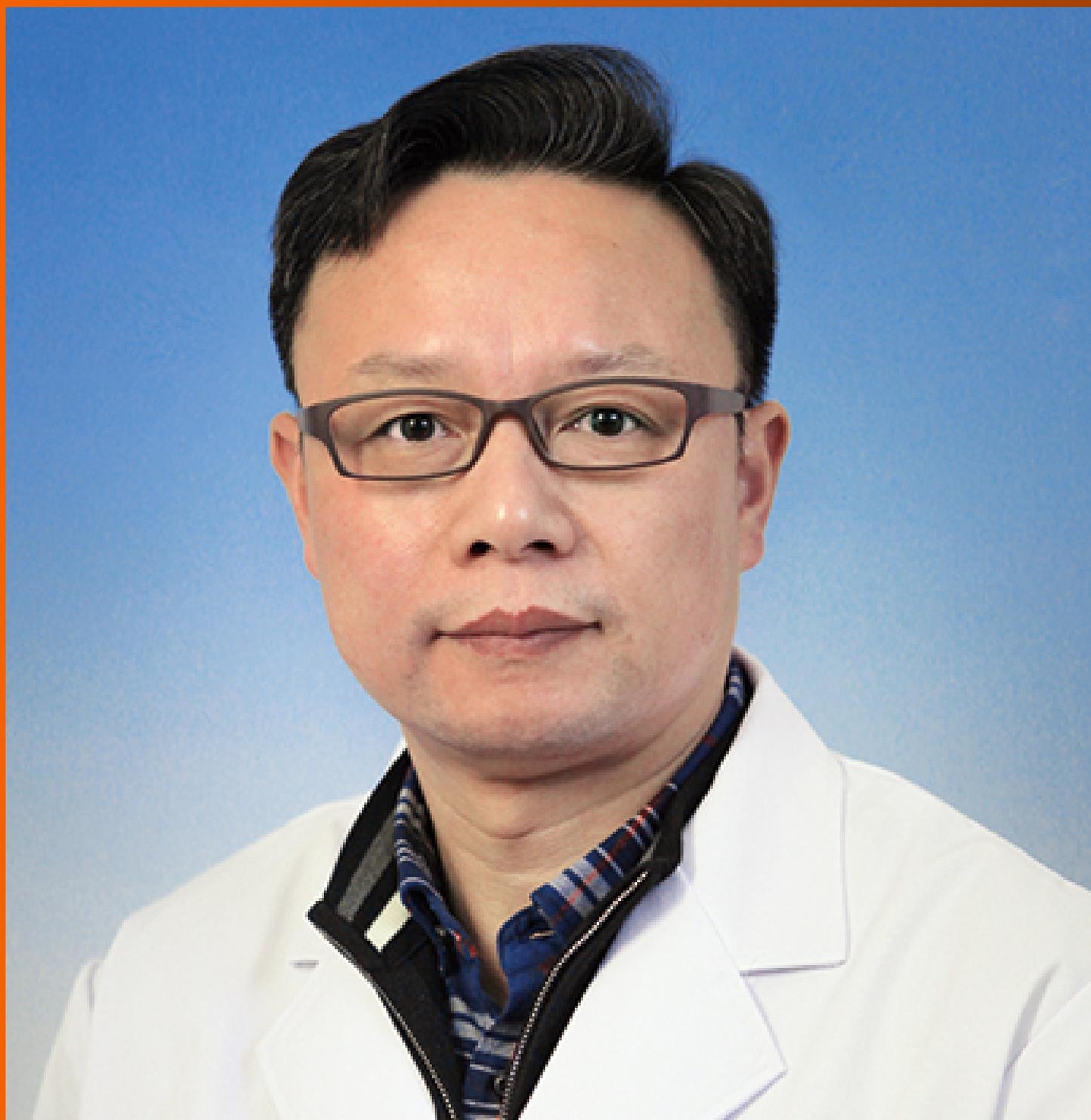


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Conversion hepatectomy for hepatocellular carcinoma with main portal vein tumour thrombus after lenvatinib treatment: A case report

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) accompanied by portal vein tumour thrombus (PVTT) presents an aggressive disease course, worsening liver function reserve, and a high recurrence rate. Clinical practice guidelines recommend systemic therapy as the first-line option for HCC with portal invasion. However, to achieve longer survival in these patients, the treatment strategy should be concluded with removal of the tumour by locoregional therapy. We experienced a case of initially unresectable HCC with main PVTT converted to radical hepatectomy after lenvatinib treatment.

