Review

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The multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus

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SUMMARY Portal vein tumor thrombus (PVTT) is one of the most common complications of hepatocellular carcinoma (HCC), which refers to the advanced stage of HCC and indicates an extremely poor prognosis. Monotherapy cannot effectively prolong the survival benefit of patients with HCC-PVTT characterized by a high recurrence rate. With great progress in the area of immune and molecular targeted therapy, there comes a promising era of multidisciplinary management of HCC. Survival benefits can be achieved based on accurate diagnosis, staging, and multidisciplinary management. Additionally, in terms of the presence of controversy about the standard treatment algorithm and the absence of universal treatment guidelines, a multidisciplinary management program may afford the best hope for HCC-PVTT patients *via* appropriate implement of various treatment protocols.

Keywords hepatocellular carcinoma, portal vein tumor thrombus, management

1. Introduction

As the sixth most common cancer and the fourth leading cause of cancer-related deaths, liver cancer, which is intractable to treat and has a high rate of recurrence, seriously threatens the health of people around the world (*1*), simultaneously poses a great challenge to the liver disease specialists. Hepatocellular carcinoma accounts for about 75-85% of liver cancer with aggressive biological characteristics invading the portal vein, causing one of the most common complications of HCC- portal vein tumor thrombus (PVTT). It is commonly accepted that PVTT indicates a poor prognosis with median overall survival (MST) of 2.7-4.0 months without any intervention implemented (*2*). According to the Barcelona liver cancer staging system (BCLC staging), HCC with PVTT refers to the BCLC C stage and the only modality of treatment patients can benefit from is oral sorafenib with MST of 6.5 months (*3,4*). However, the BCLC staging system has not defined the extent of PVTT, which is significantly related to prognosis after treatment. There are only two classifications about PVTT, the Japanese Vp classification and the Chinese Cheng's classification worldwide (*5*). Referring to the classification based on the extent of PVTT, patients that may obtain better survival benefits from surgical resection can be selected. Numerous studies have demonstrated the significant survival benefit of surgical resection, and the postoperative 5-year survival ranges from 10% to 59% (*6-10*), Unfortunately, nearly half (44-62%) of patients with HCC will develop PVTT, and only a few of them can obtain a curative operation after being carefully selected. Therefore, it is necessary to identify such patients that can achieve better survival through surgical treatment and meanwhile provide more active treatment suggestions for other unresectable HCC patients with PVTT to prolong survival time and quality of life.

2. Multidisciplinary management program of hepatocellular carcinoma

In China, approximately 80% of patients with HCC have a background of hepatitis B virus (HBV) infection and various degrees of liver function damage. In recent years, with great progress in surgical technique, locoregional therapy, radiation therapy, molecular targeted, and immune therapy, through the combination of these treatment modalities, the outcome of HCC patients complicated by PVTT has significantly improved. In terms of heterogeneity and multiple treatment protocols of patients with HCC-PVTT under the absence of established guidelines, it is important

to achieve better cooperation and collaboration from different disciplines through a multidisciplinary management paradigm, subsequently making individual suggestions for patients with HCC-PVTT (*11,12*). The HCC multidisciplinary team (MDT) consists of hepatologist, medical oncologists, surgical oncologists, diagnostic radiologists, pathologists, interventional radiologists, and radiation oncologists, which formulate treatment strategies by referring to the Chinese expert consensus on multidisciplinary diagnosis and treatment of HCC with PVTT (*13*)

