

The Prognostic Comparison Between Hepatocellular Carcinoma with Portal Vein Tumor Thrombus and Bile Duct Cancer Thrombus After Liver Resection

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Background and Objective: Hepatocellular carcinoma (HCC) often invades the portal vein and its branches to form portal vein tumor thrombus (PVTT), and it rarely spreads into the bile ducts to cause bile duct tumor thrombus (BDTT). However, the clinical prognosis of patients with the two types of tumor thrombus is different. In this manuscript, we plan to compare the prognosis of HCC with PVTT and BDTT for further clinical treatment.

Patients and Methods: A total of 60 patients including 48 HCC cases with PVTT and 12 HCC cases with BDTT were enrolled in the study. The medical records were collected from participants. The follow-up was performed in 3 years post-hepatectomy. Statistical analysis was performed to explore the relationship between tumor thrombus with clinicopathological characteristics, to determine the significant preoperative factors influencing overall survival (OS) and time to recurrence (TTR), and to establish the survival and recurrent curves.

Results: HCC with BDTT or PVTT often combined with viral hepatitis B, accompanied by varying degrees of cirrhosis, and high AFP level (68.3%), complete tumor capsule (76.7%), and larger tumor size (85.0%). Furtherly, patients with HCC and BDTT tended to have higher total bilirubin (TB) and more possibility of lymph node metastases. The multivariate Cox hazard analyses also revealed that both tumor size and tumor thrombus could be taken as independent prognostic indicators of HCC patients. Survival curves showed that the 1-, 2- and 3-year OS or DFS rates of HCC patients with BDTT were significantly lower than those of HCC patients with PVTT, respectively.

Conclusion: Tumor thrombus is an independent risk factor for poor survival and high recurrence in HCC. HCC patients with BDTT had shorter overall survival and higher tumor recurrence rate compared to HCC patients with PVTT.

Keywords: hepatocellular carcinoma, portal vein tumor thrombus, bile duct cancer thrombus, prognosis

Synopsis

Our study observes the prognosis of HCC with portal vein tumor thrombus (PVTT) and HCC with bile duct tumor thrombus (BDTT) to provide a reference for further clinical treatment. Our observations suggest that liver cancer with PVTT or BDTT is an independent risk factor for poor survival and high recurrence in HCC. HCC patients with BDTT had shorter overall survival and higher tumor recurrence rate compared to HCC patients with PVTT. It should be diagnosed and treated as early and precise as possible to improve the prognosis of the patients.

Introduction

Hepatocellular carcinoma, as an extremely malignant tumor, is the second most lethal malignancy worldwide, and responsible for more than 700,000 deaths annually.^{1,2} Owing to the prevalence of hepatitis B and C, the incidence rate of liver cancer is higher in Asia.² Unlike other digestive system tumors that are prone to invade lymph nodes, HCC is considered as its characteristic of a strong propensity to invade the surrounding liver vasculature.²⁻⁴ The portal vein and its branches, as a most common invasion place of HCC, are found to be invaded in about 31.4%~34% of all HCC patients according to clinical data.⁴ According to the European Association for the Study of the Liver/the American Association for the Study of the Liver Disease/Barcelona Clinic for Liver Cancer (EASL/AASLD/BCLC) Staging System and treatment guidelines, the portal vein invasion, or portal vein tumor thrombosis (PVTT), is regarded as being indicative of an advanced stage of the disease with almost little hope to be cured.⁵⁻⁷ The only proposed treatment option for this group of patients is molecular-targeted therapy drug including sorafenib and lenvatinib.^{7,8} However, the reported median survival time (MST) of patients with advanced HCC treated with sorafenib or lenvatinib is as short as 9.8 or 11.5 months.⁹ Conversely, more aggressive anticancer treatments are recommended for selected patients with HCC and PVTT by Chinese, Japanese, South Korean, and Asia-Pacific clinical practice guidelines.¹⁰⁻¹³ The surgical resection is recommended by the Chinese expert consensus for some patients with HCC and PVTT limited to a first-order branch of the main portal vein or above.¹⁰ Meanwhile, some promising survival outcomes being reported using surgical resection and other modalities including molecular target therapy, radiotherapy, and transcatheter arterial chemoembolization (TACE).^{10,14,15} Recently, as more aggressive therapeutic schemes developing, such as operation, interventional radiotherapy including radio-embolization, molecularly targeted therapy and other multidisciplinary treatments, the life quality is greatly improved and the survival time is prolonged gradually in some patients,^{14,15} even some of which were used as the downgrade treatment for patients without the possibilities of surgery. Recent advances in surgical techniques and perioperative management have promoted liver resection to become a reasonably safe treatment option with an acceptable mortality and morbidity rate.¹⁶⁻¹⁸ At present, the aggressive surgical resection for HCC with PVTT has been proposed in several centers.^{17,18}

