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Review Article

Portal vein tumor thrombosis in hepatocellular carcinoma patients: Is it the end?

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ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most prevalent form of cancer globally and the third leading cause of cancer-related mortality. The incidence of portal vein tumor thrombosis (PVTT) in HCC patients is 21% at one year and 46% at three years. The presence of PVTT has consistently been associated with a poor prognosis for HCC patients over the past decades. Notably, HCC prognosis is influenced not only by the presence of PVTT but also by the degree or extent of PVTT. Currently, there is a lack of global consensus or established protocols regarding the optimal management of HCC with associated PVTT. The Barcelona Clinic for Liver Cancer classifies HCC patients with PVTT as stage C, indicating an advanced stage, and limiting treatment recommendations for these patients to systemic therapy. In recent years, there has been an increase in the availability of therapeutic options for HCC patients with PVTT. Treatment modalities include systemic therapy, transarterial chemoembolization, surgical resection, stereotactic body radiotherapy, transarterial radioembolization, and liver transplantation. An ideal therapy for each patient necessitates a multidisciplinary approach. This review article presents the latest updates in managing HCC patients with PVTT.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and accounts for the third highest rate of cancer-related mortality.[1] It has been shown that 20% of patients diagnosed with HCC exhibit macrovascular invasion (MVI), particularly in cases where the tumors are deemed unresectable. The prevalence of portal vein tumor thrombosis (PVTT) in patients with cirrhosis ranges from 0.6% to 26.0%,[2] whereas in those with HCC, it varies from 20% to 44%.[3] In these instances, the likelihood of developing PVTT within 1 and 3 years of diagnosis is 21% and 46%, respectively.[4] MVI including PVTT, and/or hepatic vein invasion have been linked to a poor prognosis, as evidenced by a median survival rate of 2–5 months, even with optimal supportive treatment,[5] with an ongoing controversy about the prognostic variables for this condition.[6] There is a lack of worldwide agreement or standardized guidelines regarding the care of HCC with PVTT due to the heterogeneity of the tumor and its diverse tumor behavior, necessitating a multidisciplinary and personalized management plan for each patient. PVTT, the prevailing type of MVI, is observed in 44.0%–62.2% of patients diagnosed with HCC,[7] with a prevalence ranging from 25% to 50%.[8] The prevalence of hepatic vein tumor thrombus (HVTT) is relatively uncommon, ranging from 1.4% to 4.9%.[9] However, PVTT prevalence is underestimated, as many patients present late in the course of the disease.[10] Besides, it is found incidentally in 14% of biopsies collected from patients with HCC and in about 62% of autopsied livers.[11]

Several characteristics have been identified as independent risk factors for PVTT in patients with HCC. These risks include liver cirrhosis, a serum alkaline phosphatase level exceeding 100 IU/L, a tumor size larger than 8 cm, an incomplete tumor capsule, and invasion of neighboring organs.[12] Furthermore, it has been observed that larger tumor size, specifically those beyond 5 cm, and elevated serum alpha-fetoprotein (AFP) levels, serve as robust preoperative indicators for vascular invasion, particularly portal

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venous invasion.[13,14] Additionally, a statistically significant association was found between portal vein thrombosis (PVT) and maximum tumor diameter, as well as between multifocality and maximum tumor diameter; all three factors are independent of AFP.[15] Classification of patients with HCC according to their genomic profiling, landscape of mutations, and pathways of the development and progression into proliferative and non-proliferative types revealed that the proliferative type exhibited a high prevalence of chromosomal instability, microRNA deregulations, and aberrant epigenetic signatures. These patients showed aggressive tumor biology, elevated AFP levels, a higher incidence of MVI, and high-grade histology and poor tumor differentiation.[6] MVI involves the infiltration of tumor cells into numerous microvascular structures and signals the potential for tumor spread and metastasis within the liver, resulting in PVTT or distant metastasis.[16] MVI is a risk factor associated with postoperative recurrence and overall survival (OS) in patients,[16] serving as an indicator of a poor prognosis.[17] Accurate preoperative evaluation of MVI is essential for determining appropriate treatment strategies.[18]

This review aims to provide a comprehensive analysis and documentation of the progress in managing patients with HCC and PVTT. It will also discuss the available treatment options that have contributed to improved outcomes and prolonged survival in this complex scenario.

