



New Evidence and Perspectives on the Management of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus

Jun Yin^{#1}, Wen-Tao Bo^{#2}, Jian Sun³, Xiao Xiang⁴, Jin-Yi Lang¹,
Jian-Hong Zhong^{*4} and Le-Qun Li^{*4}

¹Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; ²Department of Hepatobiliary Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China;

³Department of Medical Affairs, Zibo Hospital of Integrated Traditional Chinese and Western Medicine, Zibo, China;

⁴Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China

Abstract

Portal vein tumor thrombosis (PVTT) is an intractable condition but common phenomenon in hepatocellular carcinoma (HCC). HCC patients with PVTT may have worse liver function, a higher chance of comorbidity related to portal hypertension, lower tolerance to treatment and poorer prognoses. In Western guidelines, patients are offered palliative treatment with sorafenib or other systemic agents because HCC with PVTT is grouped together with metastatic HCC during the planning of its management. In recent years, various treatment options have become available for patients with HCC and PVTT. Therapy has also shifted toward evidence-based treatment. However, policies for the management of HCC with PVTT have not been established. This comprehensive literature review aims to present current and available management options for patients with HCC and PVTT. Evidence is mainly based on studies published after 2010.

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Introduction

Hepatocellular carcinoma (HCC) is responsible for over 600,000 deaths annually.¹ In addition, HCC is characterized by its propensity to invade the liver vasculature. Macrovascular invasion (MVI) is one of the two types of invasion of the hepatic vasculature. MVI is gross invasion into the main portal veins or their branches, hepatic veins or their branches, or the inferior vena cava in the liver. Of these, portal vein

tumor thrombosis (PVTT) is the most common form of MVI of HCC. It is reported that approximately 10% to 60% of patients with HCC have PVTT at the time of diagnosis.^{2–4}

Patients with HCC in the presence of PVTT have much poorer prognoses than those without PVTT. The reported overall survival rates have ranged from only 2 to 4 months after supportive care.^{5,6} Clinically, HCC with PVTT is associated with large tumor size, greater tumor number, poorer tumor grade, worse liver function and higher serum alpha-fetoprotein. Combined effects by many factors will lead to poor prognosis of HCC patients with PVTT, such as impaired liver function, intrinsic aggressiveness of HCC, reduced intolerance to anti-neoplastic treatment and a high rate of developing complications related to portal hypertension. In regards to initial treatment, some official guidelines^{7–10} consider the presence of PVTT as a contraindication of hepatic resection or transarterial chemoembolization (TACE). These guidelines recommend sorafenib for patients with PVTT.^{7–10} However, other official guidelines^{11,12} consider hepatic resection or TACE as a choice of treatment for HCC patients with PVTT.

In recent decades, some new concepts in the management of HCC with PVTT have emerged.¹³ This review aims to discuss the current status and future prospect of the management of HCC with PVTT. In order to provide the newest and comprehensive clinical evidence, the PubMed database was systematically searched for randomized controlled trials, comparative or cohort studies, and case series on the treatment of HCC with PVTT. Only studies published after 2010 were analyzed.

Risk factors of PVTT formation

The formation of PVTT is a complex pathophysiological process, with multifactor, multicomponent participation. It is associated with the portal vein blood supply, physiological function and anatomical position. And, many cytokines may also take part in its formation. Changes in hemodynamics of the portal vein are the anatomical base of PVTT formation. Many HCC patients have portal hypertension, which will cause the blood flow velocity of the portal vein to slow down. After that, exfoliated cancer cells are able to stay more easily within and then adhere to the portal vein, gradually forming PVTT.

Cytokines may also produce important effects in the process of cancer cell exfoliation, sticking and plantation. The expression of serum soluble intercellular adhesion

Keywords: Hepatic resection; Hepatocellular carcinoma; Portal vein tumor thrombosis; Transarterial chemoembolization.

Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization.

