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Effect of bile duct resection on the prognosis of patients with hepatocellular carcinoma combined with extrahepatic bile duct tumor thrombus

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Abstract

Background Surgical therapy is the most optimal treatment for hepatocellular carcinoma (HCC) combined with bile duct tumor thrombus (BDTT) patients. However, whether to perform bile duct resection (BDR) is still controversial. The purpose of this multicenter research is to compare the effect of BDR on the prognosis of extrahepatic BDTT patients.

Methods We collected the data of 111 HCC patients combined with extrahepatic BDTT who underwent radical hepatectomy from June 1, 2004 to December 31, 2021. Those patients had either received hepatectomy with extrahepatic bile duct resection (BDR group) or hepatectomy without bile duct resection (NBDR group). Inverse probability of treatment weighting (IPTW) was used to reduce the potential bias between two groups and balance the influence of confounding factors in baseline data. Then compare the prognosis between the two groups of patients. Cox regression model was used for univariate and multivariate analysis to further determine the independent risk factors that influence the prognosis of HCC-BDTT patients.

Results There were 38 patients in the BDR group and 73 patients in the NBDR group. Before and after IPTW, there were no statistical significance in OS, RFS and intraoperative median blood loss between the two groups (all $P > 0.05$). Before IPTW, the median postoperative hospital stay in the NBDR group was shorter ($P = 0.046$) and the grade of postoperative complications was lower than BDR group ($P = 0.014$). After IPTW, there was no difference in postoperative hospital stay between the two groups ($P > 0.05$). The complication grade in the NBDR group was still lower than that in the BDR group ($P = 0.046$). The univariate analysis showed that TNM stage and portal vein tumor thrombus (PVTT) were significantly correlated with OS (both $P < 0.05$). Preoperative AFP level, TNM stage and prognostic nutritional index (PNI) were significantly correlated with postoperative RFS (all $P < 0.05$). Multivariate analysis showed that tumor TNM stage was an independent risk factor for the OS rate ($P = 0.014$). TNM stage, PNI and AFP were independent predictors of RFS after radical hepatectomy (all $P < 0.05$).

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Conclusions For HCC-BDTT patients, hepatocellular carcinoma resection combined with choledochotomy to remove the tumor thrombus may benefit more.

Keywords Hepatocellular carcinoma (HCC), Bile duct tumor thrombus (BDTT), Extrahepatic bile duct resection, Prognosis, Complication

Introduction

The incidence of hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) is relatively low, accounting for only 1.2–9% of all HCC cases [1–3]. Among different treatment strategies, surgical resection is considered as the first-line treatment option for HCC-BDTT patients [4, 5]. Compared with other palliative non-surgical treatments, surgical treatment can not only remove liver tumors, but also relieve biliary obstruction, which can provide patients a chance of long-term survival [5, 6]. Great progress had been made in different surgical methods for HCC-BDTT patients. Some studies suggest that anatomical liver resection is the preferred approach for patients with good liver function [7]. Some researches found extended hepatectomy can reduce the risk of tumor residual and recurrence [8, 9]. However, there is no consensus on whether to perform bile duct resection (BDR) or only remove the thrombus (Non-bile duct resection, NBDR) [10–13].

Materials and methods

This is a multicenter retrospective study. Data sources include patient imaging system, laboratory system, inpatient medical record system, paper medical record information, and telephone and letter follow-up records.

Patients and grouping

We collected the data of 111 patients with HCC combined with extrahepatic BDTT who underwent radical hepatectomy in the First Affiliated Hospital of Sun Yat-sen University, Zhujiang Hospital of Southern Medical University, the Southwest Hospital of AMU, the First Affiliated Hospital of Anhui Medical University, the First Affiliated Hospital of Nanchang University, and Fujian Provincial People Hospital from June 1, 2004 to December 31, 2021. All patients were diagnosed with extrahepatic BDTT by imaging before surgery. The inclusion criteria were: (1) pathological diagnosis of HCC and extrahepatic BDTT; (2) patients received R0 radical hepatectomy (3) absence of distant metastasis; and (4) no anticancer treatment for HCC before surgery. The exclusion criteria were: (1) patients with incomplete clinical and pathological data; (2) tumor thrombus was located in the first and above bile duct; and (3) patients who had other malignant diseases. The diagnosis of HCC and BDTT was confirmed by histopathology after surgery. The laboratory test data of all patients before and after surgery are fully recorded.

