Review article

Management strategies for advanced hepatocellular carcinoma with portal vein tumor thrombosis

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Running title: Management of HCC with PVTT

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Abstract

Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) presents a significant therapeutic challenge due to its poor prognosis and limited treatment options. This review thoroughly examines diagnostic methods, including imaging techniques and classification systems such as the Japanese Vp and Cheng's classifications, to aid in clinical decision-making. Treatment strategies encompass liver resection and liver transplantation, particularly living donor liver transplantation after successful downstaging, which have shown potential benefits in selected cases. Locoregional therapies, including hepatic arterial infusion chemotherapy, transarterial chemoembolization, transarterial radioembolization, and external beam radiation therapy, remain vital components of treatment. Recent advancements in systemic therapies, such as sorafenib, lenvatinib, and immune checkpoint inhibitors (e.g., atezolizumab plus bevacizumab) have demonstrated improvements in overall survival and progression-free survival. These developments underscore the importance of a multidisciplinary and personalized

approach to improve outcomes for patients with HCC and PVTT.

Keywords: Hepatocellular carcinoma; Immune checkpoint inhibitors; Liver transplantation; Portal vein; Therapeutic chemoembolization,

Introduction

Background

In recent years, treatment strategies for hepatocellular carcinoma (HCC) have significantly advanced, incorporating locoregional therapies, surgical resection, liver transplantation, and systemic therapies, including immunotherapy [1-3]. Despite these advancements, portal vein tumor thrombosis (PVTT) continues to pose a major challenge in the treatment of HCC. It represents a critical prognostic factor associated with advanced disease, limited therapeutic options, and poor clinical outcomes [4-6].

The American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and groups in the Asia-Pacific region have published region-specific guidelines for treating HCC with PVTT. These guidelines account for differences in clinical practices, resource availability, and patient characteristics [7-11]. Despite these efforts, a consensus on the best treatment approach has yet to be reached, making the management of HCC with PVTT a significant clinical challenge.

Objectives

This review comprehensively summarizes and analyzes treatment strategies for HCC with PVTT. By integrating the latest research evidence and clinical insights, this article provides guidance on identifying the most optimal treatment strategies for HCC with PVTT in real-world clinical settings.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Diagnosis and classification of PVTT

PVTT is the most prevalent type of macrovascular invasion in HCC, with its occurrence at diagnosis ranging from 10% to over 40% [5, 12, 13]. It can be identified via imaging techniques, particularly on three-phase contrast-enhanced computed tomography (CT) scans, where it presents as solid lesions within the portal vein across all phases. These lesions are marked by contrast enhancement during the arterial phase and subsequent washout in the portal venous phase [14]. In contrast, portal vein thrombosis (PVT), often resulting from complications related to cirrhosis or splenectomy, does not show arterial phase enhancement and can be managed with anticoagulant therapy. Thus, accurately differentiating PVTT from PVT is crucial [15]. Another diagnostic tool, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT, has proven highly effective in distinguishing between malignant and benign thrombi. Malignant thrombi show moderate to high FDG uptake, unlike their benign counterparts [16, 17]. The non-invasive diagnostic criteria for differentiating PVTT from PVT, referred to as A-VENA, rely on the presence of three or more indicators: alpha-fetoprotein levels exceeding 1000 ng/dL, venous expansion, thrombus enhancement, neovascularity, and proximity to HCC [18].

Two widely used systems for assessing the extent of PVTT are the Japanese Vp classification [19] and Cheng's classification, as illustrated in Fig. 1 [20]. The VP classification divides the extent of tumor thrombus in the portal vein into four levels: Vp1, which involves the segmental branches of the portal vein; Vp2, affecting the second-order branches; Vp3, involving the first-order branches; and Vp4, which affects the main trunk of the portal vein and/or the contralateral branch. Cheng's classification also delineates four grades: type I, where the tumor thrombus is located in the segmental or sectoral branches of the portal vein or higher; type II, involving the right or left portal vein; type III, affecting the main portal vein; and type IV, involving the superior mesenteric vein.

