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Recent advances in treatment strategies for hepatocellular carcinoma with portal vein cancer thrombus

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Abstract. – This is a review of current practices and advances in hepatocellular carcinoma (HCC) with portal vein cancer thrombus (PVTT). The treatment strategies of HCC with PVTT are non-uniform worldwide. Systemic treatment with molecularly targeted drugs and immune checkpoint inhibitors, such as sorafenib, lenflutinib, donafenib, atezolizumab plus bevacizumab, sintilimab plus IBI305, regorafenib, pembrolizumab and anti-Cytotoxic T Lymphocyte antigen 4 (CTLA-4) was recommended by guidelines, but with limited effectiveness for HCC patients with PVTT. More and more studies indicate that aggressive local or locoregional treatments, including liver resection, liver transplantation, radiation therapy, hepatic arterial infusion chemotherapy (HAIC), transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) benefit for selected HCC patients with PVTT. In recent years, the comprehensive treatment of HCC has advanced greatly. This review aims to provide an insight into the treatment modalities available for HCC patients with PVTT.

Key Words:
Hepatocellular carcinoma, Portal vein cancer thrombus, Liver resection, Liver transplantation, radiation therapy, Hepatic arterial infusion chemotherapy, Transarterial chemoembolization, Transarterial radioembolization, Systemic treatment.

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality worldwide. The proportions of HCC patients with portal vein tumor thrombus (PVTT) vary greatly in different countries, ranging from 13% to 45%. Treatment strategies are non-uniform worldwide. Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend systemic treatment with molecularly targeted drugs and immune checkpoint inhibitors as the standard treatment for HCC patients with PVTT (Barcelona Clinic Liver Cancer, BCLC)[1-3]. However, a more aggressive management approach for HCC with PVTT is being adopted based on the clinical guidelines in the Asia-Pacific region[4-6]. In recent years, the continuous progress of locoregional and systemic therapy improved the outcomes of HCC patients with PVTT. This article reviews the research progress to spark new ideas for improving the prognosis of HCC patients with PVTT.

Classification of PVTT

At present, two PVTT classifications are most widely used: the Japanese Vp[7] and the Cheng's classification[8]. The Vp classification comprises four levels based on the extent of tumor thrombus in the portal vein: Vp1, tumor thrombus involving the segmental branches of the portal vein; Vp2, tumor thrombus involving the second-order branches of the portal vein; Vp3, tumor thrombus involving the first-order branches of the portal vein; and Vp4, tumor thrombus involving the main trunk of the portal vein and/or contralateral branch of portal vein. The Cheng's classification comprises four grade: type I, presence of a tumor thrombus in segmental or sectoral branches of the portal vein or above; type II, presence of a tumor thrombus in the right/left portal vein; type III, presence of a tumor thrombus in the main portal vein; and type IV, presence of a tumor thrombus in the superior mesenteric vein.

Liver Resection and Liver Transplantation

Liver resection (LR) is widely accepted as a standard method for early HCC (BCLC 0 and A),

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however, for BCLC B or C lesions, LR remains controversial. Literature in the Asia-Pacific region have shown that LR and liver transplantation (LT) are safe and effective therapeutic options for HCC with PVTT. Kokudo et al[9] retrospectively analyzed the data of 6,474 HCC patients with PVTT in Japan from 2000 to 2007 who underwent surgery or other non-surgery treatment. The results showed that LR could prolong the survival time for HCC with PVTT, with a median survival time of 2.87 years in the LR group and 1.1 years for non-LR (p<0.001). The subgroup analysis showed that LR did not prolong overall survival (OS) in VP4 patients compared with non-surgery treatment. This study[9] also showed that cirrhosis was an important risk factor affecting the OS for LR. A systemic review[10] containing 29 studies from the USA, Europe, and East Asia, concluded that there was a significantly better OS with LR *vs.* systemic therapy alone in Vp1-2 and selected Vp3, and that the extent of thrombus was associated with prognosis. The prognosis was better if the thrombus was located in distal portal vein branches (Vp1-2). A study[11] showed that downstaging before LR was feasible in selected Vp3-4 using locoregional and systemic therapy. Another study[12] showed that LR with a wide surgical margin is associated with better outcomes than a narrow surgical margin in HCC patients with microvascular invasion. Although HCC with PVTT is conventionally considered a contraindication for LT due to the high risk of recurrence, few centers have reported positive results for LT in selected PVTT candidates. Soin et al[13] analyzed OS and recurrence-free survival (RFS) in 46 HCC patients (excluding 3 postoperative deaths) with PVTT who underwent LT with/without downstaging (n=43). The results showed that five-year OS and RFS were better in the downstaging group (n=23) than in the group without downstaging (n=20), 57% *vs.* 48% (p=0.79), 51% *vs.* 40% (p=0.35). The success rate of downstaging was 66% (25/38). Although the role of downstaging therapy in HCC patients with PVTT has been established, downstaging therapy was limited in small numbers. Future research should focus on downstage methods.