CASE SUMMARY

A 59-year-old male with chronic hepatitis C infection visited our clinic as a regular post-surgery follow-up. Contrast-enhanced abdominal computed tomography revealed a liver mass diffusely located at the lateral segment with a massive PVTT extending from the umbilical portion to the main and contralateral third-order portal branches. With the diagnosis of unresectable HCC with Vp4 (main trunk/contralateral branch) PVTT, lenvatinib was started at 12 mg/d. The computed tomography taken 3 mo after starting lenvatinib showed regression of the PVTT, which had retreated to the contralateral first-order portal branch. He tolerated the full dose without major adverse effects. With cessation of lenvatinib

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for 7 d, radical left lobectomy and PVTT thrombectomy were conducted. The patient's postoperative course was uneventful. Microscopically, the primary lesion showed fibrotic changes, with moderately to poorly differentiated tumour cells surrounded by granulation tissues in some areas. The majority of the PVTT showed necrosis. He was alive without recurrence for 8 mo.

CONCLUSION

This is the first case of HCC with Vp4 PVTT in which radical conversion hepatectomy was succeeded after lenvatinib treatment.

Key Words: Hepatocellular carcinoma; Lenvatinib; Portal vein tumour thrombus; Conversion hepatectomy; Case report

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Core Tip: Patients with hepatocellular carcinoma (HCC) with portal vein tumour thrombus demonstrate an aggressive disease course, decreased liver function reserve, and higher recurrence rates after treatment. Clinical practice guidelines recommend systemic therapy as the first-line option for HCC with portal invasion. However, to achieve longer survival in these patients, the treatment strategy should be concluded with removal of the tumour. We report the first case of HCC with main portal vein tumour thrombus, in which radical conversion hepatectomy was successfully performed after lenvatinib treatment. Lenvatinib has several strengths that validate its use for targeting conversion hepatectomy for unresectable HCC.

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INTRODUCTION

Portal vein tumour thrombus (PVTT) is a condition of hepatocellular carcinoma (HCC) that leads to the wide dissemination of tumours throughout the liver and causes a deterioration of liver function, leading to poor prognosis. PVTT is classified as Vp1 (segmentary), Vp2 (secondary order branch), Vp3 (first order branch), and Vp4 (main trunk/contralateral branch)^[1], and clinical practice guidelines recommend systemic therapy as the first-line option for HCC with portal invasion^[2,3]. Current systemic therapy for HCC consists of receptor tyrosine kinase inhibitors (TKIs) and checkpoint inhibitors^[4]. As a newly introduced TKI, lenvatinib is a multitargeted TKI that inhibits vascular endothelial growth factor receptor 1-3, platelet-derived growth factor receptor-alpha, rearranged during transfection, and stem cell factor receptor. Lenvatinib is characterized by high tumour regression and tumour necrosis effects^[4,5]. However, post progression survival is recognized as being short^[6], and the post hoc exploratory analysis disclosed severe morbidities related to lenvatinib treatment in patients with HCC with Vp4 PVTT (data not shown). To achieve longer survival in patients with advanced HCC, the treatment strategy should be concluded with removal of the tumour by locoregional therapy (LRT) because of the limitation of systemic therapy alone^[7-9]. Here, we present a case of initially unresectable HCC with Vp4 PVTT converted to radical hepatectomy after lenvatinib treatment.

CASE PRESENTATION

Chief complaints

A 59-year-old male presented to our clinic as a regular post-surgery follow-up for

HCC.

