Hepatectomy for hepatocellular carcinoma with bile duct tumor thrombus, including cases with obstructive jaundice

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Synopsis

Hepatectomy should be considered for hepatocellular carcinoma with bile duct tumor thrombus.

Abstract

Purpose: The purpose of this study was to evaluate the short- and long-term outcomes of hepatectomy for hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT), including cases with obstructive jaundice.

Methods: We reviewed 42 HCC patients with BDTT, including 6 patients who needed preoperative biliary drainage due to obstructive jaundice and 732 HCC patients without BDTT. We analyzed the impact of BDTT on the surgical outcomes and assessed the outcomes of hepatectomy for patients presenting with obstructive jaundice.

Results: HCC patients with BDTT had increased alpha-fetoprotein expression, larger tumors, more portal vein invasion status and were almost all stage III or IV. The survival of the HCC patients with BDTT was significantly inferior to that of the patients without BDTT ($p = 0.0003$). There was no significant difference in survival between HCC patients with or without BDTT when the two groups were matched by stage ($p = 0.3366$). HCC patients with BDTT that presented with obstructive jaundice demonstrated similar outcomes as HCC patients with BDTT that did not present with obstructive jaundice in terms of the overall survival rate ($p = 0.5469$). The perioperative outcomes of HCC patients with BDTT did not depend on the presence or absence of preoperative jaundice. No patients in either BDTT group demonstrated 90-day mortality in this study.

Conclusions: Hepatectomy should be considered for HCC patients with BDTT, even for

cases with obstructive jaundice because equivalent surgical outcomes as HCC without BDTT can be achieved.

Background

Hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) is rare in comparison with HCC with portal vein thrombus.[1] HCC with portal vein thrombus is often recognized and its prognosis is poor, but the prognosis of HCC with BDTT is not well recognized due to its rarity. In particular, HCC with BDTT showing obstructive jaundice is called icteric hepatoma, and this type of HCC is known to present difficult problems in the differential diagnosis of conditions such as advanced liver cirrhosis and biliary tract cancer.[2] HCC with BDTT showing obstructive jaundice leads to severe symptoms such as cholangitis and hemobilia, and can cause hepatic failure.[3-5] However, it is difficult to determine the surgical indications for patients with obstructive jaundice because jaundice due to advanced liver cirrhosis is a contraindication for hepatectomy. There have been several studies on HCC with BDTT and it is clear that surgical approach for HCC with BDTT is important. [6-8] However, it is presently unclear whether or not surgical treatment is valid for HCC with BDTT that presents with obstructive jaundice because the short- and long-term outcomes of such cases are unknown. In addition, the optimal surgical approach for HCC patients with BDTT— whether or not to preserve the bile duct —is also unclear.

In this study, we reviewed HCC patients with and without BDTT and analyzed the clinicopathological features and surgical outcomes. Furthermore, we reviewed the surgical management of patients with BDTT that present with obstructive jaundice and evaluated the

validity of the surgical approaches for this type of HCC.

Patients and Methods

Between January 1996 and May 2015, 774 HCC patients underwent several types of hepatectomy at the Department of Gastroenterological Surgery I, Hokkaido University Hospital. Forty-two of these patients (5.4%) had HCC with BDTT that was histopathologically diagnosed. BDTT positive patients were defined as those who had BDTT in the biliary tree or the intrahepatic bile duct histopathologically. BDTT negative patients were defined as those who did not have any BDTT in the biliary tree or the intrahepatic bile duct. Microscopic BDTT was defined as BDTT which developed in more than just the second branch of the intrahepatic bile duct. Macroscopic BDTT was defined as BDTT which existed in the second or the first branch of the biliary tree, or the common bile duct. There were 21 microscopic BDTT and 21 macroscopic BDTT cases in this study. Of the 42 BDTT cases, there were 6 HCC patients with BDTT who demonstrated obstructive jaundice, which required preoperative biliary drainage. Macroscopic portal vein tumor thrombus (PVTT) was defined as PVTT involving the first or the second branches or main trunk of the portal vein. There were 20 macroscopic PVTT cases among HCC patients with BDTT and 82 macroscopic PVTT cases among HCC patients without BDTT in this study. The median follow-up period of these patients was 45.4 months (range = 0.2–233.2

months).

