Original Article

Prognosis for patients with hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) after surgical treatment

Zhichuan Lin^{*}, Mingrui Han, Zhi Zhou

Department of Hepatobiliary Surgery, Zhangzhou Affiliated Hospital, Fujian Medical University, Zhangzhou, Fujian, China.

Summary Hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) is rarely seen in clinical practice, and its treatment strategies and prognosis are still a subject of debate. To ascertain the characteristics of and prognosis for HCC with BDTT, 49 patients with HCC with BDTT were studied out of 763 consecutive patients with HCC who underwent surgical treatment from July 2004 to May 2018. The clinical characteristics of and prognosis for those 49 patients were reviewed and analyzed retrospectively. Of the 49 patients, 25 underwent radical resection, 7 underwent thrombectomy through a choledochotomy, and 17 underwent palliative internal and external bile duct drainage. Results indicated that patients who underwent a radical resection had a better prognosis than patients in the other two groups, with a median survival of 19 months vs. 8 months and 3 months (p < 0.001). Moreover, the preoperative bilirubin level (p = 0.025), intraoperative blood loss (p = 0.006), tumor size (p = 0.025) 0.005), and the presence of portal and hepatic vein tumor thrombi (p = 0.021) were significant prognostic factors associated with long-term survival for patients who underwent radical resection in this study. Radical resection should be performed with adequate preoperative preparation for patients with HCC with BDTT in whom surgery is not contraindicated.

Keywords: Hepatocellular carcinoma (HCC), bile duct tumor thrombus (BDTT), surgical treatment

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with > 500,000 new cases annually, and it is the second leading cause of cancer-related mortality worldwide (1,2). The incidence of HCC is increasing worldwide and especially in Asian-Pacific countries, and half of all cases occur in China (3). HCC with bile duct tumor thrombus (BDTT) is rarely seen in clinical practice, and its incidence has been reported to be 1.2-12.9% (4-9). Due to a lack of awareness of HCC with BDTT, some patients fail to receive effective treatment. This is especially true for those with obstructive jaundice who are considered to be in the late stage of tumor progression.

*Address correspondence to:

E-mail: linzhichuan1976@163.com

The principle for surgical treatment of HCC with BDTT is the removal of primary HCC and BDTT, and active surgical resection may benefit patients (*10-12*). Patients with HCC and BDTT may undergo radical resection, thrombectomy through a choledochotomy, palliative internal and external bile duct drainage, or transarterial chemoembolization (TACE) depending on the type of BDTT. However, the treatment strategies and prognosis for patients with HCC with BDTT are still a subject of debate (*13,14*).

To ascertain the characteristics of and prognosis for HCC with BDTT, clinical features of and surgical outcomes for patients who underwent different surgical treatments were retrospectively analyzed. The prognostic factors associated with long-term survival for patients with HCC with BDTT who underwent radical resection were also analyzed in this study.

2. Patients and Methods

2.1. Patients

From July 2004 to May 2018, a total of 763 consecutive

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Dr. Zhichuan Lin, Department of Hepatobiliary Surgery, Zhangzhou Affiliated Hospital, Fujian Medical University, No. 59 Shengli West Road, Xiangcheng District, Zhangzhou, Fujian, China.

patients with HCC underwent surgical treatment out of 4,693 patients with primary HCC who were treated at Zhangzhou Hospital affiliated with Fujian Medical University. Of these patients, 49 were identified as having HCC with BDTT (Figure 1), accounting for 1.04% (49/4693) of all patients with primary HCC and 6.42% (49/763) of patients who underwent HCC resection.

The medical records of those 49 patients, including the characteristics of their underlying liver disease, tumor characteristics, and prognosis were retrospectively reviewed.

2.2. Diagnosis and classification

The workup before surgical treatment included

liver function tests, viral screening, and imaging studies. Laboratory results were obtained upon admission before surgical treatment. Tumors were evaluated using abdominal ultrasonography (US), computed tomography (CT), hepatic angiography, and magnetic resonance imaging (MRI). If necessary, direct cholangiography [percutaneous transhepatic cholangiography and drainage (PTCD) or endoscopic retrograde cholangiography (RECP)] or magnetic resonance cholangiopancreatography (MRCP) was performed before surgery to evaluate the extent of biliary invasion. Bile duct invasion by HCC was suspected when peripheral bile duct dilatation or tumor thrombus was detected on US or CT, and bile duct invasion was confirmed with direct cholangiography or MRCP as



Figure 1. Flow chart for patients included in this study. BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.

obstruction or stenosis of the biliary trees.