Treatment options for HCC with PVTT

The current evidence-based treatment algorithms for HCC patients with PVTT are presented in Figure 2.

Liver resection

Liver resection is a curative treatment for patients with HCC and, according to the Barcelona Clinic Liver Cancer (BCLC) staging system, is considered feasible only in early-stage HCC (BCLC stage 0 or A). The presence of PVTT, regardless of tumor size or extent, is classified as BCLC stage C, making liver resection contraindicated [21]. However, in the Asia-Pacific region, liver resection is performed for selected patients outside the BCLC staging system, with several studies demonstrating moderately favorable outcomes. Retrospective analyses have shown that liver resection significantly improves overall survival (OS) in patients with HCC and PVTT, particularly in those with Child-Pugh class A liver function, except in cases involving Vp4 PVTT [22]. A systematic review of [29] studies found that the median OS was longer in patients undergoing liver resection compared to those receiving systemic therapy. The location and extent of PVTT were critical factors influencing survival outcomes, with patients exhibiting distal portal vein branch invasion achieving a 5-year survival rate of 45%, while those with main trunk invasion had survival rates of less than 15% [23]. Clinical guidelines in Korea recommend liver resection for HCC patients with PVTT if the main portal trunk is not involved and liver function is well-preserved [8]. Similarly, Japanese guidelines permit liver resection in cases of portal vein invasion up to the first branch (Vp1–[3]) [9]. In China, liver resection is advised for patients with Child-Pugh class A liver function, PVTT types I or II, and an ECOG performance status of 0–1. Patients with type III PVTT are also considered eligible for liver resection either directly or after tumor downstaging through radiotherapy [7].

Liver transplantation

PVTT has traditionally been viewed as an absolute contraindication due to its strong association with high recurrence rates and poor prognosis [24, 25]. Additionally, the use of deceased donor liver transplantation in managing HCC with PVTT is limited by the scarcity of available donor organs. However, advancements in surgical techniques have led to an increased adoption of living donor liver transplantation (LDLT) for patients with HCC and PVTT. With improvements in locoregional therapies

for HCC with PVTT, liver transplantation (LT) following successful downstaging has emerged as a key area of interest. Retrospective analyses indicate that patients with segmental PVTT who underwent LDLT experienced significantly better overall survival (OS) and disease-free survival (DFS) rates than those with lobar PVTT [26]. Similarly, studies involving patients with major vascular invasion who underwent downstaging using 3D conformal radiation therapy and transarterial chemoembolization (TACE) prior to LT showed significantly higher 3-year DFS and OS rates for those meeting the Milan criteria than those who did not [26].

Hepatic artery infusion chemotherapy

Hepatic arterial infusion chemotherapy (HAIC) is a commonly used treatment for advanced HCC. This method involves delivering chemotherapeutic agents such as platinum/oxaliplatin and 5-fluorouracil directly into intrahepatic tumor lesions via a catheter or pump. HAIC is recommended for HCC patients who have major portal vascular invasion and Child-Pugh A liver function but are not eligible for hepatectomy, radiofrequency ablation (RFA), TACE, or systemic therapy [9]. A meta-analysis of six studies demonstrated that HAIC outperformed sorafenib in HCC patients with PVTT, particularly in those with types III-IV PVTT. HAIC showed better OS, progression-free survival (PFS), and disease control rate, although it was associated with higher rates of myelosuppression [27]. Additionally, a phase III randomized controlled trial (SILIUS study) from Japan reported that combining HAIC with sorafenib improved OS compared to sorafenib alone in patients with Vp4 PVTT. However, no significant difference in median OS was observed for patients with Vp1-3 PVTT [28]. Furthermore, a study comparing TACE-HAIC combined with targeted therapy and immunotherapy to TACE alone in HCC patients with PVTT showed superior outcomes for the combination group, with significantly better OS [29].