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***Correspondence to:** Jian-Hong Zhong and Le-Qun Li, Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, He Di Rd. #71, Nanning 530021, China. Tel: +86-771-5330855, Fax: +86-771-5312000, E-mail: zhongjianhong66@163.com (JHZ), xitongpingjia@163.com (LQL)

*These two authors contributed equally to this work

molecule-1 is higher in HCC patients with PVTT than in those without PVTT. Moreover, its expression is higher among those patients in which the PVTT involves the main trunk or first-order branch, as compared to those with involvement of the secondary or higher branch.¹⁴ Such results indicate that soluble intercellular adhesion molecule-1 may have important role in the formation process of PVTT.

Some clinical characteristics may also be risk factors of PVTT, such as a high level of α -fetoprotein,^{15,16} Edmondson-Steiner grade¹⁶ and low expression of plasminogen activator inhibitor.¹⁷

Clinical features and classification of PVTT

Just as the heterogeneous populations of the Barcelona Clinic Liver Cancer stage B HCC,^{18,19} cases of HCC with PVTT also consist of heterogeneous populations with different disease behaviors and prognoses. In order to advocate treatment of patients with PVTT by means of precision and personalized therapy, a universally accepted classification of PVTT is needed for the guidance of treatment strategy because patients with different types of PVTT may have different outcomes.

The first PVTT classification system developed and proposed by the Liver Cancer Study Group of Japan was published in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.^{20,21} This classification is based on the clinical characteristics, imaging findings, pathological findings and surgical outcomes, with PVTT macroscopically classified into five grades (Table 1).²⁰⁻²² Results of the 19th follow-up survey of primary liver cancer in Japan²³ revealed that the proportions of 20,850 HCC patients (from 2006 to 2007) with Vp0, Vp1, Vp2, Vp3 and Vp4 were 87.1%, 3.1%, 2.6%, 3.9% and 3.4%, respectively. Microscopic pathological findings of surgical or biopsy specimens found 72.1%, 21.5%, 3.3%, 2.2% and 0.9% had grade Vp0, Vp1, Vp2, Vp3 and Vp4 disease, respectively. Results of the 18th follow-up survey of HCC in Japan, based on more than 25,000 patients with HCC treated by resection (between 1994 and 2005), found the 5-year overall survival rates were 59.0%, 39.1%, 23.3% and 18.3% in patients with Vp0, Vp1, Vp2 and Vp3/Vp4 grade disease, respectively.²⁴

Mei *et al.*²⁵ reported a different PVTT classification system in 2006. In this, PVTT was divided among five grades, from

Table 1. PVTT classification system developed and proposed by the Liver Cancer Study Group of Japan

Classification	Definition
Vp0	No tumor thrombus in the portal vein
Vp1	Presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein
Vp2	Presence of a tumor thrombus in the second-order branches of the portal vein
Vp3	Presence of a tumor thrombus in the first-order branches of the portal vein
Vp4	Presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both)

near to distant (Table 2). Moreover, PVTTs were also divided into three pathological types according to necrotic degree of the PVTT: proliferative type, necrotic type and organized type.

The third PVTT classification system was published in 2007 by Cheng and coworkers²⁶ and has been accepted by many liver centers in China. This system includes four types of PVTT (Table 3). In a subsequent retrospective study of 441 patients who underwent partial hepatic resection with or without portal thrombectomy for HCC with PVTT, the percentages of patients with types I, II, III and IV PVTT were 32.7%, 42.9%, 19.5% and 5.0%, respectively. The corresponding 1-, 2- and 3-year overall survival rates 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 ($p < 0.001$).²⁷

According to these PVTT classification systems, hepatic resection is one of the feasible treatment options for patients with PVTT. In general, patients with minor portal vein involvement have better prognoses than those with major portal vein involvement. However, no matter which of the above classifications is used, patients' prognoses would be determined by the extent of the PVTT and its proximity to the main, or even the contralateral, portal vein.²

Monotherapy modality and prognosis

TACE or transarterial chemotherapy (TAC)

