

Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis

A systematic review and meta-analysis

Zun-Yi Zhang, MD, Ke-Shuai Dong, PhD, Er-Lei Zhang, PhD, Li-Wei Zhang, MD, Xiao-Ping Chen, PhD, Han-Hua Dong, PhD*

Abstract

Background: According to the Barcelona Clinic Liver Cancer (BCLC) staging system, the presence of portal vein tumor thrombosis (PVTT) is considered to indicate an advanced stage of hepatocellular carcinoma (HCC) with nearly no cure. Hepatic resection and transarterial chemoembolization (TACE) have recently been recommended for treatment of HCC with PVTT.

Methods: We conducted a systematic review to compare the overall survival between patients with HCC and PVTT undergoing hepatectomy, TACE or conservative treatment including sorafenib chemotherapy. The PubMed, Web of Science, and Cochrane Library databases were searched. All relevant studies were considered. Hazard ratios with 95% confidence intervals were calculated for comparison of the cumulative overall survival. Ten retrospective studies met the inclusion criteria and were included in the review.

Results: Overall survival was not higher in the hepatectomy group than TACE group. But survival rate was higher in hepatectomy group than conservative group. The subgroup analysis demonstrated that hepatectomy was superior in patients without PVTT in the main trunk than in patients with main portal vein invasion. In patients without main PVTT, hepatectomy has showed more benefit than TACE. However, there has been no significant difference between the hepatectomy and TACE groups among patients with main PVTT.

Conclusion: For patients with resectable HCC and PVTT, hepatectomy might be more effective in patients without PVTT in the main trunk than TACE or conservative treatment.

Abbreviations: BCLC = the Barcelona Clinic Liver Cancer, HCC = hepatocellular carcinoma, MeSH = medical subject heading, nRCTs = non-randomized comparative trials, PVTT = portal vein tumor thrombosis, RCTs = randomized controlled trials, ROBINS = Risk of Bias in Non-randomized Studies of Interventions, TACE = transarterial chemoembolization.

Keywords: Barcelona clinic liver cancer (BCLC) staging system, hepatectomy, hepatocellular carcinoma (HCC), portal vein tumor thrombosis (PVTT), transarterial chemoembolization (TACE)

Editor: Neil Merrett.

This work was supported by funding from the National Natural Science Foundation of China (No. 81402410; No.81802767).

The authors report no conflicts of interest.

Research Laboratory and Hepatic Surgery Center, Department of Hepatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

* Correspondence: Han-Hua Dong, Department of Hepatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jie Fang Da Dao, Wuhan 430030, China (e-mail: hanhua_dong@hotmail.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Zhang Zy, Dong Ks, Zhang El, Zhang Lw, Chen Xp, Dong Hh. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: A systematic review and meta-analysis. *Medicine* 2019;98:50(e18362).

Received: 12 August 2019 / Received in final form: 6 November 2019 /

Accepted: 14 November 2019

<http://dx.doi.org/10.1097/MD.00000000000018362>

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and one of the most prevalent causes of cancer-related death worldwide.^[1] Because of the biological characteristics of HCC, it is prone to invade intrahepatic vessels, especially the portal vein system.^[2] The reported possibility of portal vein invasion in patients with HCC at autopsy is 64.7%.^[3] However, according to the Barcelona Clinic Liver Cancer/American Association for the Study of Liver Diseases (BCLC/AASLD), portal vein invasion or portal vein tumor thrombosis (PVTT) is considered to represent an advanced stage of disease (BCLCC stage) with nearly no hope of cure.^[4] The only suggested treatment option is chemotherapy with sorafenib, but the median survival time of patients with PVTT is as short as 10.7 months.^[5] When no intervention is done, the median survival time is only 2.7 months.^[6–8]

Because of recent advances in surgical techniques and perioperative management, liver resection combined with thrombectomy has become a reasonably safe treatment option for some selected patients with acceptable mortality and morbidity rates.^[10,11] According to a study by Kokudo et al,^[4] hepatic resection could provide longer survival times for patients

with HCC and PVTT than in patients who do not undergo resection (2.45 vs 1.57 years, respectively; $P < .001$). Therefore, to improve the survival benefit of patients with HCC and PVTT, surgical intervention has been introduced in some medical centers.^[4,9] Anatomical hepatectomy is effective in eliminating the main gross tumor, and possible satellite nodules. When it is combined with thrombectomy, it could remove the thrombus from the portal vein system. This method could reduce the portal vein pressure and may help to improve liver function. Most importantly, by reducing the tumor burden, hepatectomy combined with thrombectomy could increase the effect of multimodality treatments after operation such as TACE or systematic therapy. Although the benefit of this method is obvious, its disadvantages are also of concern. When tumor thrombosis formed in portal vein system, the tumor cells spread out and were penetrating into circulation system. So, even though hepatectomy and thrombectomy were done concomitantly, HCC patients with PVTT could achieve limited survival benefits from the surgery because of tumor recurrence. Due to the short predicted survival time of HCC patient with PVTT, some researches proposed that great trauma and from surgery, damage of residual liver function, and high recurrence rate may limit the use of hepatectomy. According to a report by Ye et al,^[12] patients who undergone transarterial chemoembolization (TACE), have shown longer survival times than those who did hepatectomy combined with hepatic resection. Several other large-scale studies have described the use of aggressive surgical resection in several medical centers.^[4,9,13,14] However, the effective treatment in patients with PVTT remains controversial.

