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Treatment of hepatocellular carcinoma in patients with portal vein tumor thrombosis: Beyond the known frontiers

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Abstract

Hepatocellular carcinoma is one of the most frequent malignant tumors worldwide: Portal vein tumor thrombosis (PVTT) occurs in about 35%-50% of patients and represents a strong negative prognostic factor, due to the increased risk of tumor spread into the bloodstream, leading to a high recurrence risk. For this reason, it is a contraindication to liver transplantation and in several prognostic scores sorafenib represents its standard of care, due to its antiangiogenic action, although it can grant only a poor prolongation of life expectancy. Recent scientific evidences lead to consider PVTT as a complex anatomical and clinical condition, including a wide range of patients with different prognosis and new treatment possibilities according to the degree of portal system involvement, tumor biological aggressiveness, complications caused by portal hypertension, patient's clinical features and tolerance to antineoplastic treatments. The median survival has been reported to range between 2.7 and 4 mo in absence of therapy, but it can vary from 5 mo to 5 years, thus depicting an extremely variable scenario. For this reason, it is extremely important to focus on the most adequate strategy to be applied to each group of PVTT patients.

Key words: Portal vein tumor thrombosis; Sorafenib; Systemic chemotherapy; Transarterial chemoembolization; Transarterial radioembolization; Percutaneous ablation therapies; Combined therapies; Surgery; Liver transplantation

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Core tip: Portal vein tumor thrombosis (PVTT) is a complex anatomical and clinical condition, including patients with different prognosis according to the degree of portal system involvement, tumor biological aggressiveness, complications caused by portal hypertension, patient's clinical features and tolerance to antineoplastic treatments. For this reason, it is extremely important to focus on the most adequate treatment strategy for each group of PVTT patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors worldwide accounting for 749000 new cases/year and about 745000 deaths/year, with an incidence that ranges from less than 5 per 100000 individuals in Northern Europe, United States and Japan to over 20 per 100000 in sub-Saharan Africa and Eastern Asia^[1-3].

Portal vein tumor thrombosis (PVTT) occurs in about 35%-50% of patients^[4] and involves the main trunk at the time of diagnosis in 15%-30% of cases^[5]. However, PVTT prevalence is certainly underestimated, being incidentally found in about 62% of autopsic livers and in 14% of surgical specimens obtained from HCC patients^[6]. In those with already known history of HCC, the probability of malignant vascular infiltration is as high as 30%, decreasing to 20% in case of contemporary diagnosis of both HCC and thrombosis^[7].

The presence of PVTT is considered a strong negative prognostic factor, due to the increased risk of release into the bloodstream of cancer cells, leading to a high recurrence risk; for this reason, it is considered a contraindication to LT and is included in several HCC-prognostic scores [e.g., Barcelona-Clinic Liver Cancer (BCLC) staging system, French classification of HCC, Cancer of the Liver Italian Program (CLIP) classification, the Hong-Kong Liver Cancer (HKLC) staging system, Chinese University Prognostic Index (CUPI) score, and Japan Integrated Staging (JIS)]^[8-14]. In most of these classifications, sorafenib is the standard of care for patients with PVTT due to its antiangiogenic action related to the inhibition of the vascular endothelial growth factor (VEGF). However, sorafenib can grant only a poor prolongation of life expectancy in these patients^[15].

Recent scientific evidences lead to consider PVTT as a complex anatomical and clinical condition, including a wide range of patients with different prognosis and new treatment possibilities according to degree of the portal system involvement, tumor biological aggressiveness, patient's clinical features and tolerance to antineoplastic treatments, severity of liver dysfunction, and complications caused by portal hypertension (e.g., variceal hemorrhage). The median survival has been reported to range between 2.7 and 4 mo in absence of therapy^[16,17], but it can vary from 5 mo to 5 years according to liver function, tumor features and treatment applied, thus depicting an extremely variable scenario^[4,8]. For this reason, it is extremely important to focus on the most adequate strategy to be applied to each group of PVTT patients.

DIAGNOSTIC APPROACH TO PVTT

Ultrasound (US) examination represents the first-line imaging technique for the detection of PVTT with sensitivity and specificity of 80%-100% and diagnostic accuracy of 88%-98%^[18-20]. The thrombus appears as a hypo/isoechoic inhomogeneous material obstructing partially or completely the vessel, with an expansive aspect of the mass and difficult or absent detection of the infiltrated vascular walls. Colour and Power Doppler-US is able to detect pulsatile signs of arterial neovascularization

within the endoluminal mass, while pulsed Doppler identifies high resistance index in intralesional arterial flow^[18].

Contrast enhanced ultrasound (CEUS) represents the most sensitive and cheap method to depict neoplastic endovascular invasion, with a better diagnostic performance compared to computed tomography (CT)-scan (sensitivity 88%-100%, specificity 94%-96% in differential diagnosis between benign and neoplastic PVT)^[21]; PVTT presents a HCC-like contrast behaviour, with a rapid wash-in during arterial phase and wash-out in the portal/late phase, while benign thrombus has no contrast enhancement in all the study phases^[22].

CT-scan and magnetic resonance imaging (MRI) can distinguish between neoplastic and non-neoplastic portal thrombosis and add further information on thrombosis extension and presence of collateral vessels, with a sensitivity of 86% and 100% and a specificity of 100% and 90%, respectively. In particular, CT texture analysis and attenuation values grant the distinction between neoplastic and benign thrombosis on portal-phase CT imaging by analysing thrombus density, mean value of positive pixels and entropy^[23-27].

Percutaneous US-guided fine-needle aspiration is another simple, safe and effective diagnostic method to distinguish non-neoplastic and neoplastic portal thrombosis when a definitive diagnosis is not attained by imaging methods^[28].

Another promising tool to achieve differential diagnosis between non-malignant thrombosis and PVTT is ¹⁸F-Fluorodeoxyglucose positron emission tomography/CT (¹⁸F-FDG PET/CT), which seems to be able to identify metabolic abnormalities of the thrombus before the detection of the typical morphological and contrast enhanced signs detected on CT-scan. Hu *et al*^[29] defined thrombus malignancy by visual analysis and a maximum standardized uptake value (SUVmax) > 3.35.

CLASSIFICATION OF PVTT

PVTT classification is crucial to define a proper therapeutic approach. There are many studies describing PVTT stages according to the classifications created in different medical centers. In 2010 Ikai *et al*^[30,31] on behalf of the Liver Cancer Study Group of Japan (LCSGJ), distinguished four grades of PVTT and three grades of hepatic vein tumor involvement [Vp1: Presence of a tumor thrombus distal to the second-order branches of portal vein (but not involving them directly); Vp2: Invasion of the second-order branches of portal vein; Vp3: Presence of the thrombus in the first-order branches; Vp4: Tumor thrombus in the main trunk of the portal vein and/or a portal vein branch contralateral to the primarily involved lobe; Vv1: Tumor thrombus in a branch of the hepatic vein; Vv2: Tumor thrombus in the main trunk of the hepatic veins; Vv3: Thrombus reaching the right atrium] (Figure 1).

Another classification proposed by Cheng *et al* describes the portion of portal vein involved, identifying 4 categories: Type I₀ indicating microscopic portal invasion, Type I combining Vp1 and Vp2, Type II corresponding to Vp3, Type III and IV indicating thrombus in the main trunk and involvement of superior mesenteric vein, respectively^[32,33].

