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Guidelines for Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus in China (2021 Edition)

Juxian Sun[a] Rongping Guo[b] Xinyu Bi[c] Mengchao Wu[a] Zhaoyou Tang[d] Wan Yee Lau[a, e] Shusen Zheng[f] Xuehao Wang[g] Jinming Yu[h] Xiaoping Chen[i] Jia Fan[d] Jiahong Dong[j] Yongjun Chen[k] Yunfu Cui[l] Chaoliu Dai[m] Chihua Fang[n] Shuang Feng[o] Zhili Ji[p] Weidong Jia[q] Ningyang Jia[r] Gong Li[s] Jing Li[t] Qiu Li[u] Jiangtao Li[v] Tingbo Liang[w] Lianxin Liu[q] Shichun Lu[x] Yi Lv[y] Yilei Mao[z] Yan Meng[o] Zhiqiang Meng[A] Feng Shen[B] Jie Shi[a] Huichuan Sun[C] Kaishan Tao[D] Gaojun Teng[E] Xuying Wan[F] Tianfu Wen[G] Liqun Wu[H] Jinglin Xia[I] Mingang Ying[J] Jian Zhai[K] Leida Zhang[L] Xuewen Zhang[M] Zhiwei Zhang[N] Haiping Zhao[O] Donghai Zheng[P] Xuting Zhi[Q] Jie Zhou[R] Cuncai Zhou[S] Jian Zhou[d] Zhaochong Zeng[T] Kangshun Zhu[U] Minshan Chen[b] Jianqiang Cai[c] Shuqun Cheng[a] On behalf of Chinese Association of Liver Cancer and Chinese Medical Doctor Association

[a]Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [b]Department of Hepatobiliary Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; [c]Department of Hepatobiliary Surgery, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [d]Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Fudan University, Shanghai, China; [e]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China; [f]Department of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital, Hangzhou, China; [g]Hepatobiliary Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [h]Department of Oncology, Clinical College of Weifang Medical University, Weifang, China; [i]Hepatic Surgery Center, Tongji Medical College, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China; [j]Department of Hepatobiliary and Pancreas Surgery, Beijing Tsinghua Chang Gung Hospital (BTCH), School of Clinical Medicine, Tsinghua University, Beijing, China; [k]Department of Hepatobiliary Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [l]Department of Hepatopancreatobiliary Surgery, Second Affiliated Hospital of Harbin Medical University, Harbin, China; [m]Department of Hepatobiliary and Spleenary Surgery, The Affiliated Shengjing Hospital, China Medical University, Shenyang, China; [n]Department of Hepatobiliary Surgery, Zhujiang Hospital, First Military Medical University, Guangzhou, China; [o]Department of Radiation Oncology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [p]Department of General Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [q]Department of General Surgery, The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, China; [r]Department of Radiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [s]Department of Radiation Oncology, Beijing Tsinghua Changgung Hospital (BTCH), School of Clinical Medicine, Tsinghua University, Beijing, China; [t]Department of Hepatobiliary Surgery, Xinqiao Hospital, Third Military Medical University, Chongqing, China; [u]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [v]Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; [w]Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [x]Department of Hepatobiliary Surgery, First Medical Center of Chinese PLA General Hospital, Beijing, China; [y]Department of Hepatobiliary Surgery, The First

Karger@karger.com
www.karger.com/lic

Correspondence to:
Minshan Chen, cms64@163.com
Jianqiang Cai , caijianqiang188@sina.com
Shuqun Cheng, chengshuqun@aliyun.com

Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [Z]Department of Liver Surgery, Peking Union Medical College (PUMC) Hospital, PUMC and Chinese Academy of Medical Sciences, Beijing, China; [A]Department of Oncology, Shanghai Medical College, Fudan University Shanghai, Shanghai, China; [B]Department of Hepatic Surgery IV, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [C]Department of Liver Surgery and Transplantation, Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China; [D]Department of Hepatobiliary Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China; [E]Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China; [F]Department of Integrated Traditional Chinese and Western Medicine, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [G]Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, China; [H]Division of Hepatobiliary Pancreatic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, China; [I]Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China; [J]Department of Abdominal Surgery, Fujian Provincial Cancer Hospital, Fujian Medical University Teaching Hospital, Fuzhou, China; [K]Department of Interventional Radiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; [L]Department of Hepatobiliary Surgery Institute, Southwest Hospital, Third Military Medical University, Chongqing, China; [M]Department of Hepatobiliary and Pancreas Surgery, The Second Hospital of Jilin University, Changchun, China; [N]Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [O]Department of Hepatobiliary and Pancreas Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Huhehot, China; [P]Department of Traditional Chinese Medicine, Beijing Weida Traditional Chinese Medicine Tumor Hospital, Beijing, China; [Q]Department of General Surgery, Qilu Hospital, Shandong University, Jinan, China; [R]Department of Hepatobiliary Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China; [S]Department of Hepatobiliary Surgery, Jiangxi Provincial Cancer Hospital, Nanchang, China; [T]Department of Radiation Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; [U]Department of Minimally Invasive Interventional Radiology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Keywords