However, different from PVTT, HCC with bile duct tumor thrombus (BDTT) is a relatively rare event in clinical practice

which accounts for only 1.2±12.9% of total HCC cases.¹⁹ As a result of a lack of the right awareness of HCC with BDTT, some patients fail to receive effective treatment. Presently, the diagnosis of BDTT mainly depends on clinical symptoms, physical examinations, image studies, surgical exploration and postoperative pathological results. According to the type of BDTT, patients with HCC and BDTT may undergo radical resection, thrombectomy through a choledochotomy, palliative internal and external bile duct drainage including, or transarterial chemoembolization (TACE). Depending on the patient's condition, sometimes routine percutaneous transhepatic cholangial drainage (PTCD) or endoscopic nasobiliary drainage (ENBD) was performed before surgery to reduce the degree of jaundice. The active surgical resection may benefit some selected patients.^{20,21}

When patients with HCC have developed into portal vein tumor thrombus (PVTT) or bile duct tumor thrombus (BDTT), it was always judged that the condition has stepped into an advanced stage, furtherly followed by intrahepatic and extrahepatic metastases, portal hypertension, jaundice and ascites in a short period. If not given treatment in time, the median survival time of patients will be less than 6 months. Therefore, PVTT and BDTT are recognized as an important prognosis factor for patients with HCC. As the diagnosis imaging is developed and more awareness is improved regarding the recognition of these types of disease, the correct preoperative diagnosis and the prompt treatment are given. Due to the different biological characteristics of bile duct and portal vein tumor thrombus, the prognosis of PVTT and BDTT after surgery is different. In this article, we clarified the long-term surgical outcomes of HCC with the two types of tumor thrombus.

Patients and Methods

Patients

A total of 60 patients including 48 HCC cases with PVTT and 12 HCC cases with BDTT were enrolled in the study. Patients received curative resection for HCC at the department of General surgery, Huashan Hospital, Fudan University (Shanghai, China) between January 2014 and December 2016. All the patients meet the following inclusion criteria (a) a definite clinically diagnosed with HCC and postoperative pathological diagnosis of HCC, (b) R0 resection of all patients based on histologic examinations. The tumor thrombus is removed during surgery. (c) The TNM staging is in accordance with the AJCC/UICC 2017 TNM staging standard. (d) Classification of liver function

was graded according to Child-Pugh classification criteria. (e) Without distant metastasis, (f) patients did not receive any treatment before surgery. (g) The diagnosis of portal vein tumor thrombus was based on pathological tissue slices, preoperative imaging and confirmed in the surgery. (h) Patients were generally recommended to undergo trans-arterial chemoembolization (TACE) therapy at 1 month after surgery. All cases had complete laboratory values, imaging results, clinical and pathology data, and treatment information, including gender, age, HBsAg, cirrhosis, preoperative AFP, ALT, and tumor size, tumor number, tumor capsule, the degree of differentiation, distant metastasis, PVTT and BDTT stage, TNM staging. Clinical samples were collected from patients after obtaining informed consent in accordance with a protocol approved by the Ethics Committee of Huashan Hospital (Shanghai, China), which was in accordance with the Declaration of Helsinki.

The Classification of PVTT and BDTT

It is greatly important to select the appropriate therapeutic strategies depending on the classification of PVTT. The portal vein invasion classification (Vp) has been used worldwide since it was introduced in 1987 by the Liver Cancer Study Group of Japan.^{22,23} The Eastern Hepatobiliary classification (also known as Cheng's classification) was devised in 2007.²⁴ The Details of the Vp classification and Cheng's classification are provided in the [Supplementary Table S1](#). No such classification system has been developed yet in the west. Hepatocellular carcinoma with BDTT was classified according to the location of BDTT, as proposed by Ueda²⁵ ([Supplementary Table S1](#)). The patients with PVTT selected in this study are at the stage of Vp1-3 (Cheng's classification type I or II), while those with BDTT were classified as Ueda type I or II.