Finally, a simplified classification, divides patients with HCC and PVTT in group A (tumor thrombus in the main portal trunk or in both the left and right portal veins) and group B (involvement of either the left or the right portal vein)^[34].

TREATMENT OPTIONS FOR HCC WITH PVTT: STATE OF THE ART AND POSSIBLE FUTURE PERSPECTIVES

According to the Barcelona Clinic Liver Cancer (BCLC) classification, the recommended treatment for HCC with PVTT is sorafenib. However, many other treatment strategies have been attempted, with variable results. They include non-surgical procedures, such as systemic chemotherapy, radiation therapy, transarterial chemoembolization (TACE), microwave coagulation therapy (MCT), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and surgical options such as resection and liver transplantation (LT).

Sorafenib

Sorafenib is a multi-tyrosine-kinase inhibitor targeting Raf/Mek/Erk-pathways, vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, widely used as standard-of-care in the treatment of advanced HCC^[35]. Its efficacy has been investigated by two phase-III-trials: In the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP, studying Western




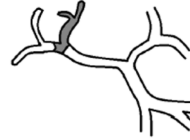




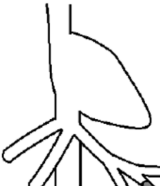

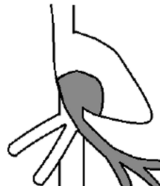
Portal vein tumor thrombosis classification according to the liver cancer study group of Japan			MSTs (yr)
VP 1: Tumour thrombus distal to the second-order branches of portal vein			2.67
VP 2: Invasion of the second-order branches of portal vein			1.51
VP 3: Thrombus in the first-order branches			0.78
VP 4: Tumour thrombus in main portal trunk or portal branch contralateral to primarily involved lobe (or both)			0.50
Vv1: Tumor thrombus in a branch of the hepatic vein			NA
Vv2: Tumor thrombus in the main trunk of the hepatic veins			NA
Vv3: Thrombus reaching the right atrium			NA

Figure 1 Portal vein tumor thrombosis classification according to the Liver Cancer Study Group of Japan.
MSTs: Median survival times; NA: Not available.

population), the median overall survival (OS) of patients with HCC and macrovascular invasion ($n = 108$ patients) was 8.1 mo *vs* 4.9 mo in the placebo group ($n = 123$ patients), while time to progression (TTP) was 4.1 mo *vs* 2.7 mo, respectively; these results were confirmed by the Asia-Pacific Trial, but, as sorafenib was only able to slightly prolong OS compared to placebo in advanced HCC (6.5 mo *vs* 4.2 mo, its effect in presence of PVTT was even smaller (5.6 mo *vs* 4.1 mo, TTP 2.7 mo *vs* 1.3 mo) in this study^[35-38]. Yau *et al*^[39] noticed a similar OS in both patients with and without PVTT treated with sorafenib. Subsequent studies in patients with PVTT classified as

Vp2-3-4 did not reveal satisfying performances. Jeong *et al*^[40] analysed the effects of sorafenib monotherapy in Vp3-4 PVTT, finding a 10% response rate and a 40% disease control rate (OS 3.1 mo; TTP 2.1 mo); the overall incidence of drug-related adverse events (AEs) was 90% and the most common AEs (grade 1-2) were dermatological, gastrointestinal and constitutional.

As regards the combination of systemic treatments with other techniques, Giorgio *et al*^[41] demonstrated a better outcome for PVTT treated with both sorafenib and RFA compared to sorafenib alone (1-2-3 year survival rates were 60%, 35% and 26% *vs* 37%, 0% and 0%, respectively); AEs were almost superimposable in the two groups [abdominal pain, hand foot skin reaction (HFSR), asthenia, diarrhoea, weight loss]. A recent multicenter phase III trial by Park *et al*^[42] demonstrated that, in advanced HCC, sorafenib combined with cTACE faced to sorafenib-alone does not achieve an increase in OS (12.8 mo *vs* 10.8 mo; HR = 0.91; 90%CI: 0.69-1.21; *P* = 0.290) but improved TTP (5.3 mo *vs* 3.5 mo; HR = 0.67; 90%CI: 0.53-0.85; *P* = 0.003), PFS (5.2 mo *vs* 3.6 mo; HR = 0.73; 90%CI: 0.59-0.91; *P* = 0.01) and tumor response rate (60.6% *vs* 47.3%, *P* = 0.005). Surprisingly, patients with Vp3-4 PVTT or invasion of other vessels seemed to have a survival benefit from sorafenib plus TACE, even though this trend was not statistically significant (HR = 0.52; 95%CI: 0.27-1.02). It is also relevant to point out that a high incidence of serious AEs was observed in the combination treatment group faced to sorafenib-alone (33.3% *vs* 19.8%, *P* = 0.006, respectively), including elevation of alanine aminotransferase (ALT), hyperbilirubinemia, ascites, HFSR, thrombocytopenia and anorexia.

It should be noted that data on the efficacy of other antiangiogenetic drugs in patients with PVTT are lacking. Indeed, in the registrative study of lenvatinib, which has been shown to be non-inferior to sorafenib for the treatment of patients with advanced HCC, patients with main portal trunk invasion were excluded^[43].

Systemic chemotherapy

Traditional chemotherapy is not usually included in HCC treatment algorithms because of its toxicity, which may be even more serious in patients with cirrhosis and liver function impairment.

Okada *et al*^[44] conducted a phase II study in which different systemic chemotherapy regimens [Tegafur, Doxorubicin, Tegafur plus Uracil, Etoposide, Mitoxantrone, Interferon-gamma, Cisplatin, 5-fluorouracil (5-FU)] were administered to 71 patients with unresectable HCC, whose response varied from 0% to 20%; median survival time was 5.6 mo, 1-year and 2-years survival rates were 23% and 5%. Among them, 22 patients had Vp4 PVTT, with a reported median survival time of 3.9 mo. Itamoto *et al*^[45] assessed hepatic arterial infusion of 5-FU and cisplatin in 7 patients with unresectable HCC and Vp3-4 PVTT: Response rate was 33%; a reduction in size or disappearance of thrombosis after chemotherapy was observed in 43% patients; mean and median survival times were 8 and 7.5 mo, respectively. No serious AEs occurred, whereas nausea and vomiting were the most common mild AEs requiring medical management. Yamasaki *et al*^[46] obtained good results in a randomized study on HCC with PVTT by the addition of leucovorin to the protocol previously experimented by Itamoto^[45], with a 56% response rate *vs* 20% (*P* = 0.022); indeed, for leucovorin arm, 1- and 2-year survival rates were 66.7% and 44.4% compared to 10% and 0% for the control group (*P* = 0.033).

Ando *et al*^[47] examined 9 patients with advanced HCC and Vp4-PVTT for the efficacy of low-dose cisplatin and 5-FU arterial infusion by subcutaneously implanted injection-port: overall response rate was 44.4%, 3-year survival rate was 40%, median survival time 10.2 mo. Only tolerable AEs occurred (nausea, loss of appetite).