Hepatocellular carcinoma · Portal vein tumor thrombus · Multidisciplinary therapy · Guideline

Abstract

Portal vein tumor thrombus (PVTT) is very common and it plays a major role in the prognosis and clinical staging of hepatocellular carcinoma (HCC). We have published the first version of the guideline in 2016 and revised in 2018. Over the past several years, many new evidences for the treatment of PVTT become available, especially for the advent of new targeted drugs and immune checkpoint inhibitors which have further improved the prognosis of PVTT. So, the Chinese Association of Liver Cancer and Chinese Medical Doctor Association revised the 2018 version of the guideline to adapt to the development of PVTT treatment. Future treatment strategies for HCC with PVTT in China would depend on new evidences from more future clinical trials.

Sun Juxian, Guo Rongping, and Bi Xinyu contributed equally to this study.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide, and China accounts for more than half of new cases and deaths related to HCC every year [1]. The latest data indicated that the morbidity and mortality rates of HCC ranked fourth and third, respectively, among all malignant tumors reported in China [2]. Given the advances in diagnosis and treatment strategies for different stages of HCC, the prognosis of HCC patients has improved. Unfortunately, 70%–80% of patients are still diagnosed at an advanced stage as there are no obvious clinical symptoms at early stages. At present, the overall prognosis of HCC is not satisfactory.

Owing to the biological characteristics of liver cancer and the anatomical characteristics of the liver, HCC is prone to invade intrahepatic vessels, especially the portal venous system. In China, the incidences of portal vein tumor thrombus (PVTT) have been reported to range from 44% to 62.2% [3]. Once developed, PVTT progresses rapidly to cause portal hypertension, hepatocellular jaundice, and intractable ascites. The median survival of HCC patients with main PVTT is 2.7 months [4]. PVTT plays a major role in the prognosis and clinical staging of HCC [5, 6].

Table 1. Grades of evidences

Grades of evidences	Description
Ia	Evidences are originated from the meta-analysis results of various RCTs
Ib	Evidences are originated from the results of at least one well-designed RCT
IIa	Evidences are originated from the results of at least one well-designed perspective non-RCT
IIb	Evidences are originated from the results of at least one well-designed interventional clinical research of other types
III	Evidences are originated from the well-designed non-interventional clinical researches, such as descriptive researches and relevant researches
IV	Evidences are originated from the reports made by the committee of experts or the clinical reports of authoritative experts

RCT, randomized controlled trial.

There have been no worldwide consensuses or guidelines on the diagnosis and treatment of HCC with PVTT. Guidelines in Europe and America follow the Barcelona Clinic Liver Cancer Staging (BCLC) and regard HCC with PVTT to be at BCLC Stage C. The guidelines also recommend treating HCC patients with PVTT with systemic therapy [7]. On the contrary, experts from Southeast Asian countries, including China opine that multidisciplinary therapy, including surgery, transcatheter arterial chemoembolization (TACE), radiotherapy (RT), molecular-targeted drugs, and/or immune checkpoint inhibitor (ICIs) should be considered to achieve more satisfactory outcomes. But the difference is that Chinese doctors tend to use more curable treatments for the same subgroup of PVTT patients.

In May 2016, the Chinese National Research Cooperative Group for Diagnosis and Treatment of Hepatocellular Carcinoma with Tumor Thrombus launched The Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (version 2016) [8] based on the existing evidences published internationally and in China at that time. In 2018, we revised the 2016 version of the guideline to adapt to the development of PVTT treatment. This version (version 2018) [9] has been widely used and recognized clinically in China.

Over the past several years, many new evidences for the treatment of PVTT become available, especially for the advent of new targeted drugs and ICIs which have further improved the prognosis of PVTT. So, the Chinese Association of Liver Cancer revised the 2018 version of the guideline to adapt to the development of PVTT treatment.

Based on internationally accepted practice, the grades of evidence we use are presented in Table 1 [10]. We also adopted the United States Preventive Service Task Force recommendations to assign 5 alphabets (A, B, C, D, and I) to denote the strength of recommendation for clinical practice (Table 2) [11].

Guideline Recommendations

Diagnosis and Classification of PVTT

PVTT is one of the most common complications of HCC. A diagnosis of HCC is a prerequisite to diagnose PVTT [12]. The imaging features of PVTT include solid lesions within the portal vein in all the phases of intravenous enhanced three-phase computed tomography, especially with an enhancement of contrast in the arterial phase and washout in the portal venous phase of the procedure [13, 14]. Clinically, PVTT should be distinguished from portal vein thrombosis (PVT), which occurs as a complication of cirrhosis or after splenectomy. PVT is not enhanced in the arterial phase. It occasionally disappears or improves after anticoagulant therapy [15].