Hepatic Arterial Infusion Chemotherapy (HAIC)

Hepatic arterial infusion chemotherapy (HAIC) delivering chemotherapeutic agents (such as oxaliplatin, 5-fluorouracil, cisplatin, gemcitabine, floxuridine, epirubicin, individually or in combination) into intrahepatic tumor lesion through a catheter or pump is one of the commonly used treatment options for advanced HCC. HAIC is recommended in HCC patients with major portal vascular invasion who are ineligible for or unresponsive to hepatectomy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and systemic therapy in Japan[14]. In a randomized comparative trial (RCT), Choi et al[15] evaluated the efficacy and safety of HAIC (n=29) compared to sorafenib (n=29) among HCC patients with PVTT. The median OS was longer in the HAIC group than in the sorafenib group (14.9 *vs.* 7.2 months, p=0.012). A meta-analysis[16] containing six studies (n=417) also found that HAIC is superior to sorafenib in HCC with PVTT with respect to OS, progression-free survival (PFS), and disease control rate (DCR), especially in HCC with types III-IV PVTT. However, HAIC caused more myelosuppression. In a RCT[17] comparing sorafenib alone with sorafenib plus HAIC was conducted in 247 patients with PVTT. The median OS was longer in the sorafenib plus HAIC group than the sorafenib alone group, 13.37 *vs.* 7.13 months (p=0.01). The median OS stratified by portal vein invasion grade in the sorafenib plus HAIC group was also longer than that in the sorafenib group (Vp1-2: 18.17 *vs.* 10.87 months, p=0.002; Vp3: 13.47 *vs.* 6.27months, p<0.001; Vp4: 9.47 *vs.* 5.5 months, p<0 .001).

A phase III RCT[18] (SILIUS study) from Japan reported that HAIC plus sorafenib (n=17) is superior to sorafenib alone (n=22) in HCC patients with Vp4 PVTT (11.4 *vs.* 6.5 months, p=0.05). However, the median OS for Vp1-3 PVTT between HAIC plus sorafenib group and sorafenib group was not statistically different (12.6 *vs.* 14.4 months p=0.218). Recently, in an RCT, Zheng et al[19] compared the efficacy of sorafenib plus HAIC *vs.* sorafenib alone for HCC with PVTT (Vp3 and Vp4) in 64 patients. The median OS was better in the sorafenib plus HAIC group (n=32) than in the sorafenib alone group (n=32), 16.3 months and 6.5 months (p<0.001). In a retrospective, PSM study, Yuan et al[20] compared TACE-HAIC combined with targeted therapy and immunotherapy (n=139) and TACE alone (n=604) for HCC with PVTT. The combination group showed significantly better OS and PFS than the TACE group, not reached *vs.* 10.4 months (p<0.001) and 14.8 *vs.* 2.3 months (p<0.001), respectively. Tumor downstaging followed by LR was significantly

more common in the combination group than in TACE group (46.3% *vs.* 4.5%, $p<0.001$).

In conclusion, HAIC was an alternative or integrative method for HCC patients with PVTT, especially for Vp3-Vp4. Combination with targeted therapy and immunotherapy has attracted significant attention. HAIC plus systemic treatment maybe an effective surgical conversion therapy strategy for unresectable HCC patients with PVTT.

Transarterial Radioembolization (TARE)

Transarterial radioembolization (TARE) is an effective method for HCC, by which radioactive yttrium-90 (Y90) contained in microspheres are delivered to HCC lesions through the feeding arteries. Hepatic artery flow is not completely blocked by TARE, which is contradistinction to TACE-occlusion of the hepatic artery as theory of treatment with risks inducing ischemic hepatitis in patients involving portal vein occluded by PVTT. The microembolic effect of TARE permits treatment in the presence of compromised portal flow. Y90 has been approved to treat HCC patients with PVTT since 2005. In 2017, a phase III RCT[21] at 25 centers in France (SARAH) compared the efficacy and safety of sorafenib (n=222, 60% with PVTT) and TARE (n=237, 53% with PVTT) in HCC patients. The SARAH trial result showed that TARE did not prolong OS compared with sorafenib, 8.0 months and 9.9 months respectively (p=0.18). The subgroup analysis of SARAH study did not show statistical difference between sorafenib and TARE for HCC with PVTT. In 2018, another phase III trial (SIRveNIB)[22] from 11 countries in Asia Pacific region also showed that TARE was no inferior to sorafenib. The median OS was 8.8 months and 10.0 months with TARE (n=182) and sorafenib (n=178), respectively (p=0.36). In 2019, in a multicenter prospective RCT study (SORAMIC), Ricke et al[23] reported that there was no statistical difference in median OS between TARE with sorafenib and sorafenib alone for advanced HCC, 12.1 months and 11.4 months (p=0.9529). Ahn et al[24] retrospectively analyzed the results of a National Cancer Database in which the trends and the outcomes of using TARE (n=1,454) and systemic therapy (n=3,915) for HCC with PVTT were compared. Promisingly, the results showed that HCC patients who received TARE had a higher OS rate than systemic treatment at 1 year (46.5% *vs.* 34.2%), 2 years (21.8% *vs.* 16.4%), and 3 years (10.4% *vs.* 9.3%). According to the 2021 NCCN guidelines[25], TARE is more suitable for HCC patients with segmental or lobar PVTT.

In summary, TARE is an alternative method for advanced HCC. However, there is still a lack of high-level evidence to test the effectiveness of TARE in HCC patients with PVTT and the effects need to be verified in large RCTs.

External Beam Radiation Therapy

Recently, the developments of radiotherapy techniques have made radiation therapy (RT) able to deliver high radiation doses to focal tumors. In several reports[26,27], three-dimensional radiation therapy (3D-CRT) and stereotactic body radiotherapy (SBRT) have been safely used in HCC with all types of PVTT. Nakazawa et al[26] retrospectively compared sorafenib with radiotherapy in 97 HCC patients with Vp3-4 PVTT. The median OS did not differ significantly between the two groups (4.3 *vs.* 5.9 months; p=0.115), respectively. After propensity score matching (PSM, n=28 per group), the median OS was better in the RT group than in the sorafenib group (10.9 *vs.* 4.8 months; p=0.025). Im et al[27] reported that the response rate of radiotherapy in HCC patients with PVTT (n=985) was 51.8% in a Korean nationwide, multicenter retrospective cohort analysis using PSM. The combination treatment of radiotherapy and TACE or HAIC (n=201) was better than radiotherapy alone (n=201) after propensity score matching, with a median OS of 10.4 months and 8.7 months, respectively (p=0.023). In a prospective RCT, Yoon et al[28] compared RT plus TACE (n=45) and sorafenib (n=45) in 90 HCC patients with PVTT. The results revealed that the median OS of RT plus TACE was 55 weeks, which was significantly higher than sorafenib (48 weeks, p=0.04). Due to the achievement of a higher biologically effective dose within a shorter duration of treatment, SBRT has often been applied instead of 3D-CRT. In an RCT, Wei et al[29] reported that RT plus LR (n=64) was better than LR alone (n=64). The 6-, 12-, 18-, and 24-months OS for RT plus LR group was 89.0%, 75.2%, 43.9%, and 27.4%, while the LR-alone group was 81.7%, 43.1%, 16.7%, and 9.4%, respectively (p<0.001). In that study, the type of PVTT was downstaged from Cheng's type III to type II or from type II to type I in 12 cases. Que et al[30] retrospectively analyzed the efficacy of SBRT plus sorafenib and SBRT alone in 54 HCC patients with PVTT. The result showed that SBRT plus sorafenib resulted in a higher median PFS (6 *vs.* 3 months), and median