In the past, TACE was especially regarded as a contraindication for the patients with PVTT in the main trunk because it has led to liver dysfunction.^[15,16] Recent studies have shown that PVTT is slowly formed and that its blood supply comes from the hepatic artery.^[17] Therefore, PVTT may not completely block the blood flow of the portal vein in most cases and TACE may be an effective treatment option for patients with HCC and PVTT. The 2010 International Hepatic-Pancreato-Biliary Association expert consensus statement has recommended; TACE as a standard treatment for advanced-stage HCC, even for patients with PVTT.^[18] However, the treatment effect of TACE compared with hepatectomy or sorafenib chemotherapy remains controversial.

We conducted a systematic review and meta-analysis of the available literature to clarify the survival benefits of hepatic resection over TACE or sorafenib chemotherapy in patients with HCC with PVTT and the survival benefits of hepatic resection in patients with HCC with or without invasion of the main trunk of the portal vein.

2. Methods

We performed a literature search using the main databases (Medline, Embase, and Cochrane Library). A computer-assisted search was conducted using the following combination of Medical Subject Heading terms (MeSH): “hepatocellular carcinoma” and “portal vein tumor thrombosis” and “hepatectomy” and “liver resection” and “transarterial chemoembolization” and “chemotherapy” and “palliative therapy” and “sorafenib.” We also checked the useful references from the articles retrieved and the main review articles. Studies that have concentrated on hepatectomy vs TACE or conservative treatment (which included sorafenib chemotherapy and/or symptomatic treatment) were selected. Each study was reviewed by 3 authors, and the

methodological criteria and results of each study were recorded. Studies were judged suitable for the meta-analysis only if they met all 3 of the following criteria:

- (1) the study was a prospective or retrospective clinical trial of hepatectomy vs TACE for treatment of HCC with PVTT;
- (2) the study contained well-defined outcomes including at least one of the following: (a) total hospital stay or (b) 1, 3, or 5-year survival rates; and
- (3) mortality and morbidity data were provided. The mortality rate was calculated as death within 30 days after the surgery or TACE treatment. Morbidity rates were calculated by the number of patients who developed least one adverse event of any nature within 30 days after the treatment. Only results fully reported in journal articles were taken into consideration.

The exclusion criteria were

- (1) non-HCC,
- (2) hepatic metastasis,
- (3) mixed malignances,
- (4) non-comparative studies, and
- (5) comparison between hepatic resection vs TACE or sorafenib for recurrent or ruptured HCC.

Of the 113 articles initially identified, 10 met the inclusion criteria. This systematic review was based on the results from these studies. The reports of all 10 trials were reviewed blindly and independently by the 3 above-mentioned authors using a standardized data abstract form. Disagreement was resolved by consensus. We did not contact the study authors for additional data. Because this study is a meta-analysis and systemic review, so ethical approval and informed consent are not necessary.

2.1. Statistical analysis

We analyzed studies addressing hepatectomy and TACE or sorafenib chemotherapy in patients with HCC and PVTT. The results were analyzed by the DerSimonian–Laird method for comparing and summarizing outcomes of individual clinical trials.^[39] The primary outcome of interest for patients with HCC undergoing hepatectomy, TACE, or sorafenib chemotherapy was the one-year survival rate. The odds ratios (ORs) or the median survival time was used as a measure of the therapeutic effect. Confidence intervals (CIs) were always calculated at 95%. Only a minority of included studies has clearly reported the hazard ratios in patients with HCC who underwent hepatic resection vs TACE or palliative treatment. Therefore, we calculated the ORs with the standard error using the calculation sheets developed by Tierney et al.^[39] The survival rates at different time points were pooled by a random-effects model or fixed-effects model, only if the studies were considered to have substantial heterogeneity. Heterogeneity between studies was assessed using the I^2 statistic and the Chi-square test. If $P < .05$, the studies were considered to have significant statistical heterogeneity. We found that no randomized controlled trials (RCTs) were included in this review. Analysis of both the advantages and disadvantages of hepatectomy and TACE or sorafenib chemotherapy for patients with HCC and tumor thrombosis was dependent upon non-randomized comparative trials (NRCTs). Although bias is more readily produced in NRCTs than RCTs, we have carefully checked the methods of the NRCTs and found that they were well designed with relatively large sample sizes and solid evidence. Although the