2.1. Resectable or downstage to resectable HCC-PVTT

Different from Western countries, HCC-PVTT tends to be addressed using potentially curative treatment, such as surgical resection in combination with various local therapy or systemic treatment, in Asia-pacific countries under careful evaluation. For those deemed as unresectable HCC with PVTT, MDT members tend to utilize multiple local or systemic therapies to downstage HCC to fall into resectable criteria, where salvage surgery can promote the prognosis (*14,15*). The MST and mortality rate ranged from 8 to 22 months, 0% to 10%, respectively, for HCC-PVTT patients who underwent surgical resection (*16*). The 3-year survival rate is approximately 11.7% in conjunction with transcatheter arterial chemoembolization (TACE) following surgery (*6*). The MST reported by different institutions varies significantly, partly due to the evaluation criteria of resectability. In this setting, the selection of patients who may potentially benefit from surgery using certain criteria is critical in clinical practice. Generally, PVTT confined to the first branch of the main portal vein trunk (MPV) or above referring to type I, or II of Cheng's classification can get better survival than type III/IV PVTT after surgical resection. Zhang *et al.* established a scoring system (EHBH-PVTT) that can identify candidates that may obtain better MST postoperatively based on four clinical variables (total bilirubin (TB), α-fetoprotein (AFP), tumor diameter, and satellite lesions) (*7*). Considering the extremely high recurrence rate and poor prognosis of PVTT, not only carefully selecting surgical candidates but combining different local or systemic therapies for neoadjuvant or adjuvant treatment is necessary to augment the pathologic response rate and survival benefit. For neoadjuvant therapy, a randomized, open-label, multicenter controlled study demonstrated that neoadjuvant three-dimensional conformal radiation therapy (3DCRT) combined surgery can obtain better overall and disease-free survival compared with surgery alone (*17*). Harris Liou *et al.* reported that using yttrium-90 (Y-90) transarterial radioembolization (TARE) combined with nivolumab for neoadjuvant therapy following liver transplantation or surgical resection, two cases of HCC with PVTT had a complete pathologic response (*18*). However, it is also argued that the tumor may progress during the interval to surgical resection especially for patients who respond poorly to neoadjuvant therapy. Additionally, pre-operative TARE, 3DCRT, and other modalities of neoadjuvant therapy may increase the difficulty of operations because of tissue adhesion arising from the side effects of radiation or chemical drugs. Therefore, it is of clinical significance to build prediction models that can identify the potential candidates responding well to neoadjuvant therapy. For adjuvant therapy, postoperative adjuvant TACE (PA-TACE) is a commonly used method to improve the postoperative long-term outcome (*19,20*). A retrospective study by propensity score matching, which included 464 patients with HCC and PVTT indicated that PA-TACE has better MST compared with surgery alone, especially for type II/III PVTT according to Cheng's classification (*21*). A subgroup analysis of systemic review and meta-analysis revealed that adjuvant TACE following surgery is associated with improved disease-free survival (DFS) and overall survival (OS) compared with surgery alone (*22*). However, subgroup analysis of the meta-analysis included only one RCT and one NRCT, allowing the adjuvant role of TACE to be controversial. The small number of RCT with PVTT is partially due to the risk of liver failure caused by TACE. However, more prospective randomized control trials are greatly needed to further illuminate the role of neoadjuvant and adjuvant therapy following surgical resection for PVTT.

2.2. Unresectable PVTT

For patients with unresectable PVTT, local therapy and systemic treatment by combination or monotherapy are the backbone to prolong survival time and improve quality of life. TACE, hepatic arterial infusion chemotherapy (HAIC), radiation therapy (RT), molecular target, and immune therapy are commonly used treatments for unresectable HCC with PVTT. In terms of this refractory complication of HCC, monotherapy is not enough. Additionally, Mechanized diagnosis and treatment based solely on established guidelines are likely to omit patients who may benefit from active treatment. With the breakthroughs of molecular targeted therapy and immune therapy, plenty of clinical trials combining various treatment methods emerged, leading to improvement of the prognosis of HCC-PVTT (*23*).

2.2.1. Locoregional therapy

TACE is the most common palliative local modality used for unresectable HCC. Theoretically, TACE is considered a relatively contraindication in patients with PVTT, especially for type III/IV PVTT, since