OS (12.5 *vs.* 7 months). However, the trends did not attain statistical significance.

In summary, RT is mainly used for PVTT involving the main trunk and/or first branches of the portal vein[31]. RT can be conducted as a bridge therapy for LR and LT[11]. However, with respect to liver function, Child-Pugh grade A-B7 would be required to tolerate RT. The optimal dose-fraction schedule is still unknown. Further prospective studies on RT with or without systemic therapies are needed to establish the role of RT.

Transarterial Chemoembolization (TACE)

Although the AASLD and EASL guidelines recommend individual systemic therapy for HCC with PVTT, TACE is the most frequent treatment of choice for HCC patients with PVTT in China, Korea, and Japan. Due to concerns that arterial embolization may cause severe ischemia and compromise remaining liver function in the setting of pre-existing occlusion of the liver's blood supply, AASLD and EASL guidelines recommend against TACE in HCC patients with PVTT. However, in Asia-Pacific countries, TACE is frequently recommended in selected patients depending on multiple factors, including portal vein collateral circulation, type of portal vein thrombus, and intact liver function. In a meta-analysis[32] with 1,933 TACE patients with PVTT, only 1% of patients experienced liver failure, and 18% of patients had post-treatment complications. Combining TACE and systemic therapy has been reported to be a safe treatment option and further improves outcomes for HCC patients with PVTT (Table I). Zhu et al[33] retrospectively analyzed the data of 91 HCC patients with PVTT who underwent TACE plus sorafenib (n=46) or TACE alone (n=45). The results showed that TACE combined with sorafenib could prolong the survival time of patients compared with TACE alone, with a median OS of 11 months and 6 months, respectively ($p<0.001$). Subgroup analysis showed that the median OS of Vp3 PVTT was 13 months and 6 months, respectively ($p=0.002$), while the median OS with Vp1-2 PVTT was 15 months and 10 months, respectively ($p=0.003$). However, there was no statistically significant difference in OS between the two groups for Vp4. Recently, a meta-analysis by Deng et al[37,] including eight studies (2103 HCC patients with PVTT), showed that TACE+sorafenib/apatinib had a better tumor response and disease control rate, and prolonged OS than TACE alone. TACE+lenvatinib was stronger than TACE+sorafenib in objective response rate (ORR) and time-to-progression (TTP), whereas it was similar in DCR and OS. The meta-analysis also showed that patients with type I and II PVTT undergoing TACE combined with tyrosine kinase inhibitors (TKI) compared with TACE alone realized prolonged OS and TTP. However, a similar benefit was not found in patients with type III PVTT. A network meta-analysis by Luo et al[38] demonstrated that TACE plus sorafenib was the most effective treatment for HCC patients with PVTT when compared with hepatectomy, TACE, sorafenib, or any combination of the two methods. The meta-analysis also showed that TACE+lenvatinib was stronger than TACE+sorafenib in ORR (60.7% *vs.* 38.9%) and median TTP, similar in DCR (96.4% *vs.* 96.3%) and OS. In an RCT, Ding et al[39] compared the efficacy and safety of TACE plus lenvatinib and TACE plus sorafenib in patients with HCC and PVTT. Patients in TACE plus lenvatinib had a higher median TTP, ORR and OS, 4.7 *vs.* 3.1 months ($p=0.029$) and 53.1% *vs.* 25.0% ($p=0.039$), 14.5 *vs.* 10.8 months ($p=0.17$), respectively.

Recently, TACE combined with TKI plus programmed cell death 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) inhibitor for HCC with PVTT was reported in several studies[40-42]. In a nationwide, retrospective, cohort, real-world study (CHANCE001) in China, Zhu et al[40] describe the efficacy and safety of 826 HCC patients who received TACE with PD-(L)1 inhibitor plus molecular targeted therapies (combination group, n=376) *vs.* TACE monotherapy (monotherapy group, n=450). After propensity score matching, the combination group showed significantly better PFS (9.5 *vs.* 8.0, $p=0.02$), OS (19.2 *vs.* 15.7 months, $p=0.001$), and ORR (60.1% *vs.* 32.0%, $p<0.001$) compared to monotherapy group, especial for patients with PVTT. A retrospective study by Xia et al[41] analyzed data from HCC patients with PVTT who were treated with TACE+apatinib+PD-1 inhibitor (n=40) or TACE+apatinib (n=69). TACE+apatinib+PD-1 inhibitor significantly improved OS, PFS, and ORR, and the adverse reactions were safe and controllable. Zou et al[42] evaluated the efficacy and safety of TACE combined with lenvatinib plus PD-1 inhibitor (n=80) *vs.* TACE combined with sorafenib plus PD-1 inhibitor (n=85) in the treatment of HCC patients with PVTT. The study showed that patients in the TACE combined with lenvatinib plus

Table I. Combinations of TACE and tyrosine kinase inhibitor with/without immune checkpoint inhibitor.

