Review Article

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

Jun Yin[#1], Wen-Tao Bo[#2], Jian Sun[3], Xiao Xiang[4], Jin-Yi Lang[1], Jian-Hong Zhong*[4] and Le-Qun Li*[4]

[1]*Department of Radiation Oncology, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China;* [2]*Department of Hepatobiliary Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China;* [3]*Department of Medical Affairs, ZiBo Hospital of Integrated Traditional Chinese and Western Medicine, Zibo, China;* [4]*Department 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.

Citation of this article: Yin J, Bo WT, Sun J, Xiang X, Lang JY, Zhong JH, *et al*. V New evidence and perspectives on the management of hepatocellular carcinoma with portal vein tumor thrombus. J Clin Transl Hepatol 2017;5(2):169–176. doi: 10.14218/JCTH.2016.00071.

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% 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.

Received: 29 November 2016; Revised: 2 March 2017; Accepted: 4 March 2017

*__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 grade[16] 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 Japan[23] 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 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 coworkers[26] 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 coworkers[28] reported that TACE could be safely performed in HCC with

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)

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 coworkers[36] 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 coworkers[44] 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 coworkers[45] 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 coworkers[46] 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 coworkers[64] 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 coworkers[66] 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 coworkers[83] 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 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.

Acknowledgements

This work was supported by Guangxi Science and Technology Development Projects (14124003–4), the National Science and Technology Major Special Project (2012ZX10002010001009), Guangxi University of Science and Technology Research Projects (KY2015LX056), the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (Z2016512, Z2015621, GZZC15–34, Z2014241), the Innovation Project of Guangxi Graduate Education (YCBZ2015030), and the Youth Science Foundation of Guangxi Medical University (GXMUYSF201302).

Conflict of interest

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

Author contributions

Manuscript design (JHZ), manuscript writing (JY, WTB, JS, XX, JYL, LQL, JHZ), final approval (JHZ).

References

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30. doi: 10.3322/caac.21387.
[2] Chan SL, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. World J Gastroenterol 2016;22:7289–7300. doi: 10.3748/wjg.v22.i32.7289.
[3] Zhong JH, You XM, Ma L, Xiang BD, Wu FX, Peng NF, *et al*. Tumor stage and primary treatment selection among patients with hepatocellular carcinoma from 2003 to 2013. Chinese Journal of Oncology Prevention and Treatment 2015;7:403–407.