The extent of PVTT is closely related to the prognosis of HCC. The HCC staging systems that are commonly used today are the TNM staging, BCLC staging, and staging of the liver cancer study group of Japan. All these staging systems accept the importance of PVTT. However, they do not further define the extent of PVTT. At present, there are two classifications for PVTT: the Japanese V_P classification [16], and the Cheng's classification as suggested by Professor Cheng Shuqun of China [17–19].

The Cheng's classification comprises four levels based on the extent of tumor thrombus in the portal vein shown on medical imagings: type I, tumor thrombus involving segmental or sectoral branches of the portal vein or above;

Table 2. Ranking of recommended opinion

Grades of evidences	Description
A	Favorable scientific evidences indicate that the medical treatment can provide clear and definite benefits to the patients; physicians are strongly recommended to administer the medical treatment to eligible patients
B	Existing evidences indicate that the medical treatment may provide moderate benefits that outweigh the potential risks; physicians may suggest or patients may carry out the said medical treatment
C	Existing evidences indicate that the medical treatment may provide only little benefits, or the benefits do not outweigh the risks; physicians may suggest or administer the said medical treatment selectively based on the patient's condition
D	Existing evidences indicate that the medical treatment would not benefit the patients, or the potential risks would outweigh the benefits; physicians are recommended not to administer the said medical treatment in patients
I	There are not enough scientific evidences, or the existing evidences cannot be used, to evaluate the benefits and risks of the said medical treatment; physicians should help the patients understand well the uncertainty of this medical treatment

type II, tumor thrombus involving the right/left portal vein; type III, tumor thrombus involving the main portal vein; and type IV, tumor thrombus involving the superior mesenteric vein. Type I_0, tumor thrombus found only under microscopy. Many studies have supported that the Cheng's classification to be more applicable than the V_P classification for disease assessment, treatment selection, and prognostic judgment in patients with PVTT [18–20], and hence it is recommended to be used for classifying the extent of PVTT.

Multidisciplinary Therapy Path for HCC with PVTT

A multidisciplinary team to coordinate diagnosis and treatment of HCC patients with PVTT provides maximal benefits to patients. The therapeutic plan for the treatment of HCC with PVTT formulated by the National Research Cooperative Group for Diagnosis and Treatment of Hepatocellular Carcinoma with Tumor Thrombus is presented in Figure 1. Patients with Child-Pugh A liver function can undergo any treatment according to the PVTT type. When the lesion is resectable and when there is no extrahepatic metastasis, patients with type I/II PVTT should undergo surgical resection of the PVTT en bloc with the primary HCC. For patients with PVTT type III, the treatment choices include surgery, TACE, and/or RT depending on the patient's preference. For unresectable lesions, patients with type I/II/III PVTT should receive RT combined with TACE or (Hepatic Arterial Infusion Chemotherapy, HAIC), and patients with type IV PVTT should receive RT or systemic therapy. Patients with Child-Pugh B liver function should first receive antiviral treatment for HCC secondary to hepatitis B or C infections. If the liver function improves to Child-Pugh A, then these patient subgroups can be treated as mentioned above. Surgery and TACE are not recommended for Child-Pugh B patients. Child-Pugh C patients should only receive supportive care. Child-Pugh A patients who have extrahepatic metastases can receive systemic treatment and/or local treatment. Sorafenib, Lenvatinib, Donafenib, Atezolizumab plus Bevacizumab, and Sintilimab plus IBI305 can be used for patients with all extents of PVTT with Child-Pugh A liver function. Regorafenib, Apatinib, Camrelizumab, and Tislelizumab are the second-line treatments of PVTT patients.

Recommended First-Line Treatment Options for PVTT

The treatment of HCC patients with PVTT is based on the patients' liver function, the stage of hepatic lesion, and the extent of PVTT. A strategy that can either eliminate or control HCC with PVTT using multimodality therapy can extend survival and improve quality of life of the patient.

Surgery

Recommendations

- Surgery is the preferred treatment in patients with Child-Pugh A, PVTT type I/II, and ECOG PS 0–1 (Evidence level IIb, Recommendation A); type III PVTT patients can undergo surgery directly (Evidence level IIb, Recommendation B) or after tumor down-staging using RT (Evidence level Ib, Recommendation A).

