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Review Article

Treatments of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Current Status and Controversy

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Abstract

The proportions of patients with hepatocellular carcinoma (HCC) involving portal vein tumor thrombus (PVTT) varies greatly in different countries or regions, ranging from 13% to 45%. The treatment regimens for PVTT recommended by HCC guidelines in different countries or regions also vary greatly. In recent years, with the progress and development of surgical concepts, radiotherapy techniques, systematic therapies (for example, VEGF inhibitors, tyrosine kinase inhibitors and immune checkpoint inhibitors), patients with HCC involving PVTT have more treatment options and their prognoses have been significantly improved. To achieve the maximum benefit, both clinicians and patients need to think rationally about the indications of treatment modalities, the occurrence of severe adverse events, and the optimal fit for the population. In this review, we provide an update on the treatment modalities available for patients with HCC involving PVTT. Trials with large sample size for patients with advanced or unresectable HCC are also reviewed.

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Introduction

Hepatocellular carcinoma (HCC) is the seventh most common malignant tumor, resulting in more than 600,000 deaths every year.[1] Due to the lack of typical symptoms and signs of early-stage HCC, HCC is often diagnosed as intermediate or advanced disease.[2] The complex hepatic vascular system, including portal vein, hepatic vein, hepatic artery and intrahepatic bile duct, may be the main reason for the invasion of hepatic vascular system growth characteristics of HCC. Macrovascular invasion (MVI) refers to obvious invasion of the main portal vein and its branches, hepatic vein and its branches, or inferior vena cava. In all types of MVI, portal vein tumor thrombus (PVTT) is the most frequent form. HCC patients with PVTT showed a worse prognoses than those without, which may be related to the high tumor invasiveness, insufficient hepatic reserve function, portal hypertension caused by PVTT and other complications. The median survival time with the best supportive care is only 4 to 6 months.[3,4]

Due to the large difference of incidence of PVTT in different regions, high tumor invasiveness, and the poor prognoses, European and American HCC guidelines do not recommend hepatic resection or transarterial chemoembolization (TACE) for patients with HCC involving PVTT. For example, the European,[5] American[6] and ESMO[7] guidelines for the diagnosis and treatment of HCC based on the Barcelona Clinical Liver Cancer (BCLC) staging system only recommend systematic treatment regimens such as targeted drugs, and even consider PVTT to be a contraindication of hepatic resection. But in recent years, the Asian HCC guidelines, in addition to the results from large sample, multicenter, randomized clinical trials, also recognized the results from real-world practice. Beyond recommending targeted drugs, nivolumab and other immunotherapy as the first-line treatment, Pan-Asian has adapted the ESMO Clinical Practice Guidelines,[8,9] Asian-Pacific guidelines,[10] and guidelines in Korea,[11] Taiwan,[12] and mainland China[13] for the diagnosis and treatment of HCC; they also suggest that local therapies, such as TACE, local radiotherapy, hepatic resection, and hepatic arterial infusion chemotherapy (HAIC), can also be used as an optional regimen for patients with PVTT.

In recent years, with the progress and development of surgical concepts, radiotherapy techniques, targeted drugs and immunotherapy, patients with HCC involving PVTT have more treatment options and their prognoses have been significantly improved.[14–17] These therapeutic methods have different mechanisms of action (Fig. 1). Therefore, this updated review summarizes the current situation, existing controversies and future development of treatment measures for HCC with PVTT. In order to provide the latest and comprehensive clinical evidence, a systematic literature search was performed in PubMed by using the keywords of 'hepatocellular carcinoma', 'advanced', 'unresectable', and 'portal

Keywords: Hepatocellular carcinoma; Portal vein tumor thrombus; Treatment modality.

Abbreviations: BCLC, Barcelona Clinical Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MVI, macrovascular invasion; ORR, objective response rate; PVTT, portal vein tumor thrombus; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

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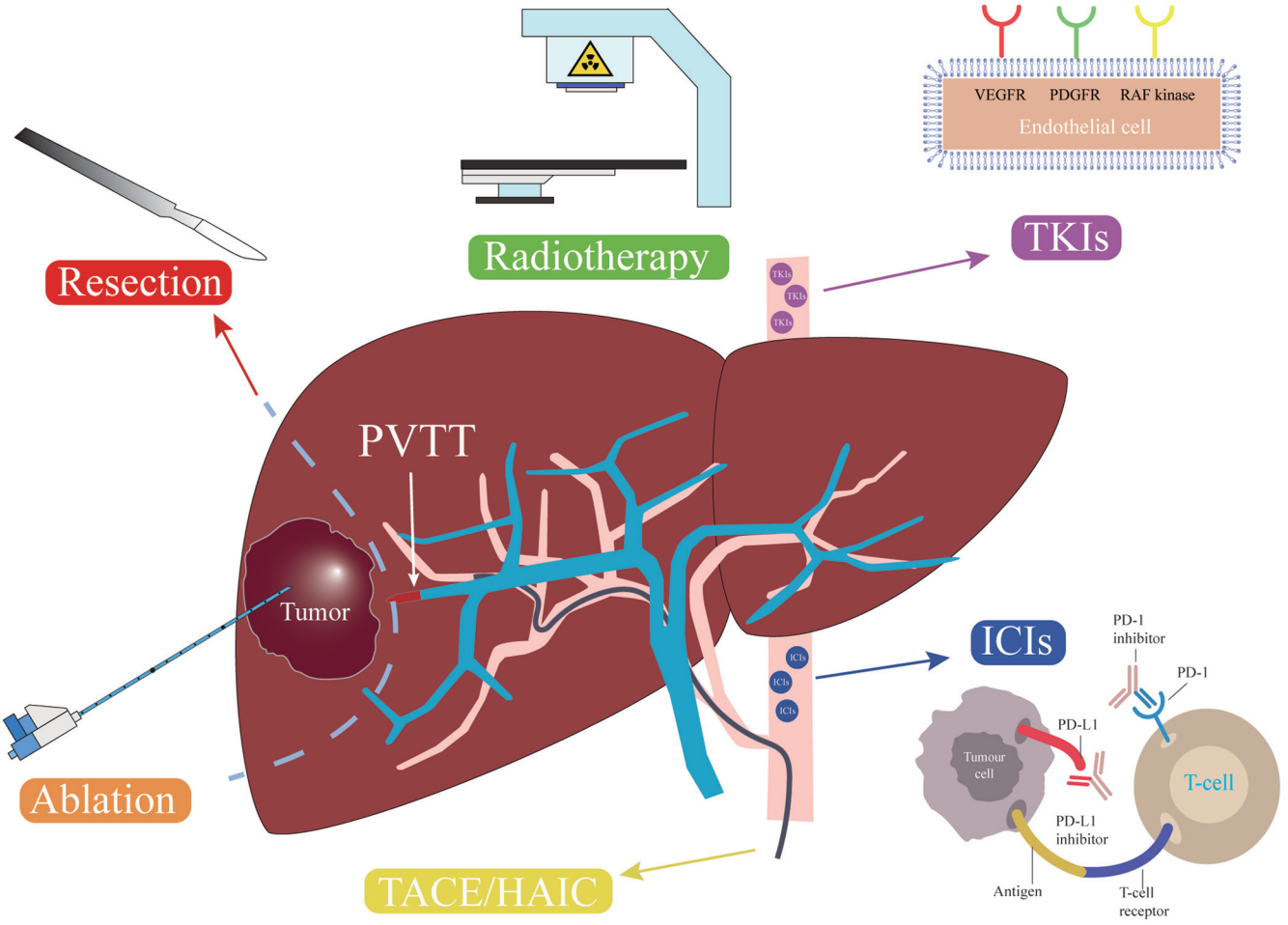