The tumor thrombus was histopathologically examined in patients with HCC with BDTT who underwent surgical treatment.

The Ueda (6) classification of HCC with BDTT was used in this study: *i*) type I: BDTT located in the secondary branch of the bile duct tree; *ii*) type II: BDTT extending to the first branch of the bile duct tree; *iii*) type IIIa: BDTT extending to the common hepatic duct; type III: an implanted tumor growing in the CBD, and iv) type IV: floating tumor debris from the ruptured tumor in CBD (*15*).

2.3. Treatment strategies

Resectability was determined based on the patient's general condition, tumor status, pre-operative liver function tests, preoperative diagnosis of the location of the primary tumors, extension of BDTT, and the future remnant liver parenchyma.

Patients with HCC with BDTT who had an unresectable tumor or in whom a lesion could not be found underwent thrombectomy through a choledochotomy.

Patients with advanced disease or disease complicated by chronic diseases and without surgical indications underwent palliative internal and external bile duct drainage (PTCD, ERCP, or intraductal stent drainage) or TACE.

2.4. Follow-up

During the first 3 months after surgical treatment, patients were re-examined every month. Afterwards, patients were re-examined every 3 months. Clinical, laboratory, and radiological data were collected during each follow-up visit.

All patients were followed until October 2018. Survival was measured from the time of surgical treatment, and death was the endpoint.

2.6. Statistical analysis

The statistical software SPSS 19.0 was used for statistical analysis. The life table method was used to estimate the survival rate, and the survival analysis was based on the log-rank (Mantel-Cox) method. Quantitative data are expressed as the mean \pm standard deviation (mean \pm S.D.). Qualitative data were tested using the Chi-square test. Statistical significance was defined as a *p* value < 0.05.

3. Results

3.1. Clinicopathological data

Forty-nine patients with HCC and BDTT were enrolled

in this study, including 43 males and 6 females with an average age of 55.51 ± 13.09 years. Out of 49 patients, 33 (67.35%) had different degrees of yellowing of the whites of the eyes and the skin as well as dark urine with elevated bilirubin levels ranging from 34.6 to 505.0 μ mol/L. Some patients had a fever, abdominal pain, bloating, pruritus, and paler stool. Thirty-two patients (65.31%) had an elevated alpha-fetoprotein (AFP) level, and 41 patients (83.67%) tested positive for hepatitis B virus surface antigen (HBsAg).

Out of 49 patients, 35 (71.43%) were diagnosed with HCC with BDTT before surgical treatment. Of the 14 remaining patients (14/49, 28.57%), 11 were misdiagnosed as having hilar cholangiocarcinoma, 1 was misdiagnosed as having ampullary carcinoma, 1 was misdiagnosed as having pancreatic head cancer, and 1 was misdiagnosed as having bile duct stones.

Results of diagnostic ultrasonography were positive in 14.29% of patients (7/49), CT results were positive in 35.00% (14/40), and MRCP results were positive in 59.18% (29/49). A biliary tumor thrombus was diagnosed with ERCP at a rate of 100% (8/8).

The tumor thrombus was histopathologically examined in patients with HCC with BDTT who underwent surgical treatment (Figure 2). HCC with BDTT was divided into the following categories: a simple tumor thrombus and a blood clot mixed with a tumor thrombus. The BDTT was yellowish, brownish, or purplish-black in color and had a pathological type identical to that of a hepatic primary tumor.

According to the Ueda classification of HCC with BDTT, 2 patients had type I tumors, 2 had type II, 42 had type III, and 3 had type IV.

3.2. Surgical treatment

Twenty-five patients underwent radical resection, 7 underwent thrombectomy through a choledochotomy, and 17 underwent palliative internal and external bile duct drainage (Figure 1).

Out of 25 patients who underwent radical resection, 2 had type I tumors, 2 had type II, and 21 had type III according to the Ueda classification. Seventeen patients underwent hemihepatectomy, including 11 who underwent hemihepatectomy plus thrombectomy through a choledochotomy (Figure 3A) and 6 who underwent biliary reconstruction (Figure 3B and 3C). Of the 6 patients who underwent biliary reconstruction, 5 underwent hemihepatectomy plus extrahepatic bile duct resection plus cholangiojejunostomy and 1 underwent left hemihepatectomy plus common hepatic duct resection plus end-to-end anastomosis of the right hepatic duct to the common bile duct. In addition, 8 patients in this group underwent HCC resection plus thrombectomy through a choledochotomy due to severe cirrhosis (Figure 3D), and the surgical margin was greater than 1 cm.