Interesting data also come from small studies using chemotherapy schemes including interferon (IFN)-alpha. Urabe *et al*^[48] treated 16 patients with HCC and Vp3-4 PVTT with a combined scheme of methotrexate, 5-FU, cisplatin and IFN-alpha 2b; the reported response rate was 46.7%, median survival was 7 mo, and the 2-year survival rate was 57.1%. Transient severe hematologic AEs were registered and more than half of patients presented grade 2 nausea or vomiting. Similar results and safety data were described by Kaneko *et al*^[49] using the same therapeutic regimen (overall response rate 45%, median survival 11 mo, 2-year survival 15%).

Some other studies showed encouraging results for the combination of subcutaneous IFN-alpha and intra-arterial 5-FU in the treatment of HCC with Vp3-4 PVTT: Response rates ranged from 43.6% to 63% and mean survival rates from 6.9 to 11.8 mo^[50-52].

Hepatic arterial infusion chemotherapy (HAIC) has been also investigated in the treatment of PVTT, because of its property to carry anticancer drug directly at the tumor site, thus limiting systemic AEs. Song *et al*^[53] showed that HAIC was more effective than sorafenib in the treatment of Vp2-4 PVTT (OS = 7.1 mo *vs* 5.5 mo, *P* = 0.011; TTP 3.3 mo *vs* 2.1 mo, *P* = 0.034); the most common AE in the sorafenib group

was HFSR (45%, mainly grade 1-2), while in the HAIC group all patients had at least grade 1 AEs, and grade 3-4 AEs were more frequent, with 98% anemia, 84% thrombocytopenia, 74% bilirubin elevation and 72% ALT elevation (68% HAIC group *vs* 27% sorafenib group).

Ikedo *et al*^[54] designed a phase II trial that proved a fair efficacy of intra-arterial cisplatin infusion in Vp3-4 PVTT, with a response rate of 28%, a mean survival time of 7.1 mo and grade 3 AEs (blood cell decrease, transient transaminases elevation) not requiring treatments. However, other similar experiences did not confirm such encouraging results^[55-56].

Another interesting perspective is offered by metronomic chemotherapy protocol (MET) that should act by preventing tumor cell proliferation and angiogenesis and stimulating the immune system.

Yang *et al*^[57] compared MET with cisplatin and 5-FU to sorafenib in the treatment of advanced HCC with PVTT, finding better outcomes as regards median survival time (158 d *vs* 117 d) and OS rate in the first group ($P = 0.029$). Main AEs in the MET group were leukopenia (48%), hyperbilirubinemia (30%), thrombocytopenia (22%), serum ALT elevation (17%); in the sorafenib group, mainly skin (28% HFSR) and gastrointestinal tract toxicity (40%), hyperbilirubinemia (36%) and increase in ALT serum levels (17%) were reported. The difference between grade 3-4 toxicity rates in both groups was not statistically significant. An Italian experience^[58] proved that MET with capecitabine was effective in improving patients' survival after sorafenib discontinuation compared to best supportive care. However, in this study, patients in the MET group showed a lower prevalence of PVTT, which represented itself a negative prognostic factor.

TACE

TACE is considered the preferential palliative therapy for multinodular HCC for patients with well-preserved liver function. TACE usefulness in PVTT, especially in type III/IV, remains uncertain, because of the limited effect on survival compared to systemic treatments and the potential risk of ischemia related post-TACE liver function failure; this risk appears increased if the collateral blood circulation surrounding the obstructed portal vein is insufficient^[59-61]. The main studies concerning TACE in PVTT patients are summarized in [Table 1](#).

A metanalysis by Xue *et al* compared TACE and conservative treatment in 1601 patients with PVTT: 6-mo and 1-year survival were better in TACE group than in supportive therapy group, with good results for both Child-Pugh A and B patients^[62]. These results were confirmed in another metanalysis by Leng *et al*^[63] including 600 patients.

A review by Silva *et al*^[63] including 13 studies with 1933 patients with PVTT treated with TACE, showed a 1-, 3-, 5-year survival of 29%, 4% and 1%, respectively. Main trunk PVTT demonstrated the worst outcome, although the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) response rates were similar in cases with main portal vein or portal vein branches thrombosis (14% *vs* 16%, $P = 0.238$).

Compared to conservative treatment, TACE allows to achieve a mean survival time of 19 mo *vs* 4 mo in type I PVTT (Vp1-2), 11.0 mo *vs* 1.43 mo in type II PVTT (Vp3), and 7.1/4.0 mo *vs* 1.3/1.0 mo in type III/IV (Vp4), respectively ($P < 0.01$)^[65]. Chung *et al* reported a median OS of 5.6 mo *vs* 2.2 mo ($P < 0.001$) in a study in which TACE arm was compared faced to supportive care arm. The best survival results were achieved in patients with Vp4. The AEs rate was 28.9%, with gastrointestinal hemorrhage more frequent in the TACE group^[66]. Another small study evidenced satisfying survival rates at 3-, 6- and 12-mo (82%, 71%, 47% respectively), with a median survival rate of 10 months and better OS in Child-Pugh A compared to Child B patients (15 mo *vs* 5 mo, respectively)^[67]. Tawada *et al*^[68] retrospectively analyzed the AEs in a group of patients with PVTT treated with TACE: The main grade 3 AEs were ALT and AST (Aspartate Aminotransferase) elevation (54.5% and 69.7%, respectively) whereas the occurrence of thrombocytopenia, hyponatremia, hyperbilirubinemia, leukopenia and anemia was rare. In this study, treatment response was evaluated by CT at one or two months after TACE, and was considered separately as "parenchymal-response" and "PVTT-response". Mean survival times were 11.1 mo *vs* 5.5 mo for parenchymal response positive patients compared to negative ones, and 14.0 mo *vs* 5.8 mo for PVTT response positive patients compared to negative ones.

TACE efficacy in the treatment of PVTT seems to be related to the degree of hepatic arterial supply to the thrombus. Indeed, patients showing a good accumulation of lipiodol after TACE presented a better response to TACE, with an OS of 10 mo *vs* 2.7 mo ($P < 0.001$)^[69].

When TACE is compared to sorafenib in BCLC-C HCC, the median OS seems to be similar (9.2 mo *vs* 7.4 mo; $P = 0.377$) but the incidence of AEs appears to be higher in the TACE group (30% *vs* 17%)^[70].