[4] Xiang X, Zhong JH, Wang YY, You XM, Ma L, Xiang BD, *et al*. Distribution of tumor stage and initial treatment modality in patients with primary hepatocellular carcinoma. Clin Transl Oncol 2017. doi: 10.1007/s12094-017-1621-6.
[5] Schöniger-Hekele M, Müller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: prognostic features and survival. Gut 2001;48:103–109. doi: 10.1136/gut.48.1.103.
[6] Jiang JF, Lao YC, Yuan BH, Yin J, Liu X, Chen L, *et al*. Treatment of hepatocellular carcinoma with portal vein tumor thrombus: advances and challenges. Oncotarget 2017. doi: 10.18632/oncotarget.15411.
[7] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379: 1245–1255. doi: 10.1016/S0140-6736(11)61347-0.
[8] European Association for Study of Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J. Cancer 2012;48: 599–641. doi: 10.1016/j.ejca.2011.12.021.
[9] Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53: 1020–1022. doi: 10.1002/hep.24199.
[10] Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, *et al*. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439–474. doi: 10. 1007/s12072-010-9165-7.
[11] Jarnagin W, Chapman WC, Curley S, D'Angelica M, Rosen C, Dixon E, *et al*. Surgical treatment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford) 2010;12:302–310. doi: 10.1111/j.1477-2574.2010. 00182.x.
[12] Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, *et al*. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–364. doi: 10.1159/ 000327577.
[13] Sun JX, Shi J, Li N, Guo WX, Wu MC, Lau WY, *et al*. Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma. Cancer Biol Med 2016;13:452–458. doi: 10.20892/j.issn.2095-3941.2016.0059.
[14] Shimizu Y, Minemura M, Tsukishiro T, Kashii Y, Miyamoto M, Nishimori H, *et al*. Serum concentration of intercellular adhesion molecule-1 in patients with hepatocellular carcinoma is a marker of the disease progression and prognosis. Hepatology 1995;22:525–531. doi: 10.1016/0270-9139 (95)90575-8.
[15] Liu Y, Wang X, Jiang K, Zhang W, Dong J. The diagnostic value of tumor biomarkers for detecting hepatocellular carcinoma accompanied by portal vein tumor thrombosis. Cell Biochem Biophys 2014;69:455–459. doi: 10. 1007/s12013-014-9817-7.
[16] Zhou L, Rui JA, Wang SB, Chen SG, Qu Q. Risk factors of poor prognosis and portal vein tumor thrombosis after curative resection of solitary hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2013;12:68–73. doi: 10. 1016/S1499-3872(13)60008-9.
[17] Zhou L, Jin Y, Cui QC, Jin KM, Zhou WX, Xing BC. Low expression of PAI-2 as a novel marker of portal vein tumor thrombosis and poor prognosis in hepatocellular carcinoma. World J Surg 2013;37:608–613. doi: 10. 1007/s00268-012-1866-8.
[18] Zhong JH, Lu SD, Wang YY, Ma L, Li LQ. Intermediate-stage HCC–upfront resection can be feasible. Nat Rev Clin Oncol 2015;12(5). doi: 10. 1038/nrclinonc.2014.122-c3.
[19] Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, *et al*. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348–359. doi: 10.1055/s-0032-1329906.
[20] Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer, 2nd ed. Tokyo: Kanehara Shuppan, 1987.
[21] Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer, second english edition. Tokyo: Kanehara & Co., Ltd., 2003.
[22] Katagiri S, Yamamoto M. Multidisciplinary treatments for hepatocellular carcinoma with major portal vein tumor thrombus. Surg Today 2014;44: 219–226. doi: 10.1007/s00595-013-0585-6.
[23] Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, *et al*. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res 2016; 46:372–390. doi: 10.1111/hepr.12697.
[24] Ikai I, Kudo M, Arii S, Omata M, Kojiro M, Sakamoto M, *et al*. Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatol Res 2010; 40:1043–1059. doi: 10.1111/j.1872-034X.2010.00731.x.
[25] Mei MH, Chen Q, Yang JH, Xu J, Qiu WJ, Zeng SE, *et al*. Clinicopathological staging of portal vein tumor thrombosis in hepatocellular carcinoma and its significance. Chin J Hepatobiliary Surg 2006;12:374–377.
[26] Shuqun C, Mengchao W, Han C, Feng S, Jiahe Y, Guanghui D, *et al*. Tumor thrombus types influence the prognosis of hepatocellular carcinoma with the tumor thrombi in the portal vein. Hepatogastroenterology 2007;54: 499–502.
