Treatment of hepatocellular carcinoma with portal vein tumor thrombus: advances and challenges

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ABSTRACT

Portal vein tumor thrombus is a frequent, challenging complication in hepatocellular carcinoma. Hepatocellular carcinoma patients with portal vein tumor thrombus may show worse liver function, less treatment tolerance and worse prognosis than patients without portal vein tumor thrombus, and they may be at higher risk of comorbidity related to portal hypertension. Western and some Asian guidelines stratify hepatocellular carcinoma with portal vein tumor thrombus together with metastatic hepatocellular carcinoma and therefore recommend only palliative treatment with sorafenib or other systemic agents. In recent years, more treatment options have become available for hepatocellular carcinoma patients with portal vein tumor thrombus, and an evidence-based approach to optimizing disease management and treatment has become more widespread. Nevertheless, consensus policies for managing hepatocellular carcinoma with portal vein tumor thrombus have not been established. This comprehensive literature review, drawing primarily on studies published after 2010, examines currently available management options for patients with hepatocellular carcinoma and portal vein tumor thrombus.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide [1], leading to over 600,000 deaths annually [1-2]. HCC shows a strong propensity to invade the liver vasculature. During so-called macrovascular invasion (MVI), tumor cells invade the main portal veins or their branches, hepatic veins or their branches, or the inferior vena cava in the liver [3-4]. Portal vein tumor thrombus (PVTT) is the most common form of MVI in HCC. Approximately 10 to 60% of HCC patients have PVTT at the time of diagnosis [5-6].

The prognosis of HCC patients is much poorer in the presence of PVTT; their overall survival is only 2-4 months with supportive care [7-8]. The worse prognosis of HCC patients with PVTT may reflect several factors, including larger tumors, more numerous tumors, poorer tumor grade, worse liver function and higher serum levels of alpha-fetoprotein. These factors likely conspire to explain the low liver function, tumor aggressiveness, low chemotherapy tolerance and high risk of complications related to portal hypertension that are often observed in HCC patients with PVTT [9].

PVTT is considered a contraindication for initial hepatic resection or transarterial chemoembolization (TACE) by many systems and associations, including the
Barcelona Clinic Liver Cancer staging system [10], the European Association for the Study of Liver Disease [11], the American Association for the Study of Liver Disease [12] and the Asian Pacific Association for the Study of the Liver [13]. These guidelines recommend sorafenib for patients with PVTT [10-13]. However, selected HCC patients with PVTT can benefit from hepatic resection or TACE, leading the American Hepato-Pancreato-Biliary Association [14] and the Japan Society of Hepatology [15] to recommend the consideration of hepatic resection or TACE for such patients.

Recent decades have seen advances in the management of HCC with PVTT, which are reviewed here. These advances and perspectives for the future are based primarily on randomized controlled trials, comparative or cohort studies and case series (not case reports) published after 2010 and indexed in PubMed.

**CLINICAL FEATURES AND CLASSIFICATION OF PVTT**

Like Barcelona Clinic Liver Cancer stage B HCC [16-17], HCC with PVTT comprises a heterogeneous family of conditions varying in clinical characteristics and prognosis. Since patients with different types of PVTT can show markedly different treatment outcomes, several efforts have been made to develop a unified classification of PVTT to allow precise, personalized therapy.

The first PVTT classification system was the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, developed by the Liver Cancer Study Group of Japan [18, 19]. This classification is based on the clinical characteristics, imaging and pathology findings and surgical outcomes. It classifies PVTT macroscopically into five grades: Vp0, no tumor thrombus in the portal vein; Vp1, presence of a tumor thrombus distal to, but not within, 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; and 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) [18-20]. Based on analysis of 20, 850 HCC patients in Japan in 2006 and 2007, the most frequent type of PVTT was Vp0, accounting for 87.1% of cases; in contrast, Vp1-Vp4 each accounted for 2.6-3.9% of cases [21]. Similar results were obtained from microscopic pathology findings of surgical or biopsy specimens. In contrast, 5-year overall survival varied to a much greater extent among the Vp classes, based on analysis of more than 25, 000 HCC patients in Japan who underwent hepatic resection between 1994 and 2005: Vp0, 59.0%; Vp1, 39.1%; Vp2, 23.3%; Vp3/4, 18.3% [22].

In 2006, Mei et al. [23] reported a second PVTT classification system, which divided PVTT into five grades from proximal to distal: 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; and type V, involving any of the types I-IV as well as extrahepatic metastasis. Moreover, the classification system divides PVTTs into three pathology types based on degree of necrosis: proliferative, necrotic and organized.