Transcatheter Arterial Chemoembolization (TACE)

HCC patients with PVTT or BDTT were generally recommended to undergo TACE at 1 month after surgery. Whether the patients followed the physician's recommendation mainly depended on their socioeconomic status and compliance with the doctors. TACE was conducted with a conventional procedure. In brief, hepatic arteriography and superior mesenteric arterial portovenography were performed first to verify whether tumor staining occurred,

especially for the operative area. The arteries supplying the tumors were catheterized superselectively as close as possible to the suspicious tumor, followed by infusion of 1 g of 5-fluorouracil, 150 mg of oxaliplatin, and 30 mg pirarubicin mixed with 5–10 mL of lipiodol. The dosage of chemotherapeutic agents or lipiodol was adjusted according to the body weight and liver function.

Statistical Analysis

The statistical analysis was performed with IBM SPSS Statistics 20 statistical software. The measurement data of normal distribution are expressed by "mean ± standard deviation", and Student's *t*-test was used to analyze quantitative variables between two groups. Fisher's exact test was used to analyze categorical data. Survival curves were established using the Kaplan–Meier method and compared using the Log-rank test. $P < 0.05$ in the results were statistically different and $P < 0.01$ was statistically significantly different by a two-tailed test.

Results

The Diagnosis and Treatment of HCC with PVTT or BDTT

Patients with liver cancer and tumor thrombus were preliminarily diagnosed by imaging including B-mode ultrasound, enhanced CT, and enhanced magnetic resonance imaging. All tumor thrombi were confined to the first branch or higher grade of the portal vein or intrahepatic bile duct did not invade or extend to the main portal vein or common hepatic duct ([Figure 1A and B](#)). After a comprehensive and detailed evaluation before the surgery, a reasonable surgical plan is made. Based on the systemic and tumor conditions, we perform liver resections on patients, including regular anatomical hepatic resection of the lobes or the segments, or local irregular liver resections, and tumor thrombus are removed as a whole during surgery. In the present study, 30 patients with PVTT and 7 patients with BDTT were treated by the anatomical hepatectomy, while 18 patients with PVTT and 5 patients with BDTT were treated by non-anatomical hepatectomy. The detailed descriptions are shown in [Supplementary Table S2](#). The tumor and tumor thrombus tissue were almost visually observed after surgery ([Figure 1A and B](#)). The final diagnosis depends on the current pathological diagnosis of the microscope.