Fig. 1. Different therapeutic methods have different mechanisms of action for patients with HCC involving PVTT. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitors.

vein tumor thrombus'. We focus our discussion herein on the phase Ib to III clinical trials related to treatment of advanced or unresectable HCC with PVTT published after January 1, 2010 (mainly full-text), as well as prospective or retrospective comparative studies with relatively large sample size.

Epidemiology of PVTT

The proportions of patients with HCC involving PVTT varies greatly in different countries or regions, which may be related to the economic living standard of the location. A study from China involving 6,241 patients with primary HCC found the proportion of PVTT was about 45%.[2] In 2014, a study in Hong Kong showed that 39.1% of 3,856 HCC patients had PVTT.[18] In 2016, a study from Italy reported that 42.0% of 5,183 HCC patients had PVTT.[19] Data from the 19th national liver cancer survey in Japan revealed that 13.0% patients with HCC were accompanied by PVTT and 4.6% by hepatic vein tumor thrombus.[20]

Classification of PVTT

Although American Joint Committee on Cancer tumor-node-metastasis, BCLC,[21] Japan Integrated Staging,[22] Hong Kong Liver Cancer,[18] ITA.LI.CA,[19] and other HCC guidelines from other countries or regions[5–13,23,24] emphasize the effect of PVTT on patients' prognoses; notably, the diversity of PVTT growth sites determines the great difference of their prognoses. Therefore, it is necessary to classify PVTT according to the scope of PVTT involvement, and then select different treatment regimens according to different types.

The first classification system of PVTT was reported by the Liver Cancer Study Group of Japan.[25,26] This system is based on the clinical features, imaging findings, pathological findings of PVTT, and patients' prognoses. PVTT is divided into five grades in this classification system (Table 1).[25,26] Since then, this classification system was cited by data from Japan's annual liver cancer census. For example, the report of the 19th Japan's annual liver cancer census[20] showed that the proportion of Vp0, Vp1, Vp3, and Vp4 were 87.1%, 3.1%, 2.6%, 3.9%, and 3.4%, respectively, according to imaging diagnosis, and 84.1%, 9.7%, 3.1%, 2.2%, and 1.0%, respectively, according to postoperative pathological diagnosis. This classification system is relatively highly recognized by scholars around the world. In 2007, another PVTT classification system was reported by scholars from China.[27] Their first version included type I to type IV (Table 2).[27,28] In 2011, type I_0 was added.[28] Recently, this classification system has been highly recog-

Table 1. PVTT classification system from the Liver Cancer Study Group of Japan[25,26]

Grade	Definition
Vp0	Absence of invasion of (or tumor thrombus in) the portal vein
Vp1	Invasion of (or tumor thrombus in) distal to the second-order branches of the portal vein, but not of the second-order branches
Vp2	Invasion of (or tumor thrombus in) second-order branches of the portal vein
Vp3	Invasion of (or tumor thrombus in) first-order branches of the portal vein
Vp4	Invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contra-lateral portal vein branch to the primarily involved lobe

PVTT, portal vein tumor thrombus.

nized by scholars in mainland China.[13,29]

Treatments for HCC with PVTT

Hepatic resection

At present, in addition to the HCC diagnosis and treatment guidelines in China[13] and Japan,[23] which have their own independent HCC staging systems, HCC guidelines in other countries or regions mostly adopt the BCLC staging system.[5–9,11,12,24] However, the indications for hepatic resection defined by the BCLC staging system in successive versions are very narrow, and HCC with PVTT has been considered contraindicated for hepatic resection.[21,30,31] Therefore, in recent years, many HCC researchers all over the world have questioned the indications of hepatic resection in the BCLC staging system. An influential study that was published in 2013 by Torzilli *et al*.[32] retrospectively analyzed clinical data of 2,046 patients who underwent hepatic resection from 10 medical centers of eastern and western countries. There were 297 (14.5%) patients with BCLC stage C disease and 275 (13.4%) patients with macrovascular invasion. Five years overall survival and recurrence-free survival were 38% and 18% after hepatic resection. Patients who underwent hepatic resection in this study had significantly better long-term overall survival than patients who underwent TACE in other studies. Therefore, Torzilli *et al*.[32] proposed that guidelines based on the BCLC system should be modified to appropriately expand indications of hepatic resection. However, the proposal of Torzilli *et al*.[32] immediately sparked a heated debate among several leading liver cancer experts. For example, Bruix,[33,34] a leading member of the BCLC group, and Mazzaferro,[35] the main founder of the Milan standard for liver transplantation, still do not agree with the proposal of Torzilli and coworkers,[32] but several surgical experts in the field of liver cancer in Asia[36–38] fully agree with Torzilli and coworkers. Moreover, the findings ofTorzilli were completely consistent with our findings that hepatic resection was associated with significantly better overall survival than TACE in selected patients with stage C HCC and preserved liver function.[39] Therefore, "we're still in an update process of the BCLC system."[40] "Surgeons should not shy away from hepatic resection when it is feasible, though they should be prepared for the fact that the procedure is technically demanding".[41]