2. Diagnosis and classification of PVTT

Diagnosing PVTT is vital in determining the prognosis and clinical staging of HCC.[19,20] From a clinical standpoint, it is essential to differentiate between malignant PVTT and benign PVT. While the current gold standard for diagnosing PVTT is the histopathological examination, clinical diagnosis mainly depends on triphasic computed tomography (triphasic CT) scans and/or magnetic resonance imaging (MRI).[21] Benign PVT is characterized by the absence of pulsations in the Doppler study, a lack of arterial enhancement in triphasic CT or MRI, and is often associated with cirrhosis following splenectomy or with coagulation disorders that may improve or resolve with anticoagulant therapy.[22,23] In contrast, the malignant criteria for PVTT include a pulsatile pattern in the Doppler study, arterial enhancement during the triphasic CT study, neo-vascularity within PVTT, and a thrombus with a diameter of >23 mm, in addition to the presence of an HCC lesion, whether in close proximity to PVTT or not.[22,24–26] Fluorine-18-fluorodeoxyglucose-positron emission tomography/CT (18F-FDG PET/CT) demonstrated favorable diagnostic efficacy in distinguishing malignant thrombus that shows a moderate to high avidity for FDG.[27,28] It was documented that maximum standardized uptake value of malignant thrombus (6.37 ± 2.67) is significantly higher than that of benign thrombus (2.87 ± 1.47; $P < 0.01$).[22] Additionally, a high serum AFP level above 1000 ng/dL is another characteristic studied in relation to PVTT.[26] Sherman *et al.*[26] developed noninvasive diagnostic criteria called the A-VENA criteria, which allow for accurate differentiation between PVTT and PVT using three or more criteria. Various research reports have established several categorization methods for PVTT.[29,30]

Currently, two primary classification systems for staging PVTT are discussed in Table 1: the Japanese classification and the Chinese Cheng's classification.[31–40] The Japanese classification categorizes tumors based on the extent of PVTT into five categories, namely Vp0-Vp4.[34] In contrast, the Chinese Cheng's classification system encompasses four levels determined by the extent of tumor thrombus, including Type I0-Type IV.[32] There's a superiority of Chinese Cheng's classification over the Japanese classification in terms of disease assessment, treatment guidance, and prognostic evaluation in PVTT.[35] Therefore, it is highly suggested that Chinese Cheng's classification be utilized to categorize the extent and impact of PVTT. More recently, Cao *et al.*[41] introduced a classification system utilizing a decision tree algorithm to address the presence of PVTT and HVTT in HCC patients. This system consists of 13 subclasses, allowing for personalized management strategies. However, the effectiveness of this system requires additional evaluation.[41]

3. The prognostic role of PVTT in patients with HCC and current management status

PVTT has been proven to be an independent factor in the unfavorable prognosis and reduced survival time in patients with HCC. Llovet *et al.*[42] investigated the natural progression of HCC with PVTT and found that the median survival time for these patients, in the absence of any therapy, is 2.7 months. Other studies have also shown that patients with HCC and PVTT have a median survival time of 2.7–4.0 months without treatment.[43,44] Additionally, a

Table 1
Comparison between classification systems of PVTT.

Aspect	Japanese classification[a]	Chinese Cheng's classification
Classification criteria	• Vp0: No tumor thrombus in the portal vein • Vp1: Presence of a tumor thrombus distal to the second-order branches of the portal vein (without direct involvement) • Vp2: Invasion of the second-order branches of the portal vein • Vp3: Presence of the tumor thrombus in the first-order branches of the portal vein • Vp4: Tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both)	• Type I0: Microscopic portal invasion • Type I: Tumor thrombus involving the segmental branches of the portal vein or above • Type II: Tumor thrombus involving the right/left portal vein • Type III: Tumor thrombus involving the main portal vein • Type IV: Tumor thrombus involving the superior mesenteric vein
Survival rates	• Vp0: 91.6%, 74.2%, and 57.6% (1-, 3-, and 5-year) • Vp1: 78.6%, 52.6%, and 38.7% • Vp2: 59.2%, 31.8%, and 23.8% • Vp3 or Vp4: 50.4%, 25.8%, and 18.4%	• Type I: 54.8%, 33.9%, and 26.7% (1-, 2-, and 3-year) • Type II: 36.4%, 24.9%, and 16.9% • Type III: 25.9%, 12.9%, and 3.7% • Type IV: 11.1%, 0%, and 0%
Application	Based solely on the presence of macroscopic hepatocellular carcinoma (HCC).	Incorporating both macroscopic portal vein tumor thrombosis (PVTT) and microscopic PVTT.
Overall assessment	Studies have demonstrated that the Chinese Cheng's classification outperforms the Japanese classification in assessing the disease, guiding treatment, and evaluating prognosis in PVTT.	
Limitations	Both classifications are strictly anatomical with regard to the portal venous system and fail to consider underlying liver function or the extent of tumor involvement within the hepatic parenchyma.	
Refs.	31, 34–38, 40	32, 33, 36, 39

[a] The Liver Cancer Study Group of Japan classified PVTT into five grades on the degree of tumor involvement.

study by Mähringer-Kunz *et al.*[45] recruited 1317 patients with HCC, of whom 484 (36.8%) had PVTT. The study found that the median survival for patients with PVTT was 7.2 months, compared to 35.7 months in those without PVTT ($P < 0.001$). According to another report, patients who presented with PVTT at the outset of the disease or due to HCC recurrence or advancement had an anticipated survival period of around three months while receiving optimal supportive treatment.[46] Moreover, the presence of PVTT does not solely determine the prognosis of HCC but is also significantly influenced by the extent of PVTT.[47] In a retrospective analysis conducted by Giannelli *et al.*,[48] 150 patients diagnosed with HCC were examined. The study revealed that PVTT emerged as the most significant and dependable adverse prognostic factor. A significant correlation was also reported between the tumor differentiation grade and vascular invasion.[49]