Clinicopathological variables

Perioperative parameters, such as age, gender, alanine aminotrandferase(ALT), aspartic transaminase(AST), alkaline phosphatase, ALP), γ-Glutamyl transpeptidase(GGT), albumin(ALB), total bilirubin(TBIL), direct bilirubin(DBIL), indirect bilirubin(IBIL), α-fetoprotein(AFP), presence or absence of PVTT, and Child-Pugh classification were collected. The number of tumors and with or without PVTT were assessed by preoperative imaging studies such as CT, ultrasound, MRI, and surgical records.

Statistical analysis

Inverse probability of treatment weighting (IPTW) was used to reduce the potential bias between the two groups and balance the effect of confounding factors of baseline data. The patient's gender, age, hepatitis, preoperative biliary drainage, preoperative AFP, preoperative TBIL, AST, GGT, PNI, Child-Pugh classification and tumor TNM staging were included. Standardized mean difference (SMD) was used to evaluate the balance of independent variables after IPTW between the two groups. SMD ≤ 10% was considered as ideal balance, and SMD ≤ 20% was considered as within the acceptable range. Kaplan–Meier survival curves were drawn and tested using the log-rank test. Statistical evaluation was performed using SPSS25.0 (IBM SPSS Inc., Chicago, IL, USA) and R4.0.3 software (Institute for Statistics and Mathematics, Vienna, Austria). Continuous variables are represented by median (interquartile range), and categorical variables are represented by quantity (percentage). The confidence interval (CI) is shown at the 95% CI.

Results

Clinicopathological characteristics

The baseline characteristics of the two groups of patients before IPTW are shown in Table 1. All hepatitis patients in this study were hepatitis B patients. Compared to the NBDR group, the BDR group had a lower proportion of female patients($P=0.048$) and hepatitis patients($P=0.014$), a higher proportion of undergoing preoperative biliary drainage($P<0.01$), lower preoperative AFP levels($P=0.001$), and a worse Child-Pugh classification($P=0.006$). After IPTW, the baseline data of the two groups were well-balanced (Table 2).

Table 1 Baseline characteristics of HCC-BDTT patients before IPWT

Variables	NBDR($n=73$)	BDR($n=38$)	*P*
Sex			**0.048**
male	59 (80.8)	36 (94.7)	
female	14 (19.2)	2 (5.3)	
Age	54.45 (9.92)	55.18 (10.18)	0.715
Hepatitis B			**0.014**
no	9 (12.3)	12 (31.6)	
yes	64 (87.7)	26 (68.4)	
Biliary drainage			**<0.001**
no	44 (60.3)	9 (23.7)	
yes	29 (39.7)	29 (76.3)	
AST(U/L)			0.090
≤37.00	9 (12.3)	1 (2.6)	
>37.00	64 (87.7)	37 (97.4)	
GGT(U/L)			0.499
≤50.00	2 (2.7)	2 (5.3)	
>50.00	71 (97.3)	36 (94.7)	
TBIL(μmol/L)			0.744
<300.00	68 (93.2)	36 (94.7)	
≥300.00	5 (6.8)	2 (5.3)	
PNI	37.40 (4.37)	37.00 (4.09)	0.642
AFP			**0.001**
≤400.00	42 (56.0)	33 (86.8)	
>400.00	33 (44.0)	5 (13.2)	
Child-Pugh stage			**0.006**
A	41 (56.2)	11 (28.9)	
B	32 (43.8)	27 (71.1)	
PVTT			0.644
no	53 (72.6)	26 (68.4)	
yes	20 (27.4)	12 (31.6)	
TNM			0.743
I	29 (39.7)	14 (36.8)	
II	8 (11.0)	7 (18.4)	
III	16 (21.9)	7 (18.4)	
IV	20 (27.4)	10 (26.3)	