In 2015, a systematic review which included 24 studies involving 4,389 patients with HCC and macrovascular invasion after hepatic resection found the median perioperative mortality was 2.7% (0–24%), the median complication rate was 30.2% (4.0–42%), the median overall survival at 1, 3, 5 years were 50%, 23% and 18%, and the corresponding median recurrence-free survival were 32%, 20% and 18%.[42] However, due to insufficient information of included studies, subgroup analysis based on PVTT classification was not performed. In 2016, a retrospective study from Japan included 6,474 patents with HCC involving PVTT.[43] In that study, 2,093 patients underwent hepatic resection, while 438 patients underwent palliative treatments. The perioperative mortality in the hepatic resection group was 3.7%. Patients in the hepatic resection group had significantly higher overall survival than those in the non-resection group among patients with Child-Pugh class A or B liver function (all $p<0.001$). Results from propensity score analysis confirmed these findings. Subgroup analysis based on PVTT classification indicated that the advantage of hepatic resection was only in patients with Vp1-3 but was not significant in patients with Vp4 (hazard ratio [HR]: 0.84, 95% confidence interval [CI]: 0.63–1.12). In 2016, a retrospective study from China established a model to select patients who would benefit most from hepatic resection.[44] The training cohort enrolled 432 HCC patients with I/II stage (Vp1-3) PVTT, while the internal validation cohort enrolled 285 patients. Patients from three other centers were assigned as three external validation cohorts (n=286, 189, and 135, respectively). The Eastern Hepatobiliary Surgery Hospital-PVTT score (≤/>3) significantly differentiated overall survival, with median survival of 17.0 and 7.9 months, respectively ($p<0.001$).[44] The study did not include patients with type III (Vp4) PVTT or those who underwent non-hepatic resection. Therefore, it is unknown whether this predictive model is appropriate for patients with type III PVTT or those receiving other treatment regimens.

Table 2. PVTT classification system from China[27,28]

Type	Definition
I_0	Tumor thrombus formation found under microscopy
I	Tumor thrombi involving segmental branches of portal vein or above
II	Tumor thrombi involving right/left portal vein
III	Tumor thrombi involving the main portal vein trunk
IV	Tumor thrombi involving the superior mesenteric vein

PVTT, portal vein tumor thrombus.

In conclusion, although hepatic resection for HCC involving PVTT is not recommended in European and American HCC guidelines,[5–7] the HCC guidelines in Asia have appropriately expanded the surgical indications.[8–13,23,24] Large-sample studies in real world settings suggest that many HCC patients with type I/II (Vp1-3) PVTT may have good long-term outcomes from hepatic resection.[43,44] However, a high rate of postoperative recurrence is one of the most striking features of hepatic resection in patients with HCC involving PVTT. In recent years, a large number of studies have shown that postoperative adjuvant TACE can significantly reduce the rate of recurrence and ultimately prolong survival time.[45–47] In addition, phase III clinical trials (e.g., Imbrave 050)[48] exploring the efficacy of adjuvant targeted agents and immune checkpoint inhibitors after hepatic resection are ongoing and the results are expected to guide clinical treatment.

Radiotherapy

In 1994, Chen *et al*.[49] from Taiwan first reported the efficacy of external radiotherapy to treat PVTT. In this study, 10 patients with unilateral PVTT received radiotherapy (3,000–5,000 cGY) using a linear accelerator under localization by real-time ultrasound. The PVTT in five patients completely disappeared; while in the other five patients, it showed partial shrinkage. However, external radiotherapy had poor precision positioning ability at that time, which could easily cause irreversible liver function damage or even liver failure. With the improvement of external radiotherapy in recent years and the rapid development of three-dimensional conformal radiotherapy, proton beam therapy, intensity-modulated radiotherapy, and stereotactic radiotherapy, the clinical application of external radiotherapy for HCC is becoming more and more extensive, and there are more and more reports in the publicly-available literature. The new version of guidelines from Europe[5] and America[6] have started to mention the application of external radiotherapy, but without specific recommendations. The ESMO guideline[7] recommended external radiation to treat early HCC. However, guidelines in Korea,[11] Taiwan,[12] and mainland China[13] recommended external radiotherapy (or combined with other treatments) to treat several stages of HCC, including that with PVTT.