TACE is a standard treatment for patients with unresectable HCC. However, TACE has been contraindicated for the treatment of patients with HCC and PVTT involving the main trunk or a first-order left or right branch of the portal vein because of the potential risk of hepatic insufficiency resulting from ischemia after TACE.⁷⁻¹⁰ In 1997, Lee and coworkers²⁸ reported that TACE could be safely performed in HCC with

Table 2. PVTT classification system in 2006 in China

Classification	Definition
Type I	Involving the first-order branch (left or right trunk of portal vein)
Type II	Involving the first-order branch (left or right trunk of portal vein) and the main trunk of the portal vein
Type III	Involving the first-order branches (left and right trunks of portal vein) and the main trunk of the portal vein
Type IV	Involving type III and the superior mesenteric vein or splenic vein
Type V	Involving any type I to IV plus extrahepatic metastasis

Table 3. PVTT classification system in 2007 in China

Classification	Definition
Type I	Involving segmental branches or above
Type II	Involving the right or left portal vein
Type III	Involving the main portal vein
Type IV	Involving the superior mesenteric vein

main trunk PVTT. However, no statistical survival benefit of TACE was detected. Since then, more and more studies have explored the role of TACE/TAC for HCC with PVTT (Table 4).²⁹⁻⁴³ The majority of studies have used TACE, rather than TAC. In addition, most studies have not reported complications and mortality. The median survival time reported is 9 (4 to 16) months, and the median 1-, 2- and 3-year overall survival rates are 48%, 32% and 18%, respectively.

Some studies have compared the efficacy of hepatic resection to TACE/TAC.^{36,38,43} The study by Liu and coworkers³⁶ included 247 HCC patients with PVTT who underwent hepatic resection and 181 who underwent TACE. The estimated 1-, 3- and 5-year overall survival rates were 85%, 68% and 61% and 60%, 42% and 33%, respectively ($p < 0.001$). In the propensity model, the overall survival benefit of hepatic resection remained significant. In addition, patients receiving TACE had a 2.044-fold increased risk of mortality compared with patients receiving hepatic resection. In another study by Peng and coworkers,³⁸ the 1-, 3- and 5-year overall survival rates of the hepatic resection and TACE groups were 42.0%, 14.1% and 11.1% and 37.8%, 7.3% and 0.5%, respectively ($p < 0.001$). On subgroup analyses, the overall survival rates of the hepatic resection group were better than those of the TACE group for type I PVTT and type II PVTT (all $p < 0.05$), but not for type III PVTT or type IV PVTT (all $p < 0.05$). The third study also found TACE was associated with worse overall survival than hepatic resection for HCC with PVTT.⁴³

In general, TACE is an option for patients with HCC and PVTT, and especially for those with a type III PVTT or a type IV PVTT. However, compared with TACE, hepatic resection provides survival benefits for selected patients with resectable HCC with PVTT and preserved liver function.

Radiotherapy

Some decades ago, conventional radiotherapy was not recommended for patients with HCC with or without PVTT because the lack of precise localized radiotherapy may have led to liver damage or even liver failure. The preliminary study in which radiotherapy was used to treat HCC with PVTT was reported by Chen and coworkers⁴⁴ in 1994. In that study, radiotherapy was demonstrated as safe, but lacked significant efficacy.⁴⁴ Many other studies appeared after 2000.

With the development of radiotherapy technology, three-dimensional conformal radiotherapy (3D-CRT) gradually became a clinical frequently-used radiotherapy strategy with low radiotoxicity. Other radiotherapy methods currently in use include proton beam therapy, intensity-modulated radiotherapy and stereotactic radiotherapy. Bae and coworkers⁴⁵ reported the results of their study of 47 patients with HCC and PVTT following 3D-CRT. The median survival time was 8 months, with a 1-year survival rate of 15% and a response rate of 40%. Rim and coworkers⁴⁶ reported that 3D-CRT was associated with 6.7% complete remission rate, 55.6% partial response rate, 31% stable disease rate and 6.7% progressive disease rate.