This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 015-0251). All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital.

Preoperative management

Preoperative management was performed according to our previous report.[9] Our algorithm, which incorporates the indocyanine green retention rate at 15 minutes (ICGR15) and remnant liver volume, was used to determine the operative procedure, as previously described. [9] If the ICGR15 is less than 15% and the resected liver volume is less than 60%, hemihepatectomy or extended hemihepatectomy can be performed. However, if the ICGR15 is less than 15% and the resected liver volume is greater than 60%, then percutaneous transhepatic portal embolization is performed before surgery. For patients with an ICGR15 of 15% to 20%, sectionectomy can be performed; for patients with an ICGR15 of 20% to 25%, segmentectomy can be performed; and for patients with an ICGR15 of 25% to 40%, a limited resection can be performed. If the ICGR15 is more than 40%, hepatectomy is contraindicated. For patients with BDTT that presented with obstructive jaundice, biliary drainage was performed first, and hepatic functional reserve was evaluated after the serum bilirubin level was < 2 mg/dl. A liver resection was secondly

performed when possible according to our algorithm.

Surgical methods

The surgical methods used for liver resection were previously described.[9] Anatomical resection was defined as a resection in which the lesion(s) are anatomically completely removed based on Couinaud's classification (segmentectomy, sectionectomy and hemihepatectomy or extended hemihepatectomy). We preserved the bile duct in all HCC patients with BDTT. Our surgical procedure is similar to bile duct-preserving surgery reported by Yamamoto et al. [10] We cut the bile duct, peeled off the tumor thrombus, closed the bile duct incision site by running sutures with 5-0 or 6-0 absorbable monofilament thread, and inserted a C-tube into the cystic duct to decompress the bile duct. We performed cholangiography to verify the absence of the tumor thrombus. Hepatectomy for HCC with BDTT in this study included two right trisectionectomies, one left trisectionectomy, five extended right hepatectomies, four extended left hepatectomies, 13 right hepatectomies, eight left hepatectomies, one central bisectionectomy, two right anterior sectionectomies, two right posterior sectionectomies, two left lateral sectionectomies, and two partial resections.

Statistical analysis

The correlation between BDTT and the clinicopathological features was evaluated using the Fisher exact test for categorical variables or the Mann-Whitney U test for continuous variables. The overall survival rates and time to recurrence were calculated using the Kaplan-Meier method and compared between groups using the log-rank test. Potential prognostic factors were identified by univariate analysis using the log-rank test. Independent prognostic factors were evaluated using a Cox proportional-hazards regression model. In this study, $p < 0.05$ was considered significant. Statistical analyses were performed using JMP (version 12 for Windows; SAS Institute, Cary, NC).

Results

Differences in the clinicopathological features and surgical outcomes according to the presence or absence of BDTT

The clinicopathological features of the HCC patients with and without BDTT are presented in Table 1. The median age, sex, proportion of hepatitis B surface antigen, proportion of hepatitis C virus antibody, Child-Pugh Classification, ICGR15, and proportion of liver cirrhosis in the patients in the BDTT-negative and BDTT-positive groups were similar. On the other hand, HCC patients with BDTT vs without BDTT demonstrated significantly different alpha-fetoprotein expression, TNM stage, tumor size, portal vein invasion status, and proportion of anatomical resection. In terms of histological

