# Concurrent bile duct resection versus concomitant thrombectomy for hepatocellular carcinoma associated with bile duct tumor thrombus: a propensity score matching analysis

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**Background:** Hepatocellular carcinoma (HCC) associated with bile duct tumor thrombus (BDTT) is uncommon in clinical practice. Surgical resection can achieve better survival than non-operative palliative treatments. However, there is great controversy regarding the optimal surgical modality, particularly regarding the approach to remove BDTT in patients with HCC with macroscopic BDTT.

**Methods:** Data from consecutive patients who underwent radical surgery for HCC and macroscopic BDTT at the Eastern Hepatobiliary Surgery Hospital and Fujian Provincial Hospital from January 2009 to December 2016 were retrospectively reviewed. The survival outcomes of patients who underwent hepatectomy combined with extrahepatic bile duct resection (the EBDR group) were compared with those of patients undergoing liver resection plus thrombectomy (the thrombectomy group) using propensity score matching (PSM). Univariate and multivariate Cox analyses were performed to identify independent prognostic factors for overall survival (OS) and recurrence-free survival (RFS).

**Results:** 217 patients included in this study were divided into two groups: the EBDR group (n=30) and the thrombectomy group (n=187). A total of 90 patients were matched by PSM with a 1:2 ratio. Before PSM, the OS and RFS rates were comparable between the two groups (for OS, P=0.517; for RFS, P=0.211). After PSM, the OS rates did not differ statistically significantly between the EBDR and thrombectomy groups (P=0.134). Nevertheless, the RFS rate of the EBDR group was significantly higher compared to that of the thrombectomy group (P=0.020). Multivariate analysis demonstrated that some traditional risk factors, such as tumor size and microscopic resection margin, were more important prognostic factors than the BDTT type.

**Conclusions:** For patients with HCC and macroscopic BDTT, hepatectomy combined with extrahepatic bile duct resection is associated with a reduced recurrence rate in comparison with concurrent thrombectomy. Further large-scale, prospective studies are warranted to evaluate the impact of different surgical modalities on these patients' survival.

**Keywords:** Bile duct tumor thrombus (BDTT); extrahepatic bile duct resection; hepatocellular carcinoma (HCC); survival outcomes; thrombectomy

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## Introduction

Hepatocellular carcinoma (HCC) is one of the most aggressive malignant neoplasms and the third leading cause of cancer-related mortality worldwide (1). Vascular invasion is very common in the development of HCC (2,3). However, the formation of bile duct tumor thrombus (BDTT) due to intrabiliary growth of HCC is relatively rare in clinical practice. The prevalence of BDTT resulting from HCC ranges only from 1.2% to 12.9% in the previous literature (4).

With great advances in perioperative management and surgical techniques in recent years, radical surgery has become a safe and effective treatment strategy for patients with HCC and BDTT, resulting in improved survival compared with conventional therapies like transarterial chemoembolization (TACE) (5). Nevertheless, great controversy on the optimal surgical method for HCC patients complicated with macroscopic BDTT, especially on the necessity of extrahepatic bile duct resection (EBDR), persists. The effect of different operative modalities on patients' survival has not been well explored. Unfortunately, due to its low incidence, available studies focusing on this issue are scarce. Most studies to date are case reports or case series including a limited number of patients, which restricts the generalizability and extrapolation of the results.

This study is based on a consecutive patient cohort from two tertiary cancer centers in China, with the aim of investigating two operative techniques (concurrent EBDR versus combined thrombectomy) and examining their influence on the long-term outcomes in HCC patients with macroscopic BDTT. In particular, independent prognostic factors affecting survival, and recurrence patterns for these patients were also analyzed.

We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6449).

## Methods

### *Study population*

Between January 2009 and December 2016, 382 patients with HCC and BDTT underwent radical surgical resection as initial treatment at the Eastern Hepatobiliary Surgery Hospital (EHBH) and Fujian Provincial Hospital (FPH). The demographic, clinical and pathologic data, recurrence status and survival outcomes were recorded in a prospectively maintained electronic database and reviewed retrospectively. To evaluate the effect of surgical methods on the long-term survival, these patients were divided into two groups based on the operative procedure. The patients who underwent hepatectomy combined with thrombectomy belonged to the thrombectomy group; the others undergoing liver resection plus EBDR were entered into the EBDR group. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Institutional Ethics Committees of EHBH and FPH (No. EHBHKY2018-01-007). Written informed consent was obtained from each of the recruited patients for their data to be used for research purposes.

The diagnosis of primary HCC was based on the up-to-date *EASL Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma* (6). The presence of BDTT was identified by preoperative imaging modalities, including abdominal ultrasonography (US), contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), or by intraoperative exploratory findings. Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) was utilized to evaluate the extent of BDTT when necessary. The specimens of HCC and BDTT were all histopathologically confirmed by two senior pathologists from the Department of Pathology of the EHBH and FPH.

### *Classification of BDTT*

BDTT was categorized as B1 (involvement of the third-order intrahepatic duct or above), B2 (invasion of the second-order branches of bile duct), B3 (extension to the first-order branches of bile duct, namely, the left or right hepatic duct), and B4 (locating to the common hepatic duct or common bile duct) according to the classification standard defined by *the liver cancer study group of Japan* (*LCSGJ*) (7).

### *Inclusion and exclusion criteria*

HCC patients with grade B1 or B2 BDTT were intentionally excluded because such an extent of BDTT could usually be removed en bloc with HCC and was not associated with changes of further surgical treatment planning.

The inclusion criteria were HCC patients with BDTT (I) diagnosed by the diagnostic criteria as mentioned above; (II) receiving radical surgery; (III) with preserved liver function of Child-Pugh class A or selected B (total scores ≤7); and (IV) complicated with type B3 and B4 BDTT.

The exclusion criteria were patients with (I) preoperative anti-cancer treatment, including TACE, local ablation, systemic chemotherapy, sorafenib, and percutaneous ethanol injection; (II) extrahepatic spread and distant metastasis, or other unrelated malignancies; (III) liver function of Child-Pugh class C; (IV) serious postoperative complications such as acute hepatic dysfunction or death within 3 months of surgery; (V) type B1 and B2 BDTT; and (VI) missing or incomplete data.