History of present illness

The patient received segmentectomy 5 and cholecystectomy for a single HCC 2 years prior.

History of past illness

He had hepatitis C virus infection with genotypes 1a which was treated with 24 wk of ledipasvir/sofosbuvir 5 years prior, and sustained virologic response rate was achieved. He received the radiofrequency ablation a year before the first hepatectomy.

Personal and family history

The patient had a history of alcohol use with 200 mL daily intake for 35 years. Since HCC was diagnosed, the patient had quitted alcohol drinking. He had no family history of cancer.

Physical examination

The patient's temperature was 36.5 °C, heart rate was 74 bpm, respiratory rate was 14 breath/min, blood pressure was 128/81 mmHg and oxygen saturation in room air was 98%. There was an operative scar for a J-shaped incision on the abdomen from the previous liver resection. No ascites and encephalopathy were detected.

Laboratory examinations

Laboratory exams were normal except for a slight increase in aspartate aminotransferase levels of 52 U/L and protein induced by des-γ-carboxy prothrombin of 107 mAU/mL. Electrocardiogram, chest X-ray and arterial blood gas were also normal.

Imaging examinations

Contrast-enhanced (CE) abdominal computed tomography (CT) revealed a liver mass diffusely located at the lateral segment with a massive PVTT extending from the umbilical portion to the main portal and the contralateral third portal branches (Vp4) (Figure 1A and B).

MULTIDISCIPLINARY EXPERT CONSULTATION

Amane Takahashi, MD, PhD, Chief Surgeon, Department of Gastroenterological Surgery, Saitama Cancer Center

As a treatment strategy, we should administer lenvatinib at a dose of 12 mg, following the clinical guidelines. The reason for choosing lenvatinib, not sorafenib was that lenvatinib demonstrated higher response rate compared with sorafenib in an open-label, phase III, multicentre, non-inferiority trial involving patients with advanced HCC (the REFLECT trial). If the PVTT exhibited shrinkage to the contralateral first portal branch, we would be able to remove the tumour surgically. We should be careful to follow the liver function during lenvatinib treatment, since the post hoc exploratory analysis revealed severe morbidities including liver failure in cases with Vp4 PVTT.

FINAL DIAGNOSIS

With the diagnosis of unresectable HCC with Vp4 PVTT, lenvatinib was started at 12 mg/d. CT taken two weeks after starting lenvatinib showed regression of PVTT (by 11%) with partial disappearance of contrast enhancement, retreating to the contralateral second-order PV (Figure 2A). At 3 mo, the PVTT regressed further to the contralateral first-order branch with more loss of contrast enhancement (by 58%), meeting the definition of partial response according to the modified Response Evaluation Criteria in Solid Tumours criteria (Figure 2B and C). During lenvatinib treatment, liver function was maintained within Child-Pugh A (5 points), and the albumin-bilirubin (ALBI) score was -3.45 to -2.93 (Grade 1). He tolerated the full dose without treatment-related adverse effects (TRAEs).