In 2007, Cheng and coworkers [24] proposed a third PVTT classification system, which is accepted by many liver centers in China. This system defines four types of PVTT: type I, involving segmental branches or above; type II, involving the right or left portal vein; type III, involving the main portal vein; and type IV, involving the superior mesenteric vein. In a retrospective study of 441 HCC patients with PVTT who underwent partial hepatic resection with or without portal thrombectomy, the following frequencies were observed for the different types of PVTT: type I, 32.7%; type II, 42.9%; type III, 19.5%; and type IV, 5.0%. 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% (P < 0.001) [25].

These three PVTT classification systems consider hepatic resection to be a feasible treatment option for HCC patients with PVTT. Prognosis is determined by the extent of the PVTT and its proximity to the main, or even contralateral, portal vein [9]. In general, patients with minor portal vein involvement have better prognosis than those with major portal vein involvement. In addition, other PVTT classification system was also proposed [26].

**MONOTHERAPIES AND ASSOCIATED PROGNOSIS**

**Hepatic resection**

In the 1980s, hepatic resection was considered an option only for patients with a tumor thrombus in a first-order branch of the portal vein that did not involve the confluence of the left and right portal veins [27, 28]. During this time, only studies from Asia reported on the safety and efficacy of hepatic resection for HCC with PVTT. Some years later, the ability of hepatic resection to treat tumor thrombus extending to the main portal trunk was reported [29, 30], and hepatic resection with or without thrombectomy to treat PVTT began to spread and be refined. It is currently a widespread practice, especially in Asian liver centers [31].

Since then, a growing number of comparative or cohort studies, mostly from Asian countries, have...
reported hepatic resection to be safe and effective for selected patients with HCC and PVTT (Table 1) [32-56]. Among these studies, the median rate of postoperative complications was 26% (range, 3-42%) and median mortality was 4.1% (range, 0-23.7%). Median survival time was 25.4 months (range, 8-64), and median rates of 1-, 2-, and 3-year overall survival were 62, 52, and 41%. Despite the large number of studies documenting good post-resection outcomes for carefully selected HCC patients with PVTT, the suitability of the procedure for such patients remains controversial [57, 58], and it is not recommended by official guidelines in the West [10-13].

These results, together with systematic study of resection outcomes according to type of PVTT, argue for expanding official guidelines to recognize hepatic resection as a first-line option for selected patients with HCC and PVTT and preserved liver function. Analysis of 1021 patients in Japan with Vp3 or Vp4 PVTT who underwent resection showed a 5-year survival rate of 18.3% [22]. Systematic review of 24 studies involving 4,389 HCC patients with MVI showed that hepatic resection was associated with median mortality of 2.7% (range, 0-24%) and median overall survival from 50% at 1 year to 18% at 5 years [59, 60]. A large retrospective study in Japan found that the median overall survival of 2,093 HCC patients with PVTT was 2.87 years after hepatic resection, compared to only 1.10 years for 4,381 HCC patients with PVTT after non-resection treatments \( (P < 0.001) \) [36]. However, hepatic resection showed no overall survival benefit for patients in whom PVTT affected the main trunk or contralateral branch (Vp3 or Vp4) [36].

The available evidence, then, suggests that resection can be considered as initial therapy for HCC patients with type I or II (Vp0-Vp3) PVTT and preserved liver function. Surgeons should consider hepatic resection when it is feasible, though they should be prepared for the fact that the procedure is technically demanding [61].

**TACE or transarterial chemotherapy**

TACE is a standard treatment for patients with unresectable HCC, but it is officially contraindicated for