### *Preoperative assessment*

General physical status, preoperative hepatic function tests including liver biochemistry, coagulation profile and Child-Pugh score, and imaging findings indicating tumor burden and location of BDTT of each individual patient were carefully assessed to determine resectability. Spiral CT scanning and three-dimensional reconstruction were employed to predict the future remnant volume of liver parenchyma. Preoperative biliary drainage was indicated in patients with a serum total bilirubin level >5 mg/dL, or in those developing critical jaundice or cholangitis due to biliary obstruction.

### *Surgical procedures*

The surgical methods for liver resection have been described in our previous studies (8,9). For the management of macroscopic BDTT, two surgical procedures were adopted depending on the relationship of BDTT with the bile duct wall. If the BDTT was loosely adherent to the wall of large bile ducts and could be easily detached, tumor thrombus was peeled off using a technique similar to the bile duct preserving surgery reported by Yamamoto *et al.* (10). Thrombectomy through choledochotomy or cut-end of the bile duct was performed carefully to avoid intractable biliary hemorrhage. The incision site was closed by running sutures and a T-tube was inserted into the cystic duct to drain oozing of blood. In cases where the BDTT was tightly adherent to the bile duct wall, extrahepatic bile duct was resected and bilioenteric reconstruction was fashioned with Roux-en-Y hepaticojejunostomy (11). After removal of BDTT, the ductal lumen was carefully inspected employing intraoperative cholangiography or choledochoscope to verify that no residual tumor was present in the bile duct and liver. The specimens of HCC and involved bile duct were labelled and sent for cytological and histopathological examination.

### *Postoperative follow-up*

Patients' postoperative surveillance and management protocols were uniformly formulated. Generally, patients were periodically followed up at the outpatient clinic once every 3 to 4 months after discharge, until death or dropout from the follow-up program. Routine follow-up items comprised laboratory tests (complete blood count, biochemical index, AFP, hepatitis virus screens) and abdominal US. If recurrence was strongly suspected, contrast-enhanced CT or MRI was required to be undertaken. When recurrence was clinically determined, patients were actively treated by repeated surgical resection or non-surgical therapies according to general status, residual liver volume and recurrence pattern of the patients. This study was censored on December 31, 2019.

### *Definition of clinicopathologic variables and survival outcomes*

Anatomic resection was defined as complete removal of all lesions based on the liver anatomy according to Couinaud's nomenclature (12). Major hepatectomy was defined as resection of three or more Couinaud liver segments. Tumor differentiation was graded according to the Edmonson-Steiner grading standard. Tumor stage was determined using *the 8th Edition of American Joint Committee on Cancer (AJCC) Staging Manual* (13). One year after surgery was used as the cut-off to distinguish early and late recurrence. OS was calculated from the date of surgery to the date of death or the date of last follow-up. RFS was calculated from the date of surgery to the date when recurrence/metastasis

was first diagnosed or the date of last follow-up.

### *Propensity score matching analysis*

Propensity score matching (PSM) analysis was adopted to minimize the selection bias and between-group heterogeneity. Potentially confounding factors that could affect survival outcomes were included in the PSM analysis. Briefly, the propensity scores based on the logistic regression model were calculated for every individual and the baseline characteristics were balanced between the two groups. The analysis was performed between the EBDR and thrombectomy groups at a 1:2 ratio, without replacement, using the nearest-neighbor matching algorithm with a caliber of 0.2. After excluding patients with PVTT, the above PSM method was also carried out for the remaining patients.

### *Statistical analysis*

Normally distributed continuous variables were expressed as means ± standard deviation (SD) and compared using the Student's *t* test. Continuous variables with a skewed distribution were reported as medians (interquartile range, IQR) and compared using the Mann-Whitney U test. Categorical data were presented as frequencies and percentages (%) and analyzed using the Chi-square test or Fisher's exact test, as appropriate. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model. Prognostic factors with a P value <0.05 in univariate analysis were incorporated into multivariate analysis. A two-tailed P value <0.05 was considered statistically significant. PSM analysis was performed using the "MatchIt" package of the R program, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). The other statistical analyses were performed using SPSS software, version 24.0 (IBM, Armonk, New York, USA).

## Results

### *Patient characteristics*

The detailed process of selecting eligible patients during the study period is displayed in the flow diagram of *Figure 1*. Eventually, 217 patients who underwent curative surgery were identified. Among these patients, there were 30 in the EBDR group and 187 in the thrombectomy group. After PSM with a 1:2 ratio, 30 patients remained in the EBDR group and 60 patients were included in the thrombectomy group.

The baseline demographic and preoperative characteristics, the operative and pathologic data of the two groups of patients before PSM are illustrated in Tables S1,S2. Before PSM, the EBDR group had a significantly greater proportion of Child-Pugh class B, well or moderate tumor differentiation and grade B4 BDTT, and had a substantially higher level of serum total bilirubin (TBil) and a lower level of albumin (ALB). After PSM, these clinicopathological features became well-balanced (*Tables 1*,*2*). Because BDTT was blocked in the main trunk of the biliary system, most patients had preoperatively elevated TBil and γ-glutamyl transpeptidase (GGT) on first hospitalization.

### *Univariate and multivariate analysis for OS and RFS*

As shown in *Table 3*, univariate and multivariate analyses of the crude cohort demonstrated that serum ALB ≤35 g/L (P<0.001), minor hepatectomy (P=0.001), tumor diameter >5 cm (P=0.016), presence of portal vein tumor thrombus (PVTT) (P=0.011) were independent risk factors for OS. Alanine aminotransferase (ALT) >44 U/L (P=0.045), minor hepatectomy (P=0.001), tumor diameter >5 cm (P=0.005), involvement of microscopic resection margin (P<0.001) were identified as independent risk factors for RFS.

### *Survival analysis of all patients*

Before PSM, the median OS time (MOST 95% CI) after surgery was 30.0 (22.4–37.6) months. The 1-, 3- and 5-year OS rates were 76.5%, 44.8% and 36.5%, respectively. The median RFS time (MRFST 95% CI) after surgical resection was 10.0 (7.2–12.8) months. The 1-, 3- and 5-year RFS rates were 44.6%, 26.6% and 22.8%, respectively (Figure S1A,B).