portal vein occlusion caused by PVTT will lead to liver failure after TACE (*24-26*). However, recent studies have demonstrated the role of TACE in well-selected patients with good liver function and adequate collateral circulation around the obstructed portal vein, which can also obtain MST of 5.6-8.7 months in all types of PVTT as reported (*27*). A retrospective study by propensity score matching suggested that TACE is associated with better 1,2 and 3-years OS rates compared with best supportive care (45.3%, 27.7%, and 19.3 *vs.* 41.1%,15.7%, and 11.6%; p = 0.002) (*28*). However, tumor necrosis caused by TACE will lead to the release of angiogenic growth factors simultaneously, which may confer a negative effect on tumor control. Combined with sorafenib and other tyrosine kinase inhibitors (TKIs), which can block angiogenic growth factors may reduce the side-effects attributed to TACE, thereby improving the outcome of TACE, theoretically. A nationwide population-based cohort study comparing TACE monotherapy with TACE plus sorafenib suggested that the TACE-sorafenib combination strategy has a better median OS (6.7 months *vs.* 12.5 months, respectively) (*29*). However, a phase III STAH trial had the opposite outcome. The median OS was 12.8 in the TACE plus sorafenib group and 10.8 months in the TACE monotherapy group (p = 0.290), which suggested that no difference was found between the two groups. As for the time to progression, progression-free survival, and tumor response rate, results were found to be better in the TACE-sorafenib group. Therefore, the effect of TACE combined with TKIs on oncological outcome in advanced HCC still needs to be further delineated by more prospective control trials. Apart from TACE combined with sorafenib, another combination protocol showing potential benefits is HAIC plus sorafenib. A randomized phase 3 trial demonstrated that sorafenib combined with HAIC using oxaliplatin, fluorouracil, and leucovorin (FOLFOX) achieved better median OS, higher response rate, and longer median progression-free survival compared to sorafenib monotherapy in patients with portal vein invasion (*30*). Except for HAIC, TARE with Yttrium-90 (Y-90) microspheres has also presented promising results on tumor control, which is characterized by minimizing damage to liver parenchyma surrounding the tumor and alteration of hepatic arterial flow (*31*). Two III-phase randomized control trials comparing TARE and sorafenib in locally advanced HCC failed to demonstrate better OS by TARE. However, better tolerance of treatment and quality of life in patients with HCC was observed in the TARE group (*32,33*). As to the combination of sorafenib with TARE, a retrospective study suggested that no significant differences in survival outcomes were identified between sorafenib plus TARE and TARE monotherapy (median overall survival 10 *vs.* 10 months; p = 0.711) (*34*). Albeit the uncertainty of TARE in treating HCC-PVTT, TARE may be used as an alternative modality to increase the surgery eligibility as well as enhance OS.

2.2.2. Systemic therapy

Sorafenib, one TKI whose effect was proved by two large RCT trials, is generally accepted to apply to patients with advanced HCC (*3,4*). Lenvatinib another TKI also deems as the first-line therapy which is no-inferior to sorafenib for advanced HCC (*35*). Nevertheless, the response rate to TKIs is low and the benefit of patients with advanced HCC from sorafenib is modest with overall survival time being extended by approximately three months (*3*). Therefore, the combination of systemic therapy with local-regional therapy is still the mainstay of the treatment protocol for advanced HCC, especially those complicated by PVTT. Recently, immune checkpoint inhibitors (ICIs) also revealed promising outcomes for advanced HCC and multiple RCTs testing the outcome of combinations with other ICIs or TKIs are ongoing. The reported response rates to ICIs monotherapy ranged from 15% to 23% and increased to approximately 30% after combination with other systemic agents (*36*). However, considering the relatively low response rate and hyper-progression caused by ICIs in a small group of patients, a further study focusing on the biomarkers for the selection of candidates is urgently needed.

3. Conclusion

Currently, HCC complicated by macro portal vein invasion is a hard to treat bottleneck, which worsens the prognosis of HCC patients. Surgical resection is still the best potential curative method for patients with HCC and PVTT under careful estimation and selection. Combination strategies are necessary to effectively control tumor burden and reduce the risk of recurrence postoperatively. In the era of multidisciplinary management, communication and cooperation between different disciplines make patients with HCC have a better survival *via* accurate diagnosis and individual treatment. In the future, more RCTs focusing on the combination of different treatments and innovative treatments need to be performed to offer more effective choices for clinical practice.