Other similar studies have also suggested that radiotherapy could improve overall survival in HCC patients with PVTT and proposed it as feasible and safe for these patients.⁴⁷⁻⁵¹ Though these small studies have suggested that such patients can benefit from liver-directed radiotherapy, strong evidence of efficacy is still lacking. Im *et al.*⁵² recently published a large multicenter study investigating the outcomes of radiotherapy in 985 patients with HCC and PVTT in the main trunk and/or first branch. The response rate of PVTT was 51.8%, and the median overall survival time was 10.2 months. Therefore, modern radiotherapy should be an option for patients with unresectable HCC and PVTT.

Table 4. Prognoses of patients with HCC and PVTT treated by transarterial chemotherapy with or without embolization

Study	Country/ region	Enrollment period	Total patients	Treatment characteristics	Median survival, mo.	Overall survival, %		
						1 yr	2 yr	3 yr
Ajit 2014	China	2011-2013	85	TACE	7	12	-	-
Chern 2014	Taiwan	2006-2012	50	TACE	11	22	10	8
Choi 2016	Korea	2003-2012	81	TACE	16	81	56	40
Gorodetski 2016	USA	2000-2013	133	TACE	5	48	-	-
Ikeda 2013	Japan	2005-2007	25	TAC	3	40	36	20
Leng 2016	Japan	1997-2012	67	TAC	12	38	20	11
Liu L 2014	China	2006-2012	188	TACE	6	38	17	3
Niu 2012	China	2007-2010	115	TACE	6	40	11	
Peng 2012	China	2006-2013	56	TACE	11	38	12	7
Song 2013	Taiwan	2003-2006	39	TAC	7	28	15	13
Tan 2015	China	2000-2008	160	TACE	28 and 15	60,80	41,59	25,37
Tawada 2014	Japan	2000-2010	81	TACE	-	45	23	20
Yang 2014	China	2011-2013	85	TACE	6	12	-	-
Ye 2014	China	2007-2009	338	TACE	13	49	37	19

"-", data not reported; ca., approximately (for data estimated from published graphs).

Abbreviations: TAC, transarterial chemotherapy; TACE, transarterial chemoembolization.

Radioembolization with yttrium-90

Radioembolization is a transarterial form of brachytherapy in which intra-arterially injected yttrium-90-loaded microspheres serve as a source for internal radiation purposes. Transarterial radioembolization with yttrium-90 is a novel therapy for HCC with PVTT. In 2015 and 2016, six comparative or cohort studies investigating the role of radioembolization with yttrium-90 for HCC with PVTT were reported.^{53–58} The median reported survival time was 8 (3 to 18) months. The median reported 1-, 2- and 3-year overall survival rates were 38%, 26% and 14%, respectively.

A systematic review was published that included fourteen clinical studies and three abstracts, involving 722 patients with HCC and PVTT.⁵⁹ The median time to progression was 5.6 months, and median disease control rate was 74.3%. The median reported value of patients with complete response, partial response and stable disease were 3.2%, 16.5% and 31.3%, respectively. The median survival time was 9.7 months. The common toxicities were fatigue, nausea/vomiting and abdominal pain; most of these, however, did not require medical intervention. Therefore, radioembolization with yttrium-90 may be a safe and effective treatment for HCC with PVTT.⁶⁰

It is important to note, however, that the current data are all based on retrospective studies or non-controlled prospective studies, and evidence from randomized controlled trials with large sample size is still needed.