Survival analysis and prognostic indicators between the two groups

Before IPTW, the 1-, 3-, and 5-year OS rates of NBDR and BDR group were 76.2%, 54.8%, 37.6% respectively and 80.8%, 54.8%, 43.1% respectively($P>0.05$) (Fig. 1). The 1-, 3-, and 5-year RFS rates of NBDR and BDR group were 41.8%, 29.6%, 29.6% respectively and 41.0%, 30.4%, 22.8%, respectively($P>0.05$) (Fig. 1). After IPTW, the 1-, 3-, and 5-year OS rates of NBDR and BDR group were 76.8%, 53.1%, 38.7% respectively and 78.9%, 48.1%, 32.6%, respectively($P>0.05$) (Fig. 2). The 1-, 3-, and 5-year RFS rates of NBDR and BDR group were 40.3%, 30.0%, 30.0% respectively and 36.6%, 25.9%, 21.2%, respectively($P>0.05$) (Fig. 2).

Before IPTW, the median intraoperative blood loss was 500 ml in both the NBDR group and the BDR group($P=0.825$). The median postoperative hospital stay was 13 days in the NBDR group, which was shorter than the median of 16.5 days in the BDR group($P=0.046$). Additionally, the NBDR group had a lower postoperative complications compared to the BDR group ($P=0.014$) (Table 3). After IPTW, there were no significant differences between the two groups in intraoperative blood loss and postoperative hospital stay (both $P>0.05$), while the BDR group still had a higher postoperative complications compared to the NBDR group ($P=0.046$) (Table 4).

Risk factor analysis of patient survival

Univariate analysis showed that TNM stage and the presence of PVTT were significantly associated with postoperative OS in patients ($P<0.05$). Multivariate analysis showed that the TNM stage of the tumor was an independent risk factor for OS (OR=3.422, 95% CI 1.28–9.16, $P=0.014$) (Table 5). Univariate and multivariate analysis showed that preoperative AFP level, TNM stage, and preoperative PNI level were significantly associated

Table 2 Baseline characteristics of HCC-BDTT patients after IPTW

Variables	NBDR($n=106.8$)	BDR($n=93.7$)	*P*
Sex			0.151
male	91.4 (85.6)	89.9 (94.9)	
female	15.4 (14.4)	4.8 (5.1)	
Age	54.21 (10.05)	52.49 (13.07)	0.607
Hepatitis B			0.561
no	15.5 (14.5)	17.7 (18.9)	
yes	91.3 (85.5)	75.9 (81.1)	
Biliary drainage			0.217
no	52.8 (49.5)	32.2 (34.4)	
yes	53.9 (50.5)	61.5 (65.6)	
AST(U/L)			0.789
≤37.00	10.3 (9.7)	6.9 (7.4)	
>37.00	96.5 (90.3)	86.8 (92.6)	
GGT(U/L)			0.758
≤50.00	2.9 (2.7)	3.5 (3.7)	
>50.00	103.9 (97.3)	90.2 (96.3)	
TBIL(μmol/L)			0.718
<300.00	100.3 (93.9)	89.5 (95.6)	
≥300.00	6.5 (6.1)	4.2 (4.4)	
PNI	37.34 (4.28)	37.53 (4.54)	0.865
AFP			0.521
≤400.00	69.6 (63.3)	66.7 (71.2)	
>400.00	39.2 (36.7)	27.0 (28.8)	
Child-Pugh stage			0.279
A	51.5 (48.2)	33.2 (35.5)	
B	55.3 (51.8)	60.5 (64.5)	
PVTT			0.784
no	78.0 (73.0)	65.7 (70.2)	
yes	28.8 (27.0)	28.0 (29.8)	
TNM			0.898
I	41.5 (38.8)	36.2 (38.7)	
II	12.8 (12.0)	15.8 (16.8)	
III	22.1 (20.7)	20.6 (22.1)	
IV	30.4 (28.5)	21.0 (22.4)	