In 2018, a systematic review including 37 studies involving 2,513 HCC patients with PVTT analyzed the differences of the efficacy and safety between different modes of radiotherapy.[50] In three groups of patients who received stereotactic radiotherapy, three-dimensional conformal radiotherapy or selective internal radiation therapy, 1-year overall survival rates were 48.5%, 43.8% and 46.5% and objective response rates (includes tumor and/or PVTT) were 70.7%, 51.3% and 33.3%, respectively. In the three-dimensional conformal radiotherapy group and the selective internal radiation therapy group, adverse events of at least grade 3 were mainly lymphopenia and bilirubin elevation. The stereotactic body radiotherapy group rarely experienced adverse events of at least grade 3. However, this study did not perform subgroup analysis based on PVTT classification. A recent retrospective study compared the efficacy of intensity-modulated radiotherapy (n=154) and stereotactic radiotherapy (n=133) for HCC patients with PVTT. The two methods were associated with similar overall survival, progression-free survival, intrahepatic control, and local control.[51] In 2018, a retrospective study compared the efficacy of 134 HCC patients with PVTT who received three-dimensional conformal radiotherapy and 189 patients who received hepatic resection.[52] In the analysis of the total sample, patients in the hepatic resection group had a significantly better overall survival than those in the radiotherapy group. Among patients with type I (Vp1-2) PVTT, hepatic resection was associated with significantly better overall survival than radiotherapy. Among patients with type II (Vp3) PVTT, patients in the two groups had similar overall survival. However, among patients with type III (Vp4) PVTT, patients in the radiotherapy group had significantly better overall survival than those in the hepatic resection group.[52] In 2016, a multicenter retrospective study (n=1,580) compared the median survival time of patients with HCC involving PVTT who received hepatic resection, TACE, TACE combined with sorafenib, or TACE combined with radiotherapy.[53] Among patients with type I (Vp1-2) PVTT, the hepatic resection group had the best overall survival. Among patients with type II (Vp3) PVTT, median survival time in the hepatic resection group and in the TACE combined with radiotherapy group were 12.5 and 10.6 months, respectively (p=0.046). Among patients with type III (Vp4) PVTT, median survival time was longer in the TACE combined with radiotherapy group than in the hepatic resection group (8.9 vs. 6.0 months, p=0.401). In 2018, a single-center randomized controlled study from Korea compared the prognoses of patients with HCC involving PVTT who received sorafenib (n=45) or TACE combined with three-dimensional conformal radiotherapy (n=45).[54] Patients in the combination group had significantly higher progression-free survival (86.7% vs. 34.3%, p<0.001), radiographic response (33.3% vs. 2.2%, p<0.001), longer median time to progression (31.0 vs. 11.7 weeks, p<0.001), and longer median survival time (55.0 vs. 43.0 weeks, p=0.04) than those in the sorafenib group. Moreover, five (11.1%) patients in the combination group had the opportunity to undergo radical hepatic resection due to tumor down staging. No patient in the combination group suspended treatment due to liver dysfunction.[54]

The SARAH study that was published in 2017 enrolled patients with local advanced HCC from 25 centers in France. There were 237 patients in the yttrium-90 radiotherapy group and 222 patients in the sorafenib group. The median survival times were similar between the two groups (8.0 vs. 9.9 months, p=0.18), and the incidence of serious adverse events were 77% and 82%.[55] Another study from Italy also found yttrium-90 radiotherapy and sorafenib provide similar overall survival.[56] The third study (n=120) investigated the safety and efficacy of yttrium-90 for patients with HCC and PVTT. The median overall survival was 14.1 months and median progression-free survival was 6.5 months.[57] A systematic review including 17 studies (n=722) showed that the median time to progression was 5.6 months, the median objective response rate was 19.7%, and the median survival time was 9.7 months in patients with HCC involving PVTT who underwent yttrium-90 internal radiotherapy.[58]

In recent years, there are some reports about the application of radiotherapy as neoadjuvant treatment of hepatic resection. In 2019, a randomized controlled study compared the efficacy of neoadjuvant three-dimensional conformal radiotherapy combined with hepatic resection (n=82) and hepatic resection alone (n=82) in HCC patients with type II/III (Vp3-4) PVTT.[59] A total of 17 (20.7%) patients in the neoadjuvant group had PVTT regression. Neoadjuvant was associated with significantly higher 2-year overall survival than hepatic resection alone (27.4% vs. 9.4%, p<0.001).

In summary, external radiotherapy has played an increasingly important role in the multidisciplinary treatment of patients with HCC involving PVTT. External radiotherapy combined with other treatments provides the greatest benefit to such patients. At present, three-dimensional conformal radiotherapy is the most widely reported external radiotherapy technique with relatively clear curative efficacy. High-level evidence has recently suggested the value of proton beam radiotherapy[60] and stereotactic radiotherapy[61]

in the treatment of small HCC, and positive results of these two methods in PVTT are expected.

Treatments via hepatic artery

The treatments of HCC through the hepatic artery mainly include yttrium-90 internal radiotherapy, TACE and HAIC. TACE is still recognized as one of the most commonly used treatments for unresectable HCC.[10–13] In the past decade, many studies have reported the efficacy of TACE to treat patients with HCC involving PVTT. Median survival time was 9 (4 to 16) months, and 1- and 3-year overall survival rates were 48% and 18%, respectively.[4,62–70] In general, patients who underwent hepatic resection had significantly better overall survival than those who underwent TACE,[67,68,71] especially for patients with type I/II (Vp1-3) PVTT.[68]

In recent years, with the wide application of targeted drugs, transarterial treatments combined with targeted drugs have been increasingly used. The TACTICS study compared the efficacy of TACE combined with sorafenib (n=80) and TACE alone (n=76) for unresectable HCC (11.8% were BCLC stage C disease). Patients in the combination group had a significantly longer median progression-free survival (25.2 vs. 13.5 months) and time-to-progression (26.7 vs. 16.4 months) than those in the TACE group.[72] A retrospective study compared the efficacy of sorafenib combined with TACE (n=164) versus sorafenib alone (n=191) for BCLC stage C HCC (51.3% involving PVTT). Patients in the combination group had significantly longer time-to-progression (2.5 vs. 2.1 months) and median survival time (8.9 vs. 5.9 months) than those in the sorafenib group.[73] A multi-center randomized controlled study compared the efficacy of sorafenib combined with HAIC (n=125) versus sorafenib alone (n=122) to treat patients with HCC involving PVTT (Vp1-4).[74] Patients in the combination group also had significantly longer median survival time (13.4 vs. 7.1 months) and median progression-free survival (7.0 vs. 2.6 months) than those in the sorafenib group. However, the combination group had a higher rate of grade 3/4 adverse events than the sorafenib group.

These studies suggest that TACE or HAIC combined with sorafenib may be good candidates for patients with HCC involving PVTT. Clinical trials of TACE or HAIC combined with other targeted drugs (such as lenvatinib, apatinib, etc.) or immune checkpoint inhibitors (such as nivolumab, trudilizumab, etc.) are ongoing (NCT03755791, NCT03778957, NCT04191889, NCT03937830, etc.), and more positive results are expected to guide clinical practice.