After PSM, the MOST (95% CI) after surgery was 24.0 (15.0–33.0) months. The 1-, 3- and 5-year OS rates were 70.0%, 39.0% and 30.2%, respectively. The MRFST (95% CI) after surgical resection was 9.0 (6.3–11.7) months. The 1-, 3- and 5-year RFS rates were 40.7%, 25.2% and 20.8%,

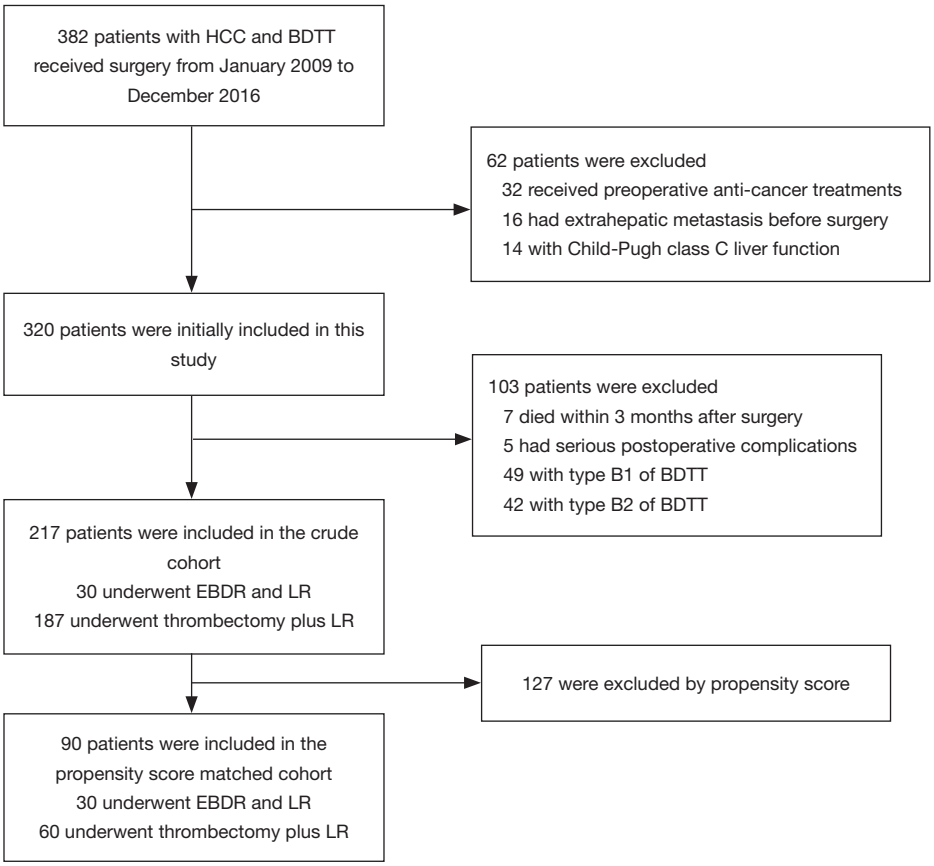


**Figure 1** Flowchart showing the selection of eligible HCC patients with macroscopic BDTT for the study. HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; EBDR, extrahepatic bile duct resection; LR, liver resection; PS, propensity scoring.

respectively (Figure S1C,D).

### *Survival analysis comparing the EBDR and thrombectomy groups*

In the crude cohort before PSM, the MOST (95% CI) after surgery was 36.0 (8.4–63.6) months for the EBDR group and 30.0 (22.6–37.4) months for the thrombectomy group. The OS was comparable between the EBDR and thrombectomy groups (1-year, 81.7% *vs.* 75.7%; 3-year, 46.9% *vs.* 44.6%; 5-year, 46.9% *vs.* 35.3%; P=0.517). The MRFST (95% CI) after surgical resection was 15.0 (4.1–25.9) months for the EBDR group and 9.0 (6.6–11.4) months for the thrombectomy group. The RFS did not differ significantly between the two groups (1-year, 57.2% *vs.* 42.6%; 3-year, 40.9% *vs.* 24.6%; 5-year, 32.7% *vs.* 21.3%; P=0.211) (*Figure 2A,B*).

In the PS-matched cohort after PSM, the MOST (95% CI) after surgery was 36.0 (8.4–63.6) months for the EBDR group and 24.0 (12.1–35.9) months for the thrombectomy group. The OS was not significantly different between the EBDR and thrombectomy groups (1-year, 81.7% *vs.* 64.5%; 3-year, 46.9% *vs.* 35.5%; 5-year, 46.9% *vs.* 21.3%; P=0.134). The MRFST (95% CI) after surgical intervention was 15.0 (4.1–25.9) months for the EBDR group and 7.0 (4.2–9.8) months for the thrombectomy group. The RFS was significantly better for the EBDR group compared with the thrombectomy group (1-year, 57.2% *vs.* 32.7%; 3-year, 40.9% *vs.* 17.7%; 5-year, 32.7% *vs.* 14.8%; P=0.020) (*Figure 2C,D*).

### *Subgroup analysis of survival for patients without PVTT*

Considering that PVTT is a well-established risk factor of long-term survival in HCC patients, survival analysis was further performed in the 174 HCC patients with BDTT