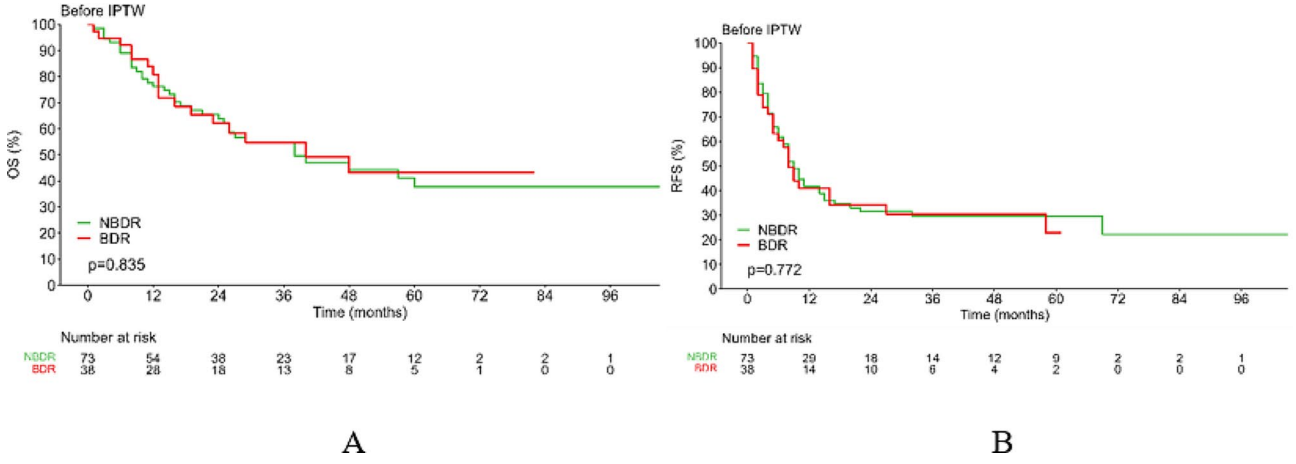

Fig. 1 (**A**) Overall survival rate and (**B**) Recurrence free survival rate of HCC-BDTT patients before IPTW in Kaplan-Meier survival analysis