[27] Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, *et al*. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011;18:74–80. doi: 10.1007/s00534-010-0314-0.
[28] Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY. The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. Cancer 1997;79:2087–2094. doi: 10.1002/(SICI) 1097-0142(19970601)79:11=2087::AID-CNCR5>3.0.CO;2-M.
[29] Ajit Y, Sudarsan H, Saumya G, Abhishek A, Navneet R, Piyush R, *et al*. Transarterial chemoembolization in unresectable hepatocellular carcinoma with portal vein thrombosis: a perspective on survival. Oman Med J 2014; 29:430–436. doi: 10.5001/omj.2014.114.
[30] Chern MC, Chuang VP, Liang CT, Lin ZH, Kuo TM. Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors. J Vasc Interv Radiol 2014;25:32–40. doi: 10.1016/j.jvir.2013.10.013.
[31] Choi JW, Kim HC, Lee JH, Yu SJ, Kim YJ, Yoon JH, *et al*. Transarterial chemoembolization of hepatocellular carcinoma with segmental portal vein tumour thrombus. Eur Radiol 2017;27:1448–1458. doi: 10.1007/s00330-016-4511-3.
[32] Gorodetski B, Chapiro J, Schernthaner R, Duran R, Lin M, Lee H, *et al*. Advanced-stage hepatocellular carcinoma with portal vein thrombosis: conventional versus drug-eluting beads transcatheter arterial chemoembolization. Eur Radiol 2017;27:526–535. doi: 10.1007/s00330-016-4445-9.
[33] Ikeda M, Okusaka T, Furuse J, Mitsunaga S, Ueno H, Yamaura H, *et al*. A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Cancer Chemother Pharmacol 2013;72:463–470. doi: 10. 1007/s00280-013-2222-x.
[34] Kim GA, Shim JH, Yoon SM, Jung J, Kim JH, Ryu MH, *et al*. Comparison of chemoembolization with and without radiation therapy and sorafenib for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. J Vasc Interv Radiol 2015;26:320–329.e326. doi: 10.1016/j.jvir.2014.10.019.
[35] Lin CC, Hung CF, Chen WT, Lin SM. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein thrombosis: impact of early response to 4 weeks of treatment. Liver Cancer 2015;4:228–240. doi: 10.1159/000367737.
[36] Liu PH, Lee YH, Hsia CY, Hsu CY, Huang YH, Chiou YY, *et al*. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. Ann Surg Oncol 2014;21:1825–1833. doi: 10.1245/s10434-014-3510-3.
[37] Niu ZJ, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, *et al*. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. Med Oncol 2012;29:2992–2997. doi: 10.1007/s12032-011-0145-0.
[38] Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS, Lau WY. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2012; 118:4725–4736. doi: 10.1002/cncr.26561.
[39] Song DS, Bae SH, Song MJ, Lee SW, Kim HY, Lee YJ, *et al*. Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 2013;19:4679–4688. doi: 10.3748/wjg. v19.i29.4679.
[40] Tan X, Xie P, Liu J, Wu H, Xie Y. Therapeutic value of transcatheter arterial chemoembolization combined with portal vein embolization for primary hepatocellular carcinoma with portal vein tumor thrombus: a pilot study. Asia Pac J Clin Oncol 2015;11:e6–e12. doi: 10.1111/ajco.12272.
[41] Tawada A, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Saito T, *et al*. Efficacy of transarterial chemoembolization targeting portal vein tumor thrombus in patients with hepatocellular carcinoma. Anticancer Res 2014;34: 4231–4237.
[42] Yang M, Fang Z, Yan Z, Luo J, Liu L, Zhang W, *et al*. Transarterial chemoembolisation (TACE) combined with endovascular implantation of an iodine-125 seed strand for the treatment of hepatocellular carcinoma with portal vein tumour thrombosis versus TACE alone: a two-arm, randomised clinical trial. J Cancer Res Clin Oncol 2014;140:211–219. doi: 10.1007/s00432-013-1568-0.
[43] Ye JZ, Zhang YQ, Ye HH, Bai T, Ma L, Xiang BD, *et al*. Appropriate treatment strategies improve survival of hepatocellular carcinoma patients with portal vein tumor thrombus. World J Gastroenterol 2014;20:17141–17147. doi: 10.3748/wjg.v20.i45.17141.
[44] Chen SC, Lian SL, Chang WY. The effect of external radiotherapy in treatment of portal vein invasion in hepatocellular carcinoma. Cancer Chemother Pharmacol 1994;33Suppl:S124–S127. doi: 10.1007/BF00686683.

