

Outcomes of resection for hepatocellular carcinoma with macroscopic bile duct tumour thrombus: A propensity score matched study

QIYU CHI¹, ZHENG SHI¹, ZHIBO ZHANG¹, XIANG ZHANG¹, LI ZHANG² and SHANGENG WENG¹

Departments of ¹Hepatopancreatobiliary Surgery and ²Pathology,
The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350005, P.R. China

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Abstract. The incidence of hepatocellular carcinoma (HCC) with bile duct tumour thrombus (BDTT) is low, and related studies, especially studies on long-term survival, are uncommon. The present study aimed to evaluate the clinicopathological characteristics, prognostic factors and postoperative long-term outcomes of BDTT in patients with HCC. The clinicopathological characteristics and postoperative long-term outcomes of patients with HCC both with and without BDTT were compared before and after propensity score matching (PSM). Prognostic risk factors were assessed by Cox proportional hazards regression analyses after PSM. Tumour stages in the BDTT group were significantly higher than those in the group without BDTT ($P=0.001$). Overall survival (OS) and recurrence-free survival (RFS) rates were significantly higher in the group without BDTT than in the BDTT group before PSM ($P<0.001$ and $P=0.003$, respectively). However, no significant difference in OS or RFS was found between the two groups after PSM ($P=0.249$ and $P=0.121$, respectively). Moreover, the median OS and RFS times of the BDTT patients who underwent tumour thrombectomy and bile duct resection were not significantly different ($P=0.891$ and $P=0.787$, respectively). In the multivariate analysis, macrovascular invasion (HR, 3.701; 95% CI, 1.313-9.10.437; $P=0.013$) was the only independent predictor of OS. Although the clinicopathological characteristics of the BDTT group suggested more advanced stage disease and poorer oncological outcomes than the group without BDTT, BDTT was not a poor prognostic factor for patients with HCC who underwent liver resection. Curative resection is recommended for patients with HCC and BDTT,

even for those with poor liver function, after proper perioperative management in order to achieve good long-term survival.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy, accounting for 600,000-700,000 deaths worldwide in 2014, and its incidence is increasing in Western countries (1,2). HCC often invades the portal vein and hepatic vein or forms a venous tumour thrombus in the inferior vena cava. However, HCC with bile duct tumour thrombus (BDTT) is relatively rare and has been identified in 0.99-13% of autopsy and surgical specimens (2-6). Once BDTT in HCC is considered as advanced liver cancer, palliative treatment is often performed due to a misunderstanding of the cause of the obstructive jaundice, cholestasis and hepatic dysfunction (7-9). The complexity of the disease causes considerable challenges for clinical diagnosis and treatment. In recent years, patients with BDTT have more often been treated with surgery in a number of medical centres due to advances in diagnosis, surgical techniques and perioperative management (4,10), and the outcomes of surgical treatment have been widely accepted to be significantly improved compared with those of palliative treatment (11,12). However, due to the rarity of the disease, the clinicopathological characteristics are not well recognized and a limited number of studies are available, especially studies regarding long-term postoperative outcomes when compared with those of patients without BDTT; the possibility of selection bias therefore remains. Furthermore, whether extrahepatic bile duct resection is necessary remains controversial.

The present study aimed to evaluate the clinicopathological features and long-term oncological outcomes of patients with HCC and macroscopic BDTT. To overcome selection bias, propensity score matching (PSM) was applied and prognostic factors after liver resection were analysed.

Patients and methods

Patients. Between January 2013 and November 2018, 773 patients with HCC underwent hepatectomy at the Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Fujian Medical University (Fuzhou,

Correspondence to: Professor Shangeng Weng, Department of Hepatopancreatobiliary Surgery, The First Affiliated Hospital of Fujian Medical University, 20 Chazhong Road, Fuzhou, Fujian 350005, P.R. China
E-mail: shangeng@sina.com

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China). Patients who had previously received locoregional therapy, such as hepatectomy (n=63), transarterial chemoembolization (TACE; n=11), radiofrequency ablation (RFA; n=4), Gamma Knife[®] treatment (n=1) or TACE combined with RFA (n=4), were excluded. Patients were also excluded if the tumour had been found to rupture (n=25), invade peripheral organs or metastasize (n=2) during the surgery. Patients whose data were incomplete or those who were lost to follow-up (n=32) were also excluded from this study. Ultimately, a total of 631 patients (age range, 20-85 years) were included in the current study, 25 (3.96%) of whom were allocated to the HCC with macroscopic BDTT group, and 606 (96.04%) of whom were allocated to the group without BDTT. The clinicopathological characteristics and survival rates of the two groups were compared. To decrease possible confounding and selection biases of the baseline characteristics in the two groups, 1:1 matching variables [age, sex, body mass index, presence of comorbidity, α -fetoprotein (AFP), hepatitis B virus, hepatitis C virus, indocyanine green retention rate at 15 min, Child-Pugh classification (13), maximum tumour size, number of tumours, cirrhosis, macrovascular invasion, microvascular invasion, tumour differentiation, American Joint Committee on Cancer (AJCC) stage (14) and resection margins] were applied using PSM. As a result, 50 patients were divided into two groups: The BDTT group (n=25) and the group without BDTT (n=25). The clinicopathological characteristics and survival rates of the two groups were compared once more after PSM and the prognostic risk factors of HCC patients who underwent liver resection were assessed by the Cox proportional hazards model after excluding other influencing factors. In addition, the curative effects on BDTT in patients with HCC who underwent tumour thrombectomy and bile duct resection were compared. The current study was approved by the Institutional Review Board of The First Affiliated Hospital of Fujian Medical University and performed in accordance with the ethical guidelines of the institute.

Preoperative evaluation and management. Primary tumours were evaluated by contrast-enhanced thin-slice computed tomography (CT) or magnetic resonance imaging (MRI) and MR cholangiopancreatography. Liver function and whether another comorbidity was present were also assessed. Liver function was evaluated using the Child-Pugh classification system. An attempt was made to convert Child-Pugh class B disease into class A disease via appropriate preoperative treatment. To improve liver function and treat cholangitis, it was necessary to perform biliary drainage by percutaneous transhepatic biliary drainage (PTBD) or to use an endoscopic retrograde cholangiopancreatography in certain patients. The serum total bilirubin (TBIL) level of patients with obstructive jaundice after appropriate preoperative management needed to decrease to <2.0 mg/dl or by >50% before major hepatectomy was performed (normal range, 0.1-1.0 mg/dl).