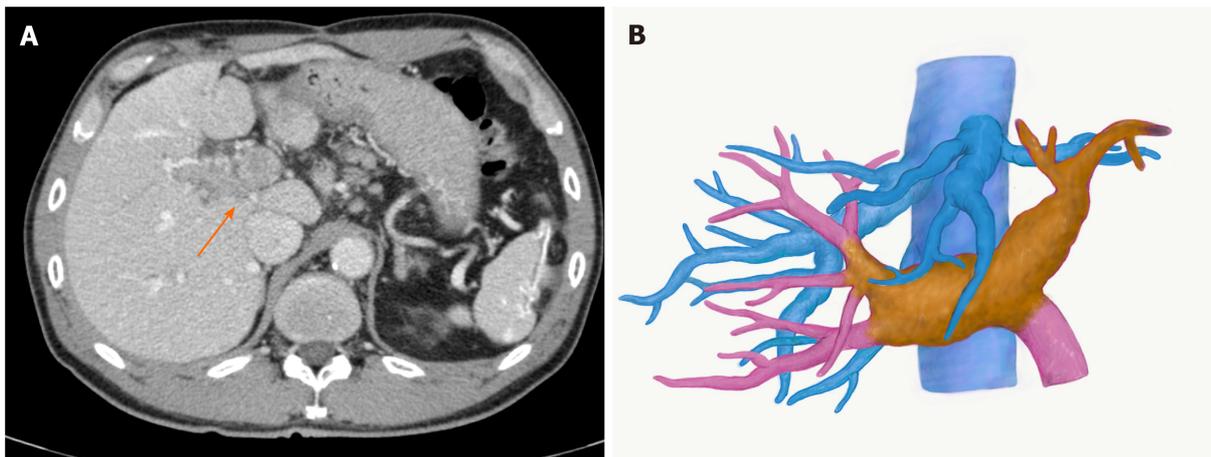


Figure 1 Images of hepatocellular carcinoma with portal vein tumour thrombus before lenvatinib treatment. A: Computed tomography image. An arrow indicates portal vein tumour thrombus; B: Three-dimensional image. The yellow mass demonstrates a viable portal vein tumour thrombus, extending to the contralateral third portal branch.

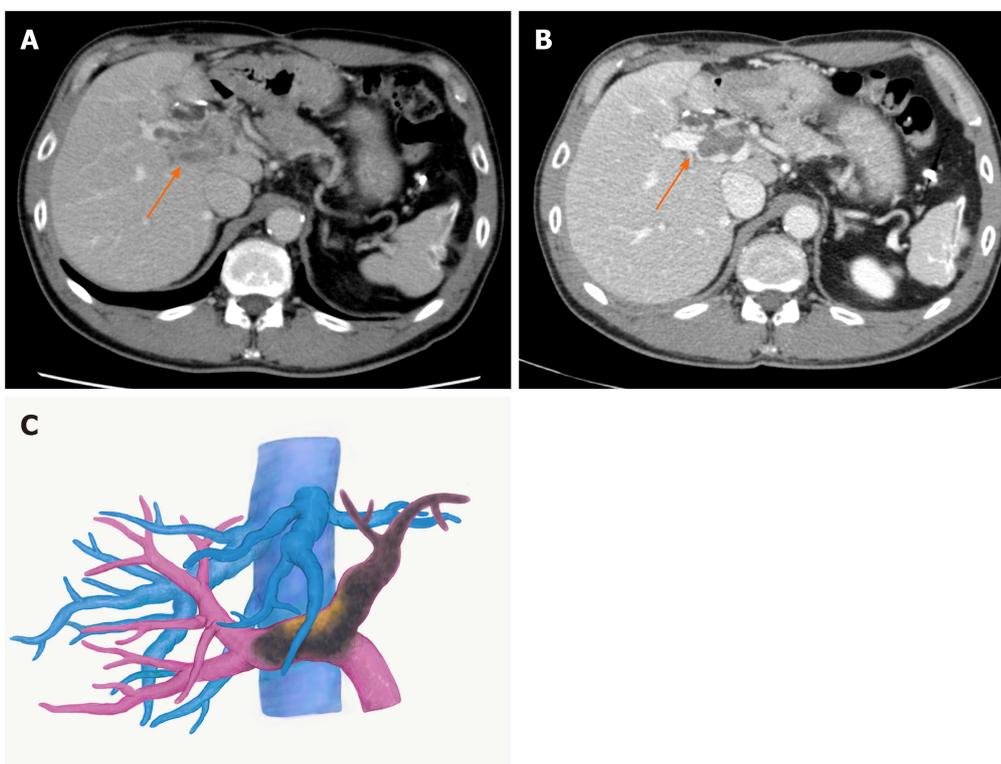


Figure 2 Images of hepatocellular carcinoma with portal vein tumour thrombus after lenvatinib treatment. A: Computed tomography image two weeks after the treatment. The portal vein tumour thrombus (PVT) showed regression with partial disappearance of contrast enhancement; B: Computed tomography image three months after the treatment; C: Three-dimensional image three months after the treatment. The PVT regressed to the contralateral first-order branch with loss of contrast enhancement. Arrows indicate PVT.