Author/trial/year	Design	Treatment	PVTT	Patients	ORR	mPFS	mOS	mTTP
Zhu et al[33] 2014	RT	T+S *vs.* T	Total Vp1-2/Vp3/Vp4	46 *vs.* 45 17/19/10 *vs.* 13/21/11	28 *vs.* 4 47/26/10 *vs.* 8/5/0	- -	11 *vs.* 6 15/13/3;10/6/3	6 *vs.* 3 7/6/0 5/3/0
Yuan et al[34] 2019	RT	T+S *vs.* T	Total I-II/III-IV	69 *vs.* 429 43/182 *vs.* 26/247	- -	- -	13 *vs.* 6 15/14 *vs.* 8/5.5	- -
Wang et al[35] 2016	RT	T+S *vs.* T	I/II/III	31/45/37 *vs.* 47/288/269	-	-	12/8.9/7 *vs.* 9.3/4.9/4	-
Ding et al[39] 2021	RCT	T+S *vs.* T+L	I-II/III-IV	25/7 *vs.* 21/11	25 *vs.* 53.1	-	-	3.1 *vs.* 4.7
Yang et al[36] 2021	RT	T+S *vs.* T+L	Vp2/Vp3/Vp4	29/17/11 *vs.* 34/16/9	38.9 *vs.* 60.7	7.4 *vs.* 8.4	12.7 *vs.* 16.4	-
Zou et al[40] 2023	RT	T+L+P *vs.* T+S+P	Vp2/Vp3/Vp4	43/28/9 *vs.* 44/32/9	41.3 *vs.* 30.6	6.3 *vs.*3.2	21.7 *vs.* 15.6	-
Lu et al[48] 2023	RCT	T+S *vs.* T+I-125 stent	Vp4	54 *vs.* 51	-	-	6.3 *vs.* 9.9	-
Xue et al[44] 2021	RT	DEB-T+L *vs.* DEB-T+S	Vp1-3	37 *vs.* 180	-	-	10.8 *vs.* 7.5	5.1 *vs.* 3.2

RT: retrospective trial; RCT: randomized comparative trial; T: TACE; S: sorafenib; L: lenvatinib; P: anti-programmed cell death 1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1); DEB-T: drug-eluting beads TACE; ORR: objective response rate; PFS: progression-free-survival; TTP: median time-to-progression. All: all patients in the study; sub: subgroup.

PD-1 inhibitor had longer median OS (21.7 *vs.* 15.6 months, p=0.0027), longer median PFS (6.3 *vs.* 3.2 months, p<0.0001), higher ORR (41.25% *vs.* 30.59%, p=0.008), and higher DCR (86.25% *vs.* 62.35%, p=0.008) than TACE combined with sorafenib plus PD-1 inhibitor.

Drug-eluting beads TACE (DEB-TACE), the combining of non-absorbable microspheres with cytotoxic drugs, are delivered to the tumor-feeding arteries and achieve sustained drug release into the tumor tissues over time in HCC patients. In a retrospective controlled study[43], DEB-TACE showed significant OS benefits (12.0 *vs.* 9.0 months, p=0.027) and longer TTP (7.0 *vs.* 4.0 months, p=0.040) than the C-TACE group.

In a propensity score matching retrospective study, Xue et al[44] compared the efficacy of TACE with drug-eluting beads (DEB-TACE) plus lenvatinib (DEB-TACE+LEN, n=37) *vs.* DEB-TACE plus sorafenib (DEB-TACE+SOR, n=180) for advanced HCC with PVTT. Patients in the DEB-TACE+LEN group had a longer OS (10.8 *vs.* 7.5 months, p=0.043) and TTP (5.1 *vs.* 3.2 months, p=0.035) than patients in the DEB-TACE+SOR group (n=180).

In summary, TACE plus TKI should be a good choice for selected HCC with PVTT. TACE plus lenvatinib produced better ORR and TTP.

Internal Radiation Therapy

In recent years, iodine-125 seed implantation or a combination of portal vein stents has been reported for the treatment of PVTT in several studies in China[45-48]. Iodine-125 seed can be implanted into PVTT by CT-guided direct percutaneous puncture implantation or endovascular iodine-125 seed-strip implantation through the percutaneous transhepatic route. A prospective, controlled, multicenter study compared the efficacy of iodine-125 seed implantation plus TACE (n=71) and TACE plus sorafenib (n=52) for HCC patients with II (Vp3) PVTT[45]. In the iodine-125 seed implantation plus TACE group, iodine-125 seeds were implanted through CT-guided percutaneous puncture. Patients in the iodine-125 seed implantation plus TACE group had significantly better overall survival than those in the TACE plus sorafenib group (13.8 *vs.* 8.3 months, p<0.001). Iodine-125 seed loaded in a 4F angiocatheter with both ends sealed can also be safely placed into the portal vein through the percutaneous transhepatic route. A retrospective study[46] comparing helical I-125 seed implantation plus TACE (n=21) and TACE alone (n=25) for HCC with main PVTT showed that the median OS in the combination group was longer than in the TACE alone group (9.8 *vs.* 5.2 months, p=0.024). Placing a stent in the portal vein can re-establish portal vein blood flow and decrease portal vein hypertension caused by PVTT. A meta-analysis[47] containing seven studies with 1,018 patients reported that a portal vein stent combined with iodine-125 seed strips had a longer stent patency time and higher survival rates compared with the portal vein stent alone for HCC with PVTT. More recently, in a multicenter RCT, Lu et al[48] compared the efficacy of irradiation stent placement with iodine-125 plus TACE (n=51) and sorafenib plus TACE (n=54). Patients in the irradiation stent placement with iodine-125 plus TACE group had longer median OS (9.9 *vs.* 6.3 months, p=0.01) and DCR (86% *vs.* 67% p=0.018) than those in the sorafenib plus TACE group. The median stent patency was 7.2 months in the irradiation stent placement with iodine-125 plus TACE group.