Besides, the abnormal expression of biomacromolecules such as circular RNAs, long non-coding RNAs, stress-inducible protein 1, and PD-L1 in HCC patients strongly correlates with MVI.[50] The increased levels of angiogenic factors in poorly differentiated HCC with high microvascular density may partially explain the stronger association between poor differentiation and vascular invasion.[51] Currently, there is a lack of universally accepted international guidelines regarding the management of HCC patients with PVTT. According to some classification systems like the Barcelona Clinic Liver Cancer (BCLC) and some treatment guidelines in Europe and America, HCC patients with PVTT are categorized as the BCLC stage C, indicating a significantly progressed stage of the disease.[52–54]

4. Available treatment options for patients with HCC and PVTT

Although there is no universally accepted guideline, many treatment options are available based on existing regional recommendations and clinical practices for patients with HCC and PVTT.[55–61] The graphical abstract illustrates these options, which will be further discussed.

4.1. Systemic therapies

Conventional cytotoxic chemotherapy is generally not recommended for patients with HCC and PVTT due to impaired liver function, limited survival benefits, and patients' intolerance to treatment.[62] In contrast, targeted therapy is regarded as the primary choice for systemic therapy in these patients, as indicated in most treatment guidelines.[52,53] Recent advances in systemic and immune therapy for HCC have led to a wide array of medications, either as a single agent or in combination.[52,54]

4.1.1. Atezolizumab-bevacizumab

The combination of atezolizumab plus bevacizumab (AteBeva) is superior to sorafenib, as proven in the IMbrave150 trial, and has become the first-line systemic treatment for untreated, unresectable HCC.[63] The powerful antitumor effect of AteBeva has been demonstrated for advanced HCC with Vp4 PVTT.[64] This drug combination may have less impact on hepatic function during the early period and has shown a good initial therapeutic response.[65] The effectiveness of AteBeva and lenvatinib was comparable for the treatment of HCC with PVTT.[66]

4.1.2. Sorafenib

It is an orally administered small-molecule multi-kinase inhibitor (MKI), authorized as the initial targeted therapy for HCC patients with PVTT based on the findings of two phase III randomized, double-blind, and placebo-controlled studies.[62,67] The median survival time (MST) of patients who received sorafenib alone was reported to be 10.7 months in the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial.[67] Another study conducted in the Asia-Pacific region reported an MST of 6.5 months.[67] The survival rate was only extended by 2–3 months compared with the placebo,[68] indicating that the observed results fell short of expectations.[55] In addition, the actual outcomes of sorafenib in real-life settings may be less favorable than those shown in controlled trials, possibly due to selection bias.[67,68] Regarding the effectiveness of sorafenib in patients with HCC and PVTT, Jeong *et al.*[69] studied the effect of sorafenib monotherapy in 30 patients and reported a median survival of 3.1 months, with a partial response observed in only three (10.0%) patients.

Sorafenib is also reported to be associated with several frequent adverse effects, including hand-foot skin reactions, gastrointestinal disturbances, and hepatic damage. These adverse events may lead to serious consequences.[69] Kuo *et al.*[70] conducted a study that recruited 113 patients. Among these patients, 56 (49.5%) were classified as Vp3 and 57 (50.5%) as Vp4. The study revealed that the incidence rate of hepatic decompensation was 18.2% for Vp3 patients and 37% for Vp4 patients. Their multivariate analysis showed that Vp4 and a baseline AFP level of $\geq$200 ng/mL were the independent variables associated with hepatic decompensation.[70] Hence, the researchers proposed that sorafenib should not be recommended as the initial therapeutic option for patients with Vp4 and elevated AFP levels.[71]

The results of a phase III STAH study indicated that the combination of sorafenib and TACE was associated with a tendency to prolong OS in HCC patients with PVTT compared to sorafenib alone, although this difference was not statistically significant.[72] Another comparative study evaluating the efficacy of TACE versus sorafenib for treating HCC patients with PVTT revealed that TACE exhibited a notably higher rate of disease control and a considerably prolonged median OS time.[73] Additionally, a report revealed a comparable disease control rate between the combined administration of sorafenib and TACE (MVT: seven months) with sorafenib monotherapy (MVT: six months).[74] In a randomized controlled trial (RCT) conducted by Giorgio *et al.*,[75] a cohort of 99 patients diagnosed with HCC, cirrhosis, and PVTT was examined. The study revealed that patients who received a combination of sorafenib and radiofrequency ablation exhibited significantly higher rates of OS at 1, 2, and 3 years (60%, 35%, and 26%, respectively) compared to those treated with sorafenib alone (37%, 0%, and 0%).[75] In a separate investigation, it was shown that the MST of HCC patients with PVTT in the primary trunk or the first branch was comparable following treatment with sorafenib (4.3 months) or radiation (5.9 months).[76]