4. The MDT of West China Hospital

Based on the BRIDGE study, a large retrospective cohort study reviewing the diagnosis and treatment data of 18,031 HCC patients from 2005 to 2012, it was indicated that patients with HCC in China have significant characteristics, including younger age of onset, more HBV infections, and relatively advanced staging. The patients with BCLC stage C and portal

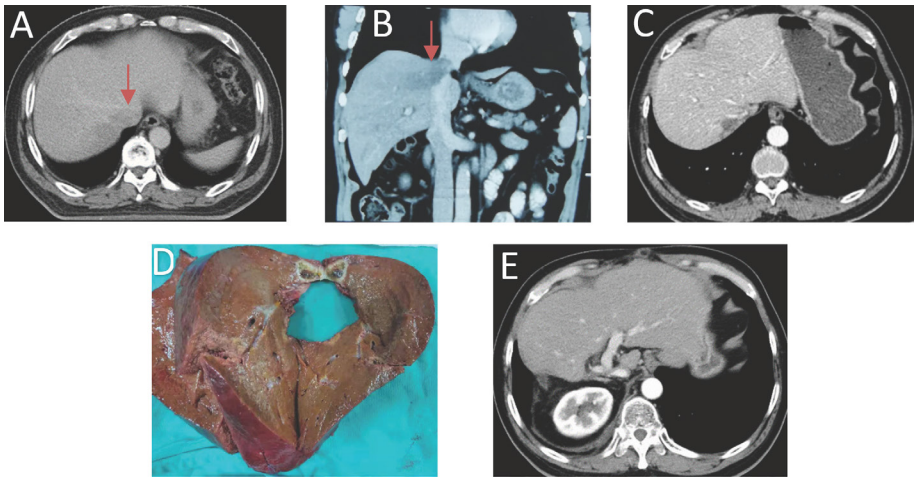

Figure 1. (A), The imaging of contrast-enhanced CT demonstrating a tumor 4.3 × 6.3 cm in diameter in the upper right posterior lobe of the liver with inferior vena cava tumor thrombus (red arrow). **(B)**, Contrast-enhanced CT demonstrating tumor invading into inferior vena cava (red arrow). **(C)**, Contrast-enhanced CT 2 months after SBRT combined with targeted therapy showed significantly decreased main tumor and thrombus. **(D)**, the specimen of resected liver. **(E)**, Contrast-enhanced CT 1 year after surgery demonstrating no obvious tumor recurrence.

vein invasion accounted for 55% and 23% of patients with HCC in the China cohort, respectively (*37*). Similarly, in our institute, the West China Hospital, there are 15,000 patients with HCC visiting the outpatient clinic annually, of whom 1,700 cases were surgically treated, and 493 cases were complicated by macro PVTT, of which 90 cases had undergone surgical resection. About 90% of HCC patients required comprehensive treatment other than surgery. Therefore, the West China Hospital launched a multidisciplinary management program for HCC, especially for HCC patients with PVTT, on March 7, 2019. In 2019, a total of 262 patients with HCC visited our MDT outpatient clinic, of which approximately 49% had a PVTT complication, 2% of patients with inferior vena cava tumor thrombus, and 2% with two kinds of tumor thrombus. Approximately 40% of patients underwent combined treatment and 6 patients underwent surgical resection after successful downstaging. While the MDT outpatient clinic can make more accurate diagnoses, comprehensive and individual treatment suggestions to patients, it saves time by avoiding the referral between different disciplines, which usually happens in traditional clinics. Even though the number of patients with vascular tumor thrombus getting curative surgery after downstage treatment is small, MDT still offers the best hope for them to prolong survival time.

5. Case presentation

Case 1

The patient was a 52-year-old Chinese man with a history of treatment for hepatitis B and child-pugh A cirrhosis presented to our center with abdominal CT examination revealing that HCC 4.3 × 6.3 cm in diameter in the upper right posterior lobe of the liver and inferior vena cava tumor thrombus. His AFP and Protein Induced by Vitamin K Absence II (PIVKA-II) were 614.1 ng/mL and 119 mAU/mL, respectively. Neoadjuvant stereotactic body radiation therapy (SBRT) combined with sorafenib (400 mg po. bid.) was planned after MDT was reviewed, in an attempt to eliminate the inferior vena cava tumor thrombus while controlling tumor growth to allow for a biologic test-of-time. The planning target volume was 40 Gy, with a fractional size of 8 Gy at five fractions per week. Imaging evaluation performed 2 months after treatment demonstrated that the size of the tumor and thrombus were significantly smaller than pre-neoadjuvant therapy with no evidence of intrahepatic tumor progression or metastatic disease (Figure 1). Laboratory results revealed that AFP decreased from 374 to 57 ng/mL and PIVKA decreased from 119 to 37 mAU/mL with well-preserved liver function. The patient subsequently underwent open right posterior lobe resection with inferior vena cava incision and tumor thrombus removal. The patient experienced no major postoperative complications and was discharged 9 days after surgery. Pathology of the resected liver tissue demonstrated negative margins and no viable malignancy. Surveillance imaging 19 months after resection demonstrated no evidence of recurrence.