In summary, iodine 125 can inhibit the growth of PVTT, and TACE plus iodine-125 seed is a feasible, safe, and effective method for HCC patients with type II PVTT. Iodine 125 can prolong stent patency time. The combination of iodine 125 with portal vein stent plus TACE provides the greatest benefit to patients with HCC and Vp4 PVTT.

Systematic Treatments

HCC is characterized by a high level of vascularization, and anti-angiogenic therapy, such as anti-vascular endothelial growth factor (VEGF), plays an important role in treatment[49]. Systemic pharmacological treatment using multi-tyrosine kinase inhibitors (sorafenib, lenvatinib, donafenib, regorafenib, and cabozantinib), anti-angiogenic antibody (ramucirumab and bevacizumab), immune checkpoint inhibitors (ICIs, such as pembrolizumab, atezolizumab, nivolumab, sintilimab, camrelizumab, tislelizumab and durvalumab) and anti-Cytotoxic T Lymphocyte antigen 4 (CTLA-4, ipilimumab and tremelimumab) for HCC have received more and more attention[50] (Table II).

First-Line Therapy

Sorafenib is considered a first-line TKI drug for BCLC stage C HCC based on the Sorafenib HCC Assessment Randomized Protocol (SHARP) study[51]. Subanalyses of SHARP study[52]

Table II. Clinical trials in first-line or second-line systemic treatment of unresectable HCC.

Author/Trial (Year) Reference	Phase	Treatment arms(all)	No. of Patients with MVI	Median OS (All)	Median OS (MVI)	Median PFS (All)	Median PFS (MVI)	ORR (All)	Adverse events≥ grade 3 (%)	Follow-up
First-line										
Llovet et al[51] SHARP (2012)	III	Sorafenib (n=299) *vs.* placebo (n=303)	Sorafenib (n=108) *vs.* placebo (n=123)	10.7 *vs.* 7.9	8.1 *vs.* 4.9	5.5 *vs.* 2.8	–	0.7 *vs.* 0.3[a]	15.2 *vs.* 10.6	–
Kudo et al[57] REFLECT (2018)	III	Lenvatinib (n=478) *vs.* Sorafenib (n=476)	Vp1-3 (Vp4 excluded)	13.6 *vs.* 12.3	–	7.4 *vs.* 3.7	–	24.1 *vs.* 9.2[b]	56.7 *vs.* 48.6	–
Finn et al[75] KEYNOTE 524 (2020)	Ib	Lenvatinib plus Pembrolizumab (n=100)	Vp1-3 (n=16)	22	–	9.3	–	36[c]	67	10.6
Qin et al[62] ZGDH3 (2021)	II/III	Donafenib (n=334) *vs.* Sorafenib (n=334)	MVI	12.1 *vs.* 10.3	–	3.7 *vs.* 3.6	–	4.6 *vs.* 2.7[c]	37.5 *vs.* 49.7	–
Ren et al[63] ORIENT-32 (2021)	II/III	Sintilimab–Bevacizumab biosimilar (n=380) *vs.* Sorafenib (n=191)	Sintilimab–Bevacizumab biosimilar (n=105) *vs.* Sorafenib (n=50)	not reached *vs.* 10.4	–	4.6 *vs.* 2.8	–	21 *vs.* 7[c]	55 *vs.* 48	10
Xu et al[77] RESCUE (2021)	II	Camrelizumab plus Apatinib as first-line (n=70) and second-line (n=120)	–	Not reached	–	5.7 *vs.* 5.5	–	34.3 *vs.* 22.5[c]	77.4	14.0
Cheng et al[60] IMbrave150 updated (2022)	III	Atezolizumab plus Bevacizumab (n=336) *vs.* Sorafenib (n=165)	Atezolizumab plus Bevacizumab (n=129) *vs.* Sorafenib (n=71)	19.2 *vs.* 13.4	14.2 *vs.* 9.7	6.9 *vs.* 4.3	6.7 *vs.* 4.2	30 *vs.* 11[c]	45.3 *vs.* 46.8	15.6
Abou-Alfa et al[74] HIMALAYA (2022)	III	Tremelimumab+ Durvalumab (n=393) *vs.* Durvalumab (n=389) *vs.* Sorafenib (n=389)	Vp4 excluded	16.4 *vs.* 16.6 *vs.* 13.8	–	3.8 *vs.* 3.7 *vs.* 4.1	–	20.1 *vs.* 17 *vs.* 5.1[c]	28.1 *vs.* 12.9 *vs.* 37.7	16.1 *vs.* 16.5 *vs.* 13.3
Kelley et al[76] COSMIC-312 (2022)	III	Cabozantinib plus Atezolizumab (n=250) *vs.* Sorafenib (n=122)	Cabozantinib plus Atezolizumab (n=51) *vs.* Sorafenib (n=20)	15.4 *vs.* 15.5	–	8.8 *vs.* 4.2	–	13 *vs.* 5[c]	76 *vs.* 57	15.8

Continued

Table II *(continued)*. Clinical trials in first-line or second-line systemic treatment of unresectable HCC.