Table 1 Outcome of transarterial chemoembolization in patients with hepatocellular carcinoma and different portal vein tumor thrombosis grades

First author, year	Patients (patients)	Treatment	PVTT Class (Vp)	Median survival time(mo)	1-yr survival rate	2-yr survival rate	3-yr survival rate	5-yr survival rate
Okazaki M, 1991	163	TACE	Vp 2 (48) Vp 3 (56) Vp 4 (59)	4.3 mo 4 mo 3.8 mo	-	-	-	-
Chung JW, 1995	83	TACE	Vp 3,4 (83)	6 mo	30%	18%	9%	-
Georgiades CS, 2005	32	TACE	Vp 3,4 (32)	9.5 mo	25%	-	-	-
Luo J, 2011	84	TACE	Vp 1,2 (40) Vp 3 (44)	10.2 mo 5.3 mo	30.9% 3.8%	9.2% 0%	-	-
Niu ZJ, 2012	115	TACE	Vp 1 (12) Vp 2 (52) Vp 3 (42) Vp 4 (9)	19 11 7.1 4	27.8%	6%	-	-
Peng ZW, 2012	402	TACE	Vp 1 (54) Vp 2 (136) Vp 3 (166) Vp 4 (46)	-	41.1% 37.9% 36.1% 30.4%	-	8.9% 6% 4.2% 4.3%	3.6% 0% 0% 0%
Ajit Y, 2014		TACE		6.2 mo	-	22%	-	-
Liu L, 2014	188	TACE	Vp 1,2 (98) Vp 3 (90)	6	38%	17%	3%	-
Liu PH, 2014	181	TACE	Vp 1,2 (181)	-	60%	-	42%	33%
Chern MC, 2014	50	TACE	Vp 1,2,3,4	6.2 mo (range, 1.7-50.9 mo)	22%	10%	8%	-
Tawada A, 2014	81	TACE	Vp 1,2,3,4	NA	45%	23%	20%	-
Ye JZ, 2014	338	TACE (86 patients)	Vp 1,2,3,4	7.0 mo	17.5%	0%	0%	-
Tan X, 2015	116	TACE (64 patients) TACE+PVE (52 patients)	Type I, II, III (according to Shi <i>et al</i>)	27.7 mo	60.9% 80.7%	41% 59%	25% 36.5%	0% 11.5%

The combination of sorafenib and TACE is reasonable considering their complementary effects: On one side, TACE determines hypoxia that could enhance the release of angiogenic factors; on the other side, sorafenib has an antiangiogenic activity (anti-VEGF-2 and 3, anti- PDGF Receptor) and suppresses tumour proliferation^[71]. A metaanalysis by Liu *et al*^[72], examining 17 studies on the combination of sorafenib and TACE in unresectable HCC compared to TACE alone, showed benefits in TTP but not in OS (TTP: 7.1-9.0 mo; OS: 12-27 mo). AEs were mainly grade 1-2 (alopecia, fatigue, nausea, diarrhoea, HFSR, haematological events, hepatotoxicity) and manageable with sorafenib dose-reduction. Heavy limitations of this analysis were represented by the wide heterogeneity of accessible data, and lack of OS and TTP in non-comparative studies that were, however, included. Furthermore, the phase II trial START performed in Asia and assessing the effectiveness of the combination of TACE with Sorafenib showed promising results in PVTT patients in terms of 3-year OS (86.1%) with acceptable rates of AEs^[73].

A retrospective study by Kim *et al*^[74] demonstrated better OS and longer TTP for patients treated with the combination of TACE and RFA than with TACE or sorafenib alone.

Zhang *et al*^[75] observed an improved outcome applying percutaneous transhepatic portal vein stenting (PTPVS) and TACE, with or without 3-dimensional conformal radiotherapy (3-DCRT): Median OS was 16.5 mo in the radiotherapy (RT) group *vs* 4.8 in the non-RT one. This study also demonstrates better results of PTPVS-TACE with 3-DCRT especially in avoiding stent re-occlusion due to tumour thrombus regrowth.

On the whole, TACE alone improves survival of selected patients with unresectable HCC, but its effectiveness in improving OS and TTP of PVTT patients is not definitively proven^[76]. The association of TACE to other treatments could provide an additional benefit by improving local control of HCC growth but further data are needed in order to demonstrate a positive influence on OS.

RT

HCC is a radio-resistant carcinoma, but, in selected patients with PVTT, RT was

demonstrated to be effective with a dose-related response^[77,78]. However, RT can lead to severe liver damage^[79]. Indeed, concerns exist upon a “veno-occlusive-disease-mimicking” radiation-induced liver disease (RILDs) characterized by jaundice, severe hypertransaminasemia, hepatomegaly and ascites appearing 2-3 mo after RT. This threatening condition still remains without specific treatments and its prognosis is potentially negative^[80]. However, a small volume of liver tissue could tolerate potentially tumoricidal high radiation doses. Indeed, Lawrence *et al.*^[81] demonstrated that the use of dose-volume histogram allows to concentrate a higher radiation dose on neoplastic tissue while sparing 2/3 of normal hepatic tissue, producing response rates 2-3 times higher faced to conventional therapy, thus obtaining a better local disease-control) and new technologies allow to achieve a highly selective target receiving high doses radiation and sparing normal tissue, thus avoiding RILDs^[82].

Some attempts to make this technique more selective and tolerable were made through the use of 3-DCRT which allows to apply radiation selectively on both tumor mass and PVTT and to avoid irradiation on the surrounding hepatic and non-hepatic tissues^[83].

Tang *et al.*^[84] compared RT to surgery in a retrospective study on 371 patients with resectable HCC and PVTT obtaining better outcomes for the RT arm: Median OS was 12.3 mo *vs* 10 mo, respectively; 1-, 2-, and 3-year OS was 51.6%, 28.4%, 19.9% for the RT group and 40.1%, 17.0%, 13.6% for the surgery group ($P = 0.029$). Other studies on Vp3-4 PVTT showed a survival rate of 5.3-7 mo, with response rates ranging between 32.6% and 83%^[78,85-88].

A study by Nakazawa *et al.*^[89] comparing RT to placebo on high grade PVTT (Vp3-4, Vv2-3), showed a 48% overall objective response rate (complete plus partial response): 56% for Vp, 50% for Vv, 20% for both Vp and Vv). Median survival time in patients receiving RT was 10 mo *vs* 3.6 mo in the control group; furthermore, 1- and 2-year cumulative survival rates were significantly higher (38% and 20.7% *vs* 8.3% and 2.7%). No grade 3-4 AEs occurred; the most common AEs were fatigue, anorexia, leukopenia and hypertransaminasemia of grade 1 or 2.

A recent study performed using the propensity score matching highlighted the superiority of RT *vs* sorafenib in patients with Vp3-4 PVTT (OS 10.9 mo *vs* 4.8 mo; $P = 0.025$); complete regression was achieved in 3.6% patients, partial response in 50.2% and stable disease in 25.6% in the RT arm. Serious AEs were more frequent in the sorafenib group (hypertransaminasemia, anorexia, nausea, HFSR), while only one case of grade 3 leukopenia occurred in patients undergoing RT^[90].

Positive results have also been reported on proton-beam therapy (PBT) in HCC with PVTT, because of the possibility to locally concentrate the radiation delivery. In a study by Sugahara *et al.*^[91] the median OS was 22 mo, with 91% 2-year local control rate and 48% 2-year survival rate; only a few patients presented grade 3 AEs, mainly consisting in leukocytopenia and thrombocytopenia. In another study 12 patients with Vp3-4 PVTT were studied after PBT: 2 of them obtained a complete response without recurrence 4.3 and 6.4 years after treatment. The remaining 10 showed partial response 1-3 mo after PBT (objective response rate 100%), with appearance of new HCC outside the irradiated volume after further 0.1-2.4 years from PBT. PFS and OS rates were 67%/24% and 88%/58% at 2 and 5 years, respectively. No grade 3 AEs were observed^[92].

Several RT techniques (3-DCRT, intensity-modulated RT, stereotactic body RT (SBRT), and RT with proton beams and carbon ion beams) showed promising outcomes in HCC patients with and without PVTT: PBT, unlike RT with X-rays, allow to precisely deliver high-dose radiations to the target volume, sparing the normal liver tissue and the surrounding organs^[93,94]. Furthermore, a metaanalysis by Qi *et al.*^[95] demonstrated a higher rate of survival for PBT compared to CRT, with lower AEs.