**Table 1** Demographic and preoperative data of patients with HCC and BDTT after PSM

| Variables | All (N=90) | EBDR group (N=30) | Thrombectomy group (N=60) | P |
|---|---|---|---|---|
| Age (years)† | 53.5 [47–60] | 54.5 [46–60] | 52 [48–60] | 0.735 |
| Gender | | | | 0.597 |
| Male | 69 (76.7%) | 22 (73.3%) | 47 (78.3%) | |
| Female | 21 (23.3%) | 8 (26.7%) | 13 (21.7%) | |
| HBsAg | | | | 0.729 |
| Positive | 68 (75.6%) | 22 (73.3%) | 46 (76.7%) | |
| Negative | 22 (24.4%) | 8 (26.7%) | 14 (23.3%) | |
| Child-Pugh class | | | | 0.227 |
| A | 38 (42.2%) | 10 (33.3%) | 28 (46.7%) | |
| B | 52 (57.8%) | 20 (66.7%) | 32 (53.3%) | |
| Biliary decompression | | | | 0.739 |
| Performed | 25 (27.8%) | 9 (31.0%) | 16 (26.7%) | |
| Not performed | 65 (72.2%) | 21 (70.0%) | 44 (73.3%) | |
| AFP (ng/mL) | | | | 0.294 |
| ≤400 | 40 (44.4%) | 11 (36.7%) | 29 (48.3%) | |
| >400 | 50 (55.6%) | 19 (63.3%) | 31 (51.7%) | |
| ALB (g/L)† | 37.3 (34.3–40.5) | 37.2 (34.4–40.6) | 37.3 (34.2–40.5) | 0.732 |
| TBil (mg/dL)† | 6.3 (1.1–11.3) | 7.2 (3.1–13.0) | 5.4 (1.0–10.9) | 0.294 |
| ALT (U/L)† | 72.8 (39.8–123.5) | 82.0 (53.7–123.8) | 65.0 (33.0–124.0) | 0.221 |
| GGT (IU/L)† | 316.0 (171.4–540.0) | 365.5 (192.5–505.1) | 297.5 (168.0–552.0) | 0.477 |
| PT (s)† | 12.7 (11.6–13.5) | 12.8 (12.2–13.5) | 12.4 (11.5–13.6) | 0.491 |

†Mann-Whitney U test; others: chi-square test. HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; EBDR, extrahepatic bile duct resection; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; ALB, albumin; TBil, total bilirubin; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; PT, prothrombin time.

but without PVTT. Before PSM, the OS and RFS rates were similar between the two groups (for OS, 1-year, 85.4% *vs.* 78.7%; 3-year, 46.2% *vs.* 47.6%; 5-year, 46.2% *vs.* 36.5%; P=0.642; for RFS, 1-year, 56.7% *vs.* 45.9%; 3-year, 41.2% *vs.* 25.8%; 5-year, 30.9% *vs.* 21.7%; P=0.412) (Figure S2A,B). After PSM, 66 patients were available. There was no significant difference in OS between the EBDR and thrombectomy groups (1-year, 85.4% *vs.* 70.6%; 3-year, 46.2% *vs.* 36.4%; 5-year, 46.2% *vs.* 18.7%; P=0.185). Nevertheless, RFS was more favorable for the EBDR group than the thrombectomy group (1-year, 56.7% *vs.* 34.7%; 3-year, 41.2% *vs.* 18.3%; 5-year, 30.9% *vs.* 13.7%; P=0.045) (Figure S2C,D).

### *Time to recurrence and site of recurrence in patients who experienced relapse*

In order to analyze the recurrence patterns, patients were categorized into various subgroups according to time to and site of recurrence.

As shown in Table S3, among the 161 patients who had recurrence during the follow-up period, 19 patients belonged to the EBDR group and the other 142 patients belonged to the thrombectomy group. 115 (71.4%) patients

**Table 2** Operative and pathologic data of patients with HCC and BDTT after PSM

| Variables | All (N=90) | EBDR group (N=30) | Thrombectomy group (N=60) | P |
|---|---|---|---|---|
| Extent of hepatectomy | | | | 0.872 |
| Major | 62 (68.9%) | 21 (70.0%) | 41 (68.3%) | |
| Minor | 28 (31.1%) | 9 (30.0%) | 19 (31.7%) | |
| Type of hepatectomy | | | | 0.370 |
| Anatomic | 48 (53.3%) | 18 (60.0%) | 30 (50.0%) | |
| Non-anatomic | 42 (46.7%) | 12 (40.0%) | 30 (50.0%) | |
| Intraoperative blood loss (mL)[†] | 400.0 (287.5–800.0) | 400.0 (275.0–850.0) | 400.0 (262.5–750.0) | 0.596 |
| Pathologic liver cirrhosis | | | | 0.654 |
| Presence | 48 (53.3%) | 15 (50.0%) | 33 (55.0%) | |
| Absence | 42 (46.7%) | 15 (50.0%) | 27 (45.0%) | |
| Tumor diameter (cm)[†] | 4.4 (3.0-6.8) | 4.8 (2.5-6.0) | 4.3 (3.0-7.0) | 0.217 |
| Number of tumor | | | | 0.551 |
| Solitary | 47 (52.2%) | 17 (56.7%) | 30 (50.0%) | |
| Multiple | 43 (47.8%) | 13 (43.3%) | 30 (50.0%) | |
| Microscopic margin involvement | | | | 0.715 |
| Positive | 19 (21.1%) | 7 (23.3%) | 12 (20.0%) | |
| Negative | 71 (78.9%) | 23 (76.7%) | 48 (80.0%) | |
| Tumor capsule | | | | 1.000 |
| Absence | 81 (90.0%) | 27 (90.0%) | 54 (90.0%) | |
| Incomplete | 5 (5.6%) | 2 (6.7%) | 3 (5.0%) | |
| Complete | 4 (4.4%) | 1 (3.3%) | 3 (5.0%) | |
| Tumor differentiation | | | | 0.551 |
| Well/moderate | 44 (48.9%) | 16 (53.3%) | 28 (46.7%) | |
| Poor/undifferentiated | 46 (51.1%) | 14 (46.7%) | 32 (53.3%) | |
| Tumor TNM stage | | | | 0.881 |
| I/II | 43 (47.8%) | 14 (46.7%) | 29 (48.3%) | |
| III/IV | 47 (52.2%) | 16 (53.3%) | 31 (51.7%) | |
| Grade of BDTT | | | | 0.553 |
| B3 | 10 (11.1%) | 2 (6.7%) | 8 (13.3%) | |
| B4 | 80 (88.9%) | 28 (93.3%) | 52 (86.7%) | |
| Concurrent PVTT | | | | 0.864 |
| Presence | 23 (25.6%) | 8 (26.7%) | 15 (25.0%) | |
| Absence | 67 (74.4%) | 22 (73.3%) | 45 (75.0%) | |

[†]Mann-Whitney U test; others: chi-square test. HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; EBDR, extrahepatic bile duct resection; TNM, tumor-node-metastasis; PVTT, portal vein tumor thrombus.