Systematic treatment

Since publication of the SHARP study in 2008,[75] systematic drugs for advanced or unresectable HCC have developed rapidly (Table 3).[75-98] Compared with placebo, sorafenib significantly prolonged median survival time for patients with advanced HCC (European and American populations, 10.7 vs. 7.9 months, p<0.001;[75] Asian Pacific population, 6.5 vs. 4.2 months, p=0.014[76]). Sorafenib is the first effective drug used as a first-line systematic therapy, but patients are prone to drug resistance. Therefore, several trials investigated the efficacy of sunitinib,[77] brivanib,[78] linifanib,[79] and sorafenib combined with erlotinib.[80] However, when comparing with sorafenib, all these trials did not meet their primary end point of overall survival. One trial comparing the efficacy of FOLFOX4 (intravenously infusional fluorouracil, leucovorin, and oxaliplatin) and doxorubicin also did not meet its primary end point of overall survival.[81] The REFLECT study analyzed the efficacy of lenvatinib in 954 patients (79% with BCLC stage C HCC) with unresectable HCC.[82] The median survival time was similar between lenvatinib and sorafenib groups (13.6 vs. 12.3 months). However, patients in the lenvatinib group had significantly longer progression-free survival than those in the sorafenib group (7.4 vs. 3.7 months), especially in Asian populations, patients with hepatitis B virus-related HCC, or those with BCLC stage C disease. Lenvatinib was the first drug with non-inferiority to sorafenib in overall survival. The ZGDH3 study[83] evaluated the safety and efficacy of donafenib versus sorafenib as first-line treatment for advanced HCC. Median survival time was significantly better in the donafenib group than in the sorafenib group (12.1 vs. 10.3, p=0.036). Compared with sorafenib (5.1%) and donafenib (4.6%), lenvatinib (18.8) was associated with the highest objective response rate (ORR) measured according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. In addition, donafenib (37.5%) was associated with lower adverse events of at least grade 3 than that of lenvatinib (56.7) or sorafenib (44.8%; Fig. 2A).

As a single-arm clinical trial, CheckMate 040 (phase I/II)[84] established the clinical indication of nivolumab, with ORR of 14.3% per RECIST v1.1. It was approved by the USA's Food and Drug Administration to be used as a second-line treatment for advanced HCC. The Checkmate 459 study[85] compared the efficacy of nivolumab and sorafenib as first-time treatments in 743 patients with advanced HCC and failed to acquire the per specified criteria. The HR of overall survival was 0.85 (95%CI: 0.72–1.02). KEYNOTE-524 (phase Ib trial) explored the efficacy of lenvatinib combined with pembrolizumab for 104 patients with unresectable HCC (68.3% with BCLC stage C HCC). The median overall survival was 22 months and the incidence of adverse events of at least grade 3 was 67%.[86] The IMbrave150 study[87] included 501 patients with unresectable HCC (82% BCLC stage C HCC) who received atezolizumab plus bevacizumab or sorafenib. Overall survival (HR: 0.58, 95% CI: 0.42–0.79), progression-free survival (HR: 0.59, 95% CI: 0.47–0.76), and ORR (27.3% vs. 11.9%) of patients who received atezolizumab plus bevacizumab were significantly better than those who received sorafenib. However, the ORR was only 8.5% among those who underwent atezolizumab monotherapy (n=59).[88] A recent phase II trial from China reported the efficacy and safety of camrelizumab plus apatinib (n=70) for patients with advanced HCC. The ORR was 34.3% but with a high incidence of adverse events of at least grade 3 (78.6%; Fig. 2A).[89]

Due to sorafenib-treated patients showing a propensity to drug resistance, some researchers have explored the efficacy and safety of other targeted drugs and immune checkpoint inhibitors as second-line systemic treatment. The RESORCE study (86.7% BCLC stage C HCC) confirmed that sorafenib followed by regorafenib extended the survival time of HCC patients to more than 26 months.[90] This survival time is encouraging. However, the ORR was only 6.6% with a high incidence of adverse events of at least grade 3 (66.3%; Fig. 2B). Another study included 707 patients (86.7% BCLC stage C HCC) who had received previous treatment with sorafenib for advanced HCC and found cabozantinib significantly prolonged median survival time (10.2 vs. 8.0 months, p=0.005) and progression-free survival (5.2 vs. 1.9 months, p<0.001) compared with placebo.[91] Also, the ORR was as low as 3.8%, and the incidence of adverse events of at least grade 3 was as high as 67.7%.[91] Ramucirumab (35.3% BCLC stage C HCC) also significantly prolonged median survival time (8.5 vs. 7.3 months, p=0.020) and progression-free survival (2.8 vs. 1.6 months, p<0.001) compared with placebo in patients with HCC and α-fetoprotein concentrations of at least 400 ng/mL who had previously received sorafenib.[92] Moreover, ramucirumab was well tolerated.[92,93] The KEYNOTE-240 study[94] (79.4% BCLC stage C HCC) compared the efficacy

Table 3. Clinical trials of first- or second-line systemic therapy for patients with advanced or unresectable HCC (sample size of at least 100 in a trial)