| Study | Country/region | Enrollment period | Total patients | Postoperative complications, % | In-hospital mortality, % | Median survival, mo. | Overall survival, % |
|-------|----------------|-------------------|----------------|--------------------------------|-------------------------|---------------------|---------------------|
|       |                |                   |                |                                |                         |                     |                     |
| Chang 2012 [32] | Taiwan | 1991-2006 | 160 | - | 2.7 | 22 | 58 | 46 | 34 |
| Chen 2012 [33] | China | 2006-2008 | 88 | 19.3 | 4.5 | 9 | 31 | 18 | 15 |
| Chok 2014 [34] | Hong Kong | 1989-2010 | 88 | 23 | 3.4 | 9 | 46 | 33 | 23 |
| Kojima 2015 [35] | Japan | 2001-2010 | 66 | - | - | 28 | 73 | 48 | 40 |
| Matono 2012 [40] | Japan | 1985-2005 | 29 | 3.0 | - | - | 36 | 62 | 42 | 24 |
| Peng 2012 [41] | China | 2002-2007 | 201 | 4.0 | 0.5 | 20 | 42 | 20 | 14 |
| Roayaie 2013 [42] | USA | 1992-2010 | 165 | - | 7.3 | 13 | 52 | 31 | 22 |
| Shi 2010 [43] | China | 2001-2003 | 406 | 32.8 | 0.2 | - | 34 | 18 | 13 |
| Tang 2013 [44] | China | 2006-2008 | 186 | 36.0 | 23.7 | 10 | 40 | 20 | 14 |
| Torzilli 2013 [46] | France, Italy, Argentina, USA | 1990-2009 | 297 | 42.0 | 3 | 36 | 76 | 56 | 49 |
| Wang 2013 [110] | China | 2003-2008 | 68 | - | 0 | 33 | 55 | - | - |
| Wei 2016 [47] | China | 2012-2014 | 74 | - | - | 14 | 74 | 40 | - |
| Xiao 2015 [49] | China | 2001-2008 | 234 | - | - | 18 | 40 | 21 | 16 |
| Ye 2014 [51] | China | 2007-2009 | 338 | - | - | 15 | 49 | 37 | 19 |
| Zhang 2014 [52] | China | 2005-2009 | 272 | 32 | 1.1 | 1.1 | 13 | 50 | 39 | 26 |
| Zhang 2016 [53] | China | 2005-2012 | 252 | 35 | 1.5 | 1.5 | 15 | 69 | 46 | 34 |
| Zheng 2016 [54] | China | 2000-2008 | 96 | 35.4 | - | - | 33 | 78 | 62 | 48 |
| Zhong 2014 [55] | China | 2000-2007 | 248 | 27.0 | 4.4 | - | 81 | 62 | 46 |
| Zhou 2015 [56] | China | - | 152 | - | - | 20 | 87 | 64 | 56 |

*Abbreviations: "-", data not reported*
HCC patients with 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 post-TACE ischemia [10-13]. In 1997, Lee and coworkers [62] reported that TACE could be safely performed on HCC patients with main-trunk PVTT, though they did not observe a significant survival benefit. Since then, an increasing number of studies have explored the role of TACE and, less often, transarterial chemotherapy (TAC) to treat HCC with PVTT (Table 2) [39, 41, 51, 63-74]. Median survival time among these studies was 9 months (range, 4-16). Median overall survival rates were 48% at 1 year, 32% at 2 years, and 18% at 3 years. Unfortunately, most of these studies did not report complications or mortality. Meta-analysis involving eight controlled trials also found TACE had potential for incurring a survival benefit for advanced HCC with PVTT, even with main portal vein obstruction [75].

Several studies suggest that hepatic resection is safer and more effective than TACE/TAC for many HCC patients with PVTT [39, 41, 51]. In one study [39], overall survival rates at 1, 3 and 5 years were significantly better for 247 HCC patients with PVTT who underwent hepatic resection (85, 68, 61%) than for 181 who underwent TACE (60, 42, and 33%; P < 0.001). The survival benefit of resection remained significant even after using propensity score matching to eliminate baseline differences between the treatment groups. The same study found that patients receiving TACE were at 2-fold higher risk of mortality than those receiving hepatic resection. Another study [41] also found overall survival rates at 1, 3, and 5 years to be significantly higher after resection (42.0, 14.1, and 11.1%) than after TACE (37.8, 7.3, and 0.5%; P < 0.001). Subgroup analysis based on type of PVTT showed that this overall survival benefit was observed among patients with type I or II PVTT (P < 0.05), but not among those with type III or IV PVTT (Cheng et al [24] types). A third study [51] found that hepatic resection was associated with better overall survival than TACE for HCC patients with PVTT.

The available evidence, then, suggests that while TACE is an option for patients with HCC and PVTT, it may be more appropriate for those with type III or IV PVTT (Cheng et al [24] types). Patients with resectable HCC, type I or II PVTT and preserved liver function may derive greater survival benefit from hepatic resection.

### Radiotherapy

Just a few decades ago, conventional radiotherapy was not recommended for HCC patients, regardless of whether they also had PVTT, out of fear that an inability to localize radiotherapy precisely could damage the liver or even cause liver failure. In 1994, Chen and coworkers [76] published preliminary results showing that radiotherapy could be used safely on HCC patients with PVTT, although it did not seem to be effective [76]. Since 2000, a growing number of studies have applied radiotherapy to HCC patients with PVTT, in part reflecting advances in radiotherapy technology, such as the advent of three-dimensional conformal radiotherapy.
(3D-CRT), which is associated with low radiotoxicity. Other radiotherapy methods include proton beam therapy, intensity-modulated radiotherapy, and stereotactic radiotherapy. Using 3D-CRT to treat 47 patients with HCC and PVTT, Bae and coworkers [77] obtained a response rate of 40%, median survival time of 8 months, and 1-year survival rate of 15%. Also using 3D-CRT, Rim and coworkers [78] reported a partial response rate of 55.6%, stable disease rate of 31%, progressive disease rate of 6.7%, and complete remission rate of 6.7%. Several additional studies have also suggested that radiotherapy is safe for HCC patients with PVTT and can improve their overall survival [79-83]. Much stronger evidence for clinical efficacy of radiotherapy has come from a much larger, multicenter study involving 985 HCC patients with PVTT in the main trunk and/or first branch [84]. The PVTT response rate was 51.8%, and median overall survival time was 10.2 months. Therefore, modern radiotherapy should be an option for patients with unresectable HCC and PVTT.