Transarterial chemoembolization

TACE is a widely utilized technique for managing unresectable HCC with PVTT [30]. It is particularly considered for patients with good liver function and sufficient collateral circulation around the obstructed portal vein [31, 32]. In patients with type III/IV PVTT, its application remains controversial due to the associated risks of liver infarction and hepatic failure, although TACE has shown potential to extend overall survival [33]. A meta-analysis of 13 trials involving 1,933 patients was conducted to assess the safety and efficacy of TACE in managing HCC with PVTT. The study found that patients with PVTT in the main portal vein trunk had significantly worse survival rates compared to those with segmental PVTT ($P < 0.001$) [34]. The limited effectiveness of TACE as a standalone therapy highlights the importance of combining it with other treatment modalities to improve OS in patients with HCC and PVTT [35]. A study comparing the effectiveness of TACE combined with radiation therapy (RT) against sorafenib therapy demonstrated that the combination therapy achieved a median OS of 12.8 months, significantly higher than the 10.0 months observed with sorafenib alone ($P=0.04$) [36]. An analysis of 25 studies, including 2,577 patients, revealed that combining TACE with RT significantly improved the 1-year survival rate compared to TACE alone [37]. This finding suggests that the TACE and RT combination could serve as a primary treatment approach for HCC patients with macrovascular invasion [38]. The median OS was significantly longer in the TACE and sorafenib combination group compared to the sorafenib monotherapy group (8.9 vs. 5.9 months, $P=0.009$), with improved OS observed in patients with macrovascular invasion (hazard ratio [HR] 0.64; 95% CI 0.44–0.92; $P=0.02$) [39]. The clinical outcomes of combining TACE with immune checkpoint inhibitors are still limited, and further research is needed to establish their efficacy and potential benefits.

Transarterial radioembolization

Transarterial radioembolization (TARE) with yttrium-90 microspheres is recognized as an effective treatment option for HCC patients with PVTT, offering a unique approach that combines microembolization with targeted radiotherapy [40]. Two phase III studies found no significant difference in OS between TARE and sorafenib [41, 42]. However, a meta-analysis of 17 trials revealed higher 6-

month and 1-year OS rates in the TARE group (76% and 47%, respectively) compared to the sorafenib group (54% and 24%) [43]. A case report suggested that concurrent TARE and combination therapy with atezolizumab plus bevacizumab could be an effective and safe treatment regimen for patients with infiltrative HCC and PVTT [44]. Nonetheless, retrospective studies and clinical trials are warranted to validate these findings. Existing evidence suggests that TARE is an effective treatment for HCC patients with PVTT, with response rates ranging from 50% to 75% and a median survival time of approximately 10 months [40]. Although internal radiotherapy is a more invasive treatment, it delivers a sustained high dose of radiation to PVTT while sparing nearby normal liver tissue, making it particularly beneficial for patients with malignant portal vein stenosis or occlusion [45].

External beam radiation therapy

For patients with unresectable HCC and all types of PVTT, RT is recommended, targeting both the primary tumor and PVTT lesions. Advances in technologies such as three-dimensional conformal RT, intensity-modulated RT, and stereotactic body RT (SBRT) have enabled higher radiation doses to be delivered to the targeted areas while protecting adjacent normal tissues [46, 47]. Target localization for RT often utilizes CT and magnetic resonance imaging fusion based on lipiodol deposition following TACE [48]. The optimal irradiation area remains a topic of debate and should be personalized. In cases where the hepatic lesion is small and PVTT is nearby, both the tumor and PVTT can be targeted simultaneously. For larger tumors or distant PVTT, irradiation may be focused exclusively on the PVTT [49]. Studies have shown that RT, either as a standalone treatment or combined with other modalities, improves survival and quality of life in these patients. When comparing sorafenib and RT in HCC patients with Vp3-4 PVTT, RT showed a significantly better median OS after propensity score matching (PSM) (10.9 vs. 4.8 months; P=0.025) [50]. Similarly, in a Korean multicenter retrospective cohort study using PSM, RT demonstrated an improved response rate in HCC patients with PVTT [51]. The efficacy of SBRT combined with sorafenib compared to SBRT alone was retrospectively assessed in patients with HCC and PVTT [52]. The findings demonstrated that the combination therapy resulted in longer median PFS (6 vs.