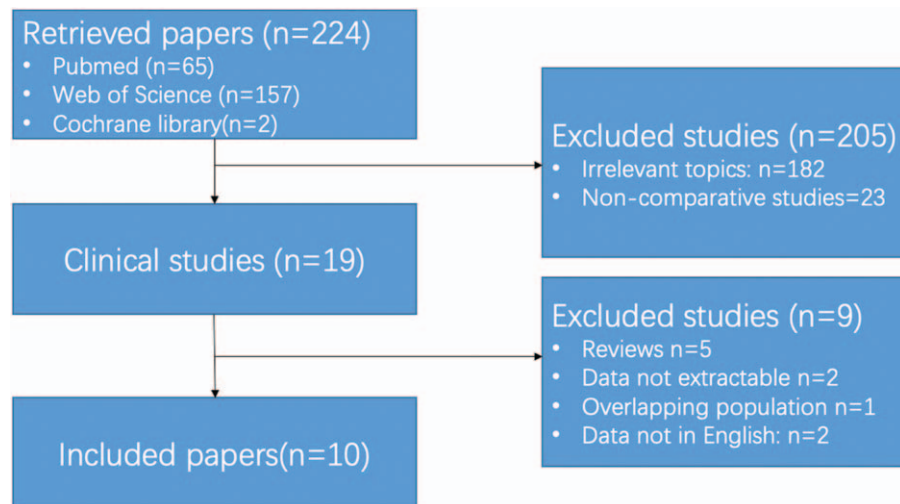


Figure 1. Flow diagram of studies identified, included, and excluded.

studies we found were limited, we still believed that this meta-analysis could show a trend in treating patients with HCC and PVTT. In this meta-analysis, a P value of $<.05$ was considered statistically significant. Funnel plots were performed to evaluate the publication bias. The meta-analysis was conducted using the statistical package Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The quality of the data collected was assessed by the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool.^[42] The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

2.2. Tumor resection and PVTT removal

Studies were included in this meta-analysis only if the tumor resection and PVTT technique performed in the studies met the following resection criterion. Regular or limited lobectomy or segmentectomy was performed in patients with adequate liver function reserve. For PVTT removal, the thrombus was resected together with the liver when the thrombus was confined within the resected liver. If the PVTT protruded into the portal vein 1–2 cm beyond the resection line, the tumor thrombi were removed through the opening of the involved portal vein stump at the surface after the tumors were resected. If the PVTT extended into the main trunk or the opposite branch and could not be taken out

completely from the opening of the portal vein stump at the resection surface, then the main trunk of the portal vein was clamped and a longitudinal incision was made at the anterior or right wall of the portal trunk. The tumor thrombi were then removed.

2.3. TACE

For studies that concentrated on TACE, conventional TACE was performed in patients with HCC and PVTT. During the treatment, a combination of 5-fluorouracil and adriamycin dispersed in lipiodol was injected, followed by embolization using gelatin sponge particles. This treatment course was repeated once every 1–2 months for 2–5 cycles.

3. Results

3.1. Characteristics of included studies

In total, 224 publications were identified using the above-described search strategy. Of these 224 publications, 19 were retrieved for detailed evaluation after scanning the title and abstract. The full text of all of these publications was read and 10 of them met all of the inclusion criteria.^[4,10,12–14,19–24] (Fig. 1) The characteristics of the eligible studies are shown in Table 1.

Table 1
Characteristics of included studies.

Study	Published year	Design	Case			Treatment benefit
			Hepatectomy	TACE	Conservative treatment	
Zhi-Yong Huang	2005	Cohort study	438	/	/	Favors hepatectomy in peripheral PVTT patients
Jie Shi	2010	Cohort study	406	/	/	Favors hepatectomy in peripheral PVTT patients
Qi Zhou	2011	Cohort study	38	10	30	Favors hepatectomy
Zhen-Wei Peng	2012	Cohort study with propensity score	201	402	/	Favors hepatectomy
Jia-Zhou Ye	2014	Cohort study	90	86	75	Favors hepatectomy
Po-Hong Liu	2014	Cohort study with propensity score	108	108	/	Favors hepatectomy
Kang Wang	2015	Cohort study with propensity score	745	604	/	Favors hepatectomy
Jung Min Lee	2015	Cohort study	40	80	52	Favors hepatectomy
Hai-Hong Ye	2016	Cohort study	54	274	57	Favors TACE
Ning-Gang Zheng	2016	Cohort study	96	134	/	Favors hepatectomy

Table 2
Summary of findings from non-randomized studies including ROBINS-I risk of bias.