[45] Bae BK, Kim JC. The response of thrombosis in the portal vein or hepatic vein in hepatocellular carcinoma to radiation therapy. Radiat Oncol J 2016; 34:168–176. doi: 10.3857/roj.2016.01669.
[46] Rim CH, Yang DS, Park YJ, Yoon WS, Lee JA, Kim CY. Effectiveness of high-dose three-dimensional conformal radiotherapy in hepatocellular carcinoma with portal vein thrombosis. Jpn J Clin Oncol 2012;42:721–729. doi: 10.1093/jjco/hys082.
[47] Lee SU, Park JW, Kim TH, Kim YJ, Woo SM, Koh YH, *et al*. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Strahlenther Onkol 2014;190:806–814. doi: 10.1007/s00066-014-0604-6.
[48] Lu XJ, Dong J, Ji LJ, Xiao LX, Ling CQ, Zhou J. Tolerability and efficacy of gamma knife radiosurgery on hepatocellular carcinoma with portal vein tumor thrombosis. Oncotarget 2016;7:3614–3622. doi: 10.18632/oncotarget.6118.
[49] Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, *et al*. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. J Radiat Res 2016;57:512–523. doi: 10.1093/jrr/rrw028.
[50] Xi M, Zhang L, Zhao L, Li QQ, Guo SP, Feng ZZ, *et al*. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One 2013;8:e63864. doi: 10.1371/journal.pone.0063864.
[51] Yeh SA, Chen YS, Perng DS. The role of radiotherapy in the treatment of hepatocellular carcinoma with portal vein tumor thrombus. J Radiat Res 2015;56:325–331. doi: 10.1093/jrr/rru104.
[52] Im JH, Yoon SM, Park HC, Kim JH, Yu JI, Kim TH, *et al*. Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumour thrombosis in a hepatitis B endemic area. Liver Int 2017;37:90–100. doi: 10.1111/liv.13191.
[53] Akinwande O, Kim D, Edwards J, Brown R, Philips P, Scoggins C, *et al*. Is radioembolization ((90)Y) better than doxorubicin drug eluting beads (DEBDOX) for hepatocellular carcinoma with portal vein thrombosis? A retrospective analysis. Surg Oncol 2015;24:270–275. doi: 10.1016/j.suronc.2015.06.008.
[54] Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, *et al*. Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. J Vasc Interv Radiol 2016;27:812–821.e822. doi: 10.1016/j.jvir.2016.01.147.
[55] Cho YY, Lee M, Kim HC, Chung JW, Kim YH, Gwak GY, *et al*. Radioembolization is a safe and effective treatment for hepatocellular carcinoma with portal vein thrombosis: a propensity score analysis. PLoS One 2016;11:e0154986. doi: 10.1371/journal.pone.0154986.
[56] de la Torre MA, Buades-Mateu J, de la Rosa PA, Lué A, Bustamante FJ, Serrano MT, *et al*. A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib. Liver Int 2016;36:1206–1212. doi: 10.1111/liv.13098.
[57] Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, *et al*. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med 2015;56:339–346. doi: 10.2967/jnumed.114.145177.
[58] Kokabi N, Camacho JC, Xing M, El-Rayes BF, Spivey JR, Knechtle SJ, *et al*. Open-label prospective study of the safety and efficacy of glass-based yttrium 90 radioembolization for infiltrative hepatocellular carcinoma with portal vein thrombosis. Cancer 2015;121:2164–2174. doi: 10.1002/cncr.29275.
[59] Jia Z, Jiang G, Tian F, Zhu C, Qin X. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Saudi J Gastroenterol 2016;22:353–359. doi: 10.4103/1319-3767.191139.
[60] Liao YY, Zhong JH, Peng NF, Li LQ, Tong TJ. Is radioembolization or sorafenib the best option for patients with hepatocellular carcinoma and portal vein invasion? Liver Int 2016;36:1715. doi: 10.1111/liv.13208.
[61] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390. doi: 10.1056/NEJMoa0708857.
[62] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25–34. doi: 10.1016/S1470-2045(08)70285-7.
[63] Jeong SW, Jang JY, Shim KY, Lee SH, Kim SG, Cha SW, *et al*. Practical effect of sorafenib monotherapy on advanced hepatocellular carcinoma and portal vein tumor thrombosis. Gut Liver 2013;7:696–703. doi: 10.5009/gnl.2013.7.6.696.
[64] Giorgio A, Merola MG, Montesarchio L, Merola F, Santoro B, Coppola C, *et al*. Sorafenib combined with radio-frequency ablation compared with sorafenib alone in treatment of hepatocellular carcinoma invading portal vein: a western randomized controlled trial. Anticancer Res 2016;36:6179–6183. doi: 10.21873/anticanres.11211.