4.1.3. Lenvatinib

It is a newly developed multi-kinase inhibitor with anti-angiogenic properties. Its effectiveness in treating advanced HCC has been demonstrated in a randomized phase III noninferiority trial.[77] Compared to sorafenib, lenvatinib showed noninferiority in terms of MST, while exhibiting a greater objective response rate and more prolonged progression-free survival (PFS). Additionally, lenvatinib was associated with tolerable side effects, such as hypertension, diarrhea, reduced appetite, and decreased weight.[77] In a case report by Takeda *et al.*,[78] after 11 months of treatment with lenvatinib for advanced HCC and PVTT, the PVTT became undetectable, and the vascularization of the primary tumor disappeared. The patient survived for over five years following the commencement of lenvatinib monotherapy. However, it is worth noting that specific adverse effects, including thrombocytopenia and proteinuria, were observed during treatment.[78]

4.1.4. Other systemic therapies

In addition to sorafenib and lenvatinib, many systemic therapies have been investigated and utilized in clinical settings as a secondary treatment option for patients with HCC and PVTT.[56] Regorafenib was the first pharmaceutical agent to demonstrate effectiveness in patients intolerant to sorafenib, albeit with an MST of just 10.6 months.[79] The most commonly observed adverse effects of regorafenib were hypertension and hand-foot skin reaction.[79] Currently, significant progress is being made in drug development, particularly in identifying biomarkers that may predict the efficacy of immunotherapies, which has become a key area of focus for future research.[80]

4.2. TACE

For a long time, TACE was avoided in patients with HCC and PVTT due to concerns about potential liver failure resulting from ischemia.[81] However, recent advancements in research have shifted this perspective.[57] In a prospective controlled trial, Lee *et al.*[82] suggested that patients with PVTT might benefit from TACE if their liver function is satisfactory (Child-Pugh A), and there is adequate collateral circulation around the obstructed portal vein.[82] A retrospective study involving 73 HCC patients with PVTT found that those who received TACE (22 with conventional TACE and 51 with drug-eluting beads TACE) had OS rates of 59% and 14% at 12 and 24 months, respectively, with a median survival of 12.3 months.[83] Drug-eluting microsphere-TACE was reported to be superior to conventional TACE for HCC patients with PVTT.[84] Subsequent studies have further examined the application of TACE in this patient population, yielding comparable results. For instance, a retrospective analysis by Chung *et al.*,[85] reviewed survival data for 125 patients with HCC and PVTT. The findings indicated that the TACE group had a significantly higher MST compared to the supportive therapy group (5.6 months *vs.* 2.2 months, $P < 0.001$).[85] Additionally, two prospective trials corroborated the notion that TACE offers a substantial survival advantage over conservative therapy.[35,86]

Nevertheless, the extent of PVTT may impact the therapeutic efficacy of TACE. Silva *et al.*[87] conducted a Meta-analysis of 13 trials, encompassing 1933 patients, to assess the safety and effectiveness of TACE in the management of HCC with PVTT. The study revealed an MST of 8 months, with a range of 5–15 months. Additionally, the incidence of liver failure and post-treatment complications were reported at 1% and 18%, respectively. The study found that patients diagnosed with PVTT in the main portal vein trunk had significantly worse survival rates compared to those with segmental PVTT ($P < 0.001$).[87] Similarly, Xiang *et al.*[88] conducted a multicenter retrospective analysis including 1040 patients. The study's findings indicated that TACE demonstrated a statistically significant enhancement in the OS rate compared to the alternative best supportive care for patients classified as type I-III. However, this improvement was not observed in patients classified as type IV.[88] Furthermore, Kim *et al.*[89] conducted a study that analyzed the survival outcomes of 331 patients with HCC and segmental PVTT with TACE as their primary treatment. Their findings indicated that TACE is not advisable for patients with significant tumor burden, extrahepatic dissemination, or Child-Pugh class B or C, due to the associated unfavorable prognosis.[89]

In a retrospective analysis conducted by Yang *et al.*,[90] the clinical data of 379 patients diagnosed with HCC and PVTT were examined. These patients underwent TACE as their initial therapy. The study revealed that patients with positive lipiodol deposition in PVTT had a significantly improved survival outcome.[90] While the aforementioned studies suggest that TACE may be considered a treatment option for HCC patients with PVTT, it is important to note that the effectiveness of TACE as a standalone therapy remains constrained, with an MST of less than ten months.[58] The use of TACE in conjunction with other treatment modalities represents a novel therapeutic approach that shows promise for enhancing the OS outcomes in patients diagnosed with HCC and PVTT. For instance, Takano *et al.*[91] documented a case study involving a patient with HCC and PVTT, who underwent curative hepatectomy after treatment with TACE and sorafenib, achieving a disease-free survival (DFS) period exceeding 12 months. Furthermore, a comprehensive analysis of 25 studies, encompassing a total of 2577 patients, revealed that those who received a combination of TACE and radiation therapy (RT) exhibited a notably superior 1-year survival rate compared to those who received TACE alone (odds ratio (OR) 1.36, 95% confidence interval (CI) 1.19–1.54).[92] Thus, combined TACE and RT may be considered as a first-line treatment option for HCC patients with MVI.[93] Chu *et al.*[94] employed propensity score matching analysis to compare the efficacy of combining TACE with RT *vs.* combining TACE with sorafenib in treating HCC patients with PVTT. The study results indicated no statistically significant differences in PFS and OS outcomes between these two combined treatment approaches.