Study	Design	Bias							Overall
		Confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	
Zhi-Yong Huang	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Jie Shi	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Qi Zhou	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Zhen-Wei Peng	Cohort study with propensity score	Low	Moderate	Low	Low	Low	Low	Low	Low
Jia-Zhou Ye	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Po-Hong Liu	Cohort study with propensity score	Low	Moderate	Low	Low	Low	Low	Low	Low
Kang Wang	Cohort study with propensity score	Low	Moderate	Low	Low	Low	Low	Low	Low
Jung Min Lee	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Hai-Hong Ye	Cohort study	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Ning-Gang Zheng	Cohort study	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate

No prospective studies were found during the search. All studies were from Asia: 1 was from Korea, 1 was from Japan, and 9 were from China. Among these studies, 2 concentrated on hepatectomy in patients with HCC with different types of PVTT. The other 9 publications focused on the treatment effect of hepatectomy vs TACE or conservative treatment for patients with HCC and PVTT. The quality of the studies was assessed by the Robins-1 tool (Table 2). Methods for handling missing data and intention-to-treat analysis were not adequately described in most of the studies. Four studies were analyzed with propensity scores.

3.2. Overall meta-analysis

The overall meta-analysis have showed no significantly higher overall survival in the hepatic resection group than in the TACE group (OR, 0.96; 95% CI, 0.44–2.11) (Fig. 2A). The

heterogeneity was statistically significant ($P < .05$, $I^2 = 94\%$). Funnel plots have demonstrated that nearly all studies lay within the 95% confidence interval (CI).

We have as well compared the treatment effect of hepatectomy and conservative treatment in patients with resectable HCC and PVTT. It has been found that the overall survival was higher in the hepatic resection group than in the conservative group (OR, 0.12; 95% CI, 0.06–0.24) (Fig. 2B). The heterogeneity was not statistically significant ($P = .16$, $I^2 = 45\%$). Funnel plots have revealed that nearly all studies lay within the 95% CI.

3.3. Subgroup analysis in patients with different types of PVTT

Among patients with HCC, the subgroup meta-analysis has proven significantly higher overall survival in those with

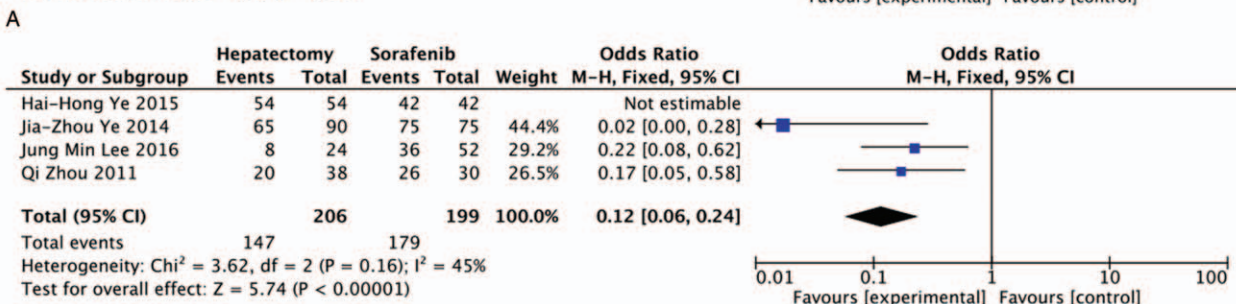
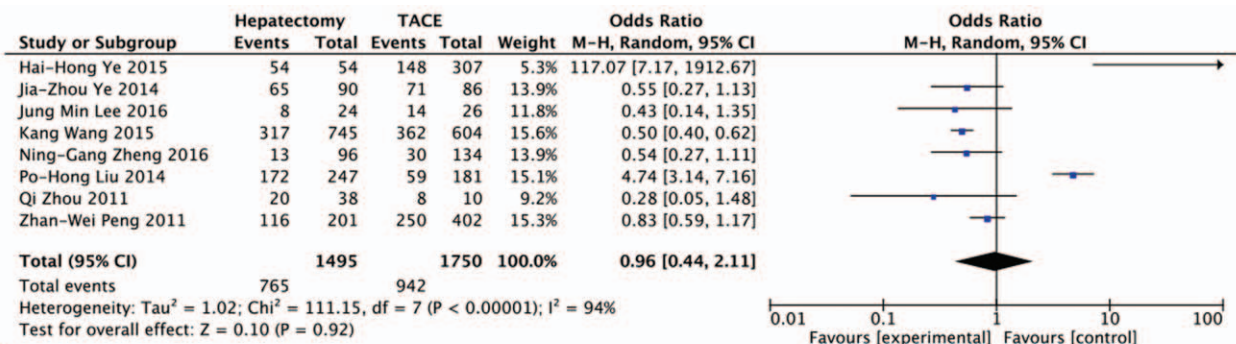


Figure 2. Forest plot and meta-analysis of overall survival. The squares are the point estimates of the hazard ratios, and the 95% confidence intervals are indicated by horizontal bars. The diamonds are the summary estimates and 95% confidence intervals from the pooled studies. (A) Results of hepatectomy compared with transarterial chemoembolization. (B) Results of hepatectomy compared with conservative treatment.