Gamma knife radiosurgery (GKR) is a type of external radiation treatment applied especially on brain lesions, focusing with gamma beams radiations precisely on the target, thus avoiding damage to surrounding healthy brain tissue. It consists in a single application whereas RT requires multiple sessions to attenuate the effects of radiations on healthy tissues. In a few Chinese cancer centers, GKR has been applied on HCC-PVTT for more than a decade. A retrospective study by Lu *et al.*^[96] identified a remarkably increased median OS of HCC-PVTT patients receiving combined TACE and GKR faced to TACE alone. A subsequent retrospective study by Lu *et al.*^[97] investigated the efficacy and safety of GKR monotherapy on PVTT-HCC, highlighting an OS advantage in both patients with branch or main PVTT (6.1 mo for GKR group *vs* 3.0 mo for supportive therapy)^[35,36]. Grade 1-2 AEs were predominant and easily managed. Despite the need of further future validation, GKR was reported to be effective on HCC with PVTT, without differences related to its extension^[97].

The combination of RT with other treatment modalities represents also an interesting approach. For example, TACE determines the necrosis of the tumor thrombus by reducing the arterial supply and stimulates G0 cells to enter into the

proliferating phase, allowing the increase of RT-related antitumor effect. The first study in patients with Vp2 PVTT was made by Chen *et al*^[98] on 10 patients who received TACE combined with RT: 6 patients died after a period ranging from 3 to 10 mo (because of advanced HCC, liver failure, HCC-rupture) while the others survived more than 6 mo. Further studies also reached satisfying response rates^[76,78,99-103].

Similarly, conventional chemotherapy could cause a significant enhancement in RT effect: Katamura *et al*^[104] compared patients treated with intra-arterial 5-FU and IFN- α alone or combined with 3D-CRT in the treatment of PVTT (patients received 3D-CRT concomitantly with the first course of intra-arterial 5-FU/IFN): In the RT group an improvement in PVTT and a reduced incidence of portal hypertension-related AEs were noticed, the objective response rate of PVTT was higher in RT group ($P = 0.012$), but the median survival time was similar to non-RT group (7.5 mo *vs* 7.9 mo). Comparing the RT and non-RT groups, a complete PVTT resolution was achieved in 19% *vs* 6%, PR in 56% *vs* 19%, SD in 25% *vs* 44%, PD in 0% *vs* 31%, respectively.

Another study claimed the superiority of surgery plus neoadjuvant RT over surgery alone in preventing tumor recurrence (1-year OS 69.0% *vs* 35.6%, 2-year OS 20.4% *vs* 0%, 6-mo RR 49.0% *vs* 88.7%, 1-year RR 77.0% *vs* 97.7%)^[83].

Finally, Nakagawa *et al*^[105] demonstrated the relevant role of RT followed by percutaneous ethanol injection (PEI), RFA or TACE in HCC with Vp2-4 PVTT, with a 50% response rate and 1-, 3- and 5-year survival rate of 45.1%, 15.2% and 5.1% respectively. **Table 2** summarizes the most important papers analyzing the effectiveness of RT alone or associated with other treatments in PVTT.

Transarterial radioembolization

Transarterial radioembolization (TARE) acts by delivering local beta radiation within HCC through the selective release of iodine-131-labeled lipiodol (¹³¹I), iodine (¹²⁵I) or yttrium (⁹⁰Y) in lobar, segmental, or subsegmental hepatic arteries supplying the tumor^[106,107]. In contrast to TACE, for which PVTT is a technical issue and an absolute contraindication in case of Vp3-4 stage due to the increased risk of liver ischemic necrosis and treatment-related death, TARE can be performed in patients with PVTT without major concerns, thanks to the minimal embolic effect of 90Y-glass microspheres and consequent lower risk of liver ischemia^[108].

In a small study on 32 patients, Shae *et al*^[109] compared the effects of TARE and TACE in a subgroup of patients with major vascular invasion, obtaining a median survival of 12 mo *vs* 9 mo (3-year survival rate 20.3% *vs* 9.7%).

TARE has also been shown to be more tolerable than TACE or Sorafenib: The most frequent AE, observed in 20-55% of patients, is post-embolization syndrome (fever, nausea, abdominal pain, malaise), which does not require medical intervention in most cases^[110]. However, in a retrospective, multicentre, therapy registry, doxorubicin drug eluting beads (DEBDOX) resulted to be safer in the treatment of unresectable HCC with PVTT, achieving better disease control (67% *vs* 20%; $P = 0.0014$) and median survival time than TARE^[111]. Furthermore, although TARE was reported to be superior to sorafenib in prolonging survival of PVTT patients in some retrospective studies^[112-115], two phase III trials (Sorafenib versus Radioembolization in Advanced Hepatocellular carcinoma - SARAH - and Selective Internal Radiation Therapy Versus Sorafenib - *SIRveNIB*)^[116,117] failed to demonstrate a significant superiority of TARE compared to sorafenib. In particular, in the SARAH study the presence of PVTT seems to favor sorafenib in term of OS.

An interesting point could be the selection of a subgroup of PVTT patients in whom the benefit of TARE could be better. In a recent paper, Spreafico *et al*^[118] developed a prognostic classification showing that patients with at least one measurable HCC lesion, PVTT non-occluding the main portal vein, absence of extra-hepatic metastasis, Child-Pugh < B7, and good performance status achieved the best therapeutic results.

Percutaneous ablation therapies

Percutaneous treatments have been proposed for HCC complicated by PVTT, but particular caution must be paid because of the potential risk of damaging portal and biliary structures. However, some preliminary attempts have been done, with discrete results.

In a study planned in 2005 when sorafenib was not available and including 35 patients with main trunk PVTT and a single HCC nodule (size 3.7-5 cm) who underwent RFA of both the HCC lesion and PVTT, the 3-year survival rate was significantly higher when compared to no treatment (77% *vs* 0%)^[41], with a mean survival time of 28.3 ± 3.8 mo *vs* 6.8 ± 0.5 mo ($P < 0.001$). A complete tumor necrosis and main portal trunk recanalization was achieved in 26 patients (74%). In another study^[119], combined treatment with RFA and TACE on HCC complicated by PVTT was reported to achieve a mean survival time of 29.5 months, with a 1-, 3-, 5-year

Table 2 Main studies on the outcome of radiotherapy alone or combined with other treatments in patients with hepatocellular carcinoma and different portal vein tumor thrombosis grades