4.3. Locoregional ablation therapies

Combination therapy of locoregional ablation with sorafenib was associated with a hazard ratio for death of 0.58 compared to sorafenib ($P < 0.001$), improved OS at 12 months (67.2% *vs.* 54.6%), and improved PFS (6.8 months *vs.* 4.3 months).[95] The National Cancer Comprehensive Network (NCCN) guidelines acknowledge that there is currently insufficient evidence to recommend systemic therapy over locoregional therapy,[96] and recent studies of locoregional therapies, such as TACE, transarterial radioembolization (TARE) and other ablative therapies, have demonstrated benefits in HCC with PVTT in select cases.[96] Over the last decade, RCTs have shown a survival benefit when ablation is added to treatment. One study compared cryotherapy plus sorafenib to sorafenib alone, demonstrating improved survival in patients with PVTT and Child-Pugh A or B (OS of 12.5 months *vs.* 8.6 months).[97] Another study compared radiofrequency ablation plus sorafenib to sorafenib alone in patients with main PVTT and Child-Pugh A, showing improved survival rates (1-, 3-, and 5-year survival rates of 63%, 30%, and 20% *vs.* a 1-year survival rate of 0%).[75,98] Additionally, a prospective study of microwave ablation following TACE for HCC with PVTT demonstrated improved OS compared to a historical cohort of patients treated with TACE (13.5 months *vs.* 9.5 months).[99]

4.4. RT

Previously, RT was not considered a suitable therapeutic option for HCC patients with PVTT due to the limited capacity of the cirrhotic liver to withstand radiation exposure.[100] However, the treatment landscape for HCC has undergone significant transformations because of the rapid advancements in precision radiation technology and the availability of novel isotopes.[101–103] Several prospective and retrospective studies have utilized RT in managing HCC and demonstrated its potential to enhance prognosis, particularly in patients with PVTT.[59,101,104,105] In their study, Yu *et al.*[106] investigated the impact of RT on the management of HCC patients with PVTT. The results have shown that patients who responded to the treatment had an MST ranging from 15 to 20 months.[106]

The study by Kishi *et al.*[107] evaluated the efficacy and safety of preoperative stereotactic body radiation therapy (SBRT) in HCC patients with PVTT, revealing a significant pathological response rate and a low occurrence of adverse effects. Additionally, an open-label RCT assessed the effectiveness of neoadjuvant three-

dimensional conformal radiotherapy (3D-CRT) in patients with HCC and PVTT following hepatectomy. This study found that the 1- and 2-year OS rates were significantly higher in the neoadjuvant 3D-CRT group compared to the surgery-alone group (75.2% and 27.4% *vs.* 43.1% and 9.4%, respectively; $P < 0.001$).[108] Furthermore, another randomized controlled study showed that postoperative adjuvant intensity modulated radiation therapy (IMRT) resulted in a substantial improvement in the OS rates at 1-, 2-, and 3-year (76.9%, 19.2%, and 11.5% compared to 26.9%, 11.5%, and 0%, respectively; $P = 0.005$).[109]

In a published Meta-analysis by Li *et al.*[110] encompassing 15 studies and 2359 patients, the researchers assessed the effectiveness and safety of several treatment modalities in patients with advanced HCC and PVTT. The treatment modalities considered in the study included SBRT, hepatic arterial infusion chemotherapy (HAIC), sorafenib, TACE, SBRT combined with TACE, 3D-CRT combined with HAIC or TACE, and TACE combined with sorafenib. The findings indicated that combining RT with HAIC or TACE resulted in superior survival outcomes compared to other treatment regimens.[110] In a retrospective analysis conducted by Im *et al.*,[111] the authors examined 985 patients with HCC and PVTT who received RT. The results indicated that the combined treatment strategy using RT was associated with improved OS compared to RT without combination therapy. Similarly, Wu *et al.*[112] proposed that combining RT and TACE is a more favorable treatment option for patients with advanced HCC and PVTT, compared to using TACE or RT as standalone therapies.[112,113]

Furthermore, Li *et al.*[114] proposed that the sequential administration of RT followed by TACE is a practical therapeutic approach for HCC patients with PVTT. Regarding the radiation dose, Im *et al.*[111] found that an equivalent radiation therapy dose of more than 45 Gy significantly improves OS.