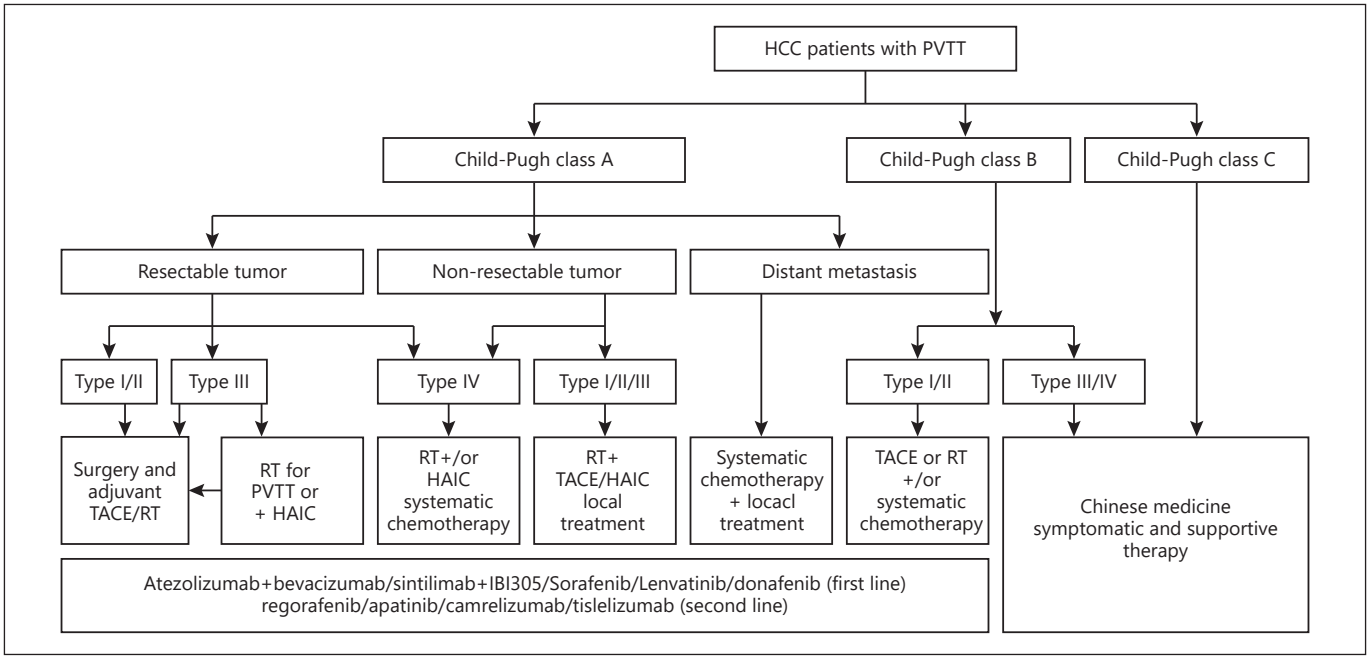

Fig. 1. Diagnosis and treatment of HCC with PVTT.

- Adjuvant TACE (Evidence level Ib, Recommendation A), RT (Evidence level Ib, Recommendation A), or molecular-targeted therapy (Evidence level IIb, Recommendation B) after surgery can be used to reduce recurrence.

Surgical treatment is considered to be potentially curative and is the preferred treatment option for HCC patients with type I/II PVTT. En bloc resection of the primary HCC and PVTT provides a potential for cure. Many studies reported that patients who had undergone surgery had a better prognosis than those treated with TACE [12, 21, 22] or TACE combined with RT [23].

Type I/II PVTT is more suitable for resection than type III/IV (Evidence level IIb) [18, 24, 25]. En-bloc resection can be performed in type I/II PVTT patients with partial hepatectomy or hemihepatectomy. For type III PVTT patients, as the PVTT has extended to the main portal vein, partial hepatectomy has to be combined with thrombectomy or main portal vein resection followed by reconstruction. At present, studies have revealed that there is no significant difference in prognosis among these surgical procedures (Evidence level IIb) [26]. Thrombectomy is by far the most commonly used surgical procedure.

The following are the recommendations for reducing recurrence rates and metastasis after surgery: (1) Preoperative small-dose RT has been reported to downstage some type III PVTT patients, reduce recurrence rate without increasing surgical risks, and reduce postoperative hepatic failure rates (Evidence level Ib) [27, 28]. (2) Adjuvant TACE after surgery has been reported to reduce recurrence rates and prolong survival of PVTT patients in a randomized controlled trial (RCT) (From January 1996 to December 2004, including 126 patients) (Evidence level Ib) [29]; but a recent meta-analysis revealed that adjuvant TACE can only increase the 1-year survival rate. (3) Adjuvant RT has been reported to reduce recurrence rates and prolong survival of PVTT patients [30] (Evidence level Ib).

Other treatment recommendations that are controversial include the following: postoperative portal vein chemotherapy [31] (Evidence level IIb), adjuvant HAIC [32] (Evidence level IIb), adjuvant molecular-targeted therapy [33] (Evidence level IIb), and postoperative intravenous chemotherapy [34] (Evidence level III).

Nonsurgical Therapies

Hepatic Artery Infusion Chemotherapy

Recommendations

- Patients with non-resectable primary tumor, type I/II/III/IV PVTT, and Child-Pugh A liver function may receive HAIC (Evidence level Ib, Recommendation B).