First author, year	Patients (patients)	Treatment	PVTT Class (Vp)	Response rate	Survival rate(yr)	Mean survival time(mo)
Tazawa, 2001	24	RT (50 Gy)+TACE	Vp3,4	50%	NA	9.7 mo
Yamada, 2001	8	RT (30 Gy)	Vp3	37.5%	NA	NA
Ishikura, 2002	20	TACE+RT (50 Gy)	Vp3	50%	25% (1-yr)	5.3 mo
Yamada K, 2003	19	TACE and 3D-RT (30Gy)	Vp3	57.9%	40.6% (1-yr), 10.2% (2-yr)	7 mo
Nakagawa, 2005	52	3D-CRT (39-60 Gy)	Vp2,3,4	NA	5.1% (5-yr)	NA
Kim DY, 2005	59	3D-CRT (39-70.2 Gy)	Vp3,4	45.8%	20.7% (2-yr)	10.7 mo
Hata, 2005	12	Proton-beam therapy (50-72 Gy)	Vp3,4	100%	88% (2-yr) 58% (5-yr)	27 mo
Lin CS, 2006	43	3D-CRT (21patients) Conventional Rtp (22 patients)	Vp3,4	83% 75%	NA NA	6.7 mo 6.0 mo
Hsu WC, 2006	53	3D-CRT+thalidomide	Vp3,4	50%	84.8% (6mo), 60.0% (1-yr), 44.6% (2-yr)	24.0 mo
Nakazawa, 2007	32	RT	Vp3-4, Vv2-3	48%	38.0% (1-yr), 20.7% (2-yr)	10.0 mo
Toya, 2007	38	3D-CRT (23.4-59.5 Gy)	Vp NA	44.7%	39.4% (1-yr)	9.6 mo (OS)
Shirai, 2009	26	3D-CRT using SPECT	Vp3,4	30.7%	30% (2-yr)	10.3 mo
Kang, 2013	101	RT+TACE TACE+RT	Vp NA	70.3%	A) 58.8% (1-yr), 29.4% (2-yr) B) 54.1% (1-yr), 27.0% (2-yr)	17 mo 15 mo
Nakazawa, 2014	97	3D-CRT (30-56 Gy)	Vp3,4	45%	NA	10.9 mo
Lee, 2014	46	3D-CRT (35-60 Gy)	Vp3,4	32.6%	66.8% (1-yr)	NA

3D-CRT: Conformal radiotherapy; Gy: Gray; NA: Not available; PVE: Portal vein embolization; PVTT: Portal vein tumor thrombosis; RT: Radiotherapy; SPECT: single photon emission computed tomography; TACE: Transarterial chemoembolization.

survival rate of 63%, 40% and 23%. Slightly inferior rates were obtained when using laser as ablation technique^[120].

Cryotherapy has also been considered as a complementary treatment to sorafenib in patients with branch and main-trunk PVTT, with a significant increase in OS (12.5 mo *vs* 8.6 mo respectively) and good safety profiles^[121].

The main limitation of ablation techniques is the extension and the location of PVTT within the portal system. Indeed, severe side effects such as neoplastic embolization, irreversible damages of vascular and biliary structures, gallbladder, gastric and duodenal walls have been occasionally reported after PVTT ablation using percutaneous ethanol injection, RFA or laser^[41,120,122]. Electrochemotherapy (ECT) is an innovative method based on local application of short and intense electric pulses that temporarily permeabilize cellular membranes, permitting the delivery of therapeutic molecules. It has been used in a small prospective case series of HCC patients with Child-Pugh A-B liver cirrhosis and Vp3-4 PVTT: Post-treatment CEUS examination and biopsy of the portal thrombus showed in all cases a complete necrosis of tumor cells without involution signs in perivascular tissues and portal endothelium. During the subsequent 12-mo follow-up, no local recurrence was detected. The main concern on this promising technique is the occurrence of thrombosis of main portal trunk and fatal late gastrointestinal haemorrhage (17% of treated patients)^[123].

Surgical approach

Since 1980s, surgical resection has been adopted for the treatment of HCC with PVTT of the first-order branches^[124]. In 1990s, Kumada *et al*^[125] reported a surgical resection of a tumor thrombus extended in the main portal trunk, describing five possible surgical approaches: (1) Hepatolobectomy, consisting in the en-bloc resection of both HCC (located either in the left or the right lobe) and PVTT (confined to the first portal branch); (2) Thrombectomy with a balloon catheter that is introduced in the clamped portal vein by an incision and used to extract the thrombus by suction or curettage; (3) Portal vein bypass, consisting in the en-bloc resection of both the involved portal branches and the thrombus when its extraction is technically complicated, followed

by the creation of a bypass-graft between portal trunk and umbilical vein; (4) Portal vein resection and anastomosis, performed in the presence of PVTT of the contralateral first branch, with an en-bloc resection of both the thrombus and the portal trunk, and the subsequent anastomosis between portal trunk and the residue of portal vein; and (5) Thrombectomy, with the extraction of the thrombus through an incision in portal wall at the bifurcation of right or left vein, while a biologic pump redirects portal and vena cava blood flow to the axillary vein; if PVTT removal is difficult, portal vein should be resected and subsequently reconstructed.

Nowadays, surgical approach to PVTT is based on three main methods: Hepatectomy, tumor thrombectomy, and *en-bloc*-resection of portal vein and thrombus with subsequent portal reconstruction. The first one represents an excellent solution in case of PVTT in the first portal branches in patients with satisfying clinical condition, as it grants a radical tumor and PVTT removal. The second one has the potential advantage of avoiding tumor residuals, but it is technically more difficult to perform, especially in case of extended thrombosis. The latter, applied to PVTT involving the bifurcation with or without the main and/or contralateral portal veins, presents high intraoperative mortality risk, but a more favorable result faced to thrombectomy that is technically less difficult, but with a higher risk of tumor residual or metastatization to the distal branches^[126,127]. A study by Chok *et al*^[128] compared these three surgical methods (hepatectomy, tumor thrombectomy, and *en-bloc*-resection of portal vein and thrombus), highlighting that median disease-free survival was 4.21, 1.51 and 3.78 mo, respectively. This implies that adjuvant treatments would be necessary to prevent the high incidence of recurrence but, unfortunately, they are still unavailable.

It should be noted that no prospective study on surgical treatment for PVTT is available to date. Some studies underlined the achievement of the same survival and disease-free survival outcomes for *en-bloc* resection of the involved liver segment and bifurcation with or without the main portal trunk compared to thrombectomy with peeling-off technique^[129-131]. Conversely, a propensity score analysis by Zhang *et al*^[132] demonstrated the superiority of *en-bloc* resection compared to thrombectomy with peeling-off resection in type I-II PVTT (mean survival time, MST 18.2 mo *vs* 10.9 mo, 1-, 3-, 5-year OS 68.9%, 34.3%, 30.8% *vs* 49.1%, 22.1%, 15.8%; recurrence rate 9.7% *vs* 23.9%, $P = 0.005$, respectively).

Back-flow thrombectomy (BFT) has been employed in order to expand therapeutic possibilities for Vp4 PVTT, which in Japan is surgically approached only in 8.8% cases, minimizing the risk of migration of floating thrombus and allowing further adjuvant treatments^[133].