Surgical strategy. The surgical strategy was determined preoperatively at the department specialist meeting (similar to a multidisciplinary team conference). Sometimes, adjustments were necessary during surgery to select a reasonable procedure based on intraoperative exploration. The basic policy for the surgical treatment of HCC in The First Affiliated Hospital of

Fujian Medical University is that if the remaining liver function is sufficient, there is an inclination to perform an anatomical resection; non-anatomical resection is recommended only when the tumour is small, the position is superficial or the remaining liver function is insufficient. Anatomical resection involved resection of the tumour with its related portal vein branches and corresponding hepatic region. The surgical treatment strategy was complete resection of the primary HCC and BDTT, trying not to remove the extrahepatic bile duct, similar to the 'peeling off technique' (10). The extrahepatic bile duct was resected only when the BDTT could not be completely peeled off or would have violated the bile duct wall.

Pathological evaluation. After the specimens were stored and fixed in 10% formalin at room temperature for 12 h, they were embedded in paraffin and cut into 5- μ m-thick sections. Hematoxylin and eosin staining (performed for 10 min at room temperature) and a light microscope (Nikon Corporation; magnification, x100, x200 and x400; analyzed using QImaging MicroPublisher 3.3 with Real-Time Viewing; Teledyne QImaging) were used. The numbers, sizes (maximum tumour diameter) and locations of the tumours were recorded during a macroscopic examination of the resected specimens by a pathologist. Moreover, the microscopic examination included determination of the histological differentiation, invasion of the bile duct (the size and location of BDTT), microvasculature and macrovasculature, the specimen margin and the presence of cirrhosis. The histological differentiation of HCC was assigned according to the Edmondson-Steiner system (15). Tumour stage was classified in accordance with the criteria of the AJCC (8th edition). HCC with macroscopic BDTT represents a tumour thrombus found in the common hepatic duct or the first to second branches of the intrahepatic bile duct. Classification of HCC with macroscopic BDTT was in accordance with the criteria of the Ueda classification (3).

Follow-up. Specially trained researchers used outpatient records and telephone calls to follow-up with the patients. After discharge from the hospital, AFP tests, ultrasound (US) and contrast-enhanced CT or MRI were performed at least every 3 months during the follow-up period. If recurrence or metastasis was observed, follow-up treatments, such as TACE, RFA, microwave ablation, reoperation and targeted drug administration, such as Sorafenib (400 mg bid), Rivatinib (8-12 mg qd) or Regorafenib (160 mg qd), were performed, as determined by the patient's condition. Survival time was calculated from the date of surgery to the date of last contact, death or collection of survival information. The follow-up deadline was May 2019.

Statistical analysis. PSM was performed with a multiple factor logistic regression model, and a calliper of 0.10 of the standard deviation of the logit was imposed. Continuous variables are reported as the mean \pm standard deviation, and categorical variables are reported as the count and percentage. Continuous variables were compared using Student's t-test or the Mann-Whitney U test as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test if necessary. Patient survival rates were analysed by the Kaplan-Meier method, and survival curves were compared between groups using the log-rank test.

Table I. Clinical features and operative procedures of patients with macroscopic BDTT.

Patient no.	Sex	Age, years	Location of tip of BDTT	Ueda type ^a	Biliary decompression	Operative procedure	Bile duct resection	Tumour thrombectomy
1	M	54	Left hepatic duct	2	No	Left hepatectomy	No	No
2	M	50	CBD	3	No	Right hepatectomy	No	Yes
3	M	67	CBD	3	Yes	Expand right hepatectomy	Yes	No
4	M	60	CBD	3	Yes	Right hepatectomy	No	Yes
5	F	61	Right hepatic duct	2	No	Right hepatectomy	No	No
6	M	55	CBD	3	Yes	Central hepatectomy	No	Yes
7	F	64	CBD	3	No	Right hepatectomy	No	Yes
8	M	65	CBD	3	Yes	Right hepatectomy	No	Yes
9	M	39	CBD	3	No	Right hepatectomy	Yes	No
10	M	65	Right hepatic duct	2	No	Right hepatectomy	No	No
11	M	68	CBD	3	No	Right hepatectomy	No	Yes
12	F	49	Left hepatic duct	2	No	Left hepatectomy	No	No
13	M	41	CBD	3	Yes	Right hepatectomy	Yes	No
14	M	61	CBD	3	Yes	Central hepatectomy	No	Yes
15	M	64	CBD	3	No	Left hepatectomy	No	Yes
16	M	59	CBD	3	No	Left hepatectomy	No	Yes
17	M	62	CBD	3	Yes	Left hepatectomy	No	Yes
18	F	44	The second branch	1	No	Right posterior section	No	No
19	F	70	The second branch	1	No	Right posterior section	No	No
20	M	58	CBD	3	No	Central hepatectomy	No	Yes
21	M	62	Right hepatic duct	2	No	Right hepatectomy	No	No
22	M	55	Left hepatic duct	2	No	Left hepatectomy	No	No
23	F	63	Left hepatic duct	2	No	Left hepatectomy	No	No
24	M	47	Left hepatic duct	2	No	Left hepatectomy	No	No
25	M	44	CBD	3	Yes	Left hepatectomy	Yes	No

^aType 3a or 3b were classified together as type 3. BDTT, bile duct tumour thrombus; CBD, common bile duct; M, male; F, female.

Patients who succumbed within 30 days of surgery were excluded from the survival analysis. Moreover, patients who underwent non-curative surgical resection were excluded from the recurrence analysis. Univariate and multivariate analyses were performed using Cox proportional hazards regression analyses. The variables found to have prognostic significance in the univariate analysis were entered into the Cox multivariate proportional hazards regression analysis to identify factors that independently predicted the HCC prognosis. $P < 0.05$ was considered to indicate a statistically significant difference. SPSS statistics software (version 24.0; IBM Corp.) was used for all statistical analyses.