Trials	Phase	Experimental arms	Follow-up duration, months	ORR according to RECIST 1.1, %	Median survival time, months	HR (95%CI) of OS	Median PFS time, months[a]	HR (95%CI) of PFS	Treatment-related adverse events of grade ≥3, %
First-line									
Llovet *et al*. 2008 (SHARP)[75]	III	Sorafenib (*n*=299) vs. placebo (n=303)	–	0.7 vs. 0.3	10.7 vs. 7.9	0.69 (0.55–0.87)	5.5 vs. 2.8	0.58 (0.45–0.74)	15.2 vs. 10.6
Cheng *et al*. 2009[76]	III	Sorafenib (*n*=150) vs. placebo (*n*=76)	–	3.3 vs. 1.3	6.5 vs. 4.2	0.68 (0.50–0.93)	2.8 vs. 1.4	0.57 (0.42–0.79)	23.5 vs. 1.3
Cheng *et al*. 2013[77]	III	Sunitinib (*n*=530) vs. sorafenib(*n*=544)	7.4 vs. 7.8	6.6 vs. 6.1	7.9 vs. 10.2	1.30 (1.13–1.50)	3.6 vs. 3.0	1.13 (0.99–1.30)	82.1 vs. 74.2
Johnson *et al*. 2013 (BRISK-FL)[78]	III	Brivanib (*n*=577) vs. sorafenib (*n*=578)	–	12.0vs. 8.8	9.5 vs. 9.9	1.06 (0.93–1.22)	4.2 vs. 4.1	1.01 (0.88–1.16)	11.7 vs. 11.3
Cainap *et al*. 2015[79]	III	Linifanib (*n*=514) vs. sorafenib (*n*=521)	–	13.0 vs. 6.9	9.1 vs. 9.8	1.05 (0.90–1.22)	5.4 vs. 4.0	0.76 (0.64–0.90)	85.3 vs. 75.0
Zhu *et al*. 2015 (SEARCH)[80]	III	Sorafenib plus erlotinib (*n*=362) vs. sorafenib plus placebo (*n*=358)	–	6.6 vs. 3.9	9.5 vs. 8.5	0.93 (0.78–1.10)	3.2 vs. 4.0	1.14 (0.94–1.37)	87.0 vs. 83.9
Qin *et al*. 2013 (FOLFOX4)[81]	III	FOLFOX4 (*n*=184) vs. doxorubicin (*n*=187)	–	8.2 vs. 2.7	6.4 vs. 5.0	0.69 (0.50–0.94)	2.9 vs. 1.8	0.62 (0.49–0.79)	37.5 vs. 49.7
El-Khoueiry *et al*. 2017 (CheckMate 040)[84]	I/II	Nivolumab dose-expansion (*n*=214) vs. dose-escalation phase (*n*=48)	–	19.6 vs. 14.6	Not reached vs. 15	–	4.0 vs. 3.4	–	18.7 vs. 25.0
Kudo *et al*. 2018 (REFLECT)[82]	III	Lenvatinib (*n*=478) vs. sorafenib (*n*=476)	27.7 vs. 27.2	18.8 vs. 6.5	13.6 vs. 12.3	0.92 (0.79–1.06)	7.4vs. 3.7	0.66 (0.57–0.77)	56.7 vs. 48.6
Yau *et al*. 2019 (CheckMate 459)[85]	III	Nivolumab (*n*=371) vs. sorafenib (*n*=372)	22.8	15.4 vs. 7.0	16.4 vs. 14.7	0.85 (0.72–1.02)	3.7 vs. 3.8	–	21.8 vs. 48.1
Qin *et al*. 2021 (ZGDH3)[83]	II/III	Donafenib (*n*=334) vs. sorafenib (*n*=334)	–	4.6 vs. 2.7[b]	12.1 vs. 10.3	0.83 (0.70–0.99)	3.7 vs. 3.6	–	37.5 vs. 49.7
Finn *et al*. 2020 (KEYNOTE 524)[86]	Ib	Lenvatinib plus pembrolizumab (*n*=100)	10.6	36.0	22.0	–	9.3	–	67
Lee *et al*. 2020 (GO30140)[88]	Ib	Atezolizumab plus bevacizumab (*n*=104) vs. atezolizumab plus bevacizumab(*n*=60) vs. atezolizumab (*n*=59)	12.4 vs. 6.6 vs. 6.7	32.7 vs. 13.3 vs. 8.5	17.1 vs. not reachedvs. not reached	–	7.4 vs. 5.7 vs. 2.0	–	52.9 vs. 36.7 vs. 13.6
Finn *et al*. 2020 (Imbrave 150)[87]	III	Atezolizumab plus bevacizumab (*n*=336) vs. sorafenib (*n*=165)	15.6	27.3 vs. 11.9	19.2 vs. 13.4	0.66 (0.54–0.85)	6.8 vs. 4.3	0.59 (0.47–0.76)	56.5 vs. 55.1
Xu *et al*. 2021 (RESCUE)[89]	II	Camrelizumab plus apatinib (*n*=70)	16.7	34.3	Not reached	–	5.7	–	78.6

(continued)

Table 3. *(continued)*

Trials	Phase	Experimental arms	Follow-up duration, months	ORR according to RECIST 1.1, %	Median survival time, months	HR (95%CI) of OS	Median PFS time, months[a]	HR (95%CI) of PFS	Treatment-related adverse events of grade ≥3, %
Second-line									
Zhu *et al*. 2015 (REACH)[93]	III	Ramucirumab (*n*=283) vs. placebo (*n*=282)	8.3 vs. 7.0	7.1 vs. 0.7	9.2 vs. 7.6	0.87 (0.72–1.05)	2.8 vs. 2.1	0.63 (0.52–0.75)	35.3 vs. 28.0
Bruix *et al*. 2017 (RESORECE)[90]	III	Regorafenib (*n*=379) vs. placebo (*n*=194)	7.0	6.6 vs. 2.6	10.6 vs. 7.8	0.63 (0.50–0.79)	3.4 vs. 1.5	0.43 (0.35–0.52)	66.3 vs. 38.3
Kudo *et al*. 2017 (S-CUBE)[97]	III	S-1 (*n*=222) vs. placebo (*n*=111)	32.4 vs. 32.9	5.4 vs. 0.9	11.1 vs. 11.2	0.86 (0.67–1.10)	2.6 vs. 1.4	0.60 (0.46–0.77)	40.5 vs. 21.6
Abou-Alfa *et al*. 2018[91]	III	Cabozantinib (*n*=470) vs. placebo (*n*=237)	–	3.8 vs. 0.4	10.2 vs. 8.0	0.76 (0.63–0.92)	5.2 vs. 1.9	0.44 (0.36–0.52)	67.7 vs. 36.3
Zhu *et al*. 2018 (KEYNOTE224)[95]	II	Pembrolizumab (*n*=104)	12.3	17.3	12.9	–	4.9	–	24.0
Zhu *et al*. 2019 (REACH-2)[92]	III	Ramucirumab (*n*=197) vs. placebo (*n*=95)	7.6	4.6 vs. 1.1	8.5 vs. 7.3	0.71 (0.53–0.95)	2.8 vs. 1.6	0.45 (0.34–0.60)	34.5 vs. 29.5
Finn *et al*. 2020 (KEYNOTE 240)[94]	III	Pembrolizumab (*n*=278) vs. placebo (*n*=135)	13.8 vs. 10.6	18.3 vs. 4.4	13.9 vs. 10.6	0.78 (0.61–0.99)	3.0 vs. 2.8	0.72 (0.57–0.90)	52.7 vs. 46.3
Yau *et al*. 2020 (CheckMate 040)[96]	I/II	Nivolumab plus ipilimumab (arm A,*n*=50; arm B, *n*=49; arm C, *n*=49)	30.7	32.0 vs. 26.5 vs. 28.6	22.8 vs. 12.5 vs. 12.7	–	–	–	53.1 vs. 28.6 vs. 31.3
Qin *et al*. 2021 (AHELP)[98]	III	Apatinib (*n*=261) vs. placebo (*n*=132)	7.6	10.7 vs. 1.5	8.7 vs. 6.8	0.79 (0.62–0.99)	4.5 vs. 1.9	0.47 (0.37–0.60)	76.2 vs. 18.9
Xu *et al*. 2021 (RESCUE)[89]	II	Camrelizumab plus apatinib (*n*=120)	14.0	22.5	Not reached	–	5.5	–	76.7