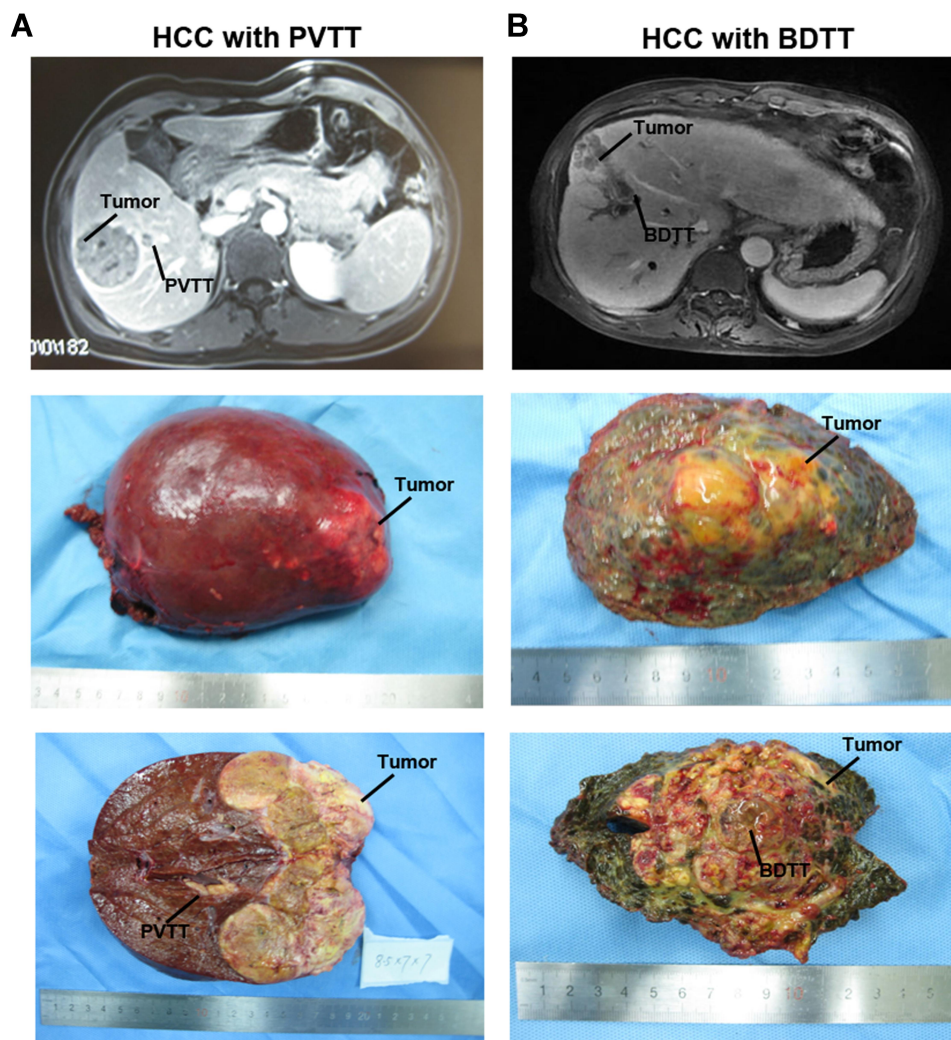


Figure 1 The Location of hepatocellular carcinoma with (A) portal vein tumor thrombus and (B) bile duct cancer thrombus in magnetic resonance imaging, naked eye specimens, and specimen sections. All tumor thrombi were confined to the first branch or higher grade of the portal vein or intrahepatic bile duct, did not invade or extend to the main portal vein or common hepatic duct. The Location of hepatocellular carcinoma and tumor thrombus in (upper) magnetic resonance imaging, (middle) naked eye specimens, and (lower) specimen sections.

The Clinicopathological Characteristics in HCC with PVTT or BDTT

The characteristics of a total of 60 patients are included in [Table 1](#). Male and the age more than 50 years old accounted for 78.3% and 83.3% of the study population, respectively. Almost all individuals (96.7%) enrolled in our research have a background of hepatitis B. At the same time, the proportion of liver cirrhosis is as high as 75%. Among the 60 patients, 48 HCC patients (80%) were accompanied by the vascular invasion of portal vein, and 12 HCC patients (20%) were diagnosed as HCC with bile duct tumor thrombus. Mostly, the patients with PVTT (80%) or BDTT (20%) had the feathers with high AFP level more than 20 ng/mL (68.3%), low CA199 level less

than 37Ku/L (76.7%), complete tumor capsule (76.7%), and tumor size more than 5 cm (85.0%). The less lymph node metastasis (90.0%) occurs to the enrolled population which is mostly diagnosed at a stage TNM III/IV (86.7%).

The Association of Tumor Thrombus with Clinicopathological Characteristics

Next, we evaluated the association between tumor thrombosis and clinicopathological characteristics of HCC patients. The correlative analysis revealed that tumor thrombus was significantly correlated with total bilirubin ($P < 0.001$) or lymph node metastasis ($P = 0.012$) ([Table 2](#)), respectively. Further analysis found that patients with liver cancer and bile duct cancer thrombus tended to have

Table 1 Clinicopathological Characteristics of HCC Patients (n=60)

Characteristics	Case Number	%
Gender		
Female	13	21.7
Male	47	78.3
Age (years)		
<50	10	16.7
≥50	50	83.3
HBsAg		
Negative	2	3.3
Positive	58	96.7
Cirrhosis		
No	15	25.0
Yes	45	75.0
ALT (U/L)		
<75	49	81.7
≥75	11	18.3
TB (μmol/L)		
≤ 200	55	91.7
>200	5	8.3
ALB (g/L)		
≥35	25	41.7
<35	35	58.3
AFP (ng/mL)		
<20	19	31.7
≥20	41	68.3
CA199 (kU/L)		
<37	46	76.7
≥37	14	23.3
Tumor size (cm)		
<5	9	15.0
≥5	51	85.0
Tumor number		
Single	44	53.5
Multiple	16	46.5
Tumor capsule		
Complete	46	76.7
None	14	23.3
tumor thrombosis		
PVTT	48	80.0
BDTT	12	20.0
Lymph node metastasis		
No	54	90.0
Yes	6	10.0

(Continued)

Table 1 (Continued).