**Radioembolization with yttrium-90**

Radioembolization is a transarterial form of brachytherapy in which yttrium-90-loaded microspheres are injected intra-arterially and generate tumor-killing radiation internally. This is a relatively new therapy for treating HCC with PVTT. Among six comparative or cohort studies [85-90] published in 2015 and 2016, median survival time of HCC patients with PVTT after radioembolization with yttrium-90 was 8 months (range, 3-18). Median overall survival was 38% at 1 year, 26% at 2 years, and 14% at 3 years. A systematic review of 14 clinical studies and three abstracts involving 722 patients with HCC and PVTT [91] reported the following median outcomes: time to progression, 5.6 months; disease control rate, 74.3%; complete response rate, 3.2%; partial response rate, 16.5%; stable disease rate, 31.3%; and survival time, 9.7 months. Frequent toxic effects were fatigue, nausea/vomiting, and abdominal pain, few of which required medical intervention.

The available evidence, then, suggests that radioembolization with yttrium-90 may be safe and effective for treating HCC with PVTT [92]. However, this evidence comes entirely from retrospective or uncontrolled prospective studies. Evidence from large, randomized controlled trials is needed.

**Sorafenib**

Sorafenib is a particularly strong example of where clinical practice does not reflect the bulk of available evidence. Following the success of sorafenib in managing advanced HCC in two clinical trials [93, 94], investigators began to explore its safety and efficacy in HCC patients with PVTT. The results consistently point to small or no clinical benefit, especially in comparison to other treatments. A study by Jeong and coworkers [95] reported median overall survival time of only 3.1 months among 30 HCC patients with Vp3 or Vp4 PVTT after sorafenib monotherapy. In a randomized controlled trial with 99 HCC patients with cirrhosis and PVTT, Giorgio and coworkers [96] found that overall survival rates at 1, 2 and 3 years were significantly higher among those receiving sorafenib and radiofrequency ablation (60, 35, 26%) than among those receiving only sorafenib (37, 0, 0%). In another study, median survival time of HCC patients with PVTT in the main trunk or the first branch was similar after sorafenib (4.3 months) or radiotherapy (5.9 months; \( P = 0.115 \)) [97]. When propensity score-matched patients were compared, median survival time was found to be significantly longer after radiotherapy (10.9 vs. 4.8 months; \( P = 0.025 \)). A study [98] comparing TAC with sorafenib to treat HCC patients with PVTT found that TAC led to a significantly higher disease control rate \( (P < 0.001) \) as well as significantly longer median overall survival time \( (7.1 \text{ vs. } 5.5 \text{ months}; \ P = 0.011) \). Another study [99] comparing the combination of sorafenib and TACE with sorafenib alone to treat HCC with main PVTT found a similar disease control rate in the two groups, as well as similar median overall survival \( (7.0 \text{ vs. } 6.0 \text{ months}; \ P = 0.544) \).

The available evidence, then, indicates that sorafenib monotherapy is inferior to other monotherapies or combination treatments. This leads us to question the wisdom of palliative sorafenib therapy for HCC patients with PVTT. The observed maximal survival benefit of fewer than 3 months [95-99] seems outweighed by the drug’s prohibitive cost and risk of adverse effects [100, 101].

**COMBINATION THERAPIES AND ASSOCIATED PROGNOSIS**

**Surgery-based multimodal treatment**

For selected patients with HCC and PVTT, hepatic resection appears to provide better outcomes than TACE/TAC, radiotherapy, radioembolization with yttrium-90, sorafenib or non-surgical combination therapies. Nevertheless, long-term overall survival after hepatic resection alone remains unsatisfactory because of the high rate of tumor recurrence and correspondingly low rate of disease-free survival [59, 102]. As a result, liver centers in the East and West are increasingly turning to combination therapies involving surgery. The rationale is that hepatic resection can eliminate the original tumor nodule and PVTT, while the non-surgical therapies can reduce the risk of recurrence. Eliminating the PVTT improves liver
function, helping patients tolerate the multiple therapies.