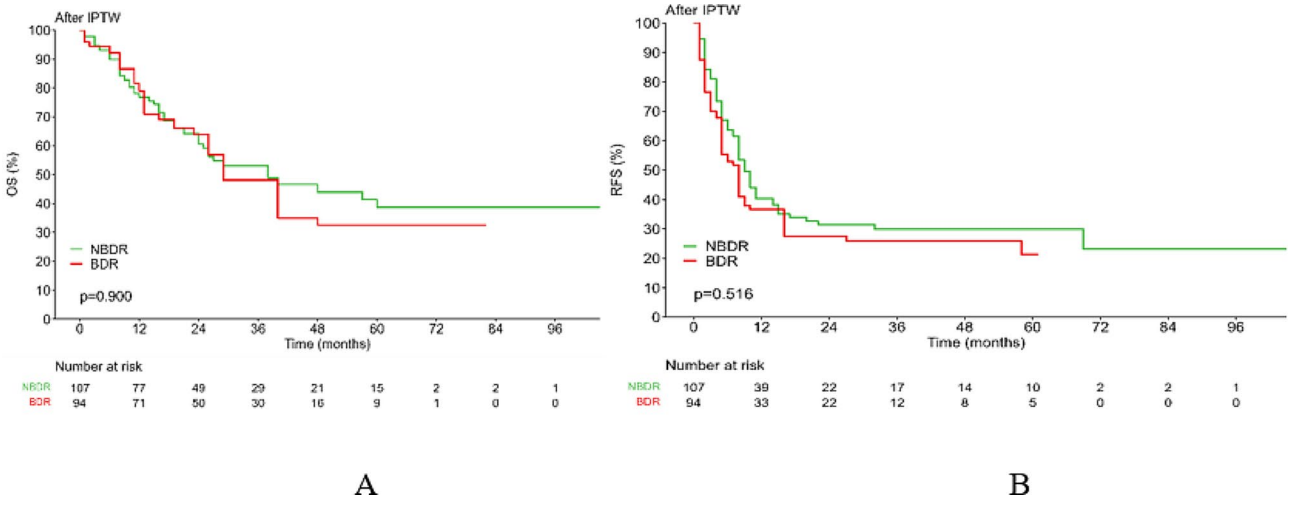

Fig. 2 (**A**) Overall survival rate and (**B**) Recurrence free survival rate of HCC-BDTT patients after IPTW in Kaplan-Meier survival analysis

Table 3 Outcome indicators of HCC-BDTT patients before IPTW

Variables	NBDR($n=73$)	BDR($n=38$)	*P*
postoperative hospital stay	13.00 [9.00, 17.00]	16.50 [11.00, 20.75]	**0.046**
intraoperative blood loss	500.00 [300.00, 1000.00]	500.00 [300.00, 1000.00]	0.825
Postoperative complications	2.00 [1.00, 3.00]	3.00 [2.00, 4.00]	**0.014**
Postoperative complications			
I	38 (52.1)	12 (31.6)	
II/III	32 (43.8)	23 (60.5)	
IV/V	3 (4.1)	3 (7.9)	

Table 4 Outcome indicators of HCC-BDTT patients before IPTW

Variables	NBDR($n=108.8$)	BDR($n=94.7$)	*P*
postoperative hospital stay	13.00 [9.00, 18.26]	16.00 [11.00, 22.93]	0.194
intraoperative blood loss	500.00 [300.00, 1000.00]	600.00 [300.00, 1200]	0.536
Postoperative complications	3.00 [1.00, 3.00]	3.00 [2.00, 4.00]	**0.046**
Postoperative complications			0.221
I	51.3 (48.1)	29.5 (31.5)	
II/III	50.2 (47.0)	53.5 (57.2)	
IV/V	5.3 (4.9)	10.6 (11.3)	

with postoperative RFS(OR=1.653, 95% CI 1.04–2.62, $P=0.033$; OR=2.197, 95% CI 1.22–3.96, $P=0.009$; OR=0.932, 95% CI 0.88–0.99, $P=0.017$) (Table 6).

Discussion

HCC patients with jaundice are often in the terminal stage of the disease and cannot tolerate surgical treatment [1, 14, 15]. However, a variety of researches have proved that obstructive jaundice caused by BDTT is not an absolute contraindication for surgery [16, 17]. As for the management of the extrahepatic bile duct, some studies suggest that preserving the bile duct provides greater benefits to the patients. Postoperative intrahepatic recurrence is common in HCC, patients often require further treatment. Performing subsequent treatments such as radiofrequency ablation and transcatheter arterial chemoembolization (TACE) after bilioenteric anastomosis may increase the risk of complications such as liver abscess, which limits the options for anticancer treatment following recurrence [11, 18, 19]. Some studies suggest that resect the extrahepatic bile duct can improve long-term survival and reduce the risk of recurrence [20, 21]. In a large-scale multi-center study conducted in Japan and Korea, extrahepatic bile duct resection was identified as a significant favorable prognostic factor for overall survival and recurrence-free survival in multivariate survival analysis. This benefit was particularly evident in patients with B4 type bile duct tumor thrombus, which is located in common hepatic duct and common bile duct [22]. This is particularly relevant for patients with primary tumors located close to the bile duct. By removing the bile duct, a better achievement of R0 resection