differentiation, there were no significant differences between the 2 groups, but there was a tendency toward poorer differentiation in the BDTT-positive group ($p = 0.061$) (Table 1). The overall 1-, 3-, and 5-year survival rates in the HCC patients with BDTT were 75.1%, 44.9%, and 36.6% in comparison with 89.0%, 72.4%, and 61.9% in the HCC patients without BDTT, respectively ($p = 0.0003$) (Fig. 1A). The median survival times (MST) of the HCC patients with and without BDTT were 2.46 and 7.62 years, respectively. Almost all HCC patients with BDTT (41 of 42 patients) were stage III or IV, and therefore when limited to stage III or IV patients there was no significant difference in the survival rate between HCC patients with or without BDTT ($p = 0.3366$) (Fig. 1B).

Risk factors for survival and recurrence in HCC patients with BDTT

In HCC patients with BDTT, univariate analysis revealed that tumor size, differentiation, and portal vein invasion were significant prognostic factors for survival, and tumor size was a significant prognostic factor for recurrence (Table 2). Multivariate analysis revealed that tumor size, differentiation, and portal vein invasion were independent prognostic factors for survival, and tumor size for recurrence (Table 2). In terms of the extent of BDTT, there was no significant difference in the survival rate between HCC patients with microscopic BDTT and HCC patients with macroscopic BDTT ($p = 0.4796$), and the MST values were 2.43 and 2.46 years, respectively (Table 2; Fig. 1C). The median

time to recurrence was 0.48 years for microscopic BDTT patients and 1.24 years for macroscopic BDTT patients, but this was also not significantly different ($p = 0.3331$) (Table 2). Among HCC patients with BDTT, there was no significant difference in the survival rate between patients with and without macroscopic PVTT ($p = 0.0820$). Among HCC patients without BDTT, there was a significant difference in survival between those with and without macroscopic PVTT ($p < 0.0001$).

Recurrence sites and treatments after hepatectomy for HCC with BDTT

The sites of first recurrence after hepatectomy and treatments are listed in Table 3. The most frequent site of recurrence was the liver (15 of 24 patients; 62.5%), and intrahepatic recurrence was most commonly treated using transcatheter arterial chemoembolization (TACE) (10 of 24 patients; 41.6%). In our present study, there was 1 case of recurrence, which developed in the form of BDTT. As a relapse treatment, this BDTT was peeled off and the bile duct was preserved. Following this relapse treatment, the patient has been without recurrence for 19 months.

Perioperative surgical outcome for patients with BDTT that present with obstructive jaundice

There were 6 patients in our current study series who needed preoperative biliary

drainage due to jaundice (Table 4). Four patients needed endoscopic nasobiliary drainage, and 2 patients needed percutaneous transhepatic biliary drainage. The maximum serum bilirubin level before biliary drainage ranged from 3.4–22.7 mg/dl, with a median concentration of 6.6 mg/dl. Liver resection for cases with obstructive jaundice included 5 right hepatectomies and 1 right anterior sectionectomy. There were no significant differences in the overall survival rate ($p = 0.5469$) among HCC patients with BDTT in terms of the presence or absence of preoperative jaundice (Table 2; Fig. 1D). The perioperative outcomes for HCC with BDTT are presented in Table 4. There were no significant differences between the 2 groups depending on the presence or absence of preoperative jaundice in terms of operation time, blood loss, anatomical resection, postoperative complications, or the postoperative hospital stays. In addition, there were no 90-day mortalities in either study group.

Discussion

HCC with BDTT is a rare phenomenon that occurs in about 2.5–3.4% of patients with HCC.[6-8] Yeh et al reported the relationship between the pathogenesis of HCC with BDTT and the microRNA-200 family. [11] HCC with BDTT reportedly demonstrates pathological features such as a higher incidence of vascular invasion and less histological differentiation.[6, 11, 12] Our present results (Table 1) are consistent with these earlier findings.