[65] Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J, *et al*. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol 2014;14:84. doi: 10.1186/1471-230X-14-84.
[66] Song DS, Song MJ, Bae SH, Chung WJ, Jang JY, Kim YS, *et al*. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol 2015;50:445–454. doi: 10.1007/s00535-014-0978-3.
[67] Zhang Y, Fan W, Wang Y, Lu L, Fu S, Yang J, *et al*. Sorafenib with and without transarterial chemoembolization for advanced hepatocellular carcinoma with main portal vein tumor thrombosis: a retrospective analysis. Oncologist 2015;20:1417–1424. doi: 10.1634/theoncologist.2015-0196.
[68] Zhong JH. The STORM trial and beyond: narrowing the horizon of adjuvant sorafenib for postoperative hepatocellular carcinoma. Tumour Biol 2015;36:8271–8272. doi: 10.1007/s13277-015-4279-0.
[69] Zhong JH, Du XK, Xiang BD, Li LQ. Adjuvant sorafenib in hepatocellular carcinoma: A cautionary comment of STORM trial. World J Hepatol 2016;8:957–960. doi: 10.4254/wjh.v8.i23.957.
[70] Lee NW, Wong J, Ong GB. The surgical management of primary carcinoma of the liver. World J Surg 1982;6:66–75. doi: 10.1007/BF01656375.
[71] Lin TY, Lee CS, Chen KM, Chen CC. Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience. Br J Surg 1987;74:839–842. doi: 10.1002/bjs.1800740931.
[72] Kumada K, Ozawa K, Okamoto R, Takayasu T, Yamaguchi M, Yamamoto Y, *et al*. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. Surgery 1990;108:821–827.
[73] Yamaoka Y, Kumada K, Ino K, Takayasu T, Shimahara Y, Mori K, *et al*. Liver resection for hepatocellular carcinoma (HCC) with direct removal of tumor thrombi in the main portal vein. World J Surg 1992;16:1172–1176; discussion 1177. doi: 10.1007/BF02067093.
[74] Li W, You X, Li L, Zhong J. Hepatic resection for hepatocellular carcinoma involving a single large tumor, multiple tumors or macrovascular invasion. Zhonghua Yi Xue Za Zhi 2015;95:3115–3118.
[75] Zhong JH, Ma L, Xiang BD, Li LQ, Yang T. We're still in an update process of the BCLC system. Ann Surg 2016. doi: 10.1097/SLA.0000000000001922.
[76] Wang HL, Cucchetti A, Zhong JH, Ye XP, Gu JH, Ma L, *et al*. Should hepatic resection be recommended to patients with hepatocellular carcinoma and portal vein invasion? J Hepatol 2016;65:1057–1058. doi: 10.1016/j.jhep.2016.07.022.
[77] Chang WT, Kao WY, Chau GY, Su CW, Lei HJ, Wu JC, *et al*. Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: extending the indication for resection? Surgery 2012;152:809–820. doi: 10.1016/j.surg.2012.03.024.
[78] Chen JS, Wang Q, Chen XL, Huang XH, Liang LJ, Lei J, *et al*. Clinicopathologic characteristics and surgical outcomes of hepatocellular carcinoma with portal vein tumor thrombosis. J Surg Res 2012;175:243–250. doi: 10.1016/j.jss.2011.03.072.
[79] Chok KS, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. World J Surg 2014;38:490–496. doi: 10.1007/s00268-013-2290-4.
[80] Kojima H, Hatano E, Taura K, Seo S, Yasuchika K, Uemoto S. Hepatic resection for hepatocellular carcinoma with tumor thrombus in the major portal vein. Dig Surg 2015;32:413–420. doi: 10.1159/000437375.
[81] Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, *et al*. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938–943. doi: 10.1016/j.jhep.2016.05.044.
[82] Lee JM, Jang BK, Lee YJ, Choi WY, Choi SM, Chung WJ, *et al*. Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. Clin Mol Hepatol 2016;22:160–167. doi: 10.3350/cmh.2016.22.1.160.
[83] Li N, Feng S, Xue J, Wei XB, Shi J, Guo WX, *et al*. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB (Oxford) 2016;18:549–556. doi: 10.1016/j.hpb.2016.04.003.
[84] Matono R, Yoshiya S, Motomura T, Toshima T, Kayashima H, Masuda T, *et al*. Factors linked to longterm survival of patients with hepatocellular carcinoma accompanied by tumour thrombus in the major portal vein after surgical resection. HPB (Oxford) 2012;14:247–253. doi: 10.1111/j.1477-2574.2011.00436.x.
[85] Roayaie S, Jibara G, Taouli B, Schwartz M. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol 2013;20:3754–3760. doi: 10.1245/s10434-013-3074-7.
[86] Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, *et al*. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol 2010;17:2073–2080. doi: 10.1245/s10434-010-0940-4.