Results

Perioperative outcomes of HCC patients with BDTT. The clinical features of the 25 HCC patients with macroscopic BDTT are shown in Table I. The common bile duct (CBD) was the most frequent location of BDTT in this study (15 patients; 60%), followed by the left hepatic duct (5 patients; 20%), the right hepatic duct (3 patients; 12%) and the second-order branch of the intrahepatic bile duct (2 patients; 8%). According to the Ueda classification, BDTT was classified as type

1 in 2 patients (8%), type 2 in 8 patients (32%) and type 3 in 15 patients (60%). No type 4 cases were included in this study. Among these patients, 11 (44%) were diagnosed with obstructive jaundice on admission. A subsequent biliary drainage procedure was performed using PTBD guided by US in 8 patients (32%), and 2 patients (8%) underwent PTBD of the right hepatic duct and then PTBD of the left hepatic duct again on postoperative days 19 and 27. Another 3 patients (12%) did not have biliary drainage as their TBIL increased in the short term and did not increase markedly before surgery. The median duration from biliary drainage to surgical treatment was 23 days (range, 13-42 days). A total of 17 patients (68%) had TBIL levels < 2.0 mg/dl at the time of surgery, and TBIL levels decreased by 14.3 ± 6.4 mg/dl at the time of preoperative biliary drainage. However, preoperative TBIL in the BDTT group was significantly higher than that in the without BDTT group (1.98 ± 1.72 vs. 1.00 ± 0.62 mg/dl; $P = 0.010$; data not shown).

The operative procedures used in the BDTT group are shown in Table I. The primary tumours were removed by right hemihepatectomy in 11 patients (44%), including an extended right hemihepatectomy in 1 patient (4%), by left hemihepatectomy in 9 patients (36%), by central hepatectomy in 3 patients

Table II. Clinicopathological characteristics before and after propensity score matching.

Variables	All patients			Propensity-matched patients		
	With BDTT (n=25)	Without BDTT (n=606)	P-value	With BDTT (n=25)	Without BDTT (n=25)	P-value
Age, years	57.08±8.98	55±11.65	0.290	57.08±8.98	55.24±9.34	0.479
Sex, n			0.164			0.269 ^a
Male	19	521		19	22	
Female	6	85		6	3	
BMI, kg/m ²	22.77±3.29	23.06±9.58	0.680	22.77±3.29	22.67±3.55	0.920
Presence of comorbidity, n			0.694			0.771
Yes	10	219		10	9	
No	15	387		15	16	
AFP, n			0.171			0.777
≤400 µg/l	14	188		14	13	
>400 µg/l	11	418		11	12	
HBV, n			0.212			0.480 ^a
Positive	19	516		19	21	
Negative	6	90		6	4	
HCV, n			1.000 ^b			1.000 ^b
Positive	0	17		0	0	
Negative	25	589		25	25	
ICGR15, %	7.53±4.36	6.96±3.87	0.396	7.53±4.36	7.25±3.66	0.810
Child-Pugh classification ^c , n			0.002 ^a			0.221 ^a
A	20	586		20	23	
B	5	20		5	2	
Maximum tumour size, cm	6.97±3.45	5.15±3.58	0.019	6.97±3.45	6.51±5.12	0.714
Number of tumours, n			0.461 ^a			1.000 ^a
Solitary	21	538		21	21	
Multiple	4	68		4	4	
Cirrhosis, n			0.001			0.145
Yes	7	366		7	12	
No	18	240		18	13	
Macrovascular invasion, n			0.002 ^a			0.440 ^a
Yes	5	31		5	3	
No	20	575		20	22	
Microvascular invasion, n			<0.001			0.089
Yes	15	153		15	9	
No	10	453		10	16	
Tumour differentiation, n			0.003 ^a			0.172 ^a
Well	0	36		0	2	
Moderate	12	429		12	15	
Poor	13	141		13	8	
AJCC stage ^c , n			0.001			0.505 ^a
I	8	403		8	12	
II	11	148		11	8	
III	6	55		6	5	
Resection margins, n			0.026 ^a			0.157 ^a
R0	21	592		21	24	
R1	4	14		4	1	

Continuous variables are presented as the mean ± SD. ^aFisher's exact test. ^bChild-Pugh classification system: Class A, 5-6 points; class B, 7-9 points. ^cStage Ia or Ib and IIIa or IIIb were classified together as stage I and III, respectively. Tumour stage was classified in accordance with the criteria of the AJCC 8th edition. AFP, α-fetoprotein; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green retention rate at 15 min; AJCC, American Joint Committee on Cancer; BDTT, bile duct tumour thrombus.

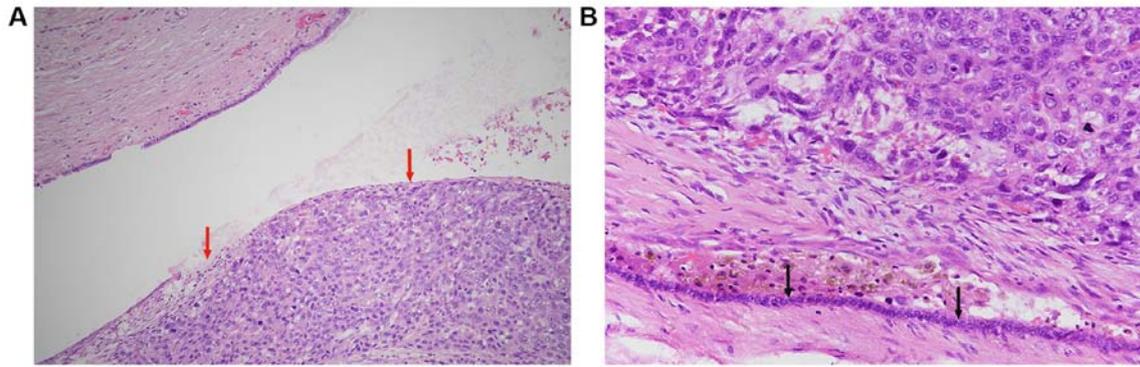


Figure 1. Histopathological findings of BDTT analyzed via hematoxylin and eosin staining. (A) BDTT (red arrow) did not adhere to the bile duct wall around it (magnification, x100). (B) The BDTT and bile duct wall are separated by fibrous tissue, and pro-fibrotic reactions are easily formed between the BDTT and bile duct epithelium (black arrow) (magnification, x400). BDTT, bile duct tumour thrombus.