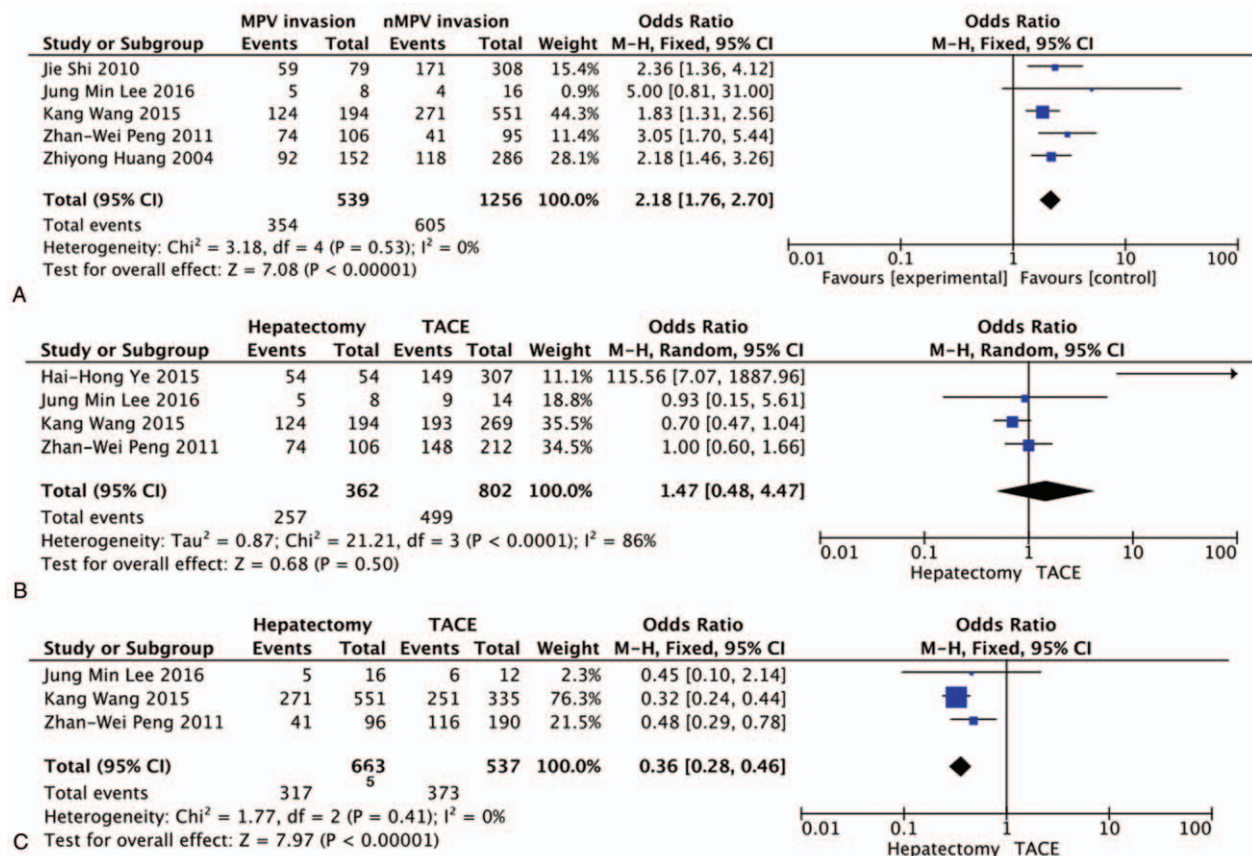


Figure 3. Forest plot and meta-analysis of overall survival for patients with hepatocellular carcinoma (HCC) with or without portal vein tumor thrombosis (PVTT) in the hepatectomy group. (A) Forest plot and meta-analysis of overall survival of patients with HCC and main PVTT in the hepatectomy group compared with transarterial chemoembolization (TACE) group. (B) Forest plot and meta-analysis of overall survival of patients with HCC and peripheral PVTT in the hepatectomy group compared with TACE group. (C).

peripheral PVTT than main PVTT (OR, 2.18; 95% CI, 1.76–2.70). The heterogeneity was not statistically significant ($P = .53$, $I^2 = 15\%$) (Fig. 3A). Funnel plots have demonstrated that nearly all studies lay within the 95% CI.

Another subgroup analysis was carried out to further evaluate the treatment effect between hepatectomy and TACE in patients with HCC with or without main PVTT. The results have demonstrated no significant difference in overall survival between the hepatectomy group and TACE group among patients with main PVTT ($P = .50$; OR, 1.47; 95% CI, 0.48–4.47) (Fig. 3B). Funnel plots have displayed that nearly all studies lay within the 95% CI. Nevertheless, the difference in overall survival was significantly different between the TACE group and hepatectomy group among patients with peripheral PVTT ($P < .0001$; OR, 0.36; 95% CI, 0.28–0.46). The heterogeneity was not statistically significant ($P = .41$, $I^2 = 0\%$) (Fig. 3C). Funnel plots have proven that nearly all studies lay within the 95% CI.