Characteristics	Case Number	%
Tumor differentiation		
I/II	23	38.3
III/IV	37	61.7
TNM stage		
I/II	8	13.3
III/IV	52	86.7

Abbreviations: HBsAg, hepatitis B surface antigen; ALT, alanine transaminase; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; CA199, Cancer antigen199; PVTT, portal vein tumor thrombus; BDTT, bile duct tumor thrombus; AFP, alpha-fetoprotein; TNM, tumor-node-metastasis staging system. Tumor differentiation was evaluated by Edmondson grade.

higher total bilirubin (TB) and more possibility of lymph node metastases. However, the two features do not exist in patients with liver cancer and portal vein tumor thrombus. There was no significant correlation between tumor thrombosis and the remaining clinical characteristics including gender, age, HBsAg (hepatitis B surface antigen), Cirrhosis, alanine transaminase (ALT), albumin (ALB), serum AFP level, serum CA199 level, tumor size, tumor number, tumor capsule, tumor differentiation, TNM stage (Table 2).

The Prognostic Value of Tumor Thrombus in HCC Patients

Furthermore, we performed the prognostic analysis in hepatocellular carcinoma with portal vein tumor thrombus and bile duct cancer thrombus after liver resection. Univariate analysis showed that tumor size and tumor thrombus were significantly associated with overall survival (OS) ($P=0.038$ and $P=0.011$, respectively) and time to recurrence (TTR) ($P=0.018$ and $P=0.005$, respectively) (Table 3). However, the other enrolled pathological features showed no association with OS or TTR. The multivariate Cox hazard analyses also revealed that both tumor size and tumor thrombus could be taken as independent prognostic indicators of HCC patients (OS: $P=0.049$ and $P=0.023$, respectively; and TTR: $P=0.030$ and $P=0.010$, respectively) (Table 3). Collectively, the results demonstrated that tumor size and tumor thrombus is an independent prognostic indicator and associated with shorter OS and TTR in HCC patients.

Kaplan-Meier survival curves showed that the 1-, 2- and 3-year overall survival (OS) rates of HCC patients with

Table 2 The Association of Tumor Thrombosis with Clinicopathological Characteristics of HCC Patients

Variable	Tumor Thrombosis (n=60)		P value
	BDTT (n=12)	PVTT (n=48)	
Gender			
Female	4(33.3%)	9(18.8%)	0.234
Male	8(66.7%)	39(81.2%)	
Age (years)			
<50	1(8.3%)	9(18.8%)	0.354
≥50	11(91.7%)	39(81.2%)	
HBsAg			
Positive	12(100.0%)	46(95.8%)	0.637
Negative	0(0.0%)	2(4.2%)	
Cirrhosis			
Yes	10(83.3%)	35(72.9%)	0.369
No	2(16.7%)	13(27.1%)	
ALT (U/L)			
<75	10(83.3%)	39(81.2%)	0.618
≥75	2(16.7%)	9(18.8%)	
TB (μmol/L)			
≤ 200	7(58.3%)	48(100.0%)	0.000
>200	5(41.7%)	0(0.0%)	
ALB (g/L)			
≥35	7(58.3%)	18(37.5%)	0.163
<35	5(41.7%)	30(62.5%)	
AFP (ng/mL)			
<20	5(41.7%)	14(29.2%)	0.307
≥20	7(58.3%)	34(70.8%)	
CA199 (kU/L)			
<37	10(83.3%)	36(75.0%)	0.426
≥37	2(16.7%)	12(25.0%)	
Tumor size (cm)			
<5	3(25.0%)	6(12.5%)	0.191
≥5	9(75.0%)	42(87.5%)	
Tumor number			
Single	11(91.7%)	33(68.8%)	0.103
Multiple	1(8.3%)	15(31.2%)	
Tumor capsule			
None	1(8.3%)	13(27.1%)	0.161
Complete	11(91.7%)	35(72.9%)	
Lymph node metastasis			
No	8(66.6%)	46(95.8%)	0.012
Yes	4(33.3%)	2(4.2%)	

(Continued)

Table 2 (Continued).