The 5-year survival rate of HCC patients with BDTT is reportedly about 30%.[7,8,12] In our current series, the 5-year survival rate of HCC patients with BDTT was 36.6%, and there was no significant difference in survival between HCC patients with or without BDTT when the two groups were matched by stage. Wong et al also reported that HCC patients with or without BDTT demonstrated similar survival rates using their matching criteria.[7] Macrovascular invasion, including portal vein invasion and hepatic vein invasion, is correlated with poor prognosis in HCC patients.[13-17] Regarding BDTT, in contrast, Esaki et al reported that macroscopic bile duct invasion demonstrates a favorable impact on patient outcomes in HCC patients with BDTT. [8] In our current series, there was no significant difference found in the survival rate and time to recurrence between HCC patients with microscopic or macroscopic BDTT. These data indicated a lower malignant potential of BDTT in comparison with vascular invasion, and that macroscopic BDTT is not a contraindication for hepatectomy. Our results also indicate that tumor size, differentiation, and portal vein invasion are independent prognostic factors for survival, and that tumor size is an independent factor for recurrence. Kasai et al have reported previously that major vascular invasion is a negative prognostic indicator for HCC patients with BDTT.[18] These results suggest that BDTT alone does not affect prognosis and only does so in conjunction with other prognostic factors, such as vascular invasion, poor differentiation, or large size.

Regarding a hepatectomy for HCC with BDTT, there is an issue about whether or

not to preserve the bile duct. Wong et al proposed extrahepatic bile duct resection for HCC with BDTT in order to minimize bile duct recurrence.[7] However, according to several reports, routine bile duct resection is not recommended unless direct invasion of the BDTT into the bile duct is suspected.[8,12,18] Shiomi et al reported that the survival of their bile duct-preserved group was similar to that of their bile duct-resected group.[19] Recently, Yamamoto et al reported using bile duct-preserving surgery for HCC with BDTT—called the "peeling off technique"[10]—which is similar to our surgical approach. One reason why preserving the bile duct is important is that BDTT demonstrates expansive growth and does not usually adhere to the bile duct wall.[10] The other reason is that treatments for recurrence, such as TACE or radiofrequency ablation (RFA), are restricted after resecting the common bile duct because liver abscess formation after TACE and RFA is relatively common when an underlying bilioenteric anastomosis is present.[20,21] As indicated in Table 3, intrahepatic recurrence is the most common recurrence after liver resection for HCC, and TACE can be performed in this circumstance after preserving the bile duct. Thus, by preserving the bile duct, the peeling-off technique is suitable for HCC with BDTT. However, careful observations must be made to check for BDTT-type recurrence. There was one patient with BDTT in our current series who presented with recurrence in the bile duct, and a salvage operation was performed to peel off the BDTT. No recurrence was noted thereafter in this case. Bile duct-preserving hepatectomy for HCC with BDTT may cause this type of

recurrence because of the direct invasion of the BDTT into the bile duct, with the BDTT remaining in the small branches of the bile ducts with intraoperative seeding along them. The selection criteria for preserving or resecting the bile duct is thus still unclear, and further studies are needed.

Jaundice affects the functional liver reserve, and cases with obstructive jaundice often presents with cholangitis and hemobilia that can cause hepatic failure.[3-5] Therefore, biliary drainage is mandatory before hepatectomy for patients with BDTT that present with obstructive jaundice. We perform preoperative biliary drainage at our hospital in accordance with the preoperative management of biliary tract cancer.[22] Biliary drainage of the remnant liver is performed until the serum bilirubin is < 2 mg/dl because a higher level than this is a contraindication for hepatectomy according to Makuuchi's criteria, and hepatectomy is performed if the functional liver reserve is sufficient.[23] In our present study, perioperative outcomes were similar between the groups depending on the presence or absence of preoperative jaundice. The postoperative complications according to the Clavien-Dindo classification[24] and the periods of the postoperative hospital stays were also similar between our 2 study groups, and there were no 90-day mortalities in either group. These data suggest that hepatectomy for patients with BDTT that present with obstructive jaundice can safely be performed if sufficient functional liver reserve remains after biliary drainage.