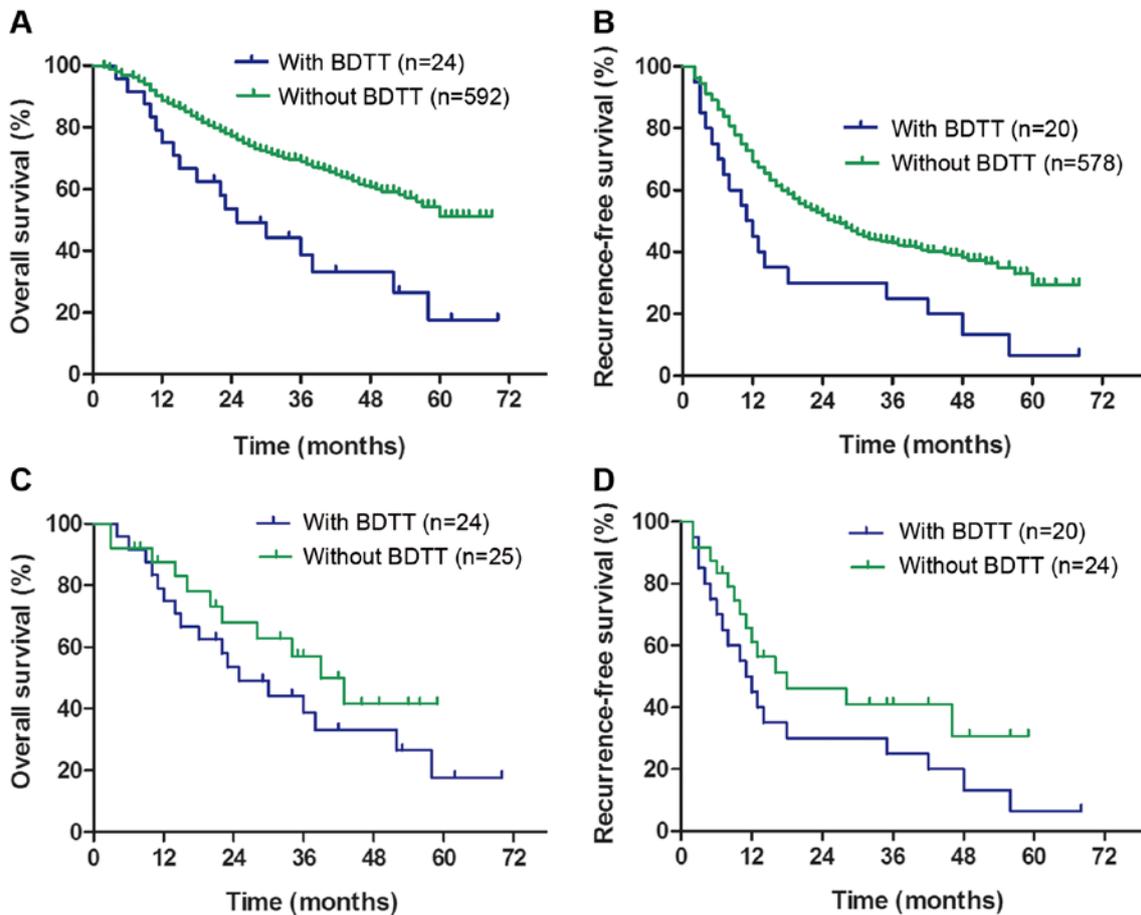


Figure 2. OS and RFS curves between two groups before and after PSM. (A) The OS of the BDTT group was significantly poorer than that of group without BDTT before PSM. (B) The RFS of the BDTT group was significantly poorer than that of the group without BDTT before PSM. (C) The OS comparison between the groups with and without BDTT revealed no significant difference after PSM. (D) The RFS comparison between the groups with and without BDTT revealed no significant difference after PSM. OS, overall survival; RFS, recurrence-free survival; PSM, propensity score matching; BDTT, bile duct tumour thrombus.

(12%) and by right posterior sectionectomy in 2 patients (8%). Caudate lobectomy was performed in 8 patients (32%). The BDTT was removed by thrombectomy either through choledochotomy or the cut end of the bile duct in 11 patients (44%), and extrahepatic bile duct resection was performed in 4 patients (16%). In the remaining 10 patients (40%), BDTTs were resected en bloc together with the primary tumour. Compared

with those in the group without BDTT, the average operative time and intraoperative blood loss in the BDTT group were significantly greater (249.67 ± 80.54 vs. 166.75 ± 55.73 min, $P < 0.001$; and 966.67 ± 917.16 vs. 352.86 ± 335.72 ml, $P = 0.012$, respectively). The perioperative mortality rate was not significantly different between the two groups (4.0 vs. 1.16%; $P = 0.287$) (data not shown).

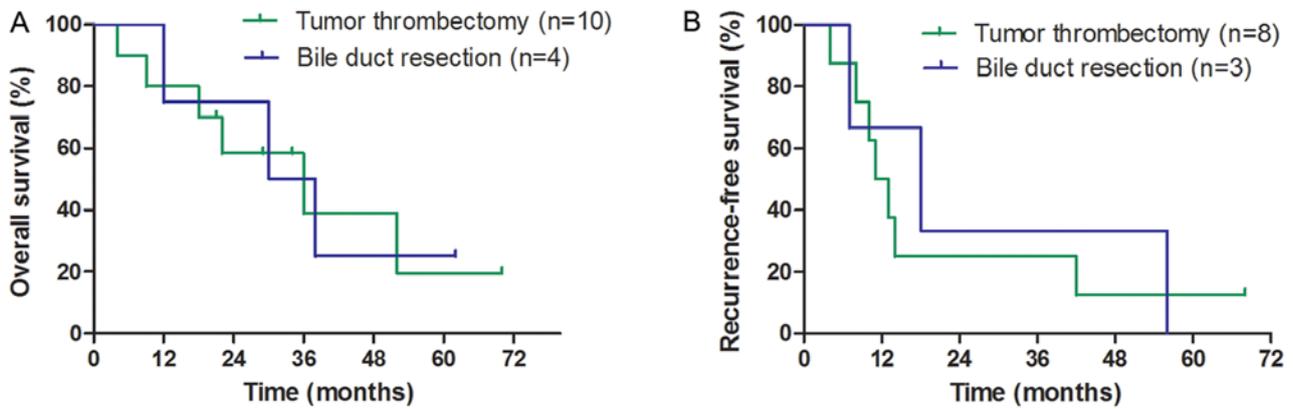


Figure 3. Postoperative OS and RFS curves for HCC patients with Ueda type 3 bile duct tumour thrombus according to bile duct resection or absence of bile duct resection. (A) OS comparison between HCC patients who underwent bile duct resection and tumour thrombectomy revealed no significant difference. (B) RFS comparison between HCC patients who underwent bile duct resection and tumour thrombectomy revealed no significant difference. OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma.