Author/Trial (Year) Reference	Phase	Treatment arms(all)	No. of Patients with MVI	Median OS (All)	Median OS (MVI)	Median PFS (All)	Median PFS (MVI)	ORR (All)	Adverse events≥ grade 3 (%)	Follow-up
Second-line										
Bruix et al[64] RESORCE (2017)	III	Regorafenib (n=379) *vs.* placebo (n=194)	Regorafenib (n=110) *vs.* placebo (n=54)	10.6 vs. 7.8	–	3.1 vs. 1.5	–	11 *vs.* 4[b]	66.3 *vs.* 38.3	7
Abou-Alfa et al[65] ELESTIAL (2018)	III	Cabozantinib (n=470) *vs.* placebo (n=327)	Cabozantinib (n=129) *vs.* placebo (n=81)	10.2 *vs.* 8.0	–	5.2 *vs.* 1.9	–	4 *vs.* 1[c]	67.7 *vs.* 36.3	–
Zhu et al[66] REACH-2 (2019)	III	Ramucirumab (n=197) *vs.* placebo group (n=95)	Ramucirumab (n=70) *vs.* placebo group (n=33)	8.5 *vs.* 7.3	–	2.8 *vs.* 1.6	–	4.6 *vs.* 1.1[c]	34.5 *vs.* 29.5	7.6
Finn et al[68] KEYNOTE 240 (2020)	III	Pembrolizumab (n=278) *vs.* placebo (n=135)	Pembrolizumab (n=36) *vs.* placebo (n=16)	13.9 *vs.* 10.6	–	3.0 *vs.* 2.8	–	18.3 *vs.* 4.4[c]	52.7 *vs.* 46.3	13.8 *vs.* 13.6
Qin et al[70] (2020)	II	Camrelizumab (n=217)	n=27	13.8	–	–	–	14.7[c]	22	12.5
Yau et al[72] Check-Mate 040 (2020)	I/II	Nivolumab plus Ipilimumab (n=50)	–	22.8	–	–	–	32[c]	53.1	30.7
Kudo et al[69] KEYNOTE-224 (2022)	II	Pembrolizumab (n=104)	n=18	13.2	–	4.9	-	18.3[c]	26	–
Ren et al[71] RANTIONALE-208 (2023)	II	Tislelizumab (n=249)	n=46	13.2	-	2.7	-	13[c]	15	12.7

MVI: macro-vascular invasion; OS: overall survival; PFS: progression-free-survival; ORR: objective response rate. [a]The level of response was measured according to the modified RECIST. [b]The level of response was measured according to modified mRECIST. [c]The level of response was measured according tomodified RECIST 1.1.

showed that among patients with macro-vascular invasion (MVI), sorafenib (n=108) significantly prolonged median (8.1 *vs.* 4.9 months) and TTP (4.1 *vs.* 2.7 months) than those who received placebo (n=123). The subgroup analysis of a phase III sorafenib Asia Pacific (AP) trial[53] showed that sorafenib (n=118) significantly prolonged median OS (5.6 *vs.* 4.1 months), TTP (2.7 *vs.* 1.3 months) and DCR (30.5% *vs.* 11.5%) in patients with MVI and/or extrahepatic metastasis than in those who received placebo (n=61). The liver without extrahepatic spread, or in those with hepatitis C virus, or a lower neutrophil-to-lymphocyte ratio was predictive of a greater OS benefit with sorafenib based on analysis of SHARP and AP trial[54]. Jeong et al[55] reported that the median OS of sorafenib monotherapy for HCC patients with Vp3 and Vp4 PVTT (n=30) was only 3.1 months. In another retrospective study, Kuo et al[56] evaluated the safety and efficacy of sorafenib monotherapy on HCC with PVTT, including 56 Vp3 and 57 Vp4. The OS of Vp3 was significantly better than Vp4 (8.1±1.0 *vs.* 3.9±1.1 months, p=0.04), but a similar PFS (2±0.03 months *vs.* 2±0.05 months, p=0.68). However, in the study[56], 60.2% of patients accepted concurrent treatments after sorafenib failure. The result proved that sorafenib monotherapy as first-line treatment was recommended for Vp4 with a higher AFP level (≥ 200 ng/ml) due to its limited survival benefit and associated with the occurrence of hepatic decompensation.

In a phase III, multicenter, non-inferiority trial (REFLECT)[57] of advanced unresectable HCC patients (n=954, 20% with MVI), lenvatinib (n=478) is proved to be non-inferior of median OS (13.6 *vs.* 12.3 months) but with a better median PFS (7.4 *vs.* 3.4 months), median TTP (8.9 *vs.* 3.7 months) and ORR (24.1% *vs.* 9.2%) as compared with sorafenib (n=476), especially in Asian populations, patients with hepatitis B virus-related HCC. Lenvatinib has been recommended as first-line therapy based on the REFLECT study. Due to the exclusion of patients with main PVTT (Vp4), its efficacy among Vp4 has not been proven. In a retrospective study, Kuzuya et al[58] compared sorafenib (n=28) and lenvatinib (n=13) as first-line therapy in HCC patients with major PVTT (Vp4). Patients in the lenvatinib group had a better ORR (53.8% *vs.* 14.3%; p=0.0193), DCR (92.3% *vs.* 35.7%; p=0.0008), TTP (269 *vs.* 53 days, p<0.0001) and median OS (not reached *vs.* 187 days; p=0.0040) than patients in the sorafenib group.

The combination of atezolizumab plus bevacizumab (Ate-Bevac) is approved as a first-line therapy for advanced HCC based on IMbrave150[59]. Recently, data from Mbrave150 was updated. In a phase III global trial[60] of advanced HCC patients (IMbrave150, n=501), after a median of 15.6 (range, 0-28.6) months of follow-up, the median OS was 19.2 months (95% CI 17.0-23.7) in the atezolizumab plus bevacizumab group and 13.4 months (95% CI 11.4-16.9) in the sorafenib group (p<0.001). The median PFS was better in the atezolizumab plus bevacizumab group than in the sorafenib group (6.9 *vs.* 4.3 months, p<0.001). Longer OS was also reported for HCC patients with MVI, 14.2 months in the atezolizumab plus bevacizumab group and 9.7 months in the sorafenib group. Treatment-related grade 3/4 adverse events occurred in 43% in the atezolizumab plus bevacizumab group and 46% in the sorafenib group, and treatment-related grade 5 events occurred in 6 (2%) and 1 (<1%) patients, respectively. Hiraoka et al[61] retrospectively compared the effect of atezolizumab plus bevacizumab and lenvatinib treatment as first-line therapy for unresectable HCC. Atezolizumab plus bevacizumab group showed better PFS and OS rates. Atezolizumab plus Bevacizumab was a priority and positioned as first-line therapy among all systemic drugs[61].