Sorafenib

After publication of the two alleged positive trials of sorafenib in patients with advanced HCC,^{61,62} the safety and efficacy profiles of sorafenib were explored for patients with HCC and PVTT. In the study by Jeong and coworkers,⁶³ the median overall survival of the 30 patients with HCC and PVTT (Vp3 or Vp4) after sorafenib monotherapy was only 3.1 months. Giorgio and coworkers⁶⁴ performed a randomized controlled trial in 99 cirrhotic patients with HCC and PVTT treated with sorafenib plus radiofrequency ablation or sorafenib alone. The 1-, 2- and 3-year overall survival rates were 60%, 35% and 26% and 37%, 0% and 0%, respectively. In the study by Nakazawa and coworkers,⁶⁵ patients with HCC and PVTT in the main trunk or the first branch had similar median survival time after sorafenib (4.3 months) or radiotherapy (5.9 months; $p = 0.115$). However, better median survival time was noted in the radiotherapy group than in the sorafenib group after propensity score matching (10.9 vs. 4.8 months; $p = 0.025$). The study by Song and coworkers⁶⁶ compared the efficacy of TAC to sorafenib in HCC patients with PVTT. The disease control rate in the TAC group was significantly higher than that in the sorafenib group ($p < 0.001$). The median overall survival was also significantly longer in the TAC group than in the sorafenib group (7.1 vs. 5.5 months; $p = 0.011$). The fifth study compared the efficacy of sorafenib plus TACE to sorafenib alone for HCC with main PVTT.⁶⁷ The disease control rate was similar between the two groups, and the median overall survival was 7.0 and 6.0 months for the sorafenib-TACE group and the sorafenib group, respectively ($p = 0.544$).

In general, the efficacy of sorafenib monotherapy is inferior to other monotherapy or combined treatments. These results lead us to question the wisdom of palliative sorafenib therapy for patients with HCC and PVTT. The greatest

survival benefit of such therapy appears to be less than 3 months.^{63–67} This slim benefit seems negligible in comparison to the prohibitive cost of sorafenib and risk of adverse effects.^{68,69}

Hepatic resection

Three decades ago, only studies from Eastern countries reported the role of hepatic resection for HCC with PVTT. In the 1980s, hepatic resection was an option only for patients with a tumor thrombus in a first-order branch of the portal vein, particularly not involving the confluence of the left and right portal veins.^{70,71} Some years later, however, the role of hepatic resection for tumor thrombus extending to the main portal trunk was reported.^{72,73} Since then, hepatic resection with or without thrombectomy for HCC with PVTT has gradually been refined and standardized to become a commonly used procedure currently, especially in Asian liver centers.⁷⁴

Though the role of hepatic resection for HCC with PVTT is still controversial^{75,76} and not recommended by Western official guidelines,^{7–10} more and more comparative or cohort studies, mostly from Asian countries, have demonstrated hepatic resection to be safe and effective for selected patients with HCC and PVTT.^{36,38,43,77–98} Most patients in those studies have been Asian. The median reported postoperative complication and mortality rates are 26% (range, 3–42%) and 4.1% (range, 0–23.7%), respectively. The median reported survival time is 25.4 (8 to 64) months, and the median 1-, 2- and 3-year overall survival rates are 62%, 52% and 41%, respectively.

From the 18th follow-up survey of primary liver cancer in Japan, which encompassed 1021 patients who underwent Vp3 or Vp4 hepatic resection, the Liver Cancer Study Group of Japan reported a survival rate of 18.3% at 5 years.²⁴ Systematic review of 24 studies involving 4389 patients with HCC with MVI showed that hepatic resection was associated with median mortality of 2.7% (range, 0–24%) and median overall survival ranging from 18% at 5 years to 50% at 1 year.^{99,100} A new large retrospective study from Japan compared overall survival of 2093 HCC patients with PVTT who underwent hepatic resection and 4381 patients who received other treatments.⁸¹ The median overall survival lengths of the two groups were 2.87 and 1.10 years ($p < 0.001$), respectively. However, hepatic resection showed no overall survival benefit among patients in whom PVTT affected the main trunk or contralateral branch (Vp3 or Vp4).⁸¹

These results argue for expanding treatment strategy in official guidelines to recognize hepatic resection as a first-line therapeutic option for selected patients with HCC and PVTT and preserved liver function, especially for those with type I or II (or Vp0-Vp3) PVTT. Surgeons should consider hepatic resection when it is feasible, although they should be prepared for the fact that the procedure is technically demanding.¹⁰¹