HAIC was developed to treat metastatic liver tumors and was known to be more effective than conventional systemic chemotherapy. Recently, HAIC was then applied to advanced HCC [35]. Commonly used chemotherapeutic agents for HAIC include platinum/oxaliplatin and 5-fluorouracil. Chemotherapeutic agents were administered every 2–4 weeks through the hepatic artery, and the patient's responses were usually evaluated every one or two cycles. A prospective randomized controlled study, including 58 HCC patients with PVTT in Korea revealed that the median OS of the HAIC group was 14.9 months, which was significantly higher than that of the Sorafenib group (7.2 months, $p = 0.012$) [36]. Lyu et al. [35] reported a single-center retrospective study demonstrating the higher objective remission rate (ORR) of HAIC compared with sorafenib (mRECIST, 47.8% vs. 9.1%, $p < 0.01$), and 26.1% of the patients in the HAIC group achieved remission to receive local treatment. HAIC may be more effective in combination with other treatments. Nagai et al. [37] studied the effect of HAIC combined with sorafenib on HCC with PVTT compared with Haic alone. The results showed that the OS of the combined treatment group was 4 months longer than that of HAIC alone ($p < 0.05$). Another study published by Onishi et al. [38] showed that the ORR in HAIC combined with RT for HCC with PVTT was significantly higher than HAIC alone (52% vs. 18%, $p < 0.05$).

Transcatheter Arterial Chemoembolization

Recommendations

- Patients with non-resectable primary tumor, type I/II PVTT, and Child-Pugh A liver function may receive TACE (Evidence level IIb, Recommendation B) alone or in combination with RT (Evidence level Ib, Recommendation A) or molecular-targeted therapy (Evidence level IIb, Recommendation A).
- Patients with Child-Pugh B liver function or type III/IV PVTT are not recommended to receive TACE (Evidence level IIb, Recommendation C).

TACE is one of the most commonly used techniques to manage nonresectable HCC with PVTT [39]. Despite the possible benefit of TACE in prolonging overall survival (4–7 months) in patients with HCC and PVTT type III/IV, the use of TACE in patients is controversial due to the risk of liver infarction and hepatic failure [40]. At present, TACE is considered for PVTT patients with good liver function with adequate collateral circulation around the obstructed portal vein [41, 42]. The overall survival rate varies greatly among patients with PVTT after TACE. The patient survival rates decreased from 82% at 3 months to 71% at 6 months and 47% at 12 months, with a median survival of 10 months. Patients with Child-Pugh A liver function had better median survival when compared to patients with Child-Pugh B (15 vs. 13 months) [43], and the complete remission rate (CR), partial remission rate, and stable disease rate were reported to be 0, 19.5–26.3%, and 42.5–62.7%, respectively [44–46]. Lipiodol and gelatin sponge are common embolizing agents used in TACE [47]. Some reports have suggested that TACE, when combined with lipiodol, is more effective than TAI or conservative treatment [39, 48]. The effectiveness of the embolizing agents depends on their size. The smaller the diameter of an embolizing agent, the better is the effect on PVTT patients and the lower is its adverse side effects [49, 50]. The use of super-selective catheterization improves therapeutic effects and reduces damages to the normal liver when compared with conventional TACE. Recently, TACE with drug-eluting beads has been introduced into a clinical application; however, its effects on HCC patients with PVTT are controversial [51].

Radiotherapy

External Beam Radiation Therapy

Recommendations

- Patients with non-resectable HCC with all types of PVTT, with Child-Pugh A or B liver function, are recommended to receive RT with the target region containing both the primary tumors and PVTT – 3DCRT or intensify-modulated RT (IMRT) 95% PTV 40–60 Gy/2–3 Gy (Evidence level IIb, Recommendation B) or SBRT 36–40 Gy/5–6 Gy (Evidence level IIb, Recommendation A).
- Patients with Child-Pugh A liver function and types I, II, and III PVTT are recommended to receive combined RT and TACE (Evidence level Ib, Recommendation A) or HAIC (Evidence level IIb, Recommendation B). The RT target region includes the primary tumor and PVTT or only the PVTT.

With the development of newer technologies such as three-dimensional conformal RT, IMRT, and three-dimensional-oriented RT (SBRT), radiation dosage to the targeted regions can be increased while giving better protection to the adjacent healthy tissues [52–54]. This allows the maximum use of RT technologies and enables their use in HCC patients with all types of PVTT.

The use of RT alone or in combination with other treatments such as TACE improved survival and quality of life in

HCC patients with PVTT. Yoon et al. [55] conducted a prospective randomized controlled study, including 90 HCC patients with PVTT and there were 45 cases in the TACE combined with RT group and 45 cases in the Sorafenib group. The results revealed that the median OS of TACE combined with RT group was 12.8 months, which was significantly higher than that of Sorafenib group (10.0 months, $p = 0.04$).