TREATMENT

After cessation of lenvatinib for 7 d, left lobectomy with PVT thrombectomy was performed. Intraoperatively, no intrahepatic satellite lesions, ascites or disseminated nodules were identified. The left hepatic artery, left PV and left hepatic duct were isolated at the hilum. After ligating and disconnecting the left hepatic artery, the right, left and main PVs were exposed. After checking the PVT by ultrasound, the PVs were clamped by Satinsky forceps (Figure 3A). Venotomy was placed at the bifurcation of the left PV, and the PVT was thrombectomized (Figure 3B). After flushing the PV with normal saline and confirming that no PVT remained, the left PV stump was closed by 6-0 proline (Figure 3C). Liver dissection was completed along the



Figure 3 Portal vein tumour thrombus thrombectomy. A: The right and the main portal veins were clamped by Satinsky forceps. Venotomy was placed at the bifurcation of the left portal vein; B: The portal vein tumour thrombus was thrombectomized; C: The left portal vein stump was closed by 6-0 proline.

middle hepatic vein. The left hepatic duct and hepatic vein were cut and closed with 6-0 proline. The specimen was finally removed.

OUTCOME AND FOLLOW-UP

The patient's postoperative course was uneventful. Macroscopically, the primary tumour at the parenchyma was obscure. The PVTT demonstrated a white to brownish nodule with a size of 60 mm × 30 mm × 25 mm (Figure 4A). Microscopically, the primary lesion demonstrated fibrotic changes with haemosiderin deposition. In some areas, moderately to poorly differentiated tumour cells and tumour cells with necrotic changes were surrounded by granulation tissues and fibrosis (Figure 4B and C). The majority of the PVTT showed necrosis (Figure 4D). According to the Union for International Cancer Control classification, the tumour was finally staged as T3 N0 M0 Stage IIIB. He is alive with no evidence of recurrence 8 mo post-surgery.

DISCUSSION

Patients with HCC with PVTT usually have an aggressive disease course, decreased liver function reserve, limited treatment options, higher recurrence rates after treatment and poor overall survival (OS). The median OS is reported to be as poor as 2-4 mo with best supporting care^[10]. The Barcelona Clinic Liver Cancer (BCLC) staging classifies patients with PVTT with Child-Pugh A or B liver function reserve as advanced HCC with BCLC stage C. The recommended treatment option for this group is systemic therapy with sorafenib or lenvatinib as the first-line treatment^[4]. LRT including hepatectomy was not recommended over systemic therapy since there was inadequate evidence to inform the balance of benefit *vs* harm^[2]. LRT could only be considered for HCC with Vp1/2, only as an option within research settings^[2]. In a Japanese nationwide surveillance study consisting of more than 6000 patients with HCC with PVTT, propensity score matching analysis demonstrated a longer median OS in the surgical group than in the non-surgery group (2.87 years *vs* 1.10 years, $P < 0.001$)^[11]. However, surgical benefit was acknowledged when PVTT was limited to the first-order branch (Vp3), and no surgical benefit was observed among patients with Vp4 PVTT. The problem in this study was that more than half of the patients with Vp3/4 underwent non-curative resection, and the impact of curative resection was not clarified in this cohort. Several retrospective studies have demonstrated survival benefits of curative hepatectomies with aggressive PV thrombectomy or *en block* resection for Vp4 PVTT^[12-14]. Hatano *et al*^[14] conducted a retrospective multi-institutional study regarding the outcome of macroscopically curative hepatic resection in 400 patients with HCC with Vp3/4 PVTT. The results demonstrated a median survival time and 5-year OS rate of 21.5 mo and 25.7%, respectively. OS time showed no statistically significant difference between Vp3 and Vp4.