**Table 3** Prognostic factors for overall survival and recurrence-free survival before PSM

| Variable | Overall survival | | | | Recurrence-free survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Preoperative factors | | | | | | | | |
| Age >55 yr | 1.24 (0.87, 1.76) | 0.230 | | | 1.00 (0.73, 1.36) | 0.973 | | |
| Gender, male | 1.50 (0.94, 2.37) | 0.087 | | | 1.26 (0.83, 1.90) | 0.277 | | |
| HBsAg, positive | 1.27 (0.86, 1.88) | 0.237 | | | 0.98 (0.70, 1.38) | 0.928 | | |
| Child-Pugh class, B | 1.06 (0.75, 1.51) | 0.737 | | | 1.05 (0.77, 1.44) | 0.765 | | |
| Biliary decompression, performed | 0.99 (0.62, 1.58) | 0.957 | | | 0.78 (0.52, 1.15) | 0.205 | | |
| AFP >400 ng/mL | 1.09 (0.77, 1.54) | 0.642 | | | 1.05 (0.77, 1.43) | 0.777 | | |
| ALB ≤35 g/L | 2.29 (1.54, 3.40) | <0.001 | 2.48 (1.65, 3.72) | <0.001 | 1.52 (1.04, 2.23) | 0.029 | | |
| TBil >3 mg/dL | 1.10 (0.78, 1.56) | 0.583 | | | 1.16 (0.85, 1.59) | 0.341 | | |
| ALT >44 U/L | 1.49 (1.03, 2.16) | 0.035 | | | 1.45 (1.04, 2.03) | 0.028 | 1.42 (1.01, 2.00) | 0.045 |
| GGT >200 IU/L | 1.17 (0.79, 1.74) | 0.433 | | | 1.17 (0.82, 1.67) | 0.382 | | |
| PT >13 s | 1.17 (0.78, 1.75) | 0.444 | | | 1.16 (0.81, 1.66) | 0.407 | | |
| Operative factors | | | | | | | | |
| Extent of hepatectomy, major | 0.60 (0.42, 0.85) | 0.004 | 0.53 (0.37, 0.76) | 0.001 | 0.65 (0.47, 0.89) | 0.008 | 0.58 (0.41, 0.80) | 0.001 |
| Type of hepatectomy, anatomic | 0.66 (0.47, 0.94) | 0.020 | | | 0.63 (0.46, 0.87) | 0.004 | | |
| Removal of BDTT, EBDR | 0.83 (0.48, 1.45) | 0.523 | | | 0.74 (0.46, 1.20) | 0.228 | | |
| Intraoperative blood loss >400 mL | 1.21 (0.85, 1.71) | 0.289 | | | 1.16 (0.85, 1.59) | 0.343 | | |
| Pathologic factors | | | | | | | | |
| Liver cirrhosis, presence | 1.06 (0.75, 1.51) | 0.732 | | | 1.06 (0.77, 1.45) | 0.720 | | |
| Tumor diameter >5 cm | 1.47 (1.03, 2.09) | 0.034 | 1.58 (1.09, 2.30) | 0.016 | 1.46 (1.06, 2.00) | 0.020 | 1.60 (1.15, 2.22) | 0.005 |
| Number of tumor, solitary | 0.91 (0.62, 1.32) | 0.612 | | | 0.96 (0.69, 1.34) | 0.808 | | |
| Microscopic margin, positive | 2.12 (1.33, 3.41) | 0.002 | | | 2.57 (1.67, 3.97) | <0.001 | 2.53 (1.63, 3.94) | <0.001 |
| Tumor capsule, absence | 1.05 (0.73, 1.52) | 0.791 | | | 1.03 (0.74, 1.45) | 0.848 | | |
| Tumor differentiation, well/moderate | 0.76 (0.52, 1.10) | 0.142 | | | 0.81 (0.59, 1.12) | 0.205 | | |
| TNM stage, I/II | 0.81 (0.57, 1.16) | 0.253 | | | 0.87 (0.63, 1.19) | 0.377 | | |
| Grade of BDTT, B4 | 1.06 (0.70, 1.59) | 0.794 | | | 1.06 (0.74, 1.52) | 0.748 | | |
| Concurrent PVTT, presence | 1.92 (1.26, 2.92) | 0.002 | 1.74 (1.13, 2.68) | 0.011 | 1.56 (1.07, 2.27) | 0.021 | | |

HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; ALB, albumin; TBil, total bilirubin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; PT, prothrombin time; BDTT, bile duct tumor thrombus; EBDR, extrahepatic bile duct resection; TNM, tumor-node-metastasis; PVTT, portal vein tumor thrombus.