Target localization suggests the use of computed tomography and MRI image fusion technology based on the area of lipiodol deposition after TACE. The clinical target volume is 4 mm larger than the diameter of the tumor area [56]. The plan target volume should be determined on the basis of a moving target, set-up error, and random error. The designation of the irradiation area is still controversial, which should be determined individually. The hepatic lesion and PVTT should be irradiated simultaneously if the hepatic lesion is small and PVTT is nearby. If the volume of the primary tumor is large or PVTT is distant to the primary tumor, only the PVTT should receive irradiation [57].

There is not enough evidence to determine the best radiation and fraction doses. The existing evidence suggests a positive correlation between total radiation dose and tumor response [58]. However, multivariate analysis only showed response to RT to be associated with survival [58, 59]. Image-guided IMRT should be applied if available, which is better than conventional 3D-CRT [60].

Radiation-induced liver disease (RILD) or radiation hepatitis is a subacute form of liver injury, which occurs due to overexposure of the liver to radiation [53]. The key to prevent RILD is to keep the total dose within the tolerance range limit when designing the RT plan [61]. As most HCC patients in China have a cirrhotic background, the radiation tolerance dose of the liver in these patients is lower than that in patients from other countries. The liver tolerance dose (average dose of the liver) is 23 Gy for Child-Pugh A patients and only 6 Gy for Child-Pugh B patients [62]. The most common risk factors of RILD include pre-existing poor liver function, high irradiation volume, coexisting PVT, and acute liver toxicity due to other causes [61, 62]. It is reported that individualized adaptive RT based on a direct biomarker of liver function such as ICG 15 can be used to achieve both high rates of local control and a high degree of safety without sacrificing either (Evidence level IIa) [63].

Evidence from clinical studies has shown a combination of RT and TACE produces better clinical outcomes than TACE or RT alone. The time interval between TACE and RT should not exceed 1 month [64]. When TACE is combined with RT, the order of the treatments given should be decided clinically. As the effect on liver function is less in patients receiving RT first than those receiving TACE first, with similar treatment outcomes, RT should be given before TACE [65]. A combination of RT and HAIC might be more effective than HAIC alone [38], but it needs to be demonstrated by further RCTs.

Internal Radiation Therapy

Recommendations

- Patients with nonresectable primary tumors; types I, II, and III PVTT; and Child-Pugh A liver function could be treated with transarterial arterial radio-embolization (TARE) (Evidence level IIb, Recommendation C) or portal veins I^{125} seed implantation (Evidence level IIb, Recommendation B).

Patients treated with I^{125} particle seeds implanted in the portal vein and TACE have been reported to have better survival outcomes when compared to patients treated with TACE alone. This combination therapy also improved the reperfusion rate of portal vein significantly [66]. Another study showed I^{125} seeds followed by TACE significantly improved the median survival and progression-free survival rates when compared to I^{125} alone ($p = 0.037$ and 0.002, respectively) [67]. TARE with yttrium-90 (Y^{90}) microspheres are considered to be a viable treatment option in HCC patients with PVTT. TARE has been shown to produce better long-term survival outcomes than TACE [68]. However, The SARAH trial revealed that the overall survival did not significantly differ between the Sorafenib group and TARE group for advanced HCC patients [69]. Furthermore, there is no uniform dosage standard at present for internal radiation therapy.

Systematic Therapy

Recommendations

- Nucleoside analogs are recommended in PVTT patients with HBsAg positive regardless of whether or not HBV DNA is positive (Evidence level Ia, Recommendation A).
- Atezolizumab plus Bevacizumab, Sorafenib, Lenvatinib, Donafenib, and Sintilimab plus IBI305 are recommended as the basic drug for PVTT patients with Child-Pugh A liver function (Evidence level Ib, Recommendation A). Regorafenib, Apatinib, Camrelizumab, and Tislelizumab are recommended as the second-line treatment for PVTT patients with Child-Pugh A liver function (Evidence level Ib, Recommendation A).

- Chemotherapy is recommended in PVTT patients (Evidence level IIb, Recommendation B) with extrahepatic metastasis and Child-Pugh A liver function.

Persistent HBV infection is an important poor risk factor for occurrence, progression, recurrence, and death in patients with HCC secondary to HBV infection. Antiviral therapy reduces postoperative recurrence and improves survival of HCC patients [70]. Antiviral therapy should also be given to PVTT patients [71, 72].

Sorafenib, Lenvatinib, and Donafenib are universally accepted therapy that effectively prolong survival in patients with advanced HCC (Evidence level Ib) [73–75]. All have been listed by the National Medical Products Administration (NMPA) as the first-line treatment option in patients with advanced HCC. The STORM was a phase 3, double-blind, randomized, placebo-controlled study, which evaluated the effectiveness of sorafenib as adjuvant therapy to surgery. When compared to placebo, sorafenib did not show any significant improvement in the median recurrence-free survival (33.3 vs. 33.7 months, $p = 0.26$), suggesting that adjuvant sorafenib to be ineffective [76]. The effectiveness of Sorafenib and TACE combination has also been controversial [77–80]. Regorafenib, Apatinib is recommended as the second-line treatment for PVTT patients (Evidence level Ib) [81, 82]. Cabozantinib [83] and Ramucirumab (AFP >400 μg/L) [84] were only approved by FDA as second-line targeted drugs.