[a]The level of response was measured according tomodified RECIST 1.1. [b]The method of response was not reported. CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

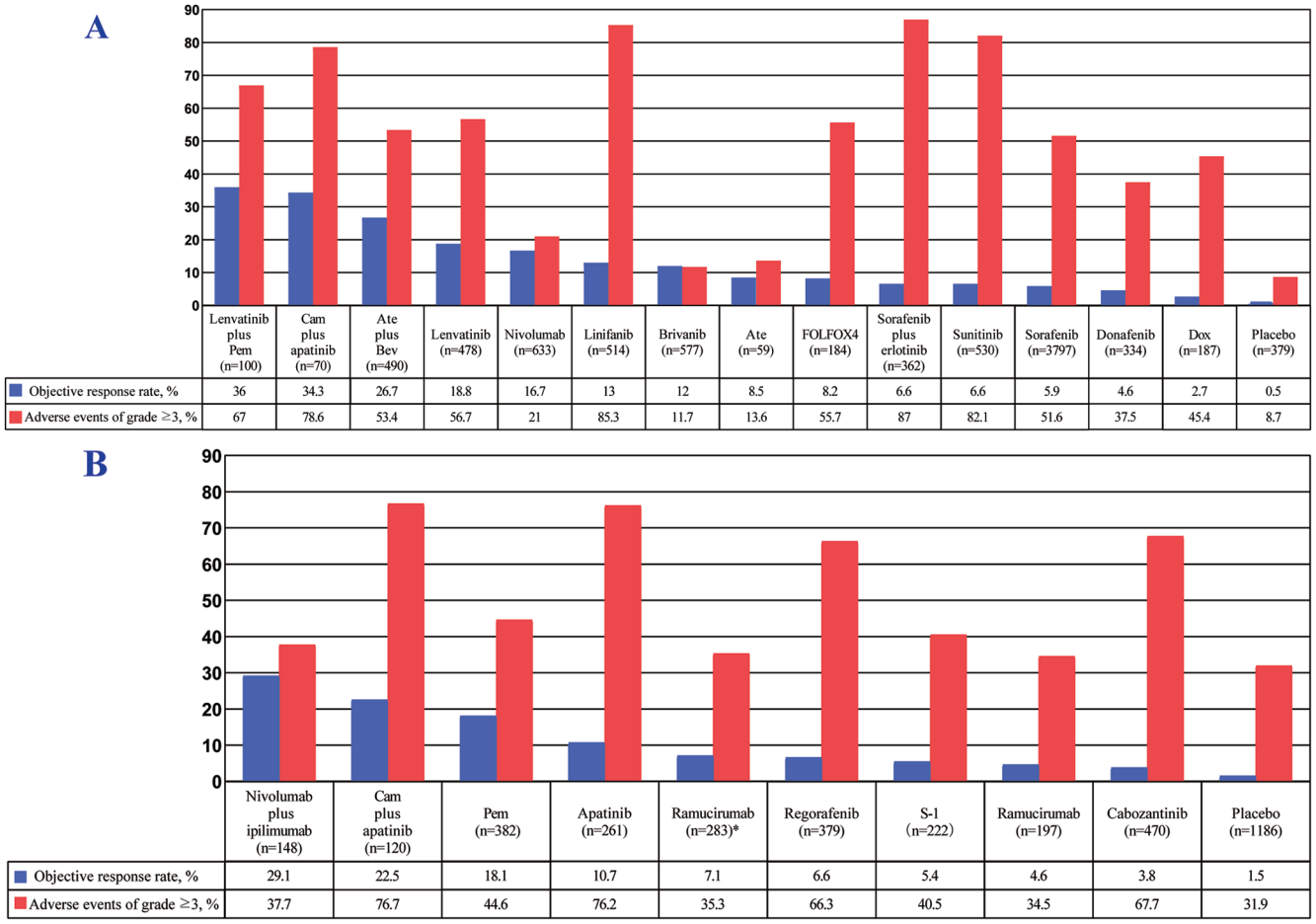

Fig. 2. Percentages of ORRs and adverse events of at least grade 3 in clinical trials of systematic therapy for advanced or unresectable HCC. (A) First-line therapy. (B) Second-line therapy. The level of response was measured according to RECIST 1.1. The total sample size equals the sum of the sample sizes for each trial. Percentages were obtained by the number of cases (ORR or adverse eventsof grade ≥3) in each trial divided by the total sample size of trials. *For patients with α-fetoprotein concentrations of at least 400 ng/mL. Ate, atezolizumab; Bev, bevacizumab; Cam, camrelizumab; Dox, doxorubicin; FOLFOX4, intravenously infusional fluorouracil, leucovorin, and oxaliplatin; Pem, pembrolizumab.