In addition, Iodine-125 (^{125}I) seed implantation, a type of brachytherapy, has been extensively studied for treating HCC with PVTT, yielding positive therapeutic outcomes.[115] In clinical practice, ^{125}I seed implantation is commonly combined with TACE or portal vein stent procedures.[115,116] Yuan *et al.*[115] conducted a Meta-analysis of eight studies comprising 1098 patients, aiming to assess the effectiveness and safety of ^{125}I seed implantation in patients with HCC and PVTT. The analysis results demonstrated that the combination of ^{125}I seed implantation and TACE significantly enhanced the survival rate of these patients and reduced the risk of mortality, without increasing the rate of adverse events.[115] Furthermore, another retrospective study showed that the integration of endovascular implantation of ^{125}I seed with stent insertion, TACE, and sorafenib may provide superior OS and PFS outcomes compared to the combination of TACE and sorafenib in patients with HCC and PVTT.[117]

TARE utilizing yttrium-90 (90Y) is a specialized therapeutic approach that combines microembolic surgery with radiotherapy.[46] Existing data indicates that TARE is a reliable and efficient therapeutic approach for patients diagnosed with HCC and PVTT. The response rates seen with TARE in these patients range from 50% to 75%, and the MST is estimated to be around ten months.[46] The results of two phase III studies indicated no statistically significant difference in OS between TARE and sorafenib.[118,119] A more comprehensive Meta-analysis including 17 trials revealed that the 6-month and 1-year OS rates were 76% and 47% in the TARE group, respectively, which were higher compared to the sorafenib group (with rates of 54% and 24%).[120] The commonest adverse events associated with TARE are abdominal discomfort, nausea, and exhaustion.[120] In their study, Spreafico *et al.*[121] reported a significant correlation between bilirubin level, the extent of PVTT, and tumor load with the prognosis of patients with HCC and PVTT after TARE. Based on their findings, the authors developed a prognostic stratification system to effectively identify appropriate candidates for this treatment.[121] This predictive model has been validated through two retrospective single-center studies, and its efficacy is recommended to be further assessed in prospective studies.[122,123]

In contrast to external radiotherapy, internal radiotherapy is a more invasive procedure.[124] Nevertheless, it offers the advantage of continuously delivering a high radiation dose to the PVTT while minimizing harm to adjacent healthy liver tissues. This is particularly beneficial for individuals with malignant stenosis or occlusion of the portal vein. Combining internal radiotherapy with a portal vein stent effectively alleviates portal hypertension and serves as a preventive measure against the reoccurrence of PVTT within the portal vein.[124–126]

However, the optimal choice between external radiation and internal radiotherapy for patients with HCC and PVTT remains uncertain. A retrospective study conducted by Tan *et al.*[124] demonstrated that the combination of internal irradiation and TACE resulted in a longer OS than the combination of external radiotherapy and TACE. The median OS was reported to be 13.1 months for the former group, whereas it was 8.0 months for the latter group.[124]

4.5. Liver resection

Liver resection is considered the primary therapeutic approach for patients with HCC, as it offers the most favorable opportunity for achieving a cure.[52] Nevertheless, the BCLC staging system classifies the presence of PVTT, regardless of its size, as a contraindication for surgery.[53] Despite this, numerous centers have suggested and implemented aggressive surgical resection as a treatment option for certain selected patients with HCC and PVTT, taking into account advancement in surgical techniques.[127,128]

The potential utilization of surgical intervention may be considered viable when both hepatic mass and the PVTT can be completely resected without distant metastases or liver function impairment.[127] Hepatectomy and thrombectomy procedures are performed based on the specific characteristics of the tumor and the existing PVTT.[127]

Embolic resection of PVTT is typically performed when the PVTT is located within the liver resection line, specifically categorized as type I to II or Vp1 to Vp3. This surgical approach can include segmental hepatectomy and hemi hepatectomy. Conversely, if the PVTT extends beyond the resection line (Type III to IV or Vp4), a combination of hepatectomy and thrombectomy may be considered.[127] Portal vein excision and repair are recommended when the PVTT invades the main portal vein wall.[60,129] Until now, several studies have assessed the effectiveness of surgical intervention in patients with HCC and PVTT, as presented in Table 2.[32,130–137]

4.6. Liver transplantation

Numerous studies have extensively evaluated liver transplantation (LT) as a potential treatment option for HCC patients with PVTT. However, PVTT continues to be regarded as an absolute contraindication due to its significance as a predictor of high recurrence rates and unfavorable prognosis.[138,139] Recently, several centers have attempted to perform LT in patients with HCC accompanied by PVTT. Cumulative data analysis has demonstrated that LT may confer a survival advantage for certain HCC patients with PVTT.[140]

In their study, Xu *et al.*[141] conducted a retrospective analysis of survival data of 24 patients with HCC and PVTT who underwent deceased donor LT (DDLT). They compared the outcomes of these patients with those of 27 patients who underwent liver resection.