The application of ICIs has created a new era in the systematic treatment of advanced HCC, especially in combination with TKI. In the global multicenter phase III clinical trial (IMBrave 150) study [85], the ORR of Atezolizumab plus Bevacizumab (T+A) was 30%, which was significantly higher than that of Sorafenib group, while the risk of death and disease progression decreased by 35% and 34%, respectively. In another multicenter phase III clinical trial (ORIENT-032) [86, 87], the ORR of Sintilimab plus IBI305 was 21%, and the risk of death and disease progression were reduced by 43.1% and 43.5% respectively when compared with Sorafenib group. T+A (evidence level Ib) and Sintilimab plus IBI305 (evidence level Ib) have been approved by NMPA as the first-line treatment of advanced HCC. Camrelizumab [88] and Tislelizumab [89] are recommended as the second-line treatment for PVTT patients (Evidence level Ib). Pembrolizumab [90, 91] and Nivolumab Plus Ipilimumab [92] were only approved by FDA as second-line targeted drugs. At present, the clinical research on immunotherapy has made rapid progress [93–98], including Camrelizumab plus Apatinib (RESCUE), Lenvatinib plus Pembrolizumab, Tremelimumab (T) plus Durvalumab (D), Regorafenib plus Pembrolizumab, Regorafenib plus Pembrolizumab, Penpulimab with Anlotinib. Based on current evidences, Atezolizumab plus Bevacizumab should be a priority and positioned as 1st-line therapy among all systemic drugs.

Before the treatment of ICIs, the medical history taking, physical examination, laboratory, and imaging examination must be done to evaluate the tumor burden and organ function (heart, lung, liver, kidney, endocrine system, and so on) of the patients comprehensively. Immune-related adverse events should be monitored during ICIs treatment, including delayed toxicity after treatment. In case of immune-related adverse events, please refer to the NCCN Guidelines for Management of Immunotherapy-Related Toxicities [99]. The research on ICIs is very active in the field of HCC. The future version of this guideline will also be modified according to the corresponding research results.

The EACH study demonstrated that FOLFOX 4 (an oxaliplatin-containing chemotherapy) provided partial cure in patients with advanced HCC (including PVTT patients). FOLFOX 4 might be administered in patients with good liver function and tolerance (Evidence level Ib) [100]. A phased II prospective study revealed that mFOLFOX4 combined with Sorafenib would be more effective, but the results need further validation [101].

Local Treatment

Recommendations

- Local ablation therapies should be recommended in PVTT patients with caution; further studies are warranted (Evidence level III, Recommendation C). Local ablation therapies may be combined with TACE and molecular-targeted therapy (Evidence level IIb, Recommendation B).

The local ablation therapies include percutaneous ethanol injection, radiofrequency ablation, and laser ablation. These therapies may be adopted to reduce tumor load and recanalization of portal vein. However, local therapies must be used cautiously as there is a risk of damaging the portal vein wall and bile duct. In addition, a high recurrence rate of PVTT has been reported within a short period of time (Level III evidence) [102, 103]. Therefore, it is suggested to combine local ablation therapies with other treatments such as TACE and molecular-targeted therapy to improve the curative effect (Level II evidence) [104–106].

Symptomatic and Supportive Treatment

Recommendations

- Symptomatic and supportive treatment is recommended in patients with Child-Pugh C liver function, with massive ascites or gastrointestinal bleeding due to esophageal varices and hepatic encephalopathy (Evidence level Ia, Recommendation A).

Portal vein stenting may be adopted to recanalize blood flow in the portal veins of PVTT patients, with resultant increase in blood flow to the liver, but without reducing the tumor load. In patients with PVTT, portal vein stenting can result in improved liver functions, reduced portal vein pressure, and at the same time, win time for other therapies such as RT and TACE to act (Evidence level III) [107, 108].

Most complications of PVTT result from portal hypertension. The common complications include upper gastrointestinal hemorrhage, ascites, hypersplenism, hepatorenal syndrome, and hepatic failure. For therapeutic methods, please refer to the article on treatment of portal hypertension [109]. In addition, Chinese medicine [110, 111] such as Huaier granule and Cidan could also be used for PVTT patients with nonresectable primary tumors.

Tumor Down-Staging of HCC with PVTT

Recommendations

- Tumor down-staging is suggested for non-resectable HCC patients with all types of PVTT, with Child-Pugh A liver function and more clinical trials need to be carried out (Evidence level IIb, Recommendation A).

Tumor down-staging of HCC with PVTT is an important way to improve the survival of PVTT patients. Especially in recent years, with the significant progress of various non-surgical treatment methods, such as immunotherapy, molecular-targeted therapy, RT, and HAIC, the down-staging success rate of PVTT patients has been significantly improved, which has greatly prolonged the survival time of certain PVTT patients. It is one of the main directions of PVTT clinical research. At present, the most reported down-staging therapy is based on RT, ICIs, and molecular-targeted therapy.