Additional evidence for the efficacy of surgery-based combination therapy comes from a study [38] comparing 45 HCC patients with main PVTT who underwent both neoadjuvant 3D-CRT and hepatic resection, with 50 patients who received hepatic resection alone. The combination approach was associated with significantly lower rates of HCC recurrence (hazard ratio [HR], 0.36) and HCC-related death (HR 0.32). Such combination therapy may also be effective with adjuvant TACE or TAC [103-105]. Future studies should further explore surgery-based multimodal therapy.

**Multimodal treatment without surgery**

Combination therapies that do not involve surgery are essential for managing HCC, particularly HCC with PVTT. They can be less traumatic than surgical approaches and offer lower risk of mortality and more rapid recovery; on the other hand, they are only palliative. Several nonsurgical multimodal treatments have been reported, such as sorafenib and radiofrequency ablation, sorafenib and TACE/TAC, radiotherapy and TACE, as well as TACE and microwave or ethanol ablation. The combination of TACE and radiotherapy is the most frequently used nonsurgical multimodal treatment based on several studies (Table 2) [96, 106-109]. The relative efficacy of different combination therapies is difficult to assess because few studies have performed parallel comparisons, and comparisons across studies may be unreliable because of differences in patient characteristics.

**CONCLUSIONS**

The available evidence suggests that hepatic resection may be appropriate first-line therapy for many HCC patients with Vp1-3 PVTT and preserved liver function, which would provide them access to a potentially curative treatment. In contrast, no curative treatment is currently available for HCC with Vp4 PVTT. Resection-based combination therapies may also be effective for many patients with HCC and PVTT, as long as preserved liver function is adequate. Future research is needed to optimize the type, dosing and timing of neoadjuvant or adjuvant treatments administered with hepatectomy in different HCC patients with PVTT. Future studies should focus on optimizing patient selection criteria for various combination therapies in order to maximize the benefits of resection. For patients with unresectable HCC and PVTT, then TACE/TAC, radiotherapy, or radioembolization with yttrium-90 should be considered. Future recommendations for managing HCC with PVTT must be based on clear evidence from large, well-designed, randomized controlled trials.

**Abbreviations**

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

**Author contributions**

Manuscript design (JFJ), manuscript writing (JFJ, YCL, BHY, JY, XL, LC, and JHZ), final approval (all authors).

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**CONFLICTS OF INTEREST**

There is no conflict of interest.

**REFERENCES**

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115-132.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7-30.
3. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, Labow DM, Llovet JM, Schwartz ME. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology. 2009;137:850-855.
4. Yuan BH, Yuan WP, Li RH, Xiang BD, Gong WF, Li LQ, Zhong JH. Propensity score-based comparison of hepatic resection and transarterial chemoembolization for patients with advanced hepatocellular carcinoma. Tumour Biol. 2016;37:2435-2441.
5. Zhong JH, Peng NF, You XM, Ma L, Xiang X, Wang YY, Gong WF, Wu FX, Xiang BD, Li LQ. Tumor stage and primary treatment of hepatocellular carcinoma at a large tertiary hospital in China: A real-world study. Oncotarget. 2017;8:18296-18302. doi: 10.18632/oncotarget.15433.
6. Quirk M, Kim YH, Saab S, Lee EW. Management of hepatocellular carcinoma with portal vein thrombosis. World J Gastroenterol. 2015;21:3462-3471.
7. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma.
rationale for the design and evaluation of therapeutic trials. Hepatology. 1999;29:62-67.
8. Schoniger-Hekele M, Muller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: prognostic features and survival. Gut. 2001;48:103-109.
9. 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.
10. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Eur J Cancer. 2012;48:599-641.
11. 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.
12. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020-1022.
13. Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shima S, Cheng AL, Ji JD, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4:439-474.
14. Jamagin W, Chapman WC, Curley S, D’Angela M, Rosen C, Dixon E, Nagorney D; American Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract. Surgical treatment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford). 2010;12:302-310.
15. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojio M, Makuuchi M; HCC Expert Panel of Japan Society of Hepatology. 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.
16. Zhong JH, Lu SD, Wang YY, Ma L, Li LQ. Intermediate-stage HCC—upfront resection can be feasible. Nat Rev Clin Oncol. 2015;12.
17. Bolondi L, Burroughs A, Dufour JF, Galle PR, Massaferr V, Picaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis. 2012;32:348-359.
18. Liver Cancer Study Group of Japan. The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 2nd ed, Kanehara Shuppan, Tokyo. 1987 (In Japanese).
19. 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.
20. Katagiri S, Yamamoto M. Multidisciplinary treatments for hepatocellular carcinoma with major portal vein tumor thrombus. Surg Today. 2014;44:219-226.
21. Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, Takayama T, Nakashima O, Matsui O, Matsuyama Y. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res. 2016;46:372-390.
22. Ikai I, Kudo M, Arai S, Omata M, Kojio M, Sakamoto M, Takayasu K, Hayashi N, Makuuchi M, Matsuyama Y, Monden M. Report of the 18th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res. 2010;40:1043-1059.
23. Mei MH, Chen Q, Yang JH. Clinicopathological staging of portal vein tumor thrombus in hepatocellular carcinoma and its significance. Chin J Hepatobiliary Surg. 2006;12:374-377.
24. Shuqun C, Mengchao W, Han C, Feng S, Jiahe Y, Guanghui D, Wenming C, Peijun W, Yuxiang Z. Tumor thrombus types influence the prognosis of hepatocellular carcinoma with the tumor thrombi in the portal vein. Hepatogastroenterology. 2007;54:499-502.
25. Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci. 2011;18:74-80.
26. Xu JF, Liu XY, Wang S, Wen HX. Surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus: a novel classification. World J Surg Oncol. 2015;13:86.
27. Lee NW, Wong J, Ong GB. The surgical management of primary carcinoma of the liver. World J Surg. 1982;6:66-75.
28. 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.
29. Kumada K, Ozawa K, Okamoto R, Takayasu T, Yamaguchi M, Yamamoto Y, Higashiyama H, Morikawa S, Sasaki H, Shimahara Y. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. Surgery. 1990;108:821-827.
30. Yamaoka Y, Kumada K, Ino K, Takayasu T, Shimahara Y, Mori K, Tanaka A, Morimoto T, Taki Y, Washida M. 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.
31. Li W, You XM, Li LQ, Zhong JH. Hepatic resection for hepatocellular carcinoma involving a single large tumor, multiple tumors or macrovascular invasion. Zhonghua Yi Xue Za Zhi. 2015;95:3115-3118.
32. Chang WT, Kao WY, Chao SY, Su CW, Lei HJ, Wu JC, Hsia CY, Lui WY, King KL, Lee SD. 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.
33. Chen JS, Wang Q, Chen XL, Huang XH, Liang L, Jie H, Huang QJ, Li DM, Cheng ZX. Clinicopathologic characteristics and surgical outcomes of hepatocellular carcinoma with portal vein tumor thrombosis. J Surg Res. 2012;175:243-250.
34. 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.