Seven patients underwent thrombectomy through a



Figure 2. Histopathological examination of the tumor thrombus in patients with HCC with BDTT who underwent surgical treatment. (A) BDTT; (B) HCC with BDTT; (C) Postoperative pathology: HCC with BDTT. BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.



Figure 3. Surgical treatment of patients with HCC with BDTT. (A), Hemi hepatectomy plus thrombectomy through a choledochotomy; (B), Left lateral hepatic lobectomy plus thrombectomy through a choledochotomy; (C), Hemi hepatectomy plus right Roux-en-Y hepaticojejunostomy; (D), Thrombectomy through a choledochotomy. BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.

choledochotomy, including 4 with type III tumors and 3 with type IV according to the Ueda classification.

A total of 17 patients underwent palliative internal and external bile duct drainage, including 5 who underwent ERCP plus biliary stenting, 4 who underwent TACE, 3 who underwent PTCD, 2 who underwent ERCP plus TACE, 2 who underwent PTCD plus TACE, and 1 who underwent PTCD plus ERCP. All 17 patients had type III tumors according to the Ueda classification.

3.3. Perioperative outcome

The operating time, intraoperative blood loss, rate

of blood transfusion, duration of postoperative hospitalization, surgical complications, and mortality for the 25 patients who underwent radical resection and 7 patients who underwent thrombectomy through a choledochotomy are shown in Table 1.

Two of these patients died of liver failure after surgery. Both of the 2 patients had intraoperative blood loss of greater than 1,500 mL, liver failure occurred 1 week after surgery, and they died within 2 months after surgery although they received supportive treatment including artificial liver support.

Eight patients developed surgical complications, including 2 who had gastric bleeding due to a stress

Items	Patients who underwent radical resection $(n = 25)$	Patients who underwent thrombectomy through a choledochotomy $(n = 7)$		
Operating time (mean ± S.D.) (min)	333.00 ± 260.00	194.28 ± 15.39		
Intraoperative blood loss (mean \pm S.D.) (mL)	962.00 ± 856.26	175.57 ± 69.86		
Rate of blood transfusion (%)	60	0		
Duration of postoperative hospitalization (days)	19.68 ± 10.21	10.71 ± 4.98		
Rate of surgical complications (%)	32.00	14.86		
Surgical mortality rate	8.00	0		

Table 1. Perioperative outcome for patients with HCC with BDTT who underwen	t radical resection or thrombectomy
through a choledochotomy	

BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.



Figure 4. Survival curve for patients with HCC with BDTT receiving different treatments. BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.

ulcer and were cured after treatment, 3 who had subphrenic effusion, and 3 who had a pulmonary infection. All 8 patients recovered with treatment.

3.4. Prognosis: Survival

The 49 patients with HCC with BDTT had a 1-year survival rate of 42.86% (21/49), a 3-year survival rate of 18.37% (9/49), and a 5-year survival rate of 12.24% (6/49).

The 25 patients who underwent radical resection had a median survival of 19 months and a 1-year survival rate of 68.00% (17/25), a 3-year survival rate of 32.00% (8/25), and a 5-year survival rate of 24.00% (6/25).

The 7 patients who underwent thrombectomy through a choledochotomy had a median survival of 8 months and a 1-year survival rate of 28.57% (2/7), a 3-year survival rate of 14.29% (1/7), and a 5-year survival rate of 0% (0/7).

The 17 patients who underwent palliative internal and external bile duct drainage had a median survival of 3 months and a 1-year survival rate of 5.89% (1/17), a 3-year survival rate of 0% (0/17) (1/7), and a 5-year survival rate of 0% (0/17).

The survival curves for patients who received above different treatments are shown in Figure 4 (p < 0.001).