In conclusion, a hepatectomy should be considered for HCC patients with BDTT,

including cases with obstructive jaundice, because equivalent surgical outcomes as HCC without BDTT can be achieved if their functional liver reserve is sufficient.

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Figure Legends

Figure 1. (A) Correlation between BDTT and the clinical outcomes of HCC patients after surgery. The HCC patients with BDTT demonstrated poorer overall survival than patients without BDTT. (B) Correlation between BDTT and the clinical outcomes of HCC patients after surgery when limited to stage III or IV patients. There was no significant difference in the survival rate between stage III or IV HCC patients with BDTT and patients without BDTT. (C) Correlation between microscopic and macroscopic BDTT and the clinical outcomes of HCC patients after surgery. There was no significant difference in the survival rate between HCC patients with microscopic BDTT and HCC patients with macroscopic BDTT. (D) Correlation between preoperative jaundice and the clinical outcomes of HCC patients with BDTT after surgery. There was no significant difference in the survival rate between cases with and without obstructive jaundice.

Table 1 Correlations between clinicopathological features and BDTT

Variable		BDTT-negative (n = 732)	BDTT-positive (n = 42)	*p* value
Age†				0.428
		64 (18-90)	61.5 (44-80)	
Gender				1.000
	Female	127	7	
	Male	605	35	
HBs antigen				1.000
	Negative	444	26	
	Positive	288	16	
HCV antibody				0.240
	Negative	490	32	
	Positive	242	10	
Child-Pugh Classification				0.162
	A	709	39	
	B	23	3	
ICG R15 †				0.061
		13.7 (2.5-94.4)	13.7 (2.7-33.3)	
Liver cirrhosis				1.000
	Absence	513	30	
	Presence	219	12	
AFP (ng/ml)†				0.015
		18.6 (0-1816620)	97.3 (1.5-624717)	
TNM Stage				<0.0001
	I or II	356	1	
	III or IV	376	41	
Tumor size (cm)†				0.004
		4.2 (0.3-22)	5 (1.5-22.5)	
Differentiation				0.061
	Well	116	2	
	Moderate	468	27	
	Poor	148	13	
Portal vein invasion				<0.0001
	Absence	546	9	
	Presence	186	33	
Anatomical resection				0.0004
	no	203	2	
	yes	529	40	

Abbreviations: BDTT, bile duct tumor thrombus; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15

† Expressed as median (range)

Table 2 Univariate and multivariate analyses of prognostic factors for HCC with BDTT