[87] Tang QH, Li AJ, Yang GM, Lai EC, Zhou WP, Jiang ZH, *et al*. Surgical resection versus conformal radiotherapy combined with TACE for resectable hepatocellular carcinoma with portal vein tumor thrombus: a comparative study. World J Surg 2013;37:1362–1370. doi: 10.1007/s00268-013-1969-x.
[88] Tang ZY, Zhou BH, Wang W, Du G, Liu ZY, Li J, *et al*. Curative analysis of several therapeutic methods for primary hepatocellular carcinoma with portal vein tumor thrombus. Hepatogastroenterology 2015;62:703–709.
[89] Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, *et al*. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg 2013;257:929–937. doi: 10.1097/SLA.0b013e31828329b8.
[90] Wei XB, Xu J, Li N, Yu Y, Shi J, Guo WX, *et al*. The role of three-dimensional imaging in optimizing diagnosis, classification and surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. HPB (Oxford) 2016;18:287–295. doi: 10.1016/j.hpb.2015.10.007.
[91] Wu ZJ, Cai J, Xu AB, Su XQ, Wang XQ, Zhang YX, *et al*. Combined three-dimensional conformal radiotherapy plus transcatheter arterial chemoembolization and surgical intervention for portal vein tumor thrombus in patients with hepatocellular carcinoma. Zhonghua Yi Xue Za Zhi 2011;91:2841–2844.
[92] Xiao CZ, Wei W, Guo ZX, Li SH, Zhang YF, Wang JH, *et al*. A prognosis model for patients with hepatocellular carcinoma and portal vein tumor thrombus following hepatic resection. Oncol Lett 2015;10:2787–2794. doi: 10.3892/ol.2015.3677.
[93] Yamamoto Y, Ikoma H, Morimura R, Shoda K, Konishi H, Murayama Y, *et al*. Post-hepatectomy survival in advanced hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 2015;21:246–253. doi: 10.3748/wjg.v21.i1.246.
[94] Zhang T, Huang JW, Bai YN, Wu H, Zeng Y. Recurrence and survivals following hepatic resection for hepatocellular carcinoma with major portal/hepatic vein tumor thrombus. Hepatol Res 2014;44:761–768. doi: 10.1111/hepr.12185.
[95] Zhang YF, Le Y, Wei W, Zou RH, Wang JH, OuYang HY, *et al*. Optimal surgical strategy for hepatocellular carcinoma with portal vein tumor thrombus: a propensity score analysis. Oncotarget 2016;7:38845–38856. doi: 10.18632/oncotarget.8642.
[96] Zheng N, Wei X, Zhang D, Chai W, Che M, Wang J, *et al*. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. Medicine (Baltimore) 2016;95:e3959. doi: 10.1097/MD.0000000000003959.
[97] Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, *et al*. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg 2014;260:329–340. doi: 10.1097/SLA.0000000000000236.
[98] Zhou L, Rui JA, Wang SB, Chen SG, Qu Q. Clinicopathological predictors of poor survival and recurrence after curative resection in hepatocellular carcinoma without portal vein tumor thrombosis. Pathol Oncol Res 2015;21:131–138. doi: 10.1007/s12253-014-9798-2.