Clinicopathological characteristics before and after PSM.

The clinicopathological characteristics of the two groups before and after PSM are shown in Table II. The proportion of females and AFP levels in the BDTT group seemed to be higher, but these results did not reach statistical significance. Fewer patients had a Child-Pugh A classification in the BDTT group than in the group without BDTT just before surgery ($P=0.002$), which corresponds to the aforementioned result that the preoperative TBIL level in the BDTT group was significantly higher than that in the group without BDTT. The numbers of tumours were not significantly different between the two groups, while the tumour diameter in the BDTT group was significantly larger than that in the group without BDTT ($P=0.019$). In the BDTT group, 5 patients (20%) had macrovascular invasion and 15 patients (60%) had microvascular invasion, with both values being significantly higher than those in the group without BDTT ($P=0.002$ and $P<0.001$, respectively). The Edmondson-Steiner grade and AJCC stage in the BDTT group were also significantly higher than those in the group without BDTT ($P=0.003$ and $P=0.001$, respectively). However, the presence of cirrhosis was significantly lower in the BDTT group than in the group without BDTT ($P=0.001$).

The imbalance in clinicopathological characteristics between the two groups indicates that the data between the two groups were incomparable before PSM. To balance this difference, the clinicopathological indices were set as matching covariates for PSM. The aforementioned variables were not significantly different between these two groups after PSM ($P>0.05$), indicating that the two sets of data were comparable (Table II).

Postoperative pathological features. Although the most common location of BDTT was the CBD (60%) in the present study, BDTT rarely invaded the wall of the CBD histologically. The underlying epithelium of the resected large bile ducts was well preserved based on the histological examination of the 4 patients who underwent extrahepatic bile duct resection in this study. One of the postoperative histopathological findings was that BDTT did not usually adhere to the CBD. The cancer cells in BDTT were flaky and solid, the cells had obvious atypia and pleomorphism, and pathological mitosis was not

uncommon (Fig. 1A). Although the tumour cells were scattered and haemosiderin deposition was evident, suggesting old bleeding, biliary epithelial cells were still continuous and intact, and were protected by profibrotic reactions (Fig. 1B).

Postoperative long-term outcomes. Patients who died perioperatively were excluded from the survival analysis. The median follow-up duration was 32 months (range, 1-70 months). The cumulative 1-, 3- and 5-year overall survival (OS) rates in the group without BDTT (88.61, 69.01 and 51.16%, respectively) were significantly higher than those in the BDTT group (75.00, 38.67 and 17.68%, respectively) ($P<0.001$; Fig. 2A). The cumulative 1-, 3- and 5-year recurrence-free survival (RFS) rates in the group without BDTT (69.32, 43.01 and 29.40%, respectively) were significantly higher than those in the BDTT group (45.00, 25.00, and 6.67%, respectively) ($P=0.003$; Fig. 2B). However, no significant differences in the cumulative 1-, 3- and 5-year OS or RFS rates were identified between the two groups after PSM (OS: 87.62, 57.07 and 41.61%, respectively, vs. 75.00, 38.67 and 17.68%, respectively; $P=0.249$; Fig. 2C; RFS: 61.09, 41.01 and 30.76%, respectively, vs. 45.00, 25.00 and 6.67%, respectively; $P=0.121$; Fig. 2D). These results illustrate that covariates other than BDTT also affect the RFS and OS rates.

In the BDTT group, the median OS and RFS times of patients who underwent tumour thrombectomy and bile duct resection were not significantly different (OS: 36 vs. 30 months, respectively; $P=0.891$; Fig. 3A; RFS: 11 vs. 18 months, respectively; $P=0.787$; Fig. 3B). A total of 17 HCC (68.0%) patients with BDTT experienced recurrence during the follow-up; intrahepatic recurrence was the most common type [12/17 (70.59%)], followed by combined intrahepatic and extrahepatic recurrence [3/17 (17.65%)] and extrahepatic recurrence [2/17 (11.76%)], both of which were in the lungs (data not shown). None of the patients who underwent tumour thrombectomy exhibited peritoneal dissemination, and only one of these patients experienced bile duct recurrence and underwent re-resection.

Univariate and multivariate analyses of OS. Univariate and multivariate analyses were performed by Cox proportional

Table III. Univariate and multivariate cox proportional analysis for overall survival.

Variables	n	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Group							
Without BDTT	25	1.000					
With BDTT	24	1.558	0.727-3.341	0.254			
Age, years							
<60	31	1.000					
≥60	18	1.230	0.5745-2.633	0.593			
Gender							
Male	40	1.000					
Female	9	1.242	0.464-3.323	0.666			
Presence of comorbidity							
No	31	1.000					
Yes	18	1.151	0.543-2.441	0.715			
AFP, µg/l							
<400	26	1.000					
≥400	23	1.617	0.764-3.423	0.209			
HBV virus antigen							
Negative	9	1.000					
Positive	40	1.005	0.405-2.498	0.991			
ICGR15^a, %							
≤10	22	1.000					
>10	8	2.417	0.703-8.307	0.161			
Child-Pugh classification							
A	42	1.000					
B	7	1.655	0.666-4.113	0.278			
Maximum tumour size, cm							
>5	24	1.000					
≥5	25	1.614	0.743-3.506	0.226			
Number of tumours							
Solitary	41	1.000					
Multiple	8	1.717	0.725-4.065	0.219			
Cirrhosis							
No	31	1.000					
Yes	18	1.27	0.587-2.747	0.544			
Macrovascular invasion							
Negative	41	1.000			1.000		
Positive	8	4.613	1.944-10.947	0.001	3.220	1.184-8.756	0.022
Microvascular invasion							
Negative	24	1.000			1.000		
Positive	25	2.942	1.350-6.413	0.007	1.728	0.737-4.051	0.208
Tumour differentiation							
Well ^b	2	-	-	-	-	-	-
Moderate	27	1.000			1.000		
Poor	20	2.302	1.081-4.905	0.031	2.150	0.968-4.775	0.06
Resection margins							
R0	44	1.000			1.000		
R1	5	5.715	2.065-15.819	0.001	2.563	0.789-8.326	0.117