3.5. Prognostic factors for long-time survival of patients who underwent radical resection

Patient No.	Age	TBIL	DBIL	Tumor location	Size	Intraoperative blood loss	Vascular tumor thrombus	Surgical approach	Postoperative relapse	Treatment after relapse	Survival (months)
1	58	198	117	III, IV	3.0 × 3.0	600	-	Left hepatocellular carcinoma resection with thrombectomy through a choledochotomy	6	Left hemi hepatectomy plus right Roux-en-Y hepaticojejunostomy	172
2	54	176	114	Ι	4.0 × 3.0	500	-	Left hemi hepatectomy with thrombectomy through a choledochotomy	-	-	140
3	50	169	100	II, III, IV	4.0 × 3.0	500	-	Left hemi hepatectomy plus right Roux-en-Y hepaticojejunostomy	-	-	133
4	42	16	10	V	4.0 × 4.0	800	-	Right hemi hepatectomy with thrombectomy through a choledochotomy	65	TACE	126
5	39	11	6	IVb	3.0 × 2.5	100	-	Resection of liver segment IVb	-	-	66
6	15	61	32	II, III	2.5 × 1.0	150	-	Left hemi hepatectomy plus end-to-end anastomosis of the right hepatic duct to the common bile duct	-	-	63

Table 2. Data from 6 patients with HCC with BDTT who underwent radical resection

BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma, TACE, transarterial chemoembolization.

Out of 25 patients who underwent radical resection, 6 without portal vein and hepatic vein tumor thrombus are still alive with a long-term survival of more than 60 months (Table 2). Of the 6 patients, 4 lived for 120 months, and the longest survival was 172 months to date. No portal or hepatic vein tumor thrombi were found in these patients.

Of these patients, patient 1 underwent HCC resection (junction of segments III and IV) plus thrombectomy through a choledochotomy. Recurrence of a thrombus in the left hepatic duct 6 months after surgery resulted in multiple tumors in the residual left lobe of the liver. Left hemihepatectomy plus liver hilar bile duct resection with right Roux-en-Y hepaticojejunostomy was performed. The patient has survived 172 months after surgery. Patient 4 was diagnosed with HCC of right hepatic segment VII 65 months after surgery and underwent TACE. No new lesions were detected during the 61 months of follow-up. The patient has survived 126 months after surgery. Patient 5 was the only patient with a type II tumor who recovered considerably after surgery and who has survived 66 months after surgery. Patient 6 was a 15-year-old patient who underwent left hemihepatectomy plus common hepatic duct resection with end-to-end anastomosis of the right hepatic duct to the common bile duct. The biliary tract

was reconstructed during surgery, and the patient has survived for 63 months.

Analysis with the Mantel-Cox model indicated that the preoperative bilirubin level (p = 0.025), intraoperative blood loss (p = 0.006), tumor size (p = 0.005), and presence of portal and hepatic vein tumor thrombi (p = 0.021) were significant prognostic factors associated with long-term survival for patients who underwent radical resection in this study (Table 3).

4. Discussion

Of 49 patients with HCC with BDTT, 25 underwent radical resection, 7 underwent thrombectomy through a choledochotomy, and 17 underwent palliative internal and external bile duct drainage. Patients who underwent a radical resection had a better prognosis than patients in the other two groups (p < 0.001). Moreover, the preoperative bilirubin level, intraoperative blood loss, tumor size, and presence of portal and hepatic vein tumor thrombi were identified as prognostic factors associated with long-term survival for patients who underwent a radical resection

The principle for surgical treatment of HCC with BDTT is the removal of primary HCC and BDTT. Active surgical resection may benefit patients (10-12).

Variable	Number of patients	Survival (months)	Log-rank (Mantel-Cox), p value
Sex			
Male	21	$4 \ 7.750 \pm 25.041$	0.906
Female	4	56.951 ± 16.068	
Age			
\geq 50 years	16	31.603 ± 10.102	0.772
< 50 years	9	34.000 ± 12.905	
HbsAg test			
Positive	20	65.386 ± 16.819	0.244
Negative	5	16.750 ± 7.609	
Degree of liver cirrhosis			0.209
Mild	5	61.286 ± 16.403	
Moderate-severe	20	19.000 ± 10.350	
Number of masses			
Single	23	61.664 ± 15.454	0.096
Multiple	2	7.500 ± 6.500	
AFP level			
\geq 400 ng/mL	10	37.500 ± 15.312	0.379
< 400 ng/mL	15	65.579 ± 19.986	
Type of liver resection			0.937
Liver lobectomy	8	28.333 ± 9.081	
Hemi hepatectomy	17	58.111 ± 16.674	
Preoperative total bilirubin level			
$\leq 200 \ \mu mol/L$	16	75.240 ± 18.864	0.025
> 200 µmol/L	9	14.286 ± 5.153	
Intraoperative blood loss			0.006
$\leq 200 \text{ mL}$	5	90.250 ± 22.493	
200-1000 mL	13	36.400 ± 20.009	
> 1000 mL	7	10.857 ± 4.748	
Size of HCC			0.005
\geq 5 cm	12	15.833 ± 2.828	
< 5 cm	13	102.958 ± 23.080	
Portal vein and hepatic vein tumor thrombus			0.021
No	20	70.012 ± 17.260	
Yes	5	10.400 ± 2.015	

Table 3. Log-rank (Mantel-Cox) tumor-free survival data for 25 patients with HCC with BDTT who underwent radical resection

BDTT, bile duct tumor thrombus; HCC, hepatocellular carcinoma.