		Univariate analysis			
		Survival		Recurrence	
Variable	n	5-years (%)	*P* value	5-years (%)	*P* value
Age			0.1616		0.9212
<60	18	48.4±12.9		73.4±12.4	
≥60	24	17.5±13.8		80.0±15.6	
Gender			0.9534		0.7030
Female	7	34.2±19.5		77.1±19.6	
Male	35	36.3±10.2		75.8±11.0	
HBs antigen			0.6415		0.2021
Negative	26	35.2±11.4		68.6±13.8	
Positive	16	40.5±14.1		86.9±11.4	
HCV antibody			0.5299		0.4165
Negative	32	39.7±10.1		76.2±10.8	
Positive	10	30.4±17.7		78.1±19.1	
Child-Pugh Classification			0.0963		0.5858
A	39	37.3±9.2		77.7±9.8	
B	3	50.0±35.3		33.3±27.2	
ICG R15 (%)			0.3298		0.3048
<10	19	55.4±12.7		45.4±11.9	
≥10	23	20.6±11.3		100.0±0.0	
Liver cirrhosis			0.6566		0.7237
Absence	30	40.4±11.8		74.1±11.5	
Presence	12	27.7±13.5		80.9±16.5	
AFP(ng/ml)			0.6637		0.9809
<20	14	36.0±10.2		76.6±18.2	
≥20	28	35.5±18.5		79.0±11.6	
TNM Stage			0.6800		0.4744
I or II	1	100.0±0.0		78.3±9.6	
III or IV	41	36.4±9.0		0.0±0.0	
Tumor number			0.3120		0.0536
Single	27	39.8±11.3		71.2±13.0	
Multiple	15	28.1±14.9		86.6±11.8	
Tumor size (cm)			0.0039		0.0001
<10	32	52.5±10.6		69.7±12.9	
≥10	10	0.0±0.0		100.0±0.0	
Differentiation			0.0321		0.7210
Well/Moderate	29	45.7±11.4		80.2±11.0	
Poor	13	19.9±12.4		73.1±20.6	
Portal vein invasion			0.0380		0.1135
Absence	9	83.3±15.2		100.0±0.0	
Presence	33	28.0±8.9		78.7±9.9	
Extent of BDTT			0.4796		0.3331
Microscopic	21	48.6±12.1		81.4±11.1	
Macroscopic	21	14.7±12.2		70.5±15.5	
Anatomical resection			0.6666		0.4673
no	2	50.0±35.3		100.0±0.0	
yes	40	36.2±9.2		75.0±10.6	
Preoperative jaundice			0.5469		0.2828
no	36	35.3±9.1		79.2±9.3	
yes	6	50.0±35.3		20.0±17.8	

	Multivariate analysis		
	Survival		
	HR	95% CI	*P* value
Tumor size	2.940	1.111-7.704	0.0304
Differentiation	2.737	1.033-6.989	0.0431
Portal vein invasion	7.235	1.075-197.74	0.0401
	Recurrence		
	HR	95% CI	*P* value
Tumor size	3.448	1.139-10.539	0.0288

Abbreviations: BDTT, bile duct tumor thrombus; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; HR, hazard ratio; CI, confidence interval

Table 3 Recurrence site and its treatment after hepatectomy for HCC with BDTT

	Treatment (Number of cases)					
The first recurrence site	TACE	Resection	Systemic chemotherapy	Radiation	Best supportive care	Total
Liver	10	2	0	0	3	15
Lung	0	2	1	0	0	3
Liver and lung	0	0	0	0	2	2
Bone	0	0	0	1	1	2
Lymph node	0	0	0	1	0	1
Bile duct	0	1	0	0	0	1
Total	10	5	1	2	6	24

Abbreviations: BDTT, bile duct tumor thrombus; TACE, transcatheter arterial chemoembolization