A retrospective single-arm study conducted by Serenari et al. [112] showed that up to 29.4% of PVTT patients treated with TARE had achieved down-staging and had the opportunity to receive liver transplantation. Another retrospective study [113] on PVTT patients compared the efficacy of TARE with Sorafenib. The results showed that the down-staging rate of TARE was 24.4%, which was significantly higher than that of Sorafenib. The efficacy of HAIC on PVTT has been mentioned above, and it may obtain a higher down-staging rate when combined with RT. The retrospective study of Hamaoka et al. [114] showed that the down-staging rate of RT combined with HAIC was 14%, and the survival time of patients undergoing surgery was significantly longer than that of non-surgical patients. Another retrospective study [115] showed that the down-staging rate of PVTT by RT combined with HAIC was 26.5%, and the pathology of PVTT of all patients undergoing surgery showed complete necrosis.

Tumor down-staging based on ICIS and targeted drugs is an important research direction to improve the down-staging rate of PVTT. At present, more clinical trials need to be carried out using various new schemes. A retrospective single-arm study conducted by Huang et al. [116] showed that the ORR of Lenvatinib combined with PD-1 was 54.5% for PVTT and 32.8% for hepatic tumors. Of the 17 PVTT patients who achieved ORR, 6 (18.1%) underwent surgery. Postoperative pathology showed that 66.7% of PVTT achieved pathological complete necrosis. A real-world study by Tsai et al. [117] included 28 patients with PVTT. The ORR of PD-1 combined with TKI was 50%, including 2 cases of CR and 1 case underwent surgery. He et al. [118] reported an RCT study that compared the efficacy of HAIC combined with Sorafenib and Sorafenib monotherapy in the treatment of PVTT. The results showed that the effective rate of the combined treatment group was significantly better than that of Sorafenib monotherapy, and 12.8% of the patients in the combined treatment group were successfully downstaged.

For patients who were successfully down-staged, it is suggested that targeted drugs should be stopped for more than 1–2 weeks, ICIs should be stopped for more than 2–4 weeks, and Bevacizumab should be stopped for more than 6 weeks before surgery. If TACE is performed, the operation should be performed 4 weeks after the last treatment and if low-dose RT is performed, surgery should be performed 3 weeks after the last RT.

Future Outlook

It is necessary to develop a treatment guideline in China as HCC patients with PVTT in China are different from those in Europe and America in terms of etiology and biological behavior. Although treatment of HCC patients with PVTT is still controversial, new evidences are being gathered. Similar to the multidisciplinary approach of HCC treatment in the United States (the American Asso-

ciation for the Study of Liver Diseases practice guidelines) and Europe (the European Association for the Study of the Liver – European Organization for Research and Treatment of Cancer) for HCC management, we have adopted a multidisciplinary approach for HCC with PVTT. This treatment approach when combined with early diagnosis, will enable a larger number of patients to receive an appropriate treatment based on the stage of the disease.

In our Guide meetings, the following principles in clinical practice are emphasized: (1) Multidisciplinary treatment should be used in HCC patients with PVTT to achieve better results. (2) Prolongation of overall survival is the most important target and the chance of cure is low. Emphasis should also be given to the quality of life of these patients. The treatment complication rate should be kept at a minimum. (3) The targeted and immunotherapy of advanced HCC has made rapid progress, which needs to be extended to the clinical application of PVTT for the first time, and carry out relevant clinical trials. (4) Tumor downstaging can greatly prolong the survival time of PVTT patients. It is also one of the research hotspots of HCC at present. More clinical trials need to be carried out by using new technologies and medicines.

There are a huge number of PVTT patients in China, and the evidence-based level of the existing guideline recommendations is still low. Therefore, in the future, we should make full use of China's case resources, update the new stage of PVTT (such as Liu-Cheng's PVTT stage system [119]) in combination with the latest treatment progress, such as targeted and immune therapy, and carry out more randomized controlled studies to verify more effective diagnosis and treatment methods of PVTT. The molecular mechanisms underlying the genesis and development of PVTT also need to be studied to lay the foundation for more future effective treatment. The role of Chinese traditional medicine in the treatment of PVTT as an adjuvant to other therapeutic options such as surgical treatment, TACE, or RT should be evaluated.

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Statement of Ethics

Our manuscript complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. In the manuscript, all authors state that subjects have given their written informed consent and that the study protocol was approved by the institute's committee on human research. The paper is approved by the Chinese Association of Liver Cancer (20210928).

Conflict of Interest Statement

The authors have no conflicts of interest to declare. Pro. Jia Fan is an Associate Editor of Liver Cancer.

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Author Contributions

All the authors planned the study and contributed to the interpretation of the data, revisions, and gave input at all stages of the study. All the authors have approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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