Variable	Tumor Thrombosis (n=60)		P value
	BDTT (n=12)	PVTT (n=48)	
Tumor differentiation			
I/II	6(50.0%)	17(35.4%)	0.272
III/IV	6(50.0%)	31(64.6%)	
TNM stage			
<5	2(16.7%)	6(12.5%)	0.507
≥5	10(83.3%)	42(87.5%)	

Notes: Analysis was conducted using χ^2 tests and Fisher's exact tests. Bold indicates significant values.

Abbreviations: HBsAg, hepatitis B surface antigen; ALT, alanine transaminase; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; CA199, Cancer antigen199; PVTT, portal vein tumor thrombus; BDTT, bile duct tumor thrombus; AFP, alpha-fetoprotein; TNM, tumor-node-metastasis staging system. Tumor differentiation was evaluated by Edmondson grade.

BDTT (41.7%, 33.3% and 33.3%, respectively) were significantly lower than HCC patients with PVTT (57.6%, 54.6% and 54.6%, respectively) ($P = 0.0212$, Figure 2A). In addition, the 1-, 2- and 3-year tumor recurrence rates of HCC patients with BDTT (51.3%, 80.5% and 90.3%, respectively) were significantly higher than HCC with PVTT group (36.6%, 52.3% and 72.4%, respectively) ($P = 0.0246$, Figure 2B). The results showed that HCC patients with BDTT had shorter overall survival (OS) and higher tumor recurrence rate compared to HCC patients with PVTT.

Discussion

Hepatocellular carcinoma is one of the most fatal malignancies worldwide. Owing to the biological characteristics of liver cancer and the anatomical characteristics of the liver, it is prone to invade intrahepatic vessels, especially the portal venous system, rarely in the bile duct system.

Once PVTT is developed, and then it progressed rapidly to cause portal hypertension, hepatocellular jaundice, and intractable ascites, which seriously affect the prognosis of patients. Therefore, according to the situation, appropriate interventions are given to these patients. However, it is of great importance to decide the appropriate therapeutic strategies by the classification of PVTT. At present, the Vp classification and Cheng's classification of PVTT have been introduced and used worldwide.²²⁻²⁴ The treatment strategies for patients who have HCC with PVTT differ substantially between the west (Europe and America) and the east (Asia-Pacific region). According to

Table 3 Univariate and Multivariate Analyses of Factors Associated with OS and TTR of HCC Patients (n=60)

Clinical Variables	Overall Survival		Time To Recurrence	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analysis				
Gender (female versus male)	0.93(0.16–6.35)	0.126	1.62(0.52–4.23)	0.312
Age (≥ 50 versus < 50 years)	0.72(0.37–1.92)	0.592	1.06(0.35–2.45)	0.913
HBsAg(positive versus negative)	1.28(0.73–4.12)	0.985	3.03(0.84–6.32)	0.518
Cirrhosis (yes versus no)	0.75(0.32–2.20)	0.649	0.81(0.39–2.52)	0.754
ALT (≥ 75 versus < 75 U/L)	1.03(0.93–3.56)	0.802	1.29(0.85–3.11)	0.843
TB(≤ 200 versus $> 200\mu\text{mol/L}$)	0.63(0.35–1.57)	0.348	0.98(0.36–2.69)	0.711
ALB(≥ 35 versus < 35 g/L)	0.87(0.32–1.85)	0.707	0.61(0.23–1.54)	0.602
AFP (≥ 20 versus < 20 ng/mL)	1.62(0.74–2.35)	0.816	0.79(0.66–1.62)	0.412
CA199 (≥ 37 versus < 37 kU/L)	0.55(0.29–1.07)	0.078	0.96(0.65–1.56)	0.681
Tumor size (≥ 5 cm versus < 5 cm)	3.00(1.06–8.41)	0.038	3.32(1.42–9.21)	0.018
Tumor number (multiple versus single)	0.49(0.18–1.26)	0.131	1.25(0.46–2.14)	0.263
Tumor capsule (complete versus none)	0.77(0.20–1.83)	0.467	0.82(0.47–2.26)	0.614
Tumor thrombus (PVTT versus BDTT)	4.61(1.44–9.26)	0.011	3.43(1.29–9.67)	0.005
Lymph node metastasis (yes versus no)	0.98(0.35–6.57)	0.936	2.31(0.27–9.49)	0.442
Tumor differentiation (III/IV versus I–II)	0.86(0.38–2.25)	0.621	0.73(0.39–1.48)	0.256
TNM stage (III/IV versus I/II)	0.92(0.17–4.39)	0.865	0.56(0.22–1.46)	0.225
Multivariate analysis				
Tumor size (≥ 5 cm versus < 5 cm)	2.86(0.92–8.36)	0.049	3.15(1.28–9.02)	0.030
Tumor thrombus (PVTT versus BDTT)	3.71(1.24–8.47)	0.023	2.93(1.11–7.89)	0.010