[99] Zhong JH, Rodríguez AC, Ke Y, Wang YY, Wang L, Li LQ. Hepatic resection as a safe and effective treatment for hepatocellular carcinoma involving a single large tumor, multiple tumors, or macrovascular invasion. Medicine (Baltimore) 2015;94:e396. doi: 10.1097/MD.0000000000000396.
[100] Zhong JH, Ke Y, Wang YY, Li LQ. Liver resection for patients with hepatocellular carcinoma and macrovascular invasion, multiple tumours, or portal hypertension. Gut 2015;64:520–521. doi: 10.1136/gutjnl-2014-308139.
[101] Zhong JH, Torzilli G, Xing H, Li C, Han J, Liang L, *et al*. Controversies and evidence of hepatic resection for hepatocellular carcinoma. BBA Clin 2016;6:125–130. doi: 10.1016/j.bbacli.2016.10.001.
[102] Chitapanarux T, Phornphutkul K. Risk Factors for the Development of Hepatocellular Carcinoma in Thailand. J Clin Transl Hepatol 2015;3:182–188. doi: 10.14218/JCTH.2015.00025.
[103] Zhong JH, Zhong QL, Li LQ, Li H. Adjuvant and chemopreventive therapies for resectable hepatocellular carcinoma: a literature review. Tumour Biol 2014;35:9459–9468. doi: 10.1007/s13277-014-2443-6.
[104] Zhong JH, Ma L, Li LQ. Postoperative therapy options for hepatocellular carcinoma. Scand J Gastroenterol 2014;49:649–661. doi: 10.3109/00365521.2014.905626.
[105] Peng BG, He Q, Li JP, Zhou F. Adjuvant transcatheter arterial chemoembolization improves efficacy of hepatectomy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Am J Surg 2009;198:313–318. doi: 10.1016/j.amjsurg.2008.09.026.
[106] Zhang X, Wang K, Wang M, Yang G, Ye X, Wu M, *et al*. Transarterial chemoembolization (TACE) combined with sorafenib versus TACE for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. Oncotarget 2017. doi: 10.18632/oncotarget.15075.
[107] Kang J, Nie Q, Du R, Zhang L, Zhang J, Li Q, *et al*. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Mol Clin Oncol 2014;2:43–50. doi: 10.3892/mco.2013.196.
[108] Long J, Zheng JS, Sun B, Lu N. Microwave ablation of hepatocellular carcinoma with portal vein tumor thrombosis after transarterial chemoembolization: a prospective study. Hepatol Int 2016;10:175–184. doi: 10.1007/s12072-015-9673-6.
[109] Nagai H, Mukozu T, Ogino YU, Matsui D, Matsui T, Wakui N, *et al*. Sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombus. Anticancer Res 2015;35:2269–2277.
[110] Wang K, Guo WX, Chen MS, Mao YL, Sun BC, Shi J, *et al*. Multimodality treatment for hepatocellular carcinoma with portal vein tumor thrombus: a large-scale, multicenter, propensity mathching score analysis. Medicine (Baltimore) 2016;95:e3015. doi: 10.1097/MD.0000000000003015.