Case 2

A 51-year-old male with a history of treated hepatitis B and Child-Pugh A cirrhosis presented to our institution with a left and right liver lobe giant HCC and intrahepatic metastasis. The diameter of the largest tumor in the left lobe increased from 9.1 × 6.1 cm to 10.3 × 7.1 cm and serum PIVKA-II rose from 9,108 mAU/mL to 15,153 mAU/mL with a normal AFP after sorafenib treatment of two weeks and the first TACE. MDT members decided to perform a second TACE, and then use PD-1 inhibitor (camrelizumab) combined with Lenvatinib, because of the insensitivity of sorafenib

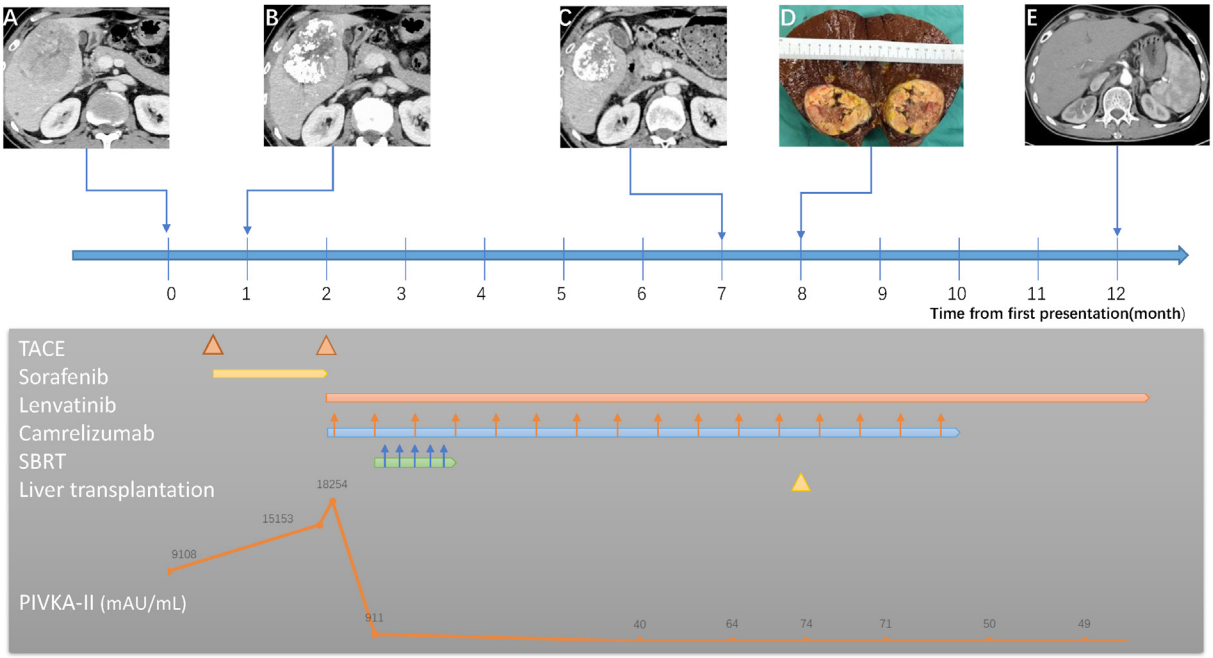

Figure 2. The figure demonstrates the variation of treatment procedures and tumor marker level with the passage of time. Blue line in the middle of the figure represents the timeline. The images of CT and postoperative specimen are presented above the timeline. (A), Contrast-enhanced CT of liver revealing the left and right liver lobe giant HCC (9.1 × 6.1 cm) combined with intrahepatic metastasis. **(B)**, Contrast-enhanced CT demonstrating the diameter of the lesion increased from 9.1 × 6.1 cm to 10.3 × 7.1 cm after 3 weeks treatment of TACE combined with sorafenib. **(C)**, Contrast-enhanced CT demonstrating a significant decrease of main tumor after 5 months treatment of targeted and immune therapy. **(D)**, Contrast-enhanced CT 4 months after liver transplantation demonstrating no obvious tumor recurrence. **(E)**, The resected specimen of diseased liver. CT: computed tomography; TACE: transcatheter arterial chemoembolization; SBRT: stereotactic body radiation therapy. PIVKA-II: protein induced by vitamin K absence II