Table 5 Prognostic factors for overall survival of HCC-BDTT patients

Variables	Univariate-analysis		multivariate analysis	
	HR(95%CI)	*P*	HR(95%CI)	*P*
Sex		0.651		
male	reference			
female	0.840 (0.394, 1.789)			
Age	0.976 (0.952, 1.001)	0.059		
Hepatitis		0.097		
no	reference			
yes	2.185 (0.868, 5.497)			
Biliary drainage		0.579		
no	reference			
yes	1.165 (0.679, 2.001)			
AST(U/L)		0.810		
≤37.00	reference			
>37.00	0.893 (0.354, 2.249)			
GGT(U/L)		0.724		
≤50.00	reference			
>50.00	0.775 (0.188, 3.190)			
TBIL(μmol/L)		0.277		
<300.00	reference			
≥300.00	1.668 (0.663, 4.193)			
PNI	0.938 (0.878, 1.001)	0.055		
AFP		0.087		
≤400.00	reference			
>400.00	1.609 (0.933, 2.773)			
Child-Pugh stage		0.825		
A	reference			
B	1.063 (0.619, 1.824)			
BDR		0.841		
no	reference			
yes	0.943 (0.529, 1.679)			
PVTT		**0.020**		0.849
no	reference			
yes	1.969 (1.115, 3.478)		0.919 (0.383, 2.200)	
TNM				
I	reference		reference	
II	0.877 (0.325, 2.365)	0.795	0.900 (0.323, 2.512)	0.841
III	3.185 (1.648, 6.154)	**0.001**	3.422 (1.278, 9.162)	**0.014**
IV	1.405 (0.670, 2.950)	0.368	1.425 (0.671, 3.027)	0.357

can be achieved, preventing tumor recurrence along the bile duct and avoiding the potential spread of tumor cells during the thrombectomy procedure.

In this study, there was no statistically significant difference in OS and RFS between the two groups before and after IPTW. Cox regression analysis showed that the resection of the extrahepatic bile duct did not significantly affect the OS and RFS of the patients. However, there was a statistical difference in the grade of postoperative complications between the two groups before and after IPTW, with the BDR group having a significantly higher grade of postoperative complications compared to the NBDR group. Additionally, the BDR group had a longer postoperative hospital stay before IPTW. Therefore, we believe that complete resection of the primary liver tumor is more important compared to extrahepatic bile duct resection. This may because invasion of the bile duct wall is rare, and resection of the extrahepatic bile duct may lead to more severe postoperative complications, prolonging hospital stay and causing psychological and economic distress to the patients. Moreover, if patients undergone extrahepatic bile duct resection, they are at increased risk of intestinal flora retrograde invasion into the liver due to the loss of the Oddi sphincter. This increases the risk of liver abscess and ischemic cholangitis during subsequent treatments. Therefore, the management of HCC with BDTT requires a comprehensive evaluation of the tumor characteristics, including

Table 6 Prognostic factors for recurrence free survival of HCC-BDTT patients

Variables	Univariate-analysis		multivariate analysis	
	HR(95%CI)	*P*	HR(95%CI)	*P*
Sex		0.159		
male	reference			
female	0.605 (0.300, 1.218)			
Age	0.605 (0.300, 1.218)	0.079		
Hepatitis		0.480		
no	reference			
yes	1.249 (0.674, 2.315)			
Biliary drainage		0.157		
no	reference			
yes	1.386 (0.882, 2.177)			
AST(U/L)		0.240		
≤37.00	reference			
>37.00	0.658 (0.327, 1.323)			
GGT(U/L)		0.620		
≤50.00	reference			
>50.00	1.430 (0.347, 5.895)			
TBIL(μmol/L)		0.327		
<300.00	reference			
≥300.00	1.575 (0.635, 3.909)			
PNI	0.920 (0.871, 0.972)	**0.003**	0.932 (0.879, 0.987)	**0.017**
AFP		**0.007**		**0.033**
≤400.00	reference		reference	
>400.00	1.875 (1.190, 2.954)		1.653 (1.041, 2.624)	
Child-Pugh stage		0.086		
A	reference			
B	1.490 (0.945, 2.349)			
BDR				
no	reference			
yes	1.074 (0.668, 1.725)	0.769		
PVTT		0.177		
no	reference			
yes	1.402 (0.859, 2.291)			
TNM				
I	reference		reference	
II	1.471 (0.692, 3.128)	0.316	1.160 (0.535, 2.515)	0.707
III	2.813 (1.585, 4.992)	**<0.001**	2.197 (1.217, 3.963)	**0.009**
IV	1.254 (0.698, 2.252)	0.449	1.267 (0.706, 2.275)	0.428