^aIn the early years, some patients did not undergo the ICG15 test so n=30 only. ^bDue to the small number of cases in these groups, the survival analysis was meaningless. HR, hazard ratio; CI, confidence interval; AFP, α-fetoprotein; HBV, hepatitis B virus; ICGR15, indocyanine green retention rate at 15 min; BDTT, bile duct tumour thrombus.

hazards regression in 49 patients who underwent PSM. The univariate analysis revealed that macrovascular invasion (HR, 4.613; $P=0.001$), microvascular invasion (HR, 2.942; $P=0.007$), tumour differentiation (HR, 2.302; $P=0.031$) and resection margins (HR, 5.715; $P=0.001$), rather than BDTT (HR, 1.558; $P=0.254$), significantly affected OS (Table III). These potential risk factors were further examined by multivariate Cox proportional hazards regression analysis. The results revealed that macrovascular invasion (HR, 3.220; 95% CI, 1.184-8.756; $P=0.022$) was the only independent predictor of OS (Table III).

Discussion

Manifestations of jaundice in patients with HCC are thought to be caused by massive tumour infiltration of the liver parenchyma or advanced underlying liver cirrhosis (16,17). Sometimes, precisely distinguishing the cause of jaundice is difficult in clinical practice (18); therefore, patients with BDTT and jaundice are often forced to receive conservative treatment, thus missing the opportunity for suitable treatment with a potential chance of a complete response. This is mainly due to insufficient understanding of the clinicopathological characteristics of the tumour. Although a general consensus indicates that the oncological prognosis of surgical treatment is significantly improved compared with that of palliative treatment (11,12), studies on the surgical treatment of HCC with BDTT are uncommon, especially studies regarding postoperative long-term outcomes. Whether the postoperative survival of patients with HCC and BDTT is equal to that of patients with HCC and no BDTT (2,8,18-24) and whether the extrahepatic bile duct should be removed remain controversial (9,25,26).

As reported in previous studies (24,27,28), compared with HCC without BDTT, HCC with BDTT demonstrates clinicopathological features such as a longer tumour diameter, a higher incidence of vascular invasion and a higher Edmondson-Steiner grade, AJCC stage and Child-Pugh classification; however, cirrhosis is less common (28), which may be associated with the biological behaviour of HCC with BDTT. The current results (Table II) before PSM are consistent with these earlier findings, which decreases the comparability of these studies. PSM could have balanced the confounding variables and reduced the impact of selection biases, and the results would have been similar to those of randomized controlled studies (29,30). The clinicopathological features between the two groups after PSM were not significantly different, which increased the comparability between groups. Therefore, PSM was used to control for selection bias in the current study, increasing the credibility of the research results.

Another notable area for comparison is whether postoperative survival among HCC patients with BDTT is equal to that among HCC patients without BDTT. Yang *et al* (21) reported that the median OS time in the BDTT group (16.6 months) was significantly worse than that in the group without BDTT (84.0 months). Other studies (8,22,23) have also illustrated that, compared with the OS in the group without BDTT, the OS of the BDTT group was significantly poorer. However, Shiomi *et al* (16) reported that the 3- and 5-year OS rates (47 and 28%, respectively) in the BDTT group were not significantly different from those in the group without BDTT

(63 and 48%, respectively; $P=0.190$). The reason for this difference may be that the potential impact of other variables on the postoperative survival of patients with HCC and BDTT was neglected (2,24). In the present study, the 3- and 5-year OS rates in the BDTT group were worse than those in the group without BDTT before PSM. However, no significant difference was observed between the two groups after PSM. These results show that when matching other variables and balancing selection bias, BDTT does not affect the long-term survival of patients with HCC who receive liver resection.

The RFS rates in the BDTT group were significantly worse than those in the group without BDTT before PSM in the present study, which is consistent with the results of previous studies (8,21). However, Kim *et al* (22) reported that RFS rates between the two groups were not significantly different. Similarly, in the current study, no significant differences in RFS rates were found between the two groups after PSM. These results indicate that BDTT does not affect postoperative RFS in patients with HCC. Tumour recurrence is generally accepted to affect survival in patients with HCC who undergo surgery with curative intent. Zeng *et al* (7) also reported that tumour recurrence was an unfavourable prognostic factor for OS. BDTT did not affect postoperative RFS in patients with HCC, which indirectly illustrates that it is not an unfavourable prognostic factor for OS after surgery. All the results indicate that BDTT in HCC has low indolent malignant potential and is not a contraindication for liver resection.

HCC with portal vein tumour thrombus (PVTT) is recognized as a relatively advanced-stage disease regardless of the criteria of the Barcelona Clinic for Liver Cancer Staging System (31) or the AJCC 8th Edition. HCC patients with PVTT have a highly unfavourable prognosis with regard to macrovascular invasion, often causing the widespread dissemination of cancer cells and leading to intrahepatic metastasis, which is considered an important mechanism of intrahepatic recurrence (32,33). In the present study, the results of the multivariate analysis revealed that macrovascular invasion was one of the independent prognostic risk factors for the long-term survival of HCC patients after resection, which is similar to the results of previous studies (28). These findings may be associated with the highly aggressive biological behaviour of HCC with macrovascular invasion. Non-curative liver resection was deemed another independent unfavourable risk factor for postoperative long-term survival in HCC patients in the univariate analysis, but not in the multivariate analysis, in the present study. The reason for this finding may be that the number of patients who underwent non-curative resection was insufficient, and its statistical weight was inadequate. Therefore, we hypothesize that when the number of non-curative surgical resections increases, non-curative resection may increase the risk of impaired long-term postoperative survival, which is a theory that is widely accepted by some surgeons (34,35). Therefore, if associated conditions are permitted, curative resection is recommended when the liver function of these patients is sufficient after appropriate preoperative management.