Notes: Analysis was conducted using univariate analysis or multivariate Cox proportional hazards regression. Bold indicates significant values.

Abbreviations: HBsAg, hepatitis B surface antigen; ALT, alanine transaminase; TB, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; CA199, Cancer antigen 199; PVTT, portal vein tumor thrombus; BDTT, bile duct tumor thrombus; AFP, alpha-fetoprotein; TNM, tumor-node-metastasis staging system; CI, confidence interval. Tumor differentiation was evaluated by Edmondson grade.

western guidelines, the molecular-targeted treatment is recommended for HCC patients with PVTT. Sorafenib was the first molecularly targeted agent to be approved for first-line treatment for patients with advanced HCC by the US Food and Drug Administration (FDA) and the

European Medicines Agency (EMA) in 2007, and lenvatinib was approved in 2018.^{7,8} In addition, regorafenib,²⁶ cabozantinib²⁷ and ramucirumab²⁸ are approved by the FDA and EMA for the second-line treatment of patients with advanced HCC, especially after sorafenib and

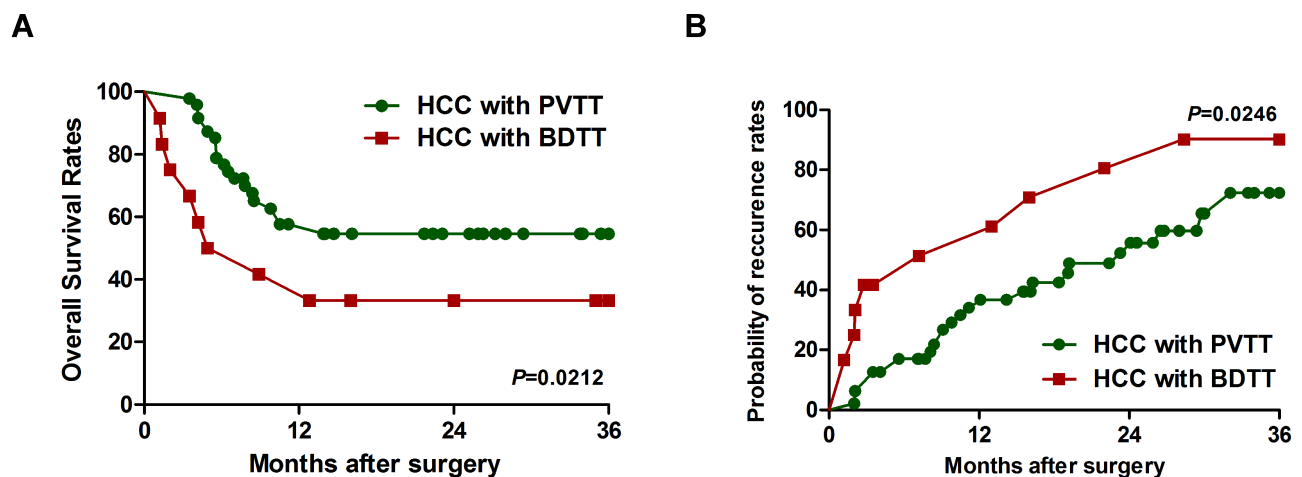


Figure 2 The prognostic comparison between hepatocellular carcinoma with portal vein tumor thrombus and bile duct cancer thrombus after liver resection by the analysis of Kaplan-Meier curves. Kaplan-Meier curves showed that HCC patients with bile duct cancer thrombus had (A) shorter overall survival and (B) higher tumor recurrence rate compared to HCC patients with portal vein tumor thrombus. P values were calculated by Log-rank test.