the extent of infiltration into the bile duct, to determine the most appropriate surgical strategy and optimize the chances of achieving complete resection. Close collaboration between surgeons, radiologists, and pathologists is necessary to ensure accurate preoperative assessment and intraoperative decision-making.

The findings of Cox regression analysis are consistent with many prognostic studies on liver cancer patients. The results suggest that for HCC-BDTT patients, traditional risk factors such as tumor size, number, vascular invasion, and AFP levels are more important prognostic factors than whether or not the extrahepatic bile duct is resected. Increasing evidence suggests that systemic inflammation and nutritional disturbances promote cancer development through inhibiting cell apoptosis, promoting angiogenesis, and damaging DNA [23]. Lymphocyte depletion and/or hypoalbuminemia contribute to lower survival rates in tumor patients. PNI is a comprehensive measure of patients' immune and nutritional status, and has been proven to be an independent prognostic factor for various types of cancer, such as gastric cancer, colorectal cancer [24], pancreatic cancer [25], and hepatocellular carcinoma [26, 27]. Increasing evidence suggests that preoperative PNI can predict the overall survival of HCC patients undergoing surgical treatment, particularly in patients with underlying liver cirrhosis [28, 29]. Therefore, improving preoperative nutritional

and immune status is an important factor in enhancing postoperative survival.

It needs to be acknowledged that this study has some limitations. This study is a national multicenter study, and there may be differences in treatment philosophies among different centers. Since some data from other centers were not collected in this study, it cannot exclude the possibility of some potential confounding factors not being included in the study. Additionally, as a retrospective study, many prognostic indicators, such as postoperative treatment methods and measures for recurrent cases, may not have been followed up. In the future, prospective multicenter studies should be designed to assess a larger patient population in order to address these limitations.

Conclusion

For patients with extrahepatic BDTT, routine resection of the extrahepatic bile duct is not required unless the tumor thrombus is tightly adhered to the bile duct wall and difficult to separate intraoperatively. Attention should be paid to perioperative management and meticulous surgical techniques, including enhancing the patient's nutritional reserve during the perioperative period. Medication and biliary drainage should be used to reduce the patient's bilirubin level and improve liver functional reserve. During the surgery, efforts should be made to achieve radical resection of the primary lesion and careful separation of the tumor thrombus from the bile duct to minimize intraoperative bleeding. Postoperative care and antimicrobial therapy should be emphasized to reduce the occurrence of complications such as bile leak, biliary infection, and intra-abdominal abscess.

Abbreviations

HCC	Hepatocellular carcinoma
BDTT	Bile duct tumor thrombus
PVTT	Portal vein tumor thrombus
AFP	α-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TBIL	Total bilirubin
DBIL	Direct bilirubin
ALB	Albumin
γ-GGT	γ-glutamyl transpeptidase
WBC	White blood cells
PLT	Platelets
CT	Computerized tomography
MRI	Magnetic resonance imaging

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Author contributions

XY wrote the main manuscript text and QZL, JLW and YCP prepared figures and tables. QL and TL participated in data collection. JPC, LHC, WC and LJL participated in the design of the subject. All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The present study was carried out in accordance with the principles of the Declaration of Helsinki. This retrospective study was approved by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all patients prior to treatment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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