after 6 weeks of treatment. The patient was started on the second TACE, camrelizumab (200mg *iv.* every two weeks) combined with Lenvatinib (8 mg po. qd.), and underwent SBRT with a planning target volume of 5,000 cGy and a fraction size of 1,000 cGy. Imaging demonstrated a complete response, with PIVKA-II decreased from 18,254 mAU/mL to 40 mAU/mL within 4 months and well-preserved liver function. Subsequently, the patient underwent liver transplantation 2 months later (Figure 2). Liver explant pathology revealed complete necrosis. The patient was discharged postoperatively after 3 weeks with normal liver graft function. Imaging evaluation demonstrated no evidence of tumor recurrence within 6 months of follow-up.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394-424.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391:1301-1314.
3. Llovet JM, Ricci S, Mazzaferro V, *et al.* Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378-390.
4. Cheng AL, Kang YK, Chen Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10:25-34.
5. Mähringer-Kunz A, Steinle V, Düber C, Weinmann A, Koch S, Schmidtmann I, Schotten S, Hinrichs JB, Graafen D, Pinto Dos Santos D, Galle PR, Kloeckner R. Extent of portal vein tumour thrombosis in patients with hepatocellular carcinoma: The more, the worse? Liver Int. 2019; 39:324-331.

6. Chen ZH, Zhang XP, Lu YG, *et al.* Actual long-term survival in HCC patients with portal vein tumor thrombus after liver resection: a nationwide study. Hepatol Int. 2020; 14:754-764.
7. Zhang XP, Gao YZ, Chen ZH, Chen MS, Li LQ, Wen TF, Xu L, Wang K, Chai ZT, Guo WX, Shi J, Xie D, Wu MC, Yee Lau W, Cheng SQ. An Eastern Hepatobiliary Surgery Hospital/Portal Vein Tumor Thrombus Scoring System as an Aid to Decision Making on Hepatectomy for Hepatocellular Carcinoma Patients With Portal Vein Tumor Thrombus: A Multicenter Study. Hepatology. 2019; 69:2076-2090.
8. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, Kudo M, Ku Y, Sakamoto M, Nakashima O, Kaneko S, Kokudo N. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016; 65:938-943.
9. Huo L, Wei W, Yan Z, Lei Z, Xie Y, Gong R, Huang S, Jia N, Xia Y. Short-term and long-term outcomes of liver resection for HCC patients with portal vein tumor thrombus. Cell Biosci. 2019; 9:23.
10. Lin DX, Zhang QY, Li X, Ye QW, Lin F, Li LL. An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. J Cancer Res Clin Oncol. 2011; 137:139-149.
11. Zhang Z, Lai E, Zhang C, Yu H, Liu Z, Wan B, Liu L, Tian Z, Deng H, Sun Q, Chen XJIjos. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. Int J Surg. 2015; 20:8-16.
12. Marrero JA. Multidisciplinary management of hepatocellular carcinoma: where are we today? Semin Liver Dis. 2013; 33 Suppl 1:S3-10.
13. Cheng S, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). Liver Cancer. 2020; 9:28-40.
14. Hamaoka M, Kobayashi T, Kuroda S, Iwako H, Okimoto S, Kimura T, Aikata H, Nagata Y, Chayama K, Ohdan H. Hepatectomy after down-staging of hepatocellular carcinoma with portal vein tumor thrombus using chemoradiotherapy: A retrospective cohort study. Int J Surg. 2017; 44:223-228.
15. Lau WY, Ho SK, Yu SC, Lai EC, Liew CT, Leung TW. Salvage surgery following downstaging of unresectable hepatocellular carcinoma. Ann Surg. 2004; 240:299-305.
16. Sakamoto K, Nagano H. Surgical treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus. Hepatol Res. 2017; 47:957-962.
17. Wei X, Jiang Y, Zhang X, *et al.* Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study. J Clin Oncol. 2019; 37:2141-2151.