Table 2
Outcomes of liver resection in HCC patients with PVTT.

Author, year	Study design	Number of participants	Interventions	*Median survival time (MST, months)	*Overall survival (OS)
Kudo, *et al.* (2020).[130]	Retrospective	29,081	Patients treated with resection, transcatheter arterial chemoembolization (TACE), and local ablation therapy	Vp0: 97.0 Vp1: 61.2 Vp2: 25.9 Vp3/Vp4: 15.7	–
Hatano, *et al.* (2018).[131]	Retrospective	400	Patients underwent macroscopic curative resection with adjuvant hepatic arterial infusion chemotherapy	Vp3: 24.7 Vp4: 18.1	5-year OS rates: 25.7%.
Kokudo, *et al.* (2016).[132]	Retrospective	2093	Patients underwent liver resection	Vp1: 49.6 Vp2: 29.9 Vp3: 18.9 Vp4: 10.9	The survival benefit was not statistically significant, except in patients with PVTT invading the main trunk or contralateral branch. The postoperative 90-day mortality rate in the liver resection group was 3.7% (68 patients).
Zheng, *et al.* (2016).[133]	Retrospective	230	96 patients underwent hepatic resection, and 134 patients underwent TACE	33	OS rates at 1-, 3-, and 5-year in the hepatic resection group were 86.5%, 60.4%, and 33.3%, respectively, which were significantly higher than those in the TACE group (1-year: 77.6%; 3-year: 47.8%; and 5-year: 20.9%; $P = 0.021$).
Zhang, *et al.* (2016).[134]	Retrospective	252	Patients with HCC and type I/II PVTT underwent hepatic resection, divided into two groups based on whether they received en bloc resection ($n = 113$) or peeling-off resection ($n = 139$).	15	En-bloc resection is safe and confers a survival advantage compared to peeling-off resection in HCC patients with PVTT. 1-year OS rates: 69% 2-year OS rates: 46% 3-year OS rates: 34%
Wei, *et al.* (2016).[135]	Retrospective	74	Patients underwent hepatic resection	14	1-year OS rates: 74% 2-year OS rates: 40% 3-years OS rates: –
Xiao, *et al.* (2015).[136]	Prospective	234	Patients underwent hepatic resection	18	1-year OS rates: 40% 2-year OS rates: 21% 3-year OS rates: 16%
Ye, *et al.* (2014).[137]	Retrospective	338	Divided into four groups: conservative treatment group ($n = 75$), the TACE group ($n = 86$), hepatic resection group ($n = 90$), and hepatic resection with postoperative TACE group ($n = 87$).	15	1-year OS rates: 49% 2-year OS rates: 37% 3-year OS rates: 19%
Shi, *et al.* (2011).[32]	Retrospective	441	Patients underwent partial hepatectomy	–	1-, 2-, and 3-year OS rates for types I to IV PVTT were 54.8%, 33.9%, and 26.7%; 36.4%, 24.9%, and 16.9%; 25.9%, 12.9%, and 3.7%; and 11.1%, 0%, and 0%, respectively

*Note: MST refers to the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, at which half of the patients in a group diagnosed with the disease are still alive. In a clinical trial, measuring the median survival is one way to see how well a new treatment works. OS refers to the length of time from the date of diagnosis or the start of treatment for a disease, such as cancer, during which patients diagnosed with the disease are still alive. Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis.

The OS rates at six months, one year, and two years were 66.7%, 29.5%, and 23.6% for the LT group, compared to 33.3%, 22.2%, and 14.8% for the resection group, respectively ($P = 0.0335$). However, it is worth noting that the tumor recurrence rate was as high as 66.7% in the LT group.[141]

Zhou *et al.*[11] compared LT with other treatment modalities for patients with HCC and PVTT. They reported that the LT group's one-year and three-year OS rates were 30% and 10%, respectively. These rates were superior to those observed in patients receiving conservative treatment, which yielded one-year and three-year OS rates of 12% and 4%, respectively.[11] However, the LT group's OS rates were inferior to those achieved through resection combined with adjuvant chemotherapy, which resulted in one-year and three-year OS rates of 70% and 20%, respectively.[11]

HCC patients with type 1 or 2 PVTT may be acceptable candidates for DDLT.[142] Due to the scarcity of available donor organs, the use of DDLT remains restricted when managing HCC with PVTT.

However, there has been a rise in the number of living donor LT (LDLT), offering a potential therapeutic avenue for treating HCC patients with PVTT.[61] In a retrospective study by Choi *et al.*,[61] a cohort of 34 HCC patients with PVTT who underwent LDLT was analyzed. The one-, three-, and five-year OS and DFS rates for the segmental PVTT group were 85.0%, 60.3%, 50.3%, 68.2%, 63.9%, and 63.9%, respectively. These rates were better compared to the lobar PVTT group, which had rates of 71.4%, 14.3%, 14.3%, 28.6%, 14.3%, and 14.3%, respectively.[61] Lee *et al.*[143] reported comparable findings.