of pembrolizumab and placebo for patients with advanced HCC previously treated with sorafenib. Although pembrolizumab prolonged median overall survival time (13.9 vs. 10.6 months, p=0.024) and median progression-free survival time (3.0 vs. 2.8 months, p=0.002), overall and progression-free survival did not reach statistical significance per specified criteria, which are consistent with the findings of KEYNOTE-224.[95] Another Checkmate 040 study[96] (phase I/II) included 148 HCC patients who had sorafenib resistance. In a ratio of 1:1:1, patients were randomly divided into three groups to explore the prognostic impact of different dose regimens of nivolumab combined with ipilimumab. The study found that patients who received "nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (every 3 weeks) for four cycles, followed by nivolumab 240 mg (every 2 weeks)" had the best survival time (22.8 months) and highest ORR (32.0%). The chemotherapy drug fluoropyrimidine (S-1) was also investigated as second-line therapy in patients with sorafenib-refractory advanced HCC. However, S-1 did not prolong overall survival compared with placebo.[97] The efficacy and safety of apatinib with[89] (n=120) or without[98] camrelizumab (n=261) as second-line therapy were also reported from China. The corresponding ORRs were 22.5% and 10.7%, respectively, and the incidence rates of adverse events of at least grade 3 were 76.7% and 76.2%, respectively (Fig. 2B). And last, some studies also demonstrated that metronomic capecitabine may be an efficient and safe second-line systemic therapy after sorafenib failure in patients with HCC.[99,100]

In conclusion, combination therapy with tyrosine kinase inhibitors and immune checkpoint inhibitors as first-line therapy provides the highest ORR (>30%), suggesting promise for patients with HCC involving PVTT. As second-line therapy, however, nivolumab plus ipilimumab or camrelizumab plus apatinib provides an acceptable ORR for such patients (>20%). However, when administered either as first- or second-line therapy, camrelizumab plus apatinib is associated with the highest incidence of adverse events of at least grade 3 (Fig. 2). The sample size of the underlying supporting trials should be taken into account when recommending their corresponding study findings. Therefore, the ASCO guideline on systemic therapy for advanced HCC[101] stated that atezolizumab plus bevacizumab, sorafenib, or lenvatinib may be offered as first-line treatment for most patients with advanced HCC; following first-line therapy with sorafenib or lenvatinib, second-line therapy options include cabozantinib, regorafenib or ramucirumab (for patients with α-fetoprotein ≥400 ng/mL), and pembrolizumab or nivolumab. Until now, no clinical trial or cohort study investigating systematic therapy for different classification of PVTT has been reported.

Future directions

Due to the large differences in the incidence of HCC, the different pathogenic factors of HCC, and the differences in the culture and economic living standards of the population in eastern and western countries, the recommended treatment opinions of HCC official guidelines in eastern and western countries are also not consistent. Different guidelines offer treatment recommendations based on different classification systems and points of view. In addition, future studies are expected to continue to explore markers that predict efficacy. Finally, due to the great influence of different PVTT classification on the prognosis of patients with HCC, further exploration on PVTT classification is expected in future clinical trials related to multiple kinase inhibitors and immune checkpoint inhibitors.

Many patients with HCC involving PVTT have a long-term survival benefit from the most traditional treatment, such as hepatic resection, but with high rate of postoperative recurrence. It is necessary to combine neoadjuvant or adjuvant therapy to reduce recurrence rate and ultimately improve overall survival. Adjuvant targeted agents plus immune checkpoint inhibitors after surgery may be a therapeutic direction in the future.[48] Three-dimensional conformal radiotherapy, proton radiotherapy and stereotactic radiotherapy have definite efficacy in controlling PVTT. In addition, radiotherapy acts as a strong modulator of the tumor immune microenvironment. Radiotherapy combined with immune checkpoint inhibitors augments the tumoricidal effect by upregulating the major histocompatibility complex and increasing susceptibility to T-cell-mediated cell death.[102] Radiotherapy combined with other treatment measures to control primary lesions and improve the survival time of patients is important. Although the efficacy of monotherapy with a multi-kinase inhibitor or immune checkpoint inhibitor is unsatisfactory for patients with advanced HCC, "T+A" treatment is brilliant. With the diversification of therapeutic drugs and regimens, more emphasis should be placed on multidisciplinary treatment in clinical practice, and the comprehensive treatment concept of local treatment plus systematic treatment should be strengthened. It is believed that the survival period of patients with HCC, including those complicated with PVTT, will be greatly prolonged in the future. Finally, some conventional drugs in new use, such as heparins, may also be useful for patients with HCC and PVTT.[103]

Conclusions

Hepatic resection is the most effective therapy for selected patients with HCC and PVTT, while radiotherapy, TACE, HAIC, multi-kinase inhibitors, and immune checkpoint inhibitors are also used to prolong progression-free survival so as to improve overall survival for such patients. At present, more and more clinical trials on immune checkpoint inhibitors, chimeric antigen receptor T-cell, etc., are under development or scheduled to be carried out in the near future, throughout various countries and regions around the world.[104] However, in clinical practice, both clinicians and patients need to rationally consider the indications of these drugs or regimens, the occurrence of fatal adverse events, and the optimal fit for the population.

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Conflict of interest

JHZ has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Conception and design of the study (JHZ), acquisition, analysis, or interpretation of data (JHZ, ZJD, YXT, LL, YQZ, YXZ, HTL, JLH, ZXL, LM), drafting of the manuscript (JHZ, ZJD, YXT, LL, YQZ, YXZ, HTL, JLH, ZXL, LM), critical revision of the manuscript for important intellectual content (JHZ), statistical analysis (JHZ, JLH, ZXL, ZJD), obtained funding (JHZ, LM), administrative, technical, or material support (LM), supervision (JHZ, LM). In addition, all authors participated in the data analysis and reading and approval of the final version to be published. JHZ had full access to all of the data in the study and serves as guarantor, taking full responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

All data are presented in the manuscript and no additional data are available.

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