Beyond its pathological meaning and the debates on the most proper therapeutic approach, PVTT itself has a fundamental role in defining the possible evolution of HCC. In patients with HBV-related HCC macrovascular invasion, tumor differentiation and size are all important prognostic factors^[134]. As regards surgical resection of large HCC (more than 10 cm), PVTT is an independent predictor of early recurrence-related mortality and a major negative prognostic factor^[135]. Since PVTT invading portal trunk is considered to be a sign of advanced HCC, the purpose of surgical approach is not to improve survival, but to help preventing the consequences of excessively high portal pressure (*e.g.*, variceal hemorrhage). However, even in patients with PVTT of the portal trunk, a slight improvement of survival has been reported even when compared to treatment with sorafenib^[130,136-138]. A review of 24 studies including 4389 patients with PVTT undergoing surgical resection, evidenced a 1-year OS of 50% and 5-year OS of 18%^[139,140]. Peng *et al*^[141] showed a 1-, 3- and 5-years survival rate for type I and II PVTT of 42%, 14.1%, 11.1% for surgery and 37.8%, 7.3%, 0.5% for TACE, respectively; however, the size of the surgery group was about half of the TACE group (201 *vs* 402), and the subgroups analysis presented statistically significant results only in type I and II PVTT ($P < 0.001$ and 0.002), but not in type III and IV ($P = 0.541$ and 0.371); R0 resection could be achieved in 83% patients (88/106) with HCC and PVTT but no vascular wall invasion, as already indicated by Shi *et al*^[142] who suggested thrombectomy as a proper treatment option if the tumor thrombus does not infiltrate portal venous wall. Further studies confirmed the superiority of surgery over TACE, especially in type I and II PVTT^[143,144].

Liver resection and thrombectomy have a better 5-year OS if the PVTT is confined to the first or second branch of the main portal vein rather than to portal trunk^[30,145-147]. A review analyzing 23 articles and 2412 patients noticed a substantial difference in 5-year post-resection survival related to PVTT stage: Vp1-2 45% (range: 25%-54%), Vp3 19% (range: 0%-38%), Vp4 14.5% (range: 0%-26.4%)^[148]. Wang *et al*^[149] suggested that, beyond type I and II PVTT (according to Chang's classification), surgery could be effective also in selected cases of type III PVTT. Indeed, surgery allows an *en-bloc* removal of neoplastic tissue in type I and II but in type III it is mandatory to clamp portal vein, perform a thrombectomy and subsequent washing of the vascular lumen

with saline solution, in order to remove possible neoplastic residuals.

At present, neither precise consensus nor indications have been established for each Vp-category: According to LCSGJ, Vp1-3 are candidate to resection, but Vp4 has a weak indication; taking into account Cheng's classification, type I-III could be treated by surgery, while type IV represents a contraindication. A study by Sakamoto *et al*^[125] proposed for Vp4 PVTT an *en-bloc* resection with reconstruction of the portal vein or thrombectomy. Another Japanese group^[150] underlined that only Vp3 may have benefits from surgery, while Vp4 should be treated with alternative therapies.

Yamamoto *et al*^[151,152] claimed that hepatectomy provides comparable survival rates for both Vp3-4 and Vp1-2 but in this series Vp3-4 group is really small faced to the Vp1-2 group. They also suggested that stage II-III patients [according to American Joint Committee on Cancer (AJCC)] with high serum alpha-fetoprotein levels should undergo neoadjuvant/adjuvant therapies.

A retrospective multicenter analysis of liver resection associated to thrombectomy performed in Italy did not report a significant difference of 5-year survival among Vp1, Vp2 and Vp3 patients^[153]. Roayaie *et al*^[154] reported a MST of 13.1 mo and 14% 5-year survival in patients with PVTT treated with resection, whereas in case of involvement of hepatic veins and vena cava MSTs felt to 4.7 mo. In case of HCC < 7 cm and AFP < 30 ng/mL, MST was 20 and 29 mo respectively. Prognostic elements such as tumor size, extension of vascular invasion and AFP resulted to be fundamental to define the outcome and should be considered when deciding if resection is possible. The main studies concerning the clinical outcome of patients with HCC and PVTT are reported in Table 3.

A metanalysis by Hyun *et al*^[155], examining 5986 patients from 18 studies, showed that primary hepatectomy is superior to TACE in BCLC-B/C stage HCC, with significant OS benefit (HR = 0.59; 95%CI: 0.51-0.67; $P < 0.00001$); as per BCLC-B, also in BCLC-C group, 1-, 3-, 5-years survival rates were higher for primary hepatectomy than TACE (62%, 42%, 20% *vs* 45%, 16%, 8%, respectively). Despite these intriguing results, the long-term effectiveness of surgery in advanced HCC is still to be proven, since no comparison was made between surgery versus standard systemic treatment with sorafenib in this group of patients. Zhang *et al*^[156] proposed the preoperative Eastern Hepatobiliary Surgery Hospital (EHBH) PVTT scoring system predicting accurately the prognosis after R0 LR of HCC patients with type I-II PVTT: This method could facilitate the decision between conventional systemic treatment and surgery in patients with advanced HCC because of its accuracy in selecting patients who could be advantaged by LR.

Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) is an innovative surgical technique, first developed in 2012, for the management of liver metastases in patients with potentially small residual liver volume, that reduces the time of liver hypertrophy from 4-6 wk (in case of standard portal embolization) to 7-10 d. It consists of in situ splitting of the liver along the main portal scissura or the right side of the falciform ligament, associated with right portal vein ligation^[157]: Vennarecci *et al*^[158] demonstrated its efficacy in two cases of HCCs with major vascular invasion in which the classical approach of radiological or surgical portal-vein occlusion and subsequent resection after 4-6 wk could not be performed; these patients were still alive 7 and 12 mo after surgery.

Surgery combined with other treatment methods

A combination strategy involving surgery has been reported to be more beneficial than surgery alone^[159]. However, the available data are still fragmentary and involve a limited number of cases. Then, further prospective randomized clinical trials are needed to achieve solid conclusions.

TACE following resection has been associated to a reduction in disease-recurrence and a prolongation of OS. This effect is obtained especially in patients with high-recurrence-risk such as those with large tumors and vascular invasion^[5,160-164].

Neoadjuvant RT can achieve tumor downstaging allowing surgery and improving disease-free and OS without significant radio-mediated liver-damage^[83]. In particular, PVTT seems to have a better radio-sensitivity than HCC itself (response rate 27% *vs* 13% respectively): This allows to reduce the duration of the intervention, the bleeding-risk and the possibility of micrometastatization by small thrombotic fragments during surgery^[160]. Kamiyama *et al*^[165] described the possible role of RT as neoadjuvant treatment before surgery in patients with Vp3-4 PVTT, helping to improve prognosis through the inactivation of thrombus tumor cells and consequent prevention of dissemination, with a mean survival time of 19.6 mo. Some studies also proved TARE with yttrium-90 to be effective in downstaging unresectable HCC with PVTT, increasing patients' survival^[166].