lenvatinib failure. Conversely, more aggressive anticancer treatments are recommended for selected patients with HCC by Chinese, Japanese, South Korean, and Asia-Pacific clinical practice guidelines. Surgical resection for some patients with HCC and PVTT limited to a first-order branch of the main portal vein or above were recommended in Chinese expert consensus. Using radiotherapy, transcatheter arterial chemoembolization (TACE), and other modalities were also reported to have promising survival outcomes.^{10,29,30}

HCC with bile duct tumor thrombus (BDTT) is one of the rare and special types of liver cancer which was often misdiagnosed as biliary calculi, cholangiocarcinoma, liver failure, or advanced HCC for similar clinical presentations and imaging characteristics.³¹ Currently, it is believed that the occurrence of liver cancer combined with BDTT is related to the biological characteristics of the tumor, the body's microenvironment, the human immune status, the adjacent relationship between liver cancer and bile ducts, but not to the size of liver cancer.^{32,33} Tumor cells first invade the sub-epithelium of the adjacent small bile duct, and then they grow continuously along the bile duct wall to the extrahepatic bile duct.^{32,33} The presence of BDTT usually implies a poor prognosis. Due to the misunderstandings of HCC with BDTT that these patients are already in an advanced stage, some patients fail to receive more effective treatment. In fact, as to the patients with liver cancer combined with BDTT, early diagnosis and early active surgical intervention can make them obtain satisfactory survival results.^{34,35} At present, the diagnosis of liver cancer combined with BDTT mainly depends on imaging examination including enhanced CT, MRCP and ERCP, etc., combined with clinical manifestations and intraoperative exploration, postoperative pathological examination. The commonly used Ueda classification combines surgical needs and facilitates prognosis judgment.²⁵ The simplified clinical typing is proposed by the Japanese scholar Satoh in 2000, which is suitable for clinical preliminary judgment of the location and prognosis of BDTT.³⁶ BDTT may undergo radical resection, thrombectomy through a choledochotomy, palliative internal and external bile duct drainage, or trans-arterial chemoembolization (TACE) depending on the type of BDTT.^{21,37} However, patients with HCC and BDTT have a relatively high risk of early recurrence, resulting in poor prognosis even after curative hepatic resection or liver transplantation.²¹ Therefore, postoperative preventive treatment is useful to improve the OS rate after the operation. Some observations have shown that tumor thrombectomy

through a choledochotomy is contraindicated for surgical treatment of HCC with BDTT, as this procedure might cause tumor recurrence at the site of the choledochotomy probably due to intraoperative iatrogenic implantation.³⁸ In conclusion, patients with HCC and BDTT have a relatively high rate of early recurrence after surgery. The prognosis of this type of HCC is extremely dismal, but the survival can be improved if complete tumor with BDTT clearance is achieved.

In this study, we retrospectively studied the clinicopathological features of 60 patients with HCC and PVTT or BDTT. After a comprehensive and detailed evaluation before surgery, a reasonable surgical plan was performed. All tumor thrombi were confined to the portal vein or intrahepatic bile duct of primary or higher grade and did not invade or extend to the main portal vein or common hepatic duct. We found that the clinical features of hepatocellular carcinoma with BDTT or PVTT are often combined with viral hepatitis B, accompanied by varying degrees of cirrhosis. Further analysis found that patients with liver cancer with bile duct cancer thrombus tended to have higher total bilirubin and more possibility of lymph node metastases. Tumor thrombus is an independent prognostic indicator and associated with shorter OS and TTR in HCC patients. The results furtherly showed that HCC patients with BDTT had shorter overall survival and higher tumor recurrence rate compared to HCC patients with PVTT. However, more studies with a larger number of patients of HCC with BDTT or PVTT are needed to draw the final conclusion.

In summary, the liver cancer with PVTT or BDTT is an independent risk factor for poor survival and high recurrence in HCC. HCC patients with BDTT had shorter overall survival and higher tumor recurrence rate compared to HCC patients with PVTT. It should be diagnosed and treated as early and precise as possible to improve the prognosis of the patients.

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Disclosure

The authors report no conflicts of interest for this work.

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