35. Kojima H, Hatano E, Taura K, Seo S, Yasuhashi K, Uemoto S. Hepatic Resection for Hepatocellular Carcinoma with Tumor Thrombus in the Major Portal Vein. Dig Surg. 2015;32:413-420.

36. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, Kudo M, Ku Y, Sakamoto M, Nakashima O, Kaneko S, Kokudo N; Liver Cancer Study Group of Japan. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016;65:938-943.

37. Lee JM, Jang BK, Lee YJ, Choi WY, Choi SM, Chung WJ, Hwang JS, Kang KJ, Kim YH, Chauhan AK, Park SY, Tak WY, Kweon YO, 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.

38. Li N, Feng S, Xue J, Wei XB, Shi J, Guo WX, Lau WY, Wu MC, Cheng SQ, Meng Y. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB (Oxford). 2016;18:549-556.

39. Liu PH, Lee YH, Hsia CY, Hsu CY, Huang YH, Chio YW, Lin HC, Huo TI. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. Ann Surg Oncol. 2014;21:1825-1833.

40. Matono R, Yoshiya S, Motomura T, Toshima B, Sato N, Yoshizumi T, Kayashima H, Masuda T, Yoshinari T, Taketomi A, Shirabe K, Maehara Y. 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.

41. 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.

42. Roayaie S, Jibani G, Taouli B, Schwartz M. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol. 2013;20:3754-3760.

43. Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol. 2010;17:2073-2080.

44. Tang QH, Li AJ, Yang GM, Lai EC, Zhou WP, Jiang ZH, Lau WY, Wu MC. 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.

45. Tang ZY, Zhou BH, Wang W, Du G, Liu ZY, Li J, Zhang SZ, Fu ZH. Curative Analysis of Several Therapeutic Methods for Primary Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. Hepatogastroenterology. 2015;62:703-709.

46. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, Vauthney JN, Choti MA, De Santibanes E, Donadon M, Morengi E, Makuchi M. 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.

47. Wei XB, Xu J, Li N, Yu Y, Shi J, Guo WX, Cheng HY, Wu MC, Lau WY, Cheng SQ. The role of 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.

48. Wu ZJ, Cai J, Xu AB, Su XQ, Wang QX, Zhang YX, Shao BF, Li YJ, Chu KY. [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.

49. Xiao CZ, Wei W, Guo ZX, Li SH, Zhang YF, Wang JH, Shi M, Guo RP. A prognosis model for patients with hepatocellular carcinoma and portal vein tumor thrombus following hepatic resection. Oncol Lett. 2015;10:2787-2794.