Lenvatinib was initially approved as the first-line therapy for advanced HCC in Japan in 2018. The REFLECT trial met its primary endpoint of non-inferiority to sorafenib in OS^[6]. Lenvatinib was superior to sorafenib in progression-free survival (PFS) and time to tumour progression (TTP). Although the complete response rate was low, the objective response rate (ORR) in the lenvatinib group was significantly higher than that in the sorafenib group (40.6% *vs* 12.4%, $P < 0.001$). TRAEs, including hand-

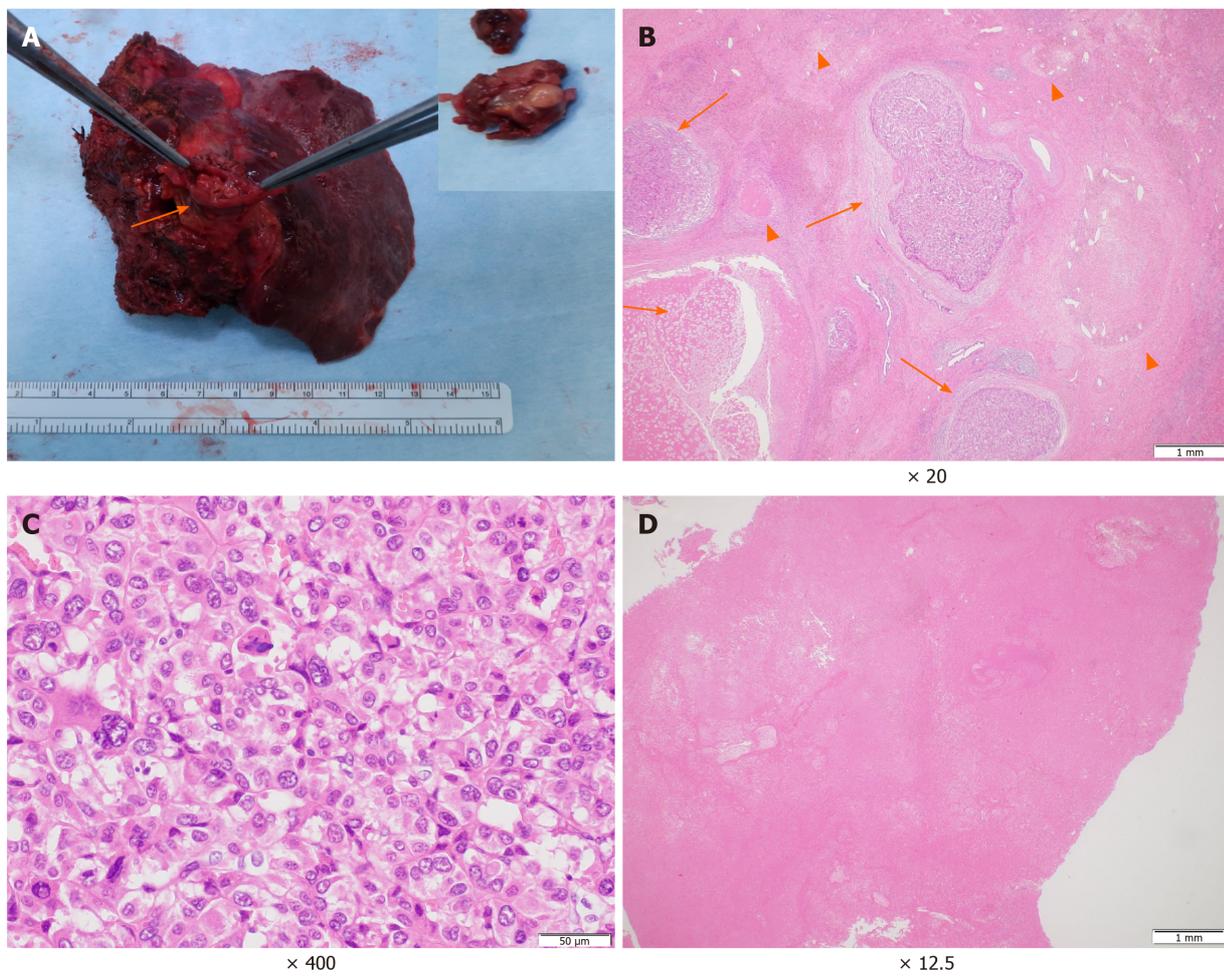


Figure 4 Macroscopic and microscopic findings of the main tumour and the portal vein tumour thrombus. A: A white to brownish nodule was found in the left portal vein (arrows). Inlet: close-up picture of the removed portal vein tumour thrombus; B: The primary lesion showed severe fibrotic change with haemosiderin deposition. In the fibrosis, the viable tumour cell nests (arrow) and the necrotic tumour lesions (arrowhead) were scattered; C: High magnification demonstrated moderately to poorly differentiated tumour cells; D: Most of the portal vein tumour thrombus showed necrotic changes.

foot syndrome, hypertension, proteinuria, and anorexia, were comparable between lenvatinib and sorafenib. These side effects are not life-threatening, and they can usually be controlled by supportive medical treatments. Subsequent studies have reported a relatively high ORR with lenvatinib of 29.4%-45.0%^[15-17]. On the other hand, the REFLECT trial excluded HCC cases that had main PV invasion, and the outcomes of this cohort were unclear. The efficacy of lenvatinib treatment for unresectable HCC with major PVTT has been reported in some case reports and retrospective studies^[18-20]. Kuzuya *et al.*^[20] compared the outcomes of advanced HCC with Vp3/4 PVTT between sorafenib and lenvatinib as the first-line systemic therapy. The ORR was significantly higher using lenvatinib (53.8% *vs* 14.3% $P = 0.0193$), and the median OS and TTP were significantly longer in the lenvatinib group than in the sorafenib group. No patient discontinued lenvatinib treatment secondary to TRAEs. These reports may characterize lenvatinib as having a relatively strong antitumour effect against HCC including PVTT, with less emergence of serious side effects.