Since the ZGDH3[62] and ORIENT-32[63] studies, donafenib and Sintilimab plus IBI305 is approved as first-line TKI drugs for advanced HCC in China.

Second-Line Therapy

The RESORCE study[64] was a randomized, double-blind, parallel-group, phase 3 trial done from 21 countries to assess regorafenib in patients with HCC who have progressed during sorafenib treatment. The median OS was 10.6 months for regorafenib (n=379) *vs.* 7.8 months for placebo (n=194) after disease progresses during sorafenib treatment in RESORCE study. The improvement in OS with regorafenib (n=110) was also better than placebo (n=57) for HCC patients with PVTT. Regorafenib has been approved as second line therapy.

Based on CELESTIAL[65] and REACH-2 studies[66], Cabozantinib and Ramucirumab has been approved as second line therapy for HCC patients who have progressed during sorafenib treatment or unable to tolerate sorafenib.

Pembrolizumab has been approved as second line therapy for HCC in the US based on a phase II trial in which the objective response was 17% (18/104

HCC patients) (KEYNOTE-224)[67]. Although the results of phase 3 trial (KEYNOTE-240)[68] study did not meet the prespecified statistical criteria, the survival benefit was favorable. The median OS was 13.9 months and 10.6 months for pembrolizumab group (n=278) and placebo group (n=135), respectively (p=0.02). The median PFS for pembrolizumab was 3.0 months *vs.* 2.8 months for pembrolizumab group and placebo group, respectively (p=0.0022). ORR was 18.3% for pembrolizumab and 4.4% for placebo. The OS and PFS were also better in pembrolizumab group (n=36) than in the placebo group (n=16) for patients with MVI. Recently, Kudo et al[69] demonstrated the final results of KEYNOTE-224 trial. The pembrolizumab showed an 18.3% ORR, a median TTP of 4.8 months, a median PFS of 4.9 months, and a median OS of 13.2 months. 25% (26/104) patients reported treatment-related adverse event grade (TRAEs) 3/4 and 1% (1/104) patients reported TRAE 5.

Camrelizumab[70] and tislelizumab[71] have been recommended as the second-line treatment for advanced HCC in China.

ICI Combinations

Several studies[72-74] investigated the possibility of combining immune checkpoint inhibitors (ICIs) and different targets.

Dual ICI therapy using PD-1/PD-L1 and anti-CTLA-4 has been used for HCC. In a I/II phase study (CheckMate 040 trial)[72], a total of 148 HCC patients who progressed during sorafenib treatment were enrolled to receive the combination of ipilimumab and nivolumab. The combination showed manageable safety, encouraging objective response rate, and durable responses. Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks, followed by nivolumab 240 mg every 2 weeks achieved a median OS of 22.8 months and ORR of 32%. The combination of nivolumab and ipilimumab (CTLA-4 ICIs) as second-line therapy for advanced HCC treatment post-sorafenib was approved in the United States based on its promising results in CheckMate 040 study[72].

In a randomized expansion, phase I/II clinical trial[73] for 332 patients with HCC who had progressed on, were intolerant to, or refused sorafenib, the T300 + D regimen [tremelimumab 300 mg plus durvalumab 1,500 mg (one dose each during the first cycle) followed by durvalumab 1,500 mg once every 4 weeks, STRIDE] demonstrated encouraging benefit-risk profile, with a median OS was 18.7 (10.8 to 27.3) months. Tolerability of T300 + D regimen was acceptable, with grade ≥3 TRAEs occurring in 37.8%. The latest phase III randomized, open-label, multicenter study (HIMALAYA)[74] revealed the superiority of tremelimumab and durvalumab combination (STRIDE arm) over sorafenib on survival benefits in 1,150 unresectable HCC patients (OS, 16.4 *vs.* 13.8 months, p=0.0035) and ORR (20.1% *vs.* 5.1%), establishing a new first-line option. There was no significant difference in the incidence of grade 3/4 TRAEs between the two arms (25.8% *vs.* 36.9%). TRAEs leading to death were slightly more common in the STRIDE arm (2.3% *vs.* 0.8%). However, the HIMALAYA trial[74] excluded HCC patients with Vp4.

ICI and TKI Combination

In a phase Ib study (KEYNOTE-524), Finn et al[75] demonstrated that lenvatinib plus pembrolizumab has promising antitumor activity in unresectable HCC. The median OS was 22 months, median PFS of 9.3 months, and a DCR>85%. Grade ≥3 treatment-related adverse events occurred in 67% (grade 5, 3%) of patients (n=100). A double-blind RCT phase III study of lenvatinib plus pembrolizumab *vs.* lenvatinib plus placebo as first-line treatment for unresectable HCC is ongoing (NCT03713593).

In a phase III trial (COSMIC-312)[76] evaluated cabozantinib plus atezolizumab (PD-L1) *vs.* sorafenib as a first-line systemic treatment for 837 advanced HCC patients at 178 centers in 32 countries. Cabozantinib and atezolizumab combination improved PFS compared with sorafenib, with median PFS 6.8 and 4.2 months (p=0.0012). The interim analysis of COSMIC-312 trial[76] showed that the median OS was 15.4 months in the cabozantinib plus atezolizumab group *vs.* 15.5 months in the sorafenib group, 1-year OS was 61.8% and 58.2%, respectively. Subgroup analyses demonstrated that PFS appeared to be longer with cabozantinib and atezolizumab combination *vs.* sorafenib in HBV-positive patients, macrovascular invasion, extrahepatic disease and in Asia patients.