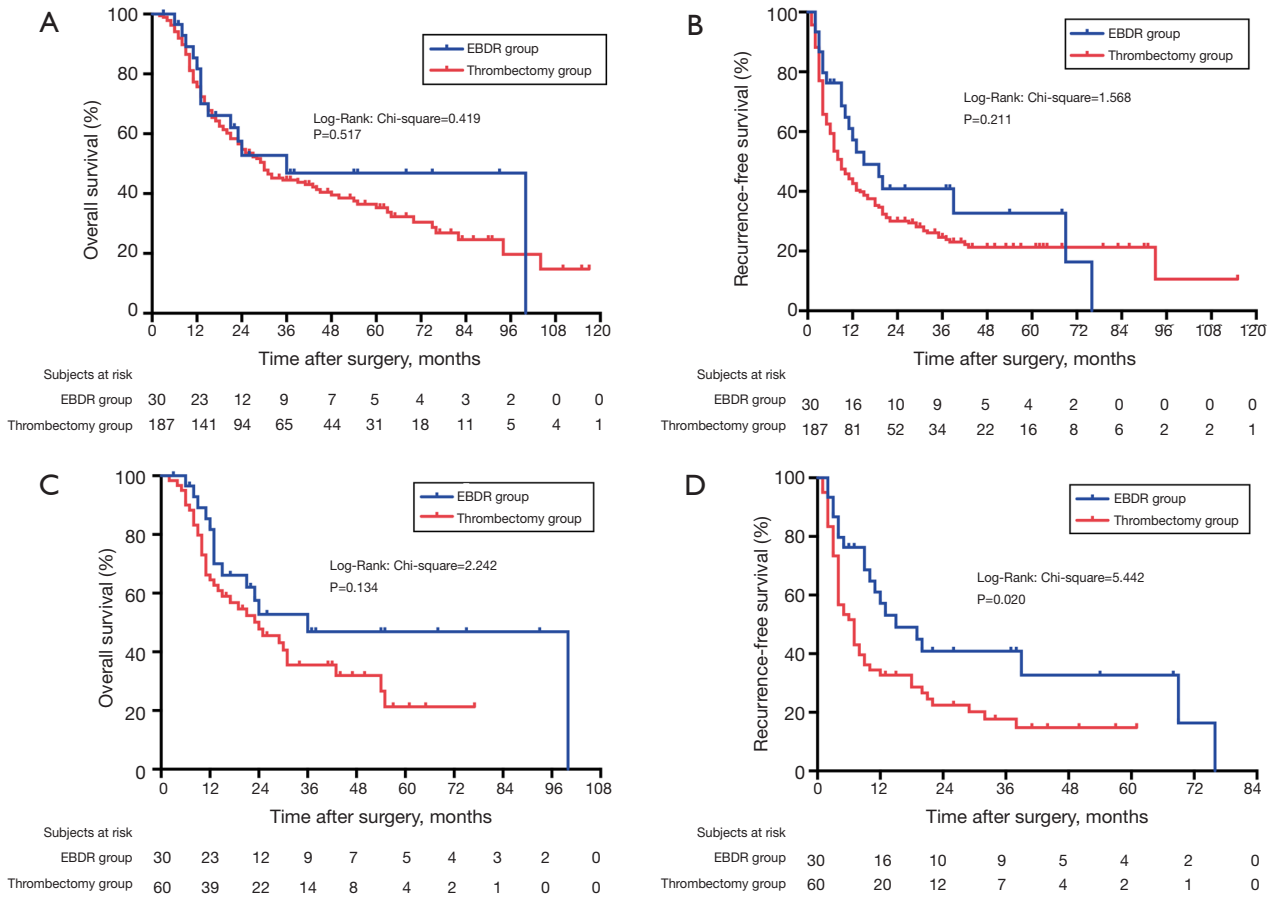


**Figure 2** Kaplan-Meier survival curves for OS and RFS in all HCC patients with BDTT. OS of HCC patients in the EBDR and thrombectomy groups (30 patients *vs.* 187 patients) before PSM (A) (P=0.517); RFS of HCC patients in the EBDR and thrombectomy groups (30 *vs.* 187 patients) before PSM (B) (P=0.211); OS of HCC patients in the EBDR and thrombectomy groups (30 patients *vs.* 60 patients) after PSM (C) (P=0.134); RFS of HCC patients in the EBDR and thrombectomy groups (30 *vs.* 60 patients) after PSM (D) (P=0.020). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; EBDR, extrahepatic bile duct resection.

experienced recurrence within the first year after surgery, among whom 11 patients were in the EBDR group and 104 patients were in the thrombectomy group. The rate of early recurrence of the thrombectomy group was relatively higher than that of the EBDR group (73.2% *vs.* 57.9%).

In terms of recurrence site, the rate of bile duct recurrence (alone or concomitant) was higher in the thrombectomy group than in the EBDR group (28.9% *vs.* 15.8%). Notably, the rate of local recurrence, defined as relapse in the liver and/or bile duct without extrahepatic dissemination, in the EBDR group was 89.4%, which was higher than that in the thrombectomy group at 84.5%; while the rate of distant spread, defined as any recurrence involving extrahepatic metastasis, was relatively higher in the thrombectomy group compared to the EBDR group (15.5% *vs.* 10.6%).

## Discussion

HCC patients associated with macroscopic BDTT can manifest unique clinical features such as obstructive jaundice, hemobilia, and acute cholangitis compared to conventional HCC without BDTT. This poses certain challenges to differential diagnoses from conditions like perihilar cholangiocarcinoma and choledocholithiasis (14-16). Sustained jaundice and hyperbilirubinemia were

considered a contraindication to aggressive surgery in the past as a result of impairment of liver function and potential risk of postoperative liver failure. However, jaundice induced by BDTT is different in nature from parenchymal cholestasis, caused by diffuse tumor infiltration or advanced liver cirrhosis, which always precludes operation because of late stage of the disease.

With rapid advances in preoperative management, especially in interventional techniques such as ERCP and percutaneous transhepatic cholangial drainage (PTCD), a considerable proportion of HCC patients with BDTT are able to be listed as candidates for radical surgery, after sufficient biliary decompression and amelioration of hepatic function. Beneficial effects of surgery on these individuals have been repeatedly documented and are well accepted. A series of retrospective studies illustrated that patients with HCC and BDTT undergoing radical surgery had significantly improved prognosis compared to those receiving non-operative management (5,17,18).

However, whether to preserve or excise extrahepatic bile duct when HCC invades large bile ducts remains a question under debate. Some authors have held that synchronous EBDR increases the chance of R0 resection and reduces the possibility of local recurrence in the biliary tract remnant (4,19-21). On the contrary, some researchers have recommended combined thrombectomy (10,22-25). This recommendation is based on the clinical finding that patients who undergo EBDR and bilioenteric anastomosis more frequently develop liver abscess when undergoing postoperative adjuvant treatment such as TACE or local ablation (26,27), thus limiting the future options for anticancer treatment.

Furthermore, the long-term prognosis of patients with HCC with macroscopic BDTT following these two distinct surgical methods is also disputed. A recent multicenter study conducted by Kim *et al.* (21) demonstrated that EBDR was a significantly positive prognostic factor for both OS and recurrence in this group of patients. Another study compared the survival of HCC patients with BDTT with similar clinicopathological profiles, which demonstrated that hepatectomy with thrombectomy was an independent negative factor of OS and RFS (20). By contrast, some other studies reported that the method of removal of BDTT did not affect the prognosis in HCC patients associated with BDTT (25,28).

In the present study, we focused on comparing the survival outcomes and investigating prognostic factors in HCC patients who underwent two different surgical procedures aiming at removal of macroscopic BDTT. Of the 217 patients who were finally included in this study, only 30 (13.8%) underwent EBDR. In order to ensure comparability between groups, PSM analyses were performed. The OS rate was comparable between the two groups before and after PSM; whereas the RFS rate was significantly better for the EBDR group following PSM. These results indicated that EBDR could potentially decrease recurrence but did not facilitate OS. Considering that PVTT is an established risk factor of HCC in this and previous studies, subgroup analyses which excluded patients complicated with PVTT were carried out. Equivalent results before and after PSM were obtained, reflecting the robustness of these findings. The results of multivariate analysis suggested that some traditional risk factors, such as tumor diameter, involvement of microscopic resection margin, and PVTT, were more prominent prognostic factors than BDTT type itself.