18. Liou H, Mody K, Boyle A, Keaveny A, Croome K, Burns J, Harnois D, Patel T, Toskich BJH. Neoadjuvant Radiation Lobectomy and Immunotherapy for Angioinvasive Hepatocellular Carcinoma Resulting in Complete Pathologic Response. J Hepatol. 2020.
19. Liu F, Guo X, Dong W, Zhang W, Wei S, Zhang S, Zhu X, Zhou W, Zhang J, Liu H. Postoperative adjuvant TACE-associated nomogram for predicting the prognosis of resectable Hepatocellular Carcinoma with portal vein Tumor Thrombus after Liver Resection. Int J Biol Sci. 2020; 16:3210-3220.
20. Zhang YF, Shang H, Zeng XL, Ji H, Li YM, Lu HW. Postoperative adjuvant chemo (embolization) therapy for hepatocellular carcinoma with portal vein tumor thrombosis. Onco Targets Ther. 2018; 11:5407-5417.
21. Liu S, Guo L, Li H, Zhang B, Sun J, Zhou C, Zhou J, Fan J, Ye Q. Postoperative Adjuvant Trans-Arterial Chemoembolization for Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombus. Ann Surg Oncol. 2018; 25:2098-2104.
22. Liang L, Li C, Diao YK, Jia HD, Xing H, Pawlik TM, Lau WY, Shen F, Huang DS, Zhang CW, Yang T. Survival benefits from adjuvant transcatheter arterial chemoembolization in patients undergoing liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. Therap Adv Gastroenterol. 2020; 13:1756284820977693.
23. Gholam PM, Iyer R, Johnson MS. Multidisciplinary Management of Patients with Unresectable Hepatocellular Carcinoma: A Critical Appraisal of Current Evidence. Cancers (Basel). 2019; 11.
24. Chung JW, Park JH, Han JK, Choi BI, Han MC, Lee HS, Kim CY. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. Radiology. 1996; 198:33-40.
25. Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, Shi M. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol. 2011; 18:413-420.
26. 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.
27. Sun JX, Shi J, Li N, Guo WX, Wu MC, Lau WY, Cheng SQ. Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma. Cancer Biol Med. 2016; 13:452-458.
28. Xiang X, Lau WY, Wu ZY, Zhao C, Ma YL, Xiang BD, Zhu JY, Zhong JH, Li LQ. Transarterial chemoembolization versus best supportive care for patients with hepatocellular carcinoma with portal vein tumor thrombus: a multicenter study. Eur J Surg Oncol. 2019; 45:1460-1467.
29. Kok V, Chen Y, Chen Y, Su Y, Ku M, Kuo J, Yoshida GJC. Sorafenib with Transarterial Chemoembolization Achieves Improved Survival *vs*. Sorafenib Alone in Advanced Hepatocellular Carcinoma: A Nationwide Population-Based Cohort Study. Cancers. 2019; 11.
30. He M, Li Q, Zou R, *et al.* Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin *vs.* Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. JAMA Oncol. 2019; 5:953-960.
31. Yang Y, Si T. Yttrium-90 transarterial radioembolization versus conventional transarterial chemoembolization for patients with hepatocellular carcinoma: a systematic review and meta-analysis. Cancer Biol Med. 2018; 15:299-310.
32. Vilgrain V, Pereira H, Assenat E, *et al.* Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017; 18:1624-1636.

33. Chow PKH, Gandhi M, Tan SB, *et al.* SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018; 36:1913-1921.
34. Facciorusso A, Bargellini I, Cela M, Cincione I, Sacco R. Comparison between Y90 Radioembolization Plus Sorafenib and Y90 Radioembolization alone in the Treatment of Hepatocellular Carcinoma: A Propensity Score Analysis. Cancers (Basel). 2020; 12.
35. Kudo M, Finn RS, Qin S, *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391:1163-1173.
36. Pinter M, Jain RK, Duda DG. The Current Landscape of Immune Checkpoint Blockade in Hepatocellular Carcinoma: A Review. JAMA Oncol. 2021; 7:113-123.
37. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015; 35:2155-2166.

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