Additionally, the use of bridging therapy before LT can assist in achieving downstaging in HCC and PVTT patients, enabling them to fulfill the necessary criteria for LT. Examples of bridging therapies that can be employed include TACE, HAIC, TARE, and concurrent chemoradiation therapy.[144] In a study by Chapman *et al.*,[145] 17 HCC patients with macrovascular invasion underwent LT following successful downstaging using TACE to meet the Milan criteria. The outcomes of this intervention were favorable, with a five-year OS rate reaching 93.8%.[145] In a report by Levi Sandri *et al.*,[146] four patients in BCLC stage C were subjected to TARE using 90Y prior to LT. All patients achieved a complete response of their PVTT and subsequently had LT. The median DFS seen in this cohort was 39.1 months.[146] Ettorre *et al.*[144] described a similar case report in which a patient with HCC and PVTT underwent TARE and subsequently

Table 3
Studies evaluating liver transplantation for HCC patients with PVTT: outcomes and characteristics.

Author, Year	Study design	Number of patients	Downstaging before LT	Type of donor	Outcomes
Yang, *et al.* (2020)[149]	Retrospective	$n = 75$ (HCC patients with PVTT (Vp1-Vp4))	No	DDLT	Three-year RFS and OS rates were 40% and 65.4% for Vp2-Vp3 PVTT patients, and 21.4% and 30.6% for Vp4 PVTT patients.
Assalino, *et al.* (2020)[150]	Retrospective	30	Yes	DDLT/ LDLT	OS rates: 76.7%, 66.2%, 59.6% at 1-, 3-, and 5-year, respectively. DFS rates were 63.3%, 56.3%, and 56.3% at 1-, 3-, and 5- year, with a median HCC RFS time of 87 months.
Soin, *et al.* (2020)[14]	Prospective	$n = 45$ (25 with PVTT, mainly Vp1-Vp3 after successful downstaging and 20 with Vp1/2 PVTT without previous treatment)	Yes	LDLT	1- and 5-year OS and RFS rates were 82%, 57%, and 77% and 51%, respectively.
Jeong, *et al.* (2017)[151]	Retrospective	17	Yes	LDLT	The rates of 1- and 3-year DFS were 70.6 and 57.8 %, respectively. 1- and 3-year OS rates were 87.4% and 60.5 %.
Choi, *et al.* (2017)[61]	Retrospective	34	No	LDLT	Lobar PVTT had dismal 5-year DFS and OS rates of 14.3%, while segmental PVTT had favorable 5-year DFS and OS rates of 63.9% and 50.3%, respectively.
Han, *et al.* (2016)[152] 2016	Retrospective	8	Yes	LDLT	1-year DFS was 87.5%.
Zhou, *et al.* (2011)[11]	Retrospective	12	No	DDLT	1- and 3-year OS rates were 30.0% and 10.0%, respectively.

Abbreviations: DDLT, deceased donor LT; DFS, disease-free survival; HCC, hepatocellular carcinoma; LT, liver transplantation; LDLT, living donor LT; OS, overall survival; PVTT, portal vein tumor thrombosis; RFS, recurrence-free survival.

had LT, exhibiting a survival period exceeding four years.[144,147] Jeng *et al.*[148] described another representative case where a patient with HCC and right main PVTT underwent DDLT following effective downstaging with multimodal therapy, achieving a survival period exceeding 20 months without any tumor recurrence or metastasis.[148]

A summary of studies evaluating LT as a treatment option for HCC patients with PVTT is shown in Table 3.[11,14,61,149–152]

5. Conclusions

To sum up, PVTT represents a significant clinical challenge in managing HCC, leading to poor outcomes and survival rates. This review has explored various treatment modalities for PVTT, including systemic therapies, TACE, locoregional therapies, and liver resection. However, the limitations of these existing methods are critical to acknowledge; there is a lack of universally accepted guidelines specific to HCC with associated PVTT, and outcomes can vary greatly due to tumor heterogeneity and individual patient response.

While immunotherapy has been recognized as a promising avenue in cancer treatment, its application in HCC and PVTT remains under research. The emerging options for immunotherapeutic agents indicate potential benefits, yet further studies are needed to integrate these with existing treatment protocols effectively.

Future directions in managing HCC with PVTT should emphasize interdisciplinary collaboration among specialists in oncological fields. Such approaches can enhance the personalization of treatment plans and lead to innovative strategies. Additionally, it is vital to improve diagnostic methods and classification systems to better stratify patients based on their specific clinical characteristics and the extent of PVTT. Addressing the limitations of current therapies through collaborative efforts and well-structured clinical trials will be essential for improving patient outcomes in this difficult-to-treat group.

Authors' contributions

Walaa Abdelhamed: Writing – original draft, Data curation. **Hend Shousha:** Writing – review & editing, Data curation. **Mohamed El-Kassas:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

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