Lastly, the recurrence patterns in patients who experienced tumor relapse were analyzed. In terms of time to recurrence, the percentage of early recurrence was relatively lower in the EBDR group, which might be attributed to the extensive clearance of micro-metastases. With respect to the positions of recurrence, the rate of local recurrence was higher in the EBDR group than in its counterpart; whereas the percentage of distant spread was the opposite. Patients suffering from local recurrence can be actively treated with re-resection, while patients who experience distant metastasis often lose the chance of reoperation and can only be managed with palliative treatment. This interesting phenomenon suggests that the selection of surgical method may exert some potential effect on the recurrence patterns in HCC patients with macroscopic BDTT. However, statistical comparisons between groups were not made due to the limitation of sample size. Additional studies are warranted to examine this clinical finding.

This study has some limitations. Firstly, despite the application of PSM analysis, selection bias and confounders inherent to the retrospective study cannot be neglected. Secondly, although this study comes from two tertiary cancer centers, the numbers of patients in the two groups differ markedly and the sample size in the EBDR group was relatively small. Therefore, prospective studies with large-scale sample size should be designed and carried out in the future, in order to further evaluate the surgical outcomes, and to select an ideal operative approach for HCC patients

with macroscopic BDTT.

## Conclusions

This PSM-based study reveals that liver resection combined with EBDR is associated with better RFS for HCC patients with macroscopic BDTT compared with hepatectomy plus thrombectomy. Concurrent EBDR can be considered as a promising strategy to reduce tumor recurrence for patients with HCC and macroscopic BDTT. However, determining the precise therapeutic role of EBDR in these patients requires more high-quality studies.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6449

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6449). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committees of the Eastern Hepatobiliary Surgery Hospital of Shanghai, China and Fujian Provincial Hospital of Fuzhou, China (No. EHBHKY2018-01-007). Written informed consent was obtained from all the patients for their data to be used for research purposes.



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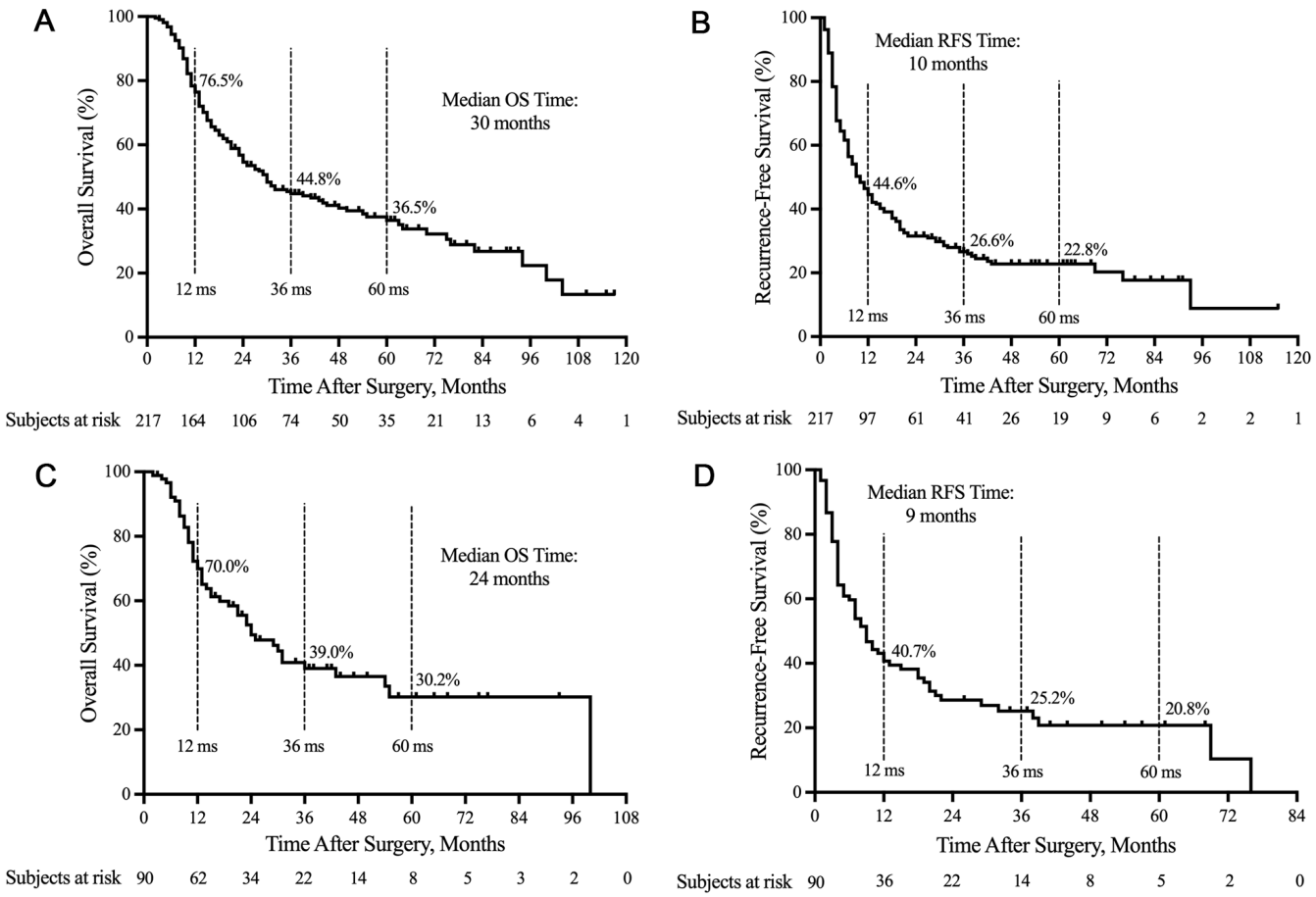


**Figure S1** Survival curves for OS and RFS in all HCC patients with BDTT. The OS of 217 patients before PSM (A); the RFS of 217 patients before PSM (B); the OS of 90 patients after PSM (C); the RFS of 90 patients after PSM (D). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus, PSM, propensity scoring match.