4. Discussion

HCC has a high possibility of portal vein invasion, which has been observed in 64.7% of patients at autopsy.^[2] PVTT is a poor prognostic factor. In 1 study, the median survival of patients with untreated HCC and PVTT was 2.7 months, while the survival in those without PVTT was 24.4 months.^[8] The BCLC staging

system suggests that in theory, sorafenib chemotherapy should be used as the only treatment for HCC.^[8] As an oral small-molecule tyrosine multi-kinase inhibitor of several intracellular proteins, sorafenib could intervene in some factors regarding tumor progression, including platelet-derived growth factor β , raf serine/threonine kinases, and vascular endothelial growth factor receptors.^[12,25,26] Vascular endothelial growth factor receptors play an important role in tumor recurrence and metastasis. Therefore, sorafenib is suggested by most guidelines for treatment of patients with HCC and PVTT in Western countries. In the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP), sorafenib has provided prolonged median survival in patients with advanced HCC (10.7 vs 7.9 months), on which the BCLC recommendations were based.^[15] However, the effective treatment for patients with HCC and PVTT remains debatable. In some Chinese medical centers, single use of sorafenib did not provide a better survival benefit than palliative treatment. For example, the 3 and 6 month survival rates were 50.9% and 29.5%, respectively, while the corresponding rates in the palliative group were 55% and 0%, respectively ($P > .05$).^[12] This may be the reason as hepatitis B virus (HBV) infection and cirrhosis are highly prevalent in Chinese patients with HCC, unlike in patients with HCC in Western countries.^[27]

The management of HCC with PVTT has become more complicated and contentious with time due to advanced

improvements in technology. Increasingly, more studies are suggesting that hepatectomy and tumor thrombectomy or TACE might be a better choice for treatment of HCC with PVTT. For example, Ye et al^[12] reported that TACE might be a better choice for patients with HCC and PVTT because the 1 year overall survival rate was 51%, in contrast to the 0% 1 year survival rate in patients who underwent hepatectomy or conservative treatment. On the other side, Wang et al^[21] reported that the 1 year overall survival rate in patients with HCC and PVTT was better after hepatectomy than after TACE or conservative treatment. Theoretically, hepatectomy combined with thrombectomy might be a safe and effective treatment for HCC because compared with other treatments, the combined former treatment provides the only hope for a cure in patients with HCC and PVTT.^[4] It may also provide the following benefits to patients with HCC and PVTT: removal of the tumor thrombus and lowering of the portal venous pressure, which prevent bleeding of esophageal varices; reduction of the tumor burden; and increased efficacy of postoperative treatments with prolonged survival.^[28–30] In the treatment algorithm of the Asian Pacific Association for the Study of the Liver (APASL), if the main portal vein is secure and the tumor is resectable, then resection is a treatment option.^[31] Furthermore, The Hong Kong Liver Cancer (HKLC) classification also recommends hepatectomy as a treatment option for patients with resectable HCC when both intrahepatic and extrahepatic vascular invasion are present. If the size of HCC is less than 5 cm with intrahepatic vascular invasion, the liver function is normal; it is categorized as Child-Pugh Class A, resection is recommended.^[32] In recent studies, the median survival time ranged from 8.9 to 33 months after hepatectomy, which seems superior to TACE.^[33,34] In theory, sustained hepatitis and cirrhosis are the 2 most common concomitant complications in patients with HCC. Since these 2 factors can jeopardize the liver function, especially in the presence of PVTT, surgeons must carefully consider whether these patients are suitable for hepatectomy.

Liver transplantation is never an option for patients with advanced HCC and PVTT according to the AASLD guidelines or Milan criteria because of decreased survival expectations. Nonetheless, several studies have focused on down staging and subsequent liver transplantation. In some reported cases, patients achieved excellent survival outcomes after radio-embolization for down staging of HCC with PVTT to meet the Milan criteria. Although the global results of these studies are outstanding, more well-designed studies are needed to evaluate the long-term outcomes of such treatments compared with hepatectomy or other methods.

In this systematic review, we have collected comparative data regarding overall survival in patients with HCC and PVTT undergoing hepatic resection, TACE, or sorafenib chemotherapy. The overall meta-analysis has proved a statistically significant survival benefit of hepatic resection over TACE or conservative treatment, including sorafenib chemotherapy. This result is coinciding with our assumption. In some recent reports and our clinical experience, the type of thrombosis is relevant to the survival benefit of patients with PVTT.^[10,29,35]