Whether extrahepatic bile duct resection for HCC with BDTT is necessary remains controversial. Moon *et al* (25) claimed that if BDTT could be successfully removed, bile duct resection may not be necessary. Moreover, Noda *et al* (28)

and Shibata *et al* (36) illustrated that the potential for serious complications, such as liver abscesses, may not be avoided when intrahepatic recurrence is treated locally after bile duct resection. Neither the median survival time nor the RFS time between the bile duct resection and tumour thrombectomy groups was significantly different in the present study, which is consistent with the results of previous studies (16,19). The surgical treatment strategy in the current study was the complete resection of primary HCC and BDTT, and it aimed not to remove the extrahepatic bile duct; this is similar to the 'peeling off technique' (10). Tumour thrombectomy is believed to have potential risks of peritoneal dissemination and recurrence in the preserved bile duct. However, Kim *et al* (37) proclaimed that thrombectomy does not significantly increase the risk of peritoneal metastasis. None of the patients who underwent tumour thrombectomy presented with peritoneal dissemination in the present study. Although bile duct recurrence was observed in one of these patients, the risks are considered minimal as the first recurrence most frequently occurs in the remnant liver and not in the bile duct, and the opportunity to undergo curative re-resection is still available.

The absence of bile duct resection for patients with HCC and BDTT may cause recurrence due to direct invasion of the tumour into the bile duct, periductal capillary plexus and lymphatic system (27,38). Recently, a multicentre study reported that bile duct resection was a significant favourable prognostic factor for recurrence, OS and survival after recurrence (37). Based on the aforementioned studies, the selection criteria for resecting the bile duct could not be too absolute, and an individualized treatment plan was required according to the condition of each patient. Whether extrahepatic bile duct resection is necessary for patients with HCC with BDTT should be further explored. Regardless of the surgical approach to remove or retain the bile duct, curative resection of the tumour is the most important aim.

The present study also has some limitations. As a retrospective case-control study, although a control group was established for direct comparisons, the number of patients with BDTT was insufficient. The reasons may be as follows: i) The incidence of HCC with BDTT is rare (2-6); ii) the biological and clinicopathological characteristics of the tumours were inadequately understood, therefore, many patients did not receive surgical treatment in the early period; and iii) the clinicopathological data of these patients were incomplete in the early period and were thus excluded from the study. Considering the rarity of HCC with BDTT, the present study is of great clinical significance, as the number of included patients exceeds that in numerous other studies (2,10,16,28,34). Although PSM was used to reduce the imbalance caused by selection bias, some unavoidable confounding variables remain. For instance, the preoperative TBIL level in the BDTT group was significantly higher than that in the group without BDTT before and after PSM. However, the impact of the preoperative TBIL level on survival was reflected in the Child-Pugh classification system, and it was not identified as an important prognostic factor for patients with BDTT. Large, multicentre, prospective, randomized, controlled trials are still needed for further validation.

Compared with those of patients without BDTT, the clinicopathological features of patients with HCC and BDTT are more advanced, and the long-term postoperative outcome of

these patients is worse. Macrovascular invasion, but not BDTT, is a significantly unfavourable risk factor for the survival of patients with HCC who undergo liver resection. Curative resection is recommended for patients with HCC and BDTT, even for those with poor liver function after proper perioperative management, in order to achieve good long-term survival.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

QC analyzed and interpreted the patient data, and was a major contributor in writing the manuscript. SW was involved in study design, study supervision and critical revision of the manuscript. ZS, ZZ and XZ analyzed and interpreted the patient data. LZ performed the histological examination of the HCC samples. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from all individuals included in the study at the time of initial data collection. The study was approved by the Institutional Review Board of The First Affiliated Hospital of Fujian Medical University and performed in accordance with the ethical guidelines of the institute.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Shehta A, Han HS, Yoon YS, Cho JY and Choi Y: Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience. *Surg Endosc* 30: 638-648, 2016.
2. Oba A, Takahashi S, Kato Y, Gotohda N, Kinoshita T, Shibasaki H, Ikeda M and Konishi M: Usefulness of resection for hepatocellular carcinoma with macroscopic bile duct tumor thrombus. *Anticancer Res* 34: 4367-4372, 2014.
3. Ueda M, Takeuchi T, Takayasu T, Takahashi K, Okamoto S, Tanaka A, Morimoto T, Mori K and Yamaoka Y: Classification and surgical treatment of hepatocellular carcinoma (HCC) with bile duct thrombi. *Hepatology* 41: 349-354, 1994.

4. Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, Takayama T, Nakashima O, Matsui O and Matsuyama Y: Report of the 19th follow-up survey of primary liver cancer in Japan. *Hepatol Res* 46: 372-390, 2016.
5. Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K and Ikari T: Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. *Cancer* 51: 863-877, 1983.
6. Meng KW, Dong M, Zhang WG and Huang QX: Clinical characteristics and surgical prognosis of hepatocellular carcinoma with bile duct invasion. *Gastroenterol Res Pract* 2014: 604971, 2014.
7. Zeng H, Xu LB, Wen JM, Zhang R, Zhu MS, Shi XD and Liu C: Hepatocellular carcinoma with bile duct tumor thrombus: A clinicopathological analysis of factors predictive of recurrence and outcome after surgery. *Medicine (Baltimore)* 94: e364, 2015.
8. Shao W, Sui C, Liu Z, Yang J and Zhou Y: Surgical outcome of hepatocellular carcinoma patients with biliary tumor thrombi. *World J Surg Oncol* 9: 2, 2011.
9. Ikenaga N, Chijiwa K, Otani K, Ohuchida J, Uchiyama S and Kondo K: Clinicopathologic characteristics of hepatocellular carcinoma with bile duct invasion. *J Gastrointest Surg* 13: 492-497, 2009.
10. Yamamoto S, Hasegawa K, Inoue Y, Shindoh J, Aoki T, Sakamoto Y, Sugawara Y, Makuuchi M and Kokudo N: Bile duct preserving surgery for hepatocellular carcinoma with bile duct tumor thrombus. *Ann Surg* 261: e123-e125, 2015.
11. Xiangji L, Weifeng T, Bin Y, Chen L, Xiaoqing J, Baihe Z, Feng S and Mengchao W: Surgery of hepatocellular carcinoma complicated with cancer thrombi in bile duct: Efficacy for criteria for different therapy modalities. *Langenbecks Arch Surg* 394: 1033-1039, 2009.
12. Lau W, Leung K, Leung TW, Liew CT, Chan MS, Yu SC and Li AK: A logical approach to hepatocellular carcinoma presenting with jaundice. *Ann Surg* 225: 281-285, 1997.
13. Bae SH, Park HC, Yoon WS, Yoon SM, Jung IH, Lee JJ, Kim JW, Seong J, Kim TH, Nam TK, *et al*: Treatment outcome after fractionated conformal radiotherapy for hepatocellular carcinoma in patients with child-pugh classification B in Korea (KROG 16-05). *Cancer Res Treat* 51: 1589-1599, 2019.
14. Abdel-Rahman O: Assessment of the discriminating value of the 8th AJCC stage grouping for hepatocellular carcinoma. *HPB (Oxford)* 20: 41-48, 2018.
15. Edmondson HA and Steiner PE: Primary carcinoma of the liver: A study of 100 cases among 48,900 necropsies. *Cancer* 7: 462-503, 1954.
16. Shiomi M, Kamiya J, Nagino M, Uesaka K, Sano T, Hayakawa N, Kanai M, Yamamoto H and Nimura Y: Hepatocellular carcinoma with biliary tumor thrombi: Aggressive operative approach after appropriate preoperative management. *Surgery* 129: 692-698, 2001.
17. Lee NW, Wong KP, Siu KF and Wong J: Cholangiography in hepatocellular carcinoma with obstructive jaundice. *Clin Radiol* 35: 119-123, 1984.
18. Mok KT, Chang HT, Liu SI, Jou NW, Tsai CC and Wang BW: Surgical treatment of hepatocellular carcinoma with biliary tumor thrombi. *Int Surg* 81: 284-288, 1996.
19. Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, Yamamoto N, Iimuro Y, Shimahara Y and Yamaoka Y: Clinicopathologic evaluation of hepatocellular carcinoma with bile duct thrombi. *Surgery* 128: 779-783, 2000.
20. Yeh CN, Jan YY, Lee WC and Chen MF: Hepatic resection for hepatocellular carcinoma with obstructive jaundice due to biliary tumor thrombi. *World J Surg* 28: 471-475, 2004.
21. Yang X, Qiu Z, Ran R, Cui L, Luo X, Wu M, Tan WF and Jiang X: Prognostic importance of bile duct invasion in surgical resection with curative intent for hepatocellular carcinoma using PSM analysis. *Oncol Lett* 16: 3593-3602, 2018.
22. Kim JM, Kwon CH, Joh JW, Sinn DH, Park JB, Lee JH, Kim SJ, Paik SW, Park CK and Yoo BC: Incidental microscopic bile duct tumor thrombi in hepatocellular carcinoma after curative hepatectomy: A matched study. *Medicine (Baltimore)* 94: e450, 2015.
23. Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Perumal SK, Balaraman K, Ramasamy R, Palaniappan R and Govindan M: Bile duct thrombi in hepatocellular carcinoma: Is aggressive surgery worthwhile? *HPB (Oxford)* 17: 508-513, 2015.
24. Wong TC, Cheung TT, Chok KS, Chan AC, Dai WC, Chan SC, Poon RT, Fan ST and Lo CM: Outcomes of hepatectomy for hepatocellular carcinoma with bile duct tumor thrombus. *HPB (Oxford)* 17: 401-408, 2015.
25. Moon DB, Hwang S, Wang HJ, Yun SS, Kim KS, Lee YJ, Kim KH, Park YK, Xu W, Kim BW, *et al*: Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: A Korean multicenter study. *World J Surg* 37: 443-451, 2013.
26. Yasunori M and Masatoshi K: Hepatocellular carcinoma with obstructive jaundice: Endoscopic and percutaneous biliary drainage. *Dig Dis* 30: 592-597, 2012.
27. Orimo T, Kamiyama T, Yokoo H, Wakayama K, Shimada S, Tsuruga Y, Kamachi H and Taketomi A: Hepatectomy for hepatocellular carcinoma with bile duct tumor thrombus, including cases with obstructive Jaundice. *Ann Surg Oncol* 23: 2627-2634, 2016.
28. Noda T, Nagano H, Tomimaru Y, Murakami M, Wada H, Kobayashi S, Marubashi S, Eguchi H, Takeda Y, Tanemura M, *et al*: Prognosis of hepatocellular carcinoma with biliary tumor thrombi after liver surgery. *Surgery* 149: 371-377, 2011.
29. Rubin DB: Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 127: 757-263, 1997.
30. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 46: 399-424, 2011.
31. Cho HJ, Kim SS, Kang SY, Yang MJ, Noh CK, Hwang JC, Lim SG, Shin SJ, Lee KM, Yoo BM, *et al*: A proposal for modification of the barcelona clinic liver cancer staging system considering the prognostic implication of performance status. *Gut Liver* 13: 557-568, 2019.
32. Vauthey JN, Klimstra D, Franceschi D, Tao Y, Fortner J, Blumgart L and Brennan M: Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. *Am J Surg* 169: 28-35, 1995.
33. Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H, Yamaguchi N and Makuuchi M: Recurrence of hepatocellular carcinoma after surgery. *Br J Surg* 83: 1219-1222, 1996.
34. Esaki M, Shimada K, Sano T, Sakamoto Y, Kosuge T and Ojima H: Surgical results for hepatocellular carcinoma with bile duct invasion: A clinicopathologic comparison between macroscopic and microscopic tumor thrombus. *J Surg Oncol* 90: 226-232, 2005.
35. Han J, Li ZL, Xing H, Wu H, Zhu P, Lau WY, Zhou YH, Gu WM, Wang H, Chen TH, *et al*: The impact of resection margin and microvascular invasion on long-term prognosis after curative resection of hepatocellular carcinoma: A multi-institutional study. *HPB (Oxford)* 21: 962-971, 2019.
36. Shibata T, Yamamoto N, Ikai I, Shimahara Y, Yamaoka Y, Itoh K and Konishi J: Choledochojejunostomy: Possible risk factor for septic complications after percutaneous hepatic tumor ablation. *AJR Am J Roentgenol* 174: 985-986, 2000.
37. Kim DS, Kim BW, Hatano E, Hwang S, Hasegawa K, Kudo A, Ariizumi S, Kaibori M, Fukumoto T, Baba H, *et al*: Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: A Korea-Japan multicenter study. *Ann Surg* 271: 913-921, 2020.
38. Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N and Nakashima T: Hepatocellular carcinoma presenting as intrabiliary duct tumor growth: A clinicopathologic study of 24 cases. *Cancer* 49: 2144-2147, 1982.



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