3 months) and median OS (12.5 vs. 7 months) than SBRT alone, although these differences were not statistically significant.

Systemic therapy

Atezolizumab with bevacizumab

The combination of atezolizumab and bevacizumab has been established as a first-line systemic therapy for unresectable HCC, as demonstrated by its superiority over sorafenib in the IMbrave150 trial [53]. This regimen has demonstrated a strong antitumor effect in advanced HCC with Vp4 PVTT and is associated with minimal impact on hepatic function in the early stages of treatment [54], along with a favorable initial response [55]. Updated efficacy and safety data from the IMbrave150 trial show that patients with macrovascular invasion (MVI) experienced improved median OS and PFS when treated with atezolizumab plus bevacizumab compared to those treated with sorafenib (Tables 1, 2) [56]. Additionally, therapeutic outcomes of atezolizumab plus bevacizumab and lenvatinib have been found comparable for managing HCC with PVTT [57]. A multicenter cohort study conducted in South Korea demonstrated that atezolizumab plus bevacizumab achieved superior 1-year survival and PFS rates compared to TACE plus RT in HCC patients with PVTT and no metastasis. These findings suggest that atezolizumab plus bevacizumab should be considered a primary treatment option for this patient group [58].

Other immune checkpoint inhibitors

Subgroup analyses from multiple clinical trials of immune checkpoint inhibitors have assessed clinical outcomes in patients with HCC and MVI (Tables 1, 2). The HIMALAYA trial evaluated the clinical outcomes of combining tremelimumab with durvalumab versus using sorafenib alone. It showed a trend toward improved OS in patients with HCC and MVI, although the results did not reach statistical significance [59]. The CARES-310 trial compared camrelizumab plus rivoceranib with sorafenib and demonstrated statistically significant improvements in both OS and PFS for patients with HCC and MVI [60]. In the context of second-line treatment, the KEYNOTE-240 trial, which compared pembrolizumab

to placebo, was the sole study to specifically analyze clinical outcomes in patients with HCC and MVI. Despite not achieving statistical significance, pembrolizumab exhibited a trend toward better OS and PFS compared to placebo [61]. Notably, unlike the IMbrave150 trial, these clinical trials excluded patients with Vp4 or type III/IV PVTT.

Sorafenib

Sorafenib, an orally administered multi-kinase inhibitor, was the first targeted therapy approved for HCC patients with PVTT, based on the results of two phase III randomized, double-blind, placebo-controlled trials [62, 63]. The SHARP trial reported a median survival time of 10.7 months [63], whereas an Asia-Pacific study reported a median survival time of 6.5 months [10]. However, real-world outcomes may be less favorable due to potential selection bias in clinical trials [10, 64]. The phase III STAH study suggested that combining sorafenib with TACE might improve OS in HCC patients with PVTT compared to sorafenib alone, although the difference was not statistically significant [65]. Additionally, a randomized controlled trial involving 99 patients with HCC, cirrhosis, and PVTT found that combining sorafenib with radiofrequency ablation significantly improved OS rates compared to sorafenib monotherapy [66].

Lenvatinib

Lenvatinib, a multi-kinase inhibitor with antiangiogenic properties, has been shown to be effective in treating advanced HCC, as evidenced by a randomized phase III noninferiority trial [67]. In comparison to sorafenib, lenvatinib not only demonstrated similar median survival times but also achieved a higher objective response rate and longer PFS [67]. Additionally, a case report highlighted that after 11 months of treatment with lenvatinib for advanced HCC with PVTT, the PVTT became undetectable, and the vascularization of the primary tumor had resolved [68].

Conclusion

The management of HCC with PVTT requires a multidisciplinary approach that incorporates locoregional therapies, systemic treatments, and surgical interventions, all tailored to the specific clinical context of each patient. Recent advancements, such as immune checkpoint inhibitors and combination strategies like TACE with RT, have shown considerable promise in enhancing clinical outcomes. These developments highlight the critical need for personalized treatment strategies to navigate the complexities and improve the prognosis for this high-risk population.