A nonrandomized, open-label, phase II trial (RESCUE)[77] evaluated the effectiveness of camrelizumab plus apatinib as first-line (n=70) and second-line (n=120) therapy in patients with advanced HCC. The ORR, PFS, and 1-year survival rate were 34.3% *vs.* 22.5%, 5.7 *vs.* 5.5 months, and 74.7% *vs.* 68.2% in first- *vs.* second-line therapy, respectively.

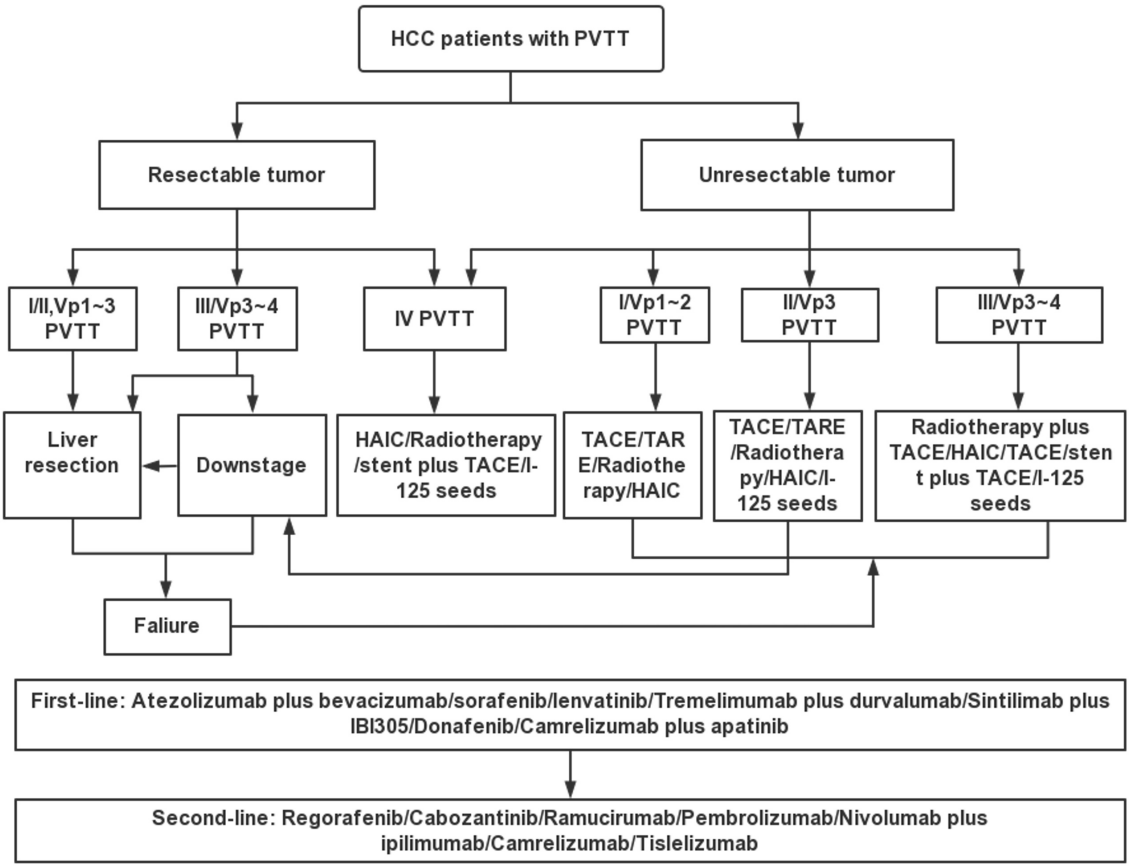

Figure 1. Treatment algorithm for HCC patients with PVTT according to the current evidence.

Multiple systemic drugs have emerged for HCC. Currently, more and more treatment strategies can be adopted according to the healthcare resources and drug availability in different countries[50]. Although there are still no robust biomarkers identified to predict response to ICIs in HCC patients, research focusing on the identification of biomarkers is ungoing[78]. Promisingly, the latest studies[78,79] have shown that gene expression profiling was correlated with the response of ICIs in HCC patients.

Conclusions

Due to different terms of etiology, biological behavior, and type of PVTT, different strategies for HCC patients with PVTT should be formulated individually in different countries. Besides systemic pharmacological therapy, local or locoregional treatments were effective and safe choices for HCC patients with PVTT (Figure 1). LR and LT with a longer OS are considered valid options in selected HCC patients with Vp1-2 PVTT. Several unresectable HCC patients have an opportunity to receive LR or LT after tumor down-staging. HAIC, radiotherapy (external and internal), TARE, and TACE are safe and effective treatment methods in HCC patients with PVTT. Atezolizumab plus bevacizumab is considered the first choice among first-line systemic therapies for HCC patients with PVTT. For patients who have progressed on first-line treatment, durvalumab plus tremelimumab may be a better choice. Excitingly, more and more clinical trials on ICIs, CTLA-4, are ongoing. The treatment of the combination of ICIs and TKI-related adverse reactions requires more attention. Local or locoregional treatments combined with systemic therapy are considered more effective treatment options.

We hope that future clinical trials or cohort studies investigating therapy strategies are stratified by portal vein invasion grade. Biomarkers to predict response to ICIs in HCC patients should receive more attention in future research

Conflict of Interest
The authors declared that they have no conflicts of interest.

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Authors' Contributions
Zhongbao Tan and Jian Zhang contributed equally to the present manuscript (conceptualization, wrote the manuscript). Zhongbao Tan revised and edited the manuscript. All authors approved the final manuscript.

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