50. Yamamoto Y, Ikoma H, Morimura R, Shoda K, Konishi H, Murayama Y, Komatsu S, Shiozaki A, Kuriu Y, Kubota T, Nakanishi M, Ichikawa D, Fujiwara H, et al. Post-hepatectomy survival in advanced hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol. 2015;21:246-253.

51. Ye JZ, Zhang YQ, Ye HH, Bai T, Ma L, Xiang BD, Li LQ. Appropriate treatment strategies improve survival of hepatocellular carcinoma patients with portal vein tumor thrombus. World J Gastroenterol. 2014;20:17141-17147.

52. 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.

53. Zhang YF, Le Y, Wei W, Zou RH, Wang JH, OuYang HY, Xiao CZ, Zhong XP, Shi M, Guo RP. 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.

54. Zheng N, Wei X, Chai W, Che M, Wang J, Du B. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. Medicine (Baltimore). 2016;95:e3959.

55. Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS, Li LQ. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg.
56. 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.

57. 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. [Epub ahead of print].

58. Wang HL, Cucchetti A, Zhong JH, Ye XP, Gu JH, Ma L, Peng NF, Li LQ. Should hepatic resection be recommended to patients with hepatocellular carcinoma and portal vein invasion? J Hepatol. 2016;65:1057-1058.

59. Zhong JH, Rodriguez 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.

60. 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.

61. Zhong JH, Torzilli G, Xing H, Li C, Han J, Liang L, Zhang H, Dai SY, Li LQ, Shen F, Yang T. Controversies and evidence of hepatic resection for hepatocellular carcinoma. BBA Clin. 2016;6:125-130.

62. Lee HS, Kim JS, Choi JJ, 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 occlusion. A prospective controlled study. Cancer. 1997;79:2087-2094.

63. Ajit Y, Sudarsan H, Saumya G, Abhishek A, Navneet R, Piyush R, Anil A, Arun G. Transarterial chemoembolization in unresectable hepatocellular carcinoma with portal vein thrombosis: a perspective on survival. Oman Med J. 2014;29:430-436.

64. 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.

65. Choi JW, Kim HC, Lee JH, Yu SJ, Kim YJ, Yoon JH, Jae HJ, Hur S, Lee M, Chung JW. Transarterial chemoembolization of hepatocellular carcinoma with segmental portal vein tumour thrombus. Eur Radiol. 2016;[Epub ahead of print].

66. Gorodetski B, Chapiro J, Scherndhaner R, Duran R, Lin M, Lee H, Lenis D, Stuart EA, Nonyane BA, Pekurovsky V, Tamrazi A, Gebauer B, Schlachter T, et al. Advanced-stage hepatocellular carcinoma with portal vein thrombosis: conventional versus drug-eluting beads transcatheter arterial chemoembolization. Eur Radiol. 2017;27:526-535.

67. Ikeda M, Okusaka T, Furuse J, Mitsunaga S, Ueno H, Yamaura H, Inaba Y, Takeuchi Y, Satake M, Arai Y. 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.

68. Kim GA, Shim JH, Yoon SM, Jung J, Kim JH, Ryu MH, Ryoo BY, Kang YK, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, 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.

69. 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.

70. Niu ZJ, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, Qi F, Zhao C. 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.

71. Song DS, Bae SH, Song MJ, Lee SW, Kim HY, Lee YJ, Oh JS, Chun HJ, Lee HG, Choi JY, Yoon SK. Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol. 2013;19:4679-4688.

72. 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.

73. Tawada A, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Saito T, Ogasawara S, Suzuki E, Maruyama H, Kanai F, Yoshikawa M, Yokosuka O. Efficacy of transarterial chemoembolization targeting portal vein tumor thrombus in patients with hepatocellular carcinoma. Anticancer Res. 2014;34:4231-4237.

74. Yang M, Fang Z, Yan Z, Luo J, Liu L, Zhang W, Wu L, Ma J, Yang Q, Liu Q. 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.

75. Xue TC, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumour thrombus: a meta-analysis. BMC Gastroenterol. 2013;13:60.