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Project administration: JP, SJY

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Conflicts of interest

There are no conflicts of interest to declare.

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Supplementary materials

Not applicable

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Figure Legends

Fig. 1. Classification of portal vein tumor thrombosis in hepatocellular carcinoma

LPV, left portal vein; RPV, right portal vein; SMV, superior mesenteric vein.

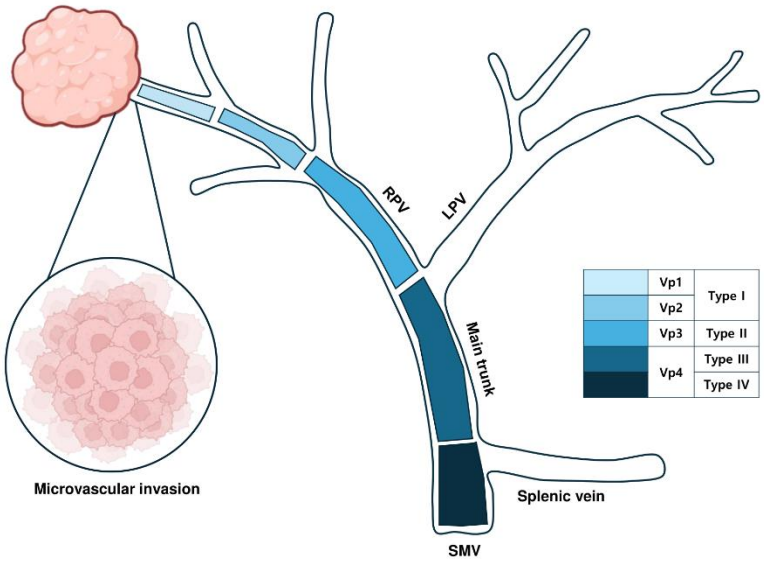
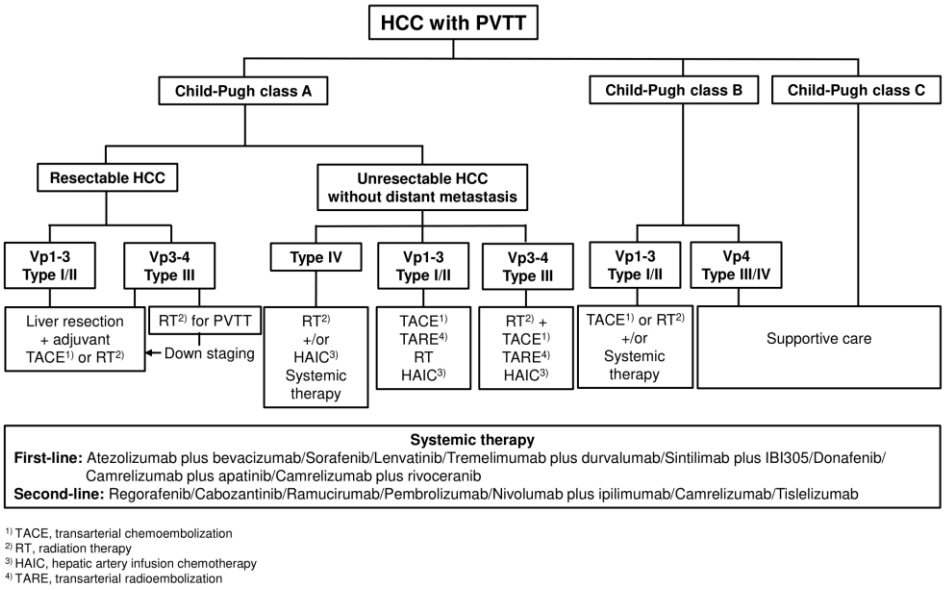


Fig. 2. Current treatment algorithm for hepatocellular carcinoma patients with portal vein tumor thrombosis

HAIC, hepatic artery infusion chemotherapy; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; RT, radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.