Other characteristics of lenvatinib treatment are the rapid antitumour effects and preservation and fast recovery of liver function^[20]. The antitumour effects of lenvatinib have been described as quick, which could be confirmed in 2 wk, and these early radiologic changes could be biomarkers to predict clinical outcomes, including OS^[16]. Another group similarly stated that the changes in arterial tumour perfusion on CE-ultrasound at 1 wk were associated with the radiological antitumour response on CE-CT at 8 wk^[21]. Regarding the preservation of liver function, patients treated with lenvatinib maintained liver functional reserves better than those treated with sorafenib^[22]. Furthermore, ALBI scores in the lenvatinib group improved faster than those in the sorafenib group^[20]. In our case, the patient tolerated the full dose while maintaining liver function without major side effects. The tumour including the PVTT showed early necrotic changes 2 wk after lenvatinib treatment.

Based on these reports, lenvatinib is characterized by the following strengths: (1) Relatively strong antitumour effect not only on the main tumour but also on PVTT; (2) Quick antitumour effects that could be noted in 1-2 wk; and (3) Preservation and early recovery of liver function with less incidence of life-threatening TRAEs. Because of these strengths, lenvatinib can be considered an optimal chemotherapeutic agent targeting radical conversion hepatectomy for unresectable HCC. The good indication might be unresectable HCC with a large size or with PV invasion. Multiple intra-extra hepatic HCC can be considered as long as curative resection is feasible, since pathological complete response is usually difficult to attain by lenvatinib alone, and the tumours can quickly regrow during the drug cessation period^[19,23]. Lenvatinib demonstrates quick antitumour effects, and it deteriorates liver function temporarily^[17]. The treatment effects on the tumour and liver function reserve should be evaluated in a short period to avoid missing the best timing for conversion. Since severe morbidities related to lenvatinib treatment were reported in advanced HCC with PVTT (data not shown), physicians should be reminded to perform careful observation during the treatment period, especially in cases with Vp3/4 PVTT, since liver function could deteriorate quickly.