A higher rate of resection is associated with significantly prolonged survival for some patients (16, 17). At the current authors' facility, the surgical procedure and scope of resection depend on the patient's liver reserve function, residual liver volume, and Ueda classification. Depending on the patient's condition, routine PTCD or endoscopic nasobiliary drainage (ENBD) was performed before surgery to reduce the degree of jaundice, and different types of liver resection were performed during surgery. Most cases of HCC with BDTT were classified as category Ueda type III. The formation of a tumor thrombus in the ipsilateral bile duct with contralateral compensatory enlargement of the liver (*i.e.*, atrophichypertrophic syndrome) makes tumor resection easier.

The surgical plan should be individually based on the degree of the close relationship between the tumor thrombus and extrahepatic biliary duct. Depending on the location of the HCC and BDTT, HCC resection or hemihepatectomy plus thrombectomy through choledochotomy is chosen. In cases where the BDTT is firmly attached to or even invades the extrahepatic bile duct wall, extrahepatic bile duct resection should be considered (15,18,19). In the current study, 2 patients who underwent HCC resection and thrombectomy through a choledochotomy had recurrence of the tumor thrombus in the left hepatic duct within 6 months after surgery, which resulted in multiple tumors in the residual left lobe of the liver. Further surgery, such as hemi hepatectomy, hilar biliary duct resection, or Roux-en-Y hepaticojejunostomy, was performed. Intraoperative cholangioscopy was used to rule out the presence of a tumor thrombus in the intrahepatic distal bile duct and as an important examination to prevent recurrence. At present, the 2 patients who underwent further surgery are in satisfactory condition. This finding indicates that surgery remains an effective treatment for tumor recurrence. Liver hilar lymph node dissection was performed in 7 patients, but metastatic lymph nodes were not noted. Thus, additional studies with larger samples need to be performed to decide whether to routinely perform hilar lymph node dissection in patients with HCC with BDTT.

Two patients of the current patients (intraoperative blood loss > 1,500 mL) had liver failure and died within

2 months after surgery after the failure of artificial liver support and other treatments. Preoperative preparation should be sufficient, with particular attention devoted to reducing the preoperative bilirubin level (and especially the direct bilirubin level), retention of an adequate residual liver volume, and reduction of intraoperative blood loss. These key factors affect patients perioperatively.

Patients with HCC with BDTT for which radical surgery is not indicated should have external and internal hepatobiliary drainage tubes placed *via* PTCD or ENBD and undergo bile duct stenting to reduce the degree of jaundice and alleviate pruritis. Transarterial embolization may be another option in this case (16, 20).

A comparative analysis of HCC with BDTT versus HCC without BDTT by Rammohan *et al.* (21) indicated that the degree of preoperative jaundice and tumor size were important factors affecting prognosis. This result was consistent with the current finding that the degree of preoperative jaundice was the main factor influencing long-term survival (p < 0.05). Analysis of the 25 patients in the current study indicated that intraoperative blood loss and portal vein and hepatic vein tumor thrombi were the main factors influencing long-term survival (p < 0.05). A vascular tumor thrombus was not noted in the 6 patients surviving long term (more than 60 months).

5. Conclusion

Surgical radical resection is the key to a favorable prognosis for patients with HCC with BDTT. In the current study, the preoperative bilirubin level, intraoperative blood loss, tumor size, and presence of portal and hepatic vein tumor thrombi were significant prognostic factors associated with long-term survival for patients who underwent radical resection. However, this study was retrospective, it had a small sample size, and it was conducted at a single center. Multicenter, prospective studies with a larger sample need to be conducted to verify the effectiveness of radical resection.

Radical resection should be performed with adequate preoperative preparation for patients with HCC with BDTT in whom surgery is not contraindicated. If radical resection is not indicated, then thrombectomy through a choledochotomy or internal and external drainage of the biliary duct and TACE should be performed to alleviate symptoms, improve quality of life, and promote longer survival.

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