We have also performed a further exploration to determine whether the type of PVTT can serve as an index for choosing the most effective treatment for patients with HCC and PVTT. We found that in patients without main PVTT, surgical treatment had a better effect than TACE and sorafenib chemotherapy. Yet, for patients with main PVTT, there was no significant

survival benefit of hepatic resection over TACE. This implies that hepatectomy might not be the best choice for patients with HCC and main PVTT. This is probably because when the PVTT extends to the main trunk, the risk of portal vein hypertension and its related diseases is higher than that in patients without main portal vein invasion.^[13,36] In other words, the beneficial effects of complete tumor ablation by hepatic resection are offset by its deteriorative effects on liver function. Moreover, HCC cells spread and become distributed throughout the portal vein system more easily in patients with main PVTT than those without main PVTT because of the different surgical treatment strategies used for these 2 conditions. In patients with HCC without main PVTT, the possibility of removing the PVTT with the tumor *en bloc* is high. In contrary, for patients with HCC with main PVTT, the tumor thrombus is usually located beyond the resection line, and suction or thrombectomy is the most frequently used strategy. Numerous researchers have reported that among patients with HCC, overall survival after surgery is shorter in those with main PVTT than peripheral PVTT.^[9,24,37] Most researches have also reported the high possibility of recurrence and liver function damage because suction or thrombectomy do not readily achieve R0 resection, even with intraoperative frozen sections. Therefore, hepatic resection might be the better choice for patients with HCC with only peripheral PVTT.

Several limitations of this meta-analysis must be acknowledged. First, all of the included studies were retrospective studies. No high-quantity prospective randomized clinical studies could be found. Thus, the results of the meta-analysis might have been influenced by selection bias. Additionally, the small number of included studies among the subgroup analyses may have also contributed to the great heterogeneity in this meta-analysis. Second, all studies included in our meta-analysis were from Asia (Japan, Korea, and China). No reports from Europe or America were found. According to the BCLC staging system, sorafenib is the only treatment that should be recommended to patients with HCC and PVTT.^[4] Therefore, hepatectomy or TACE may not be suggested to patients from Europe or America. However, for patients with HCC and PVTT in Asia, especially in China, hepatectomy, or TACE might be an accepted choice. This may be attributed to the different etiologies and biological behaviors of HCC between Eastern and Western patients. Third, therapy for HCC should be an individualized comprehensive treatment based on a surgical operation.^[38] Many therapeutic treatments for HCC are currently available. More than 1 treatment should be suggested to obtain a multidisciplinary advantage. Nevertheless, clinical research focusing on this topic is still lacking.

Several meta-analyses to date have focused on patients with HCC who underwent hepatectomy or TACE. Zhang et al^[40] have reported the survival benefits of hepatic resection vs TACE for HCC with PVTT. They have evaluated 11 studies and suggested that the survival rates favored hepatectomy over TACE in patients with HCC without main PVTT. Our study has likewise obtained the same result in the present meta-analysis. In contrast to their work, we additionally compared hepatectomy with sorafenib treatment. Hyun et al^[41] performed a meta-analysis of 18 studies, including 1 randomized controlled trial (RCT) and found that hepatectomy was associated with a better survival rate in patients with BCLC stage C HCC. However, they did not directly discuss patients with PVTT. Patients with HCC and PVTT belong to BCLC stage C, which also includes patients with extrahepatic metastasis. Yet, these findings suggest that

hepatectomy might be a meaningful choice for patients with HCC and PVTT.

5. Conclusion

This meta-analysis indicates that hepatectomy might be a better option for patients with resectable HCC and PVTT than TACE or conservative treatment, including sorafenib. On the other hand, in patients with HCC and main PVTT, hepatectomy showed no benefit over TACE or conservative treatment. Due to the lack of high-quality randomized cohort studies, more well-designed multicenter randomized clinical trials are needed to prove our outcomes.

Acknowledgments

We thank Angela Morben, DVM, ELS, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Author contributions

Formal analysis: Ke-shuai Dong.

Investigation: Zun-yi Zhang, Er-lei Zhang, Li-wei Zhang, Han-hua Dong.

Project administration: Zun-yi Zhang, Han-hua Dong.

Supervision: Xiao-ping Chen, Han-hua Dong.

Writing – original draft: Zun-yi Zhang, Ke-shuai Dong, Er-lei Zhang, Li-wei Zhang.

Writing – review & editing: Zun-yi Zhang, Han-hua Dong.