Identification of serum biomarkers for the prediction of lenvatinib response would be of significant benefit for the proper selection of patients for treatment. The post hoc exploratory analysis of the REFLECT trial revealed that the occurrence of hypertension, diarrhoea, proteinuria, or hypothyroidism was generally associated with longer OS in patients with unresectable HCC treated with lenvatinib^[24]. Another group stated that maintaining a higher relative dose intensity (RDI) in the early period after starting lenvatinib was associated with a higher ORR and longer PFS^[25]. In our case, the patient did not complain of any TRAEs that deteriorated his quality of life, and he could continue lenvatinib with RDI of 100% without decreasing the lenvatinib dose. It is reasonable to think that the high RDI might be the main reason for this significant antitumour effect, leading to PR and conversion hepatectomy.

Four conversion cases with lenvatinib treatment, including ours, were reported in the previous literature (Table 1)^[23,25,26]. Three cases were treated with lenvatinib monotherapy, and one case was treated with a combination of lenvatinib and nivolumab. Unresectable factors in these cases were large tumour size with inadequate residual liver volume, lung metastasis, and Vp4 PVTT. The duration of lenvatinib treatment in cases of large tumours and PVTT cases was short, 3-6 mo, and RDIs before conversion were all high (over 70%) in these cases. All cases demonstrated good postoperative courses with no evidence of tumour recurrence. Since the length of its market use is still short, it is necessary to gain experience and cases to clarify which cohort is suitable for targeting conversion.

Recently, there have been reports regarding the efficacy of proton beam therapy for advanced HCC with PVTT^[27,28]. Proton beam therapy has advantages in that it is less invasive to patients; however, it requires high medical expenses and a large-scale facility that is not widely available worldwide. Because of its strong and quick antitumour effects with fewer TRAEs, conversion hepatectomy using lenvatinib could be an ideal strategy. A clinical trial is currently underway in Japan regarding conversion surgery during lenvatinib administration for unresectable HCC. Several molecular targeting agents and checkpoint inhibitors are being developed and will be coming to the market soon. These sequential flows could explore a new strategy against unresectable HCC.

CONCLUSION

In conclusion, we experienced the first case of HCC with Vp4 PVTT in which radical conversion hepatectomy was successfully performed after lenvatinib treatment. Lenvatinib has several strengths that validate its use for targeting radical conversion hepatectomy for unresectable HCC. A multicentre prospective trial is needed to clarify its clinical utility.

Table 1 Case reports of conversion hepatectomy after lenvatinib treatment

Ref.	Age/sex	Background disease	Regimen	Reason for unresectivity	Former treatment	Child-Pugh classification	Duration	RDI (%)	Type of hepatectomy	Prognosis
Sato <i>et al</i> ^[23] (2019)	66/F	HCV	Lenvatinib	Large size	TACE	8 (B)	6 mo	70	Extended right hepatectomy	3 mo alive with no recurrence
Chen <i>et al</i> ^[26] (2019)	69/F	HBV	Lenvatinib, nivolumab	Large size	Sorafenib TACE	8 (B)	3.5 mo	100	Extended right hepatectomy	3 mo alive with no recurrence
Takahashi <i>et al</i> ^[25] (2019)	82/F	Non B/C	Lenvatinib	Lung metastasis	None	5 (A)	13 mo	38	Extended posterior segmentectomy	5 mo alive with no recurrence
Present study	59/M	HCV	Lenvatinib	PVTT (Vp4)	None	5 (A)	3 mo	100	Left hepatectomy	8 mo alive with no recurrence

F: Female; M: Male; HCV: Hepatitis C virus; HBV: Hepatitis B virus; PVTT: Portal vein tumour thrombus; TACE: Transarterial chemoembolization; RDI: Relative dose intensity; Vp4: Main trunk/contralateral branch.

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