1) TACE, transarterial chemoembolization
2) RT, radiation therapy
3) HAIC, hepatic artery infusion chemotherapy
4) TARE, transarterial radioembolization

Tables

Table 1. Overall survival in clinical trials of first-line or second-line systemic therapy for unresectable HCC with PVTT

Author /Trial (Year)	**Phase**	**Treatment**	**Number of patients MVI/All**	**Median OS in all patients**	**HR (95% CI) in all patients**	**Median OS with MVI**	**HR (95% CI) with MVI**	
First-line								
Cheng et al IMbrave150 updated (2022)	III	Atezolizumab plus bevacizumab	129/336	19.2 months (17.0–23.7)	0.66 (0.52–0.85)	14.2 months (11.0–19.4)	0.68 (0.47–0.98)	
		Sorafenib	71/165	13.4 (11.4–16.9)	Reference	9.7 months (6.1–13.1)	Reference	
Abou-Alfa et al HIMALAYA (2022)	III	Tremelimumab plus durvalumab	103/393	16.4 months (14.2–19.6)	0.78 (0.65–0.93)	-	0.78 (0.57–1.07)	Exclude Vp4/Type III/IV
		Durvalumab	94/389	16.6 months (14.1–19.1)	0.86 (0.73–1.03)	-	0.85 (0.62–1.17)	
		Sorafenib	100/389	13.8 months	Reference	-	Reference	

				(12.3–16.1)				
Qin et al CARES-310 (2023)	III	Camrelizumab plus rivoceranib	40/272	22.1 months (19.1–27.2)	0.62 (0.49–0.80)	-	0.56 (0.32–0.99)	Exclude Vp4/Type III/IV
		Sorafenib	52/271	15.2 months (13.0–18.5)	Reference	-	Reference	
Second-line								
Finn et al KEYNOTE 240 (2020)	III	Pembrolizumab	36/278	13.9 months (11.6–16.0)	0.78 (0.61–0.998)	-	0.57 (0.29–1.13)	Exclude Vp4/Type III/IV
		placebo	16/135	10.6 months (8.3–13.5)	Reference	-	Reference	

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; OS, overall survival; PVTT, portal vein tumor thrombosis.

Table 2. Progression-free survival in clinical trials of first-line or second-line systemic therapy for unresectable HCC with PVTT

Author /Trial (Year)	**Phase**	**Treatment**	**Number of patients MVI/All**	**Median PFS in all patients**	**HR (95% CI) in all patients**	**Median PFS with MVI**	**HR (95% CI) with MVI**	
First-line								
Cheng et al IMbrave150 updated (2022)	III	Atezolizumab plus bevacizumab	129/336	6.9 months (5.7–8.6)	0.65 (0.53–0.81)	6.7 months (5.4–8.3)	0.59 (0.43–0.83)	
		Sorafenib	71/165	4.3 months (4.0–5.6)	Reference	4.2 months (2.8–5.3)	Reference	
Abou-Alfa et al HIMALAYA (2022)	III	Tremelimumab plus durvalumab	103/393	3.8 months (3.7–5.3)	0.90 (0.77–1.05)	-	-	Exclude Vp4/Type III/IV
		Durvalumab	94/389	3.7 months (3.2–3.8)	1.02 (0.88–1.19)	-	-	
		Sorafenib	100/389	4.1 months (3.8–5.5)	Reference	-	-	

Qin et al CARES-310 (2023)	III	Camrelizumab plus rivoceranib	40/272	5.6 months (5.5–6.3)	0.52 (0.41–0.65)	-	0.55 (0.44–0.70)	Exclude Vp4/Type III/IV
		Sorafenib	52/271	3.7 months (2.8–3.7)	Reference	-	Reference	
Second-line								
Finn et al KEYNOTE 240 (2020)	III	Pembrolizumab	36/278	3.0 months (2.8–4.1)	0.72 (0.57–0.90)	-	0.80 (0.42–1.51)	Exclude Vp4/Type III/IV
		placebo	16/135	2.8 months (1.6–3.0)	Reference	-	Reference	

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PFS, pr

HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PFS, progression-free survival; PVTT, portal vein tumor thrombosis.