Sorafenib has been tested as adjuvant therapy to prevent recurrence after surgical intervention. However, the initial promising results on animal models^[167], were not

Table 3 Selected studies concerning the outcome of resective surgery in patients with hepatocellular carcinoma and different portal vein tumor thrombosis grades

First author, year	Patients (patients)	PVTT Class (Vp)	Mortality	5-yr survival rate	Median survival time (mo)
Yamaoka, 1992	29	3-4	11%	11.6% (3-yr)	NA
Ikai, 1998	26	3 4	NA	11% 4%	NA
Ohkubo, 2000	47	2-3-4	0%	23.9%	14 mo
Wu, 2000	97 15	1-2-3 4	3.1% 0%	28.5% 26.4%	NA NA
Poon, 2003	20	3-4, Vv2	5.7%	13.3%	6.0 mo
Ikai <i>et al.</i> , 2004 (21,711 patients treated from 1989 to 1999)	17,867 1609 672 679	0 1 2 3-4	NA	56.5% 34.4% 27.0% 17.3%	NA
Pawlik, 2005	102	3, Vv 2-3	5.9%	10%	11 mo
Ikai, 2006	78	3-4	3.8%	10.9%	8.9 mo
Chen, 2007	286 152	1-3 4	NA 2.6%	18.1% 0%	10.1 mo
Le Treut, 2006	26	3-4, Vv2-3	11.5%	13%	9.0 mo
Zhou, 2006	381	2-3-4	NA	12%	NA
Shi, 2011	144 189 86 22	1 2 3 4	NA	26.7% (3-yr) 16.9% (3-yr) 3.7% (3-yr) 0% (3-yr)	NA
Inoue <i>et al.</i> , 2009	20	4	0%	39.0%	NA
Ban, 2009	45	3 4	0% 0%	41.8% 20.9	20.0 mo
Kondo, 2009	5	4	0%	0%	8.0 mo
Ikai <i>et al.</i> 2010 (25,066 patients treated from 1994 to 2005)	20,195 1978 820 1,021	0 1 2 3-4	NA	59.0% 39.1% 23.3% 18.3%	NA
Shi, 2010	169 78	3 4	0.6% 0%	17.7% (3-yr) 3.6% (3-yr)	15.0 mo 10.0 mo
Wang, 2013	25	Vv3	0%	13.5%	NA
Chok, 2013	88	1-2-3-4	3.3%	11.2-14.3%	NA
Pesi, 2015	15 5 21 8 3	1 2 3 Vv2 Vv3	NA	53.3% 30.1% 20.0% NA NA	NA
Xu, 2015	16 40	A B	100% NA	0% 5.2%	NA
Kokudo, 2016	1772 1475 1942 1285	1 2 3 4	NA	NA	2.67 yr 1.51 yr 0.78 yr 0.50 yr
Kudo, 2016	1908 714 852	1 2 3-4	NA	48.2% 29.2% 25.05	NA

NA: Not available; PVTT: Portal vein tumor thrombosis.

confirmed in humans. An increased overall survival was reported in animal models and in a small series of 12 patients with HCC in the BCLC-C stage treated with sorafenib after resection faced to the 24 ones treated with surgery alone^[168].

Tang *et al.*^[169] reported that combination of surgery plus chemotherapy is effective for HCC with PVTT, increasing survival rates faced to other therapeutic strategies (chemotherapy alone, surgery alone, conservative treatment). Remarkable data were also obtained comparing hepatectomy plus thrombectomy to hepatectomy plus thrombectomy plus chemotherapy (1-year and 3-years survival rates of 47% *vs* 70% and of 22% *vs* 20%, respectively)^[6]. Nagano *et al.*^[170] also showed a 100% overall 1-year survival using subcutaneous IFN-alpha and hepatic arterial infusion of 5-FU after palliative resection of advanced HCC with PVTT.

However, none of these studies clearly demonstrates that chemotherapy increases PVTT outcome after surgery.

LT

According to international guidelines, HCC with PVTT still remains a contraindication for LT because of the elevated risk of tumor recurrence, but also because of technical difficulties and post-operative mortality^[59,171-174].

However, based upon the positive experiences with living-donor LT after successful downstaging, the role of PVTT as an absolute contraindication to LT deserves a reconsideration. A recent study reported on the use a pre-waiting list LT protocol of intensive downstaging treatment in a living donor LT program based on concurrent chemoradiotherapy (CCRT) followed by HAIC^[175]. Patients achieving successful downstaging underwent LT and median patient and graft survival was 33

months. Some important issues emerged from this study: Technical limitations due to anatomic modifications determined by downstaging treatments, the prognostic value of biomarkers (*e.g.*, AFP, PIVKA-II – protein induced by vitamin K absence or antagonist-II), the high recurrence rate (3/8 patients).

An interesting study by Levi Sandri *et al*^[176] showed encouraging results of TARE for PVTT-HCC downstaging prior to LT in four patients; DFS was 39.1 mo and in all cases complete thrombosis regression was achieved, demonstrating the potential role of TARE in tumour downstaging for LT candidates. These data underline the importance of TARE as a useful downstaging tool for PVTT-HCC opening a possible scenario for LT.

External radiation therapy has also been considered for PVTT as a bridging or downstaging therapy^[177]. A small retrospective series of 10 patients receiving hypofractionated image-guided RT (HIGRT) followed by LT, presented pathologic complete response in 27% of cases; in the others, the lesions were decreased or stable in size^[178]. Five years after LT all patients were alive and no recurrence was observed. In another study on 38 patients treated with HIGRT and LT, complete plus partial pathologic response was achieved in 68%^[179].

HCC patients with PVTT treated with resection, TACE and LT present an increased survival rate compared to those receiving conservative treatment (30% *vs* 12% at 1 year and 10% *vs* 4% at 3 years)^[6].

All these experiences contribute to endorse downstaging strategies as an essential preliminary condition to allow PVTT-HCC to undergo LT without an excessively consistent risk of recurrence.

CONCLUSION

Patients with HCC and PVTT still remain a subgroup with poor survival, despite the efforts to expand treatment indications outside the BCLC algorithm. The most evident survival advantages can be attributed to surgery and several centers are moving towards an extension of BCLC indications in these patients^[136]. Recently released guidelines by European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) reflect this new tendency and the favourable results reported by both Eastern and Western surgical groups for patients with PVTT of the first/secondary branches (Vp1/2), support the differentiation of treatment algorithms according to PVTT extension^[59,180].

The importance of the scientific debate on PVTT treatment is summarized by Wang *et al*^[181] who focus on the exiguous survival advantage offered by palliative therapies (such as sorafenib) confronted with their high health-costs. A revision of western countries guidelines is required to fully recognize hepatic resection as a valid alternative for selected cases of advanced HCC. The reason why this strategy is not yet applied probably resides in the low incidence of HCC in Western countries compared with Eastern ones and the coexistence in developed countries of several comorbidities, such as cirrhosis, resulting in the risk of poor OS after resection, thus leading either to conservative surgical strategies or to merely palliative therapies. Despite these concerns, a study by Kokudo *et al*^[182] reported a less than 4% postoperative 90-day mortality for hepatic resection in PVTT-HCC. For this reason, notwithstanding obvious technical difficulties of surgery in complex patients (*e.g.*, cirrhotic, cardiopathic ones), it should be given a larger space as a therapeutic option in patients with first-order branch PVTT and normal liver function, because of its safety and efficacy. For those with PVTT in main trunk or contralateral branches, TARE and sorafenib (alone or combined) represent the most suitable solution.

There is still a deep gap of knowledge in the field of HCC associated with PVTT as only preliminary and insufficient data are available on the effectiveness of combining neoadjuvant treatment with resection and no prospective study comparing surgery with other treatments has been reported. In the meanwhile, the involvement of a multidisciplinary tumor board is mandatory in order to provide the best therapeutic decision for complex, selected cases, considering risks and benefits in the light of residual liver function which remains a decisive factor in the orientation of therapeutic choices.

Although sorafenib represents at the present time the only recommended approach in this category of patients, it is important to remind that, for selected cases, alternative therapeutic approaches with a good safety and effectiveness profile such as surgery and TARE are available, and that the sequential and personalized combination of different treatment modalities will probably lead in the future to a deep modification of BCLC treatment pathways.

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