Table 4 Perioperative outcomes of HCC with BDTT

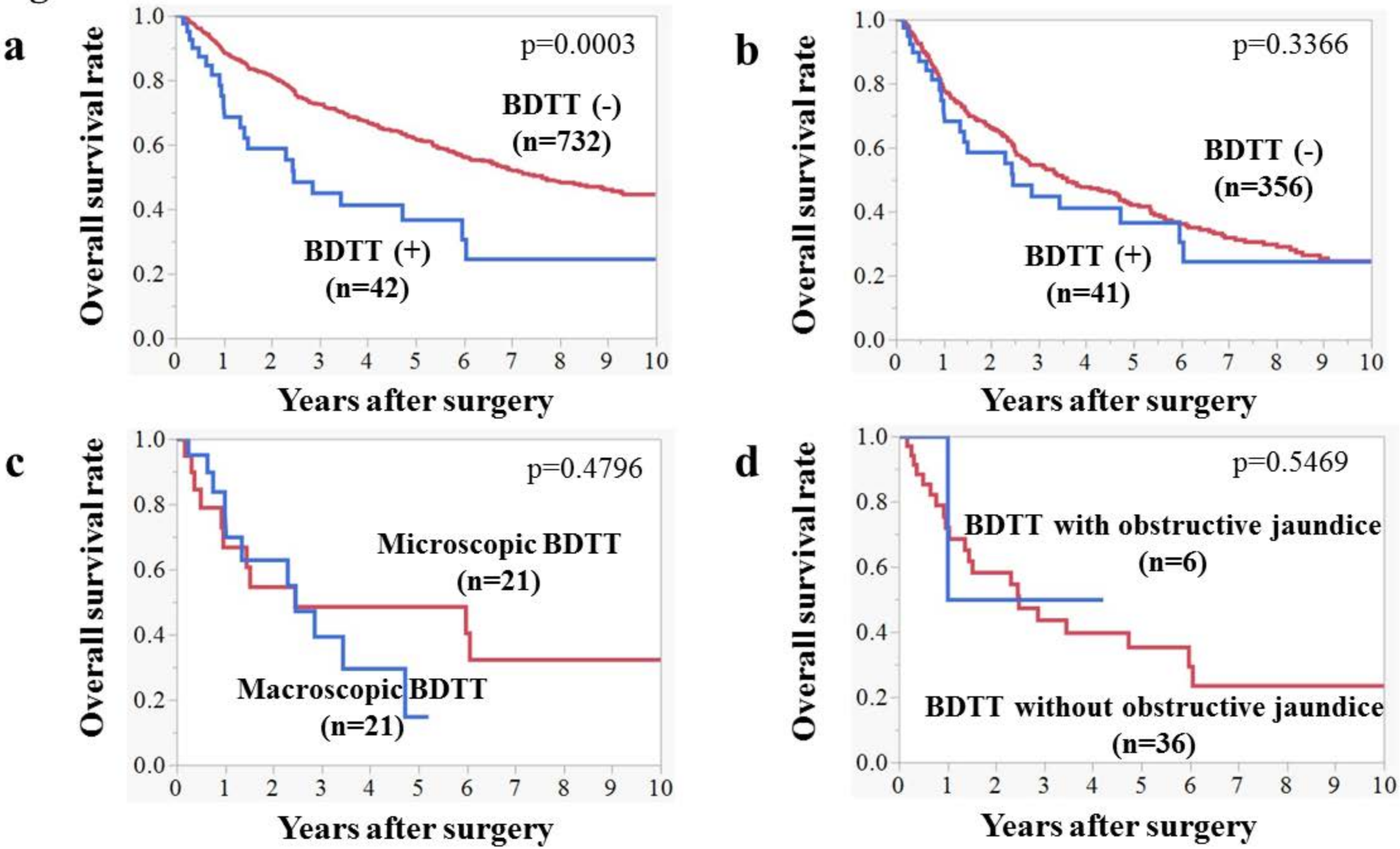
Variable		Without obstructive jaundice (n = 36)	With obstructive jaundice (n = 6)	*p* value
Operation time (min)†				0.110
		370.5 (157-1019)	324 (289-370)	
Blood loss (ml)†				0.914
		660 (40-35820)	695 (340-2155)	
Anatomical resection				1.000
	no	2	0	
	yes	34	6	
Postoperative complication‡				1.000
	III	6	0	
	IV	0	0	
Postoperative hospital stay (days)†				0.957
		22 (9-108)	22.5 (13-40)	
90days mortality				1.000
		0	0	

Abbreviations: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus

† Expressed as median (range)

‡ Clavien-Dindo grading III or IV

Figure. 1


a
Overall survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10
Years after surgery
p=0.0003
BDTT (-)
(n=732)
BDTT (+)
(n=42)
b
Overall survival rate
Years after surgery
p=0.3366
BDTT (-)
(n=356)
BDTT (+)
(n=41)
c
Overall survival rate
Years after surgery
p=0.4796
Microscopic BDTT
(n=21)
Macroscopic BDTT
(n=21)
d
Overall survival rate
Years after surgery
p=0.5469
BDTT with obstructive jaundice
(n=6)
BDTT without obstructive jaundice
(n=36)