76. Chen SC, Lian SL, Chang WY. The effect of external radiotherapy in treatment of portal vein invasion in hepatocellular carcinoma. Cancer Chemother Pharmacol. 1994;33:S124-127.
77. 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.
78. 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.
79. Lee SU, Park JW, Kim TH, Kim YJ, Woo SM, Koh YH, Lee WJ, Park SJ, Kim DY, Kim CM. Effectiveness and safety of proton beam therapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Strahlenther Onkol. 2014;190:806-814.
80. 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.
81. Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, Ishihara T, Mayahara H, Fukumoto T, Ku Y, Yamaguchi M, Sugimoto K, Sasaki R. 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.
82. Xi M, Zhang L, Zhao L, Li QQ, Guo SP, Feng ZZ, Deng XW, Huang XY, Liu MZ. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One. 2013;8:e63864.
83. 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.
84. Im JH, Yoon SM, Park HC, Kim JH, Yu Ji, Kim TH, Kim JW, Nam TK, Kim K, Jang HS, Kim KH, Kim MS, Yoon WS, et al. Radiotherapeutic strategies for hepatocellular carcinoma with portal vein tumour thrombosis in a hepatitis B endemic area. Liver Int. 2017;37:90-100.
85. Akinwande O, Kim D, Edwards J, Brown R, Philips P, Scoggins C, Martin RC 2nd. 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.
86. Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Gwak GY, Bae SH, Kim do Y, Heo J, Kim YJ. Radioembolization Is a Safe and Effective Treatment for Hepatocellular Carcinoma with Portal Vein Thrombosis: A Propensity Score Analysis. PLoS One. 2016;11:e0154986.
87. Cho YY, Lee M, Kim HC, Chung JW, Kim YH, de la Torre MA, Buades-Mateu J, de la Rosa PA, Lué A, Bustamante FJ, Serrano MT, Testillano M, Lorente S, Arenas JJ, Gil C, Íñarraíarena M, Sangro B. A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib. Liver Int. 2016;36:1206-1212.
88. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, Mesbah H, Breton M, Sulpice L, Boudjemaa K, Rohou T, Raoul JL, Clement B, Boucher E. 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.
89. Kokabi N, Camacho JC, Xing M, El-Rayes BF, Spivey JR, Knechtle SJ, Kim HS. 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.
90. 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.
91. 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.
92. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.
93. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, et al. Efficacy and safety of sorafenib monotherapy on advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25-34.
94. Jeong SW, Jung JY, Shim KY, Lee SH, Kim SG, Cha SW, Kim YS, Cho YD, Kim HS, Kim BS, Kim KH, Kim JH. Practical effect of sorafenib monotherapy on advanced hepatocellular carcinoma and portal vein tumor thrombosis. Gut Liver. 2013;7:696-703.
95. Giorgio A, Merola MG, Montesarchio L, Merola F, Santoro B, Coppola C, Gatti P, Amendola F, DI Sarno A, Calvanese A, Matteucci P, Giorgio V. 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.
96. Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J, Minamino T, Watanabe M, Kokubu S, Kozumi W. 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.
98. Song DS, Song MJ, Bae SH, Chung WJ, Jang JY, Kim YS, Lee SH, Park JY, Yim HJ, Cho SB, Park SY, Yang JM. 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.

99. Zhang Y, Fan W, Wang Y, Lu L, Fu S, Yang J, Huang Y, Yao W, Li J. Sorafenib With and Without Transarterial Chemoembolization for Advanced Hepatocellular Carcinoma With Main Portal Vein Tumor Thrombosis: A Retrospective Analysis. Oncologist. 2015;20:1417-1424.

100. Zhong JH. The STORM trial and beyond: narrowing the horizon of adjuvant sorafenib for postoperative hepatocellular carcinoma. Tumour Biol. 2015;36:8271-8272.

101. 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.

102. Chitapanarux T, Phornphutkul K. Risk Factors for the Development of Hepatocellular Carcinoma in Thailand. J Clin Transl Hepatol. 2015;3:182-188.

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.

104. Zhong JH, Ma L, Li LQ. Postoperative therapy options for hepatocellular carcinoma. Scand J Gastroenterol. 2014;49:649-661.

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.

106. Kang J, Nie Q, Du R, Zhang L, Zhang J, Li Q, Li J, Qi W. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Mol Clin Oncol. 2014;2:43-50.

107. 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.

108. Nagai H, Mukozu T, Ogino YU, Matsui D, Matsui T, Wakui N, Momiyama K, Igarashi Y, Sumino Y, Higai K. Sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombus. Anticancer Res. 2015;35:2269-2277.

109. Wang K, Guo WX, Chen MS, Mao YL, Sun BC, Shi J, Zhang YJ, Meng Y, Yang YF, Cong WM, Wu MC, Lau WY, Cheng SQ. Multimodality Treatment for Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Large-Scale, Multicenter, Propensity Matching Score Analysis. Medicine (Baltimore). 2016;95:e3015.

110. Wang JH, Kuo YH, Wang CC, Chen CL, Cheng YF, Hsu HC, Lu SN. Surgical resection improves the survival of selected hepatocellular carcinoma patients in Barcelona clinic liver cancer stage C. Dig Liver Dis. 2013;45:510-515.