References

- Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.
- Ando E, Tanaka M, Yamashita F, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. *Cancer* 2002;95:588–95.
- Poon RT, Fan ST, Lo CM, et al. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. *Ann Surg* 1999;229:216–22.
- Kokudo T, Hasegawa K, Matsuyama Y, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. *J Hepatol* 2016;65:938–43.
- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–90.
- Takizawa D, Kakizaki S, Sohara N, et al. Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. *Dig Dis Sci* 2007;52:3290–5.
- Lin DX, Zhang QY, Li X, et al. An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. *J Cancer Res Clin Oncol* 2011;137:139–49.
- Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62–7.
- Chen XP, Qiu FZ, Wu ZD, et al. Effects of location and extension of portal vein tumor thrombus on long-term outcomes of surgical treatment for hepatocellular carcinoma. *Ann Surg Oncol* 2006;13:940–6.
- Chen XP, Huang ZY. Surgical treatment of hepatocellular carcinoma in China: surgical techniques, indications, and outcomes. *Langenbecks Arch Surg* 2005;390:259–65.
- Kenjo A, Miyata H, Gotoh M, et al. Risk stratification of 7,732 hepatectomy cases in 2011 from the National Clinical Database for Japan. *J Am Coll Surg* 2014;218:412–22.
- Ye HH, Ye JZ, Xie ZB, et al. Comprehensive treatments for hepatocellular carcinoma with tumor thrombus in major portal vein. *World J Gastroenterol* 2016;22:3632–43.
- Peng ZW, Guo RP, Zhang YJ, et al. Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Cancer* 2012;118:4725–36.
- Lee JM, Jang BK, Lee YJ, et al. Survival outcomes of hepatic resection compared with transarterial chemoembolization or sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. *Clin Mol Hepatol* 2016;22:160–7.
- Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014;63:844–55.
- Yamada R, Kishi K, Sato M, et al. Transcatheter arterial chemoembolization (TACE) in the treatment of unresectable liver cancer. *World J Surg* 1995;19:795–800.
- Zhang ZM, Lai EC, Zhang C, et al. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. *Int J Surg* 2015;20:8–16.
- Schwarz RE, Abou-Alfa GK, Geschwind JF, et al. Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. *HPB (Oxford)* 2010;12:313–20.
- Ye JZ, Zhang YQ, Ye HH, et al. Appropriate treatment strategies improve survival of hepatocellular carcinoma patients with portal vein tumor thrombus. *World J Gastroenterol* 2014;20:17141–7.
- Zheng N, Wei X, Zhang D, et al. Hepatic resection or transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus. *Medicine (Baltimore)* 2016;95:e3959.
- Wang K, Guo WX, Chen MS, et al. Multimodality treatment for hepatocellular carcinoma with portal vein tumor thrombus: a large-scale, multicenter, propensity matching score analysis. *Medicine (Baltimore)* 2016;95:e3015.
- Zhou Q, Wang Y, Zhou X, et al. Prognostic analysis for treatment modalities in hepatocellular carcinomas with portal vein tumor thrombi. *Asian Pac J Cancer Prev* 2011;12:2847–50.
- Liu PH, Lee YH, Hsia CY, et al. Surgical resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. *Ann Surg Oncol* 2014;21:1825–33.
- Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol* 2010;17:2073–80.
- Jia L, Kiryu S, Watadani T, et al. Prognosis of hepatocellular carcinoma with portal vein tumor thrombus: assessment based on clinical and computer tomography characteristics. *Acta Med Okayama* 2012;66:131–41.
- Wang B, Xu H, Gao ZQ, et al. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. *Acta Radiol* 2008;49:523–9.
- Huang ZY, Liang BY, Xiong M, et al. Severity of cirrhosis should determine the operative modality for patients with early hepatocellular carcinoma and compensated liver function. *Surgery* 2016;159:621–31.
- Kojima H, Hatano E, Taura K, et al. Hepatic resection for hepatocellular carcinoma with tumor thrombus in the major portal vein. *Dig Surg* 2015;32:413–20.
- Xu JF, Liu XY, Wang S, et al. Surgical treatment for hepatocellular carcinoma with portal vein tumor thrombus: a novel classification. *World J Surg Oncol* 2015;13:86.
- Chen J, Huang J, Chen M, et al. Transcatheter arterial chemoembolization (TACE) versus hepatectomy in hepatocellular carcinoma with macrovascular invasion: a meta-analysis of 1683 patients. *J Cancer* 2017;8:2984–91.
- Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific association for the study of the liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010;4:439–74.
- Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* 2014;146:1691–700.
- Ohkubo T, Yamamoto J, Sugawara Y, et al. Surgical results for hepatocellular carcinoma with macroscopic portal vein tumor thrombosis. *J Am Coll Surg* 2000;191:657–60.
- Kondo K, Chijiwa K, Kai M, et al. Surgical strategy for hepatocellular carcinoma patients with portal vein tumor thrombus based on prognostic factors. *J Gastrointest Surg* 2009;13:1078–83.
- Ban D, Shimada K, Yamamoto Y, et al. Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. *J Gastrointest Surg* 2009;13:1921–8.
- Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;111:1018–22.
- Shaohua L, Qiaoxuan W, Peng S, et al. Surgical strategy for hepatocellular carcinoma patients with portal/hepatic vein tumor thrombosis. *PLoS One* 2015;10:e0130021.
- Zhang B, Dong W, Luo H, et al. Surgical treatment of hepato-pancreato-biliary disease in China: the Tongji experience. *Sci China Life Sci* 2016;59:995–1005.

- [39] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
- [40] Zhang XP, Wang K, Li N, et al. Survival benefit of hepatic resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. *BMC Cancer* 2017;17:902.
- [41] Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: a meta-analysis of high-quality studies. *Hepatology* 2018;68:977–93.
- [42] Jonathan AC, Sterne , Miguel A, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355: i4919.