Multimodality treatment and prognosis

Surgical multimodality treatment

HCC is a complex disease. Though hepatic resection appears to provide better outcomes than TACE/TAC, radiotherapy, radioembolization with yttrium-90, sorafenib or nonsurgical multimodality treatment for selected patients with HCC and PVTT, the long-term overall survival after hepatic resection is

Table 5. Nonsurgical multimodality treatments in patients with HCC and PVTT

Study	Country/region	Enrollment period	Sample size	Classification of PVTT	Multimodality treatment	Outcomes
Giorgio 2016	Italy	2011–2014	49	Vp4	RFA plus sorafenib	1- and 3-year OS were 60% and 26%
Kang 2014	China	2004–2008	34	Vp3 or 4	Stereotactic body radiotherapy plus TACE	Response rate was 88%
Long 2016	China	2010–2014	60	Vp1, 2 or 3	Microwave ablation plus TACE	1- and 3-year OS were 48% and 23%
Nagai 2015	Japan	2002–2009	18	Vp3 or 4	Sorafenib plus TAC	1- and 3-year OS were 36% and 18%

Abbreviations: PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; TAC, transarterial chemotherapy; TACE, transarterial chemoembolization.

still unsatisfactory because of the high rate of tumor recurrence or low rate of disease-free survival.^{99,102} Surgical multimodality treatment is now being recommended by more and more liver centers in Eastern and Western countries. On one hand, hepatic resection will eliminate the original tumor nodule and PVTT; on the other hand, eliminating the PVTT will improve liver function, consequently making a foundation for further treatment.

Li and coworkers⁸³ compared outcomes of 45 patients with HCC and main PVTT who underwent neoadjuvant 3D-CRT plus hepatic resection and 50 patients who received hepatic resection alone. They found that neoadjuvant 3D-CRT plus resection significantly decreased the rates of HCC recurrence and HCC-related death, with hazard ratios of 0.36 and 0.32, respectively. In addition, adjuvant TACE or TAC may also be a choice of treatment.^{103–105} Collectively, the available evidence indicates that surgery-based interdisciplinary therapy is effective and should be explored in future studies.

Nonsurgical multimodality treatment

Though nonsurgical multimodality treatments are palliative, they have the characteristics of less trauma, low risk of mortality and rapid recovery. Nonsurgical multimodality treatments are clearly essential for the management of HCC and are of particularly high value in cases of HCC with PVTT.¹⁰⁶ Many nonsurgical multimodality treatment types have been reported, such as sorafenib combined radiofrequency ablation, sorafenib combined TACE/TAC, radiotherapy combined with TACE or TACE combined with radiotherapy, TACE plus microwave or ethanol ablation, etc. Among these, TACE combined with radiotherapy is the most used treatment. Table 5 lists some studies of the nonsurgical multimodality treatments in patients with HCC and PVTT.^{64,107–110} Because of the heterogeneity of the included patients, however, it is hard to compare the efficacy of different nonsurgical multimodality treatment type.

Conclusions

Hepatic resection to treat HCC is associated with the best outcomes when the patient has early or intermediate stage disease and preserved liver function. For most HCC patients with Vp1–3 PVTT and preserved liver function, hepatic resection may also be the first-line therapy. However, no curative treatment is currently available for HCC with Vp4 PVTT. Currently, findings from various and worldwide studies

suggest that hepatectomy-based multiple interdisciplinary treatments are effective options for many patients with HCC and PVTT, as long as preserved liver function is adequate.

The optimal timing and details of neoadjuvant or adjuvant treatments combined with hepatectomy in patients with HCC and PVTT remains an interesting topic for future research. In the research field, there remains a need for better focusing on selection criteria to further enhance the prognostic benefits of resection. Nonetheless, for patients with unresectable HCC and PVTT, TACE/TAC, radiotherapy or radioembolization with yttrium-90 should be considered. Future recommendations must be based on clear evidence from well-designed randomized controlled trials with large sample size.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

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