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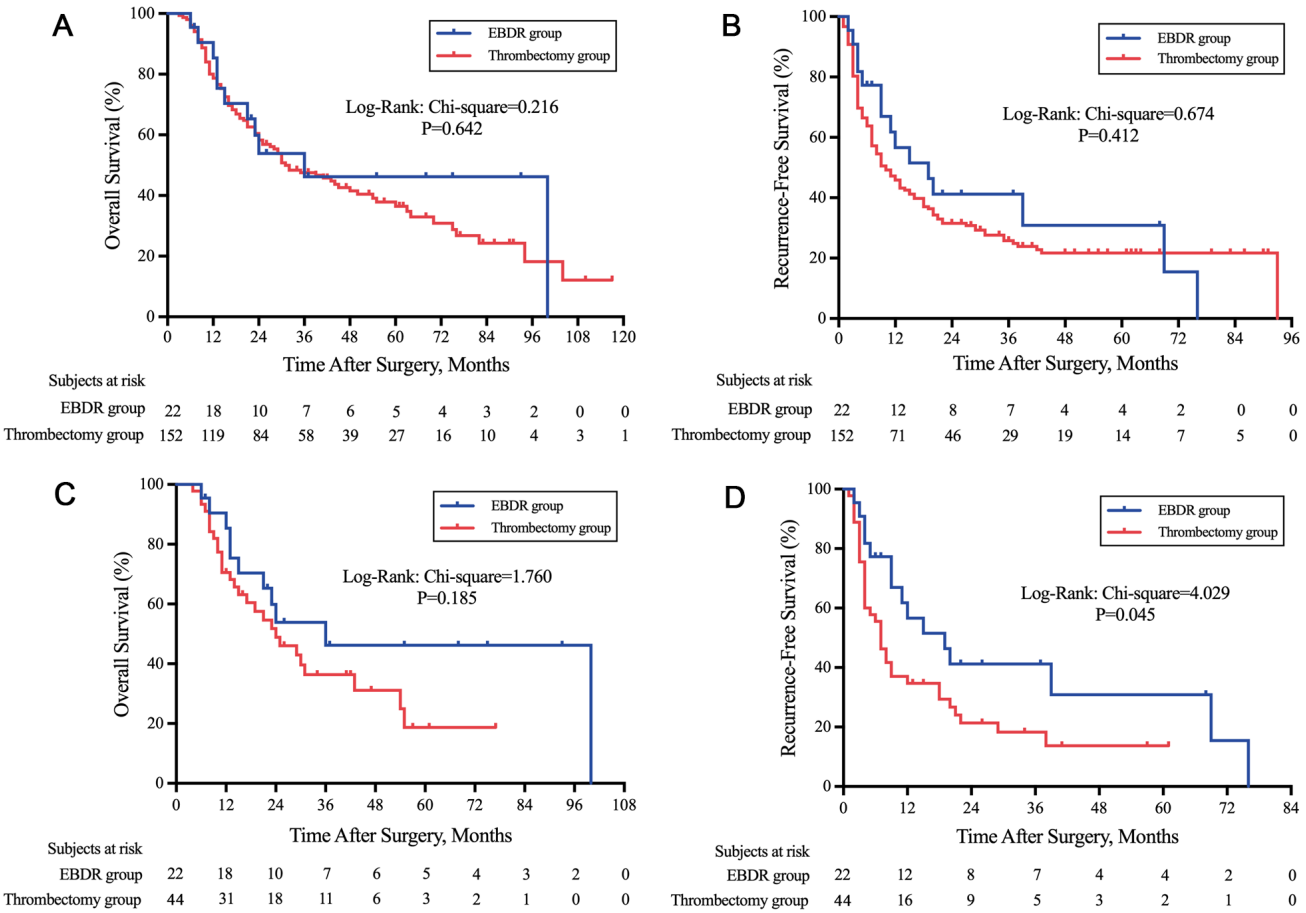


**Figure S2** Kaplan-Meier survival curves for OS and RFS in the subgroup of HCC patients with BDTT but without PVTT. OS of HCC patients in the EBDR and thrombectomy groups (22 patients *vs.* 152 patients) before PSM (A) (P=0.642); RFS of HCC patients in the EBDR and thrombectomy groups (22 *vs.* 152 patients) before PSM (B) (P=0.412); OS of HCC patients in the EBDR and thrombectomy groups (22 patients vs. 44 patients) after PSM (C) (P=0.185); RFS of HCC patients in the EBDR and thrombectomy groups (22 *vs.* 44 patients) after PSM (D) (P=0.045). OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; PVTT, portal vein tumor thrombus; EBDR, extrahepatic bile duct resection.


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**Table S1** Demographic and preoperative data of patients with HCC and BDTT before PSM

| Variables | All (217) | EBDR group (30) | Thrombectomy group (187) | P |
|---|---|---|---|---|
| Age (years)† | 52.0 (46.0-60.0) | 54.5 (46.0-60.0) | 52.0 (45.0-60.0) | 0.661 |
| Gender | | | | 0.108 |
| Male | 184 (84.8%) | 22 (73.3%) | 162 (86.6%) | |
| Female | 33 (15.2%) | 8 (26.7%) | 25 (13.4%) | |
| HBsAg | | | | 0.993 |
| Positive | 159 (73.3%) | 22 (73.3%) | 137 (73.3%) | |
| Negative | 58 (26.7%) | 8 (26.7%) | 50 (26.7%) | |
| Child-Pugh class | | | | 0.005* |
| A | 123 (56.7%) | 10 (33.3%) | 113 (60.4%) | |
| B | 94 (43.3%) | 20 (66.7%) | 74 (39.6%) | |
| Biliary decompression | | | | 0.078 |
| Performed | 40 (18.4%) | 9 (31.0%) | 31 (16.6%) | |
| Not performed | 177 (81.6%) | 21 (70.0%) | 156 (83.4%) | |
| AFP (ng/mL) | | | | 0.136 |
| ≤400 | 107 (49.3%) | 11 (36.7%) | 96 (51.3%) | |
| >400 | 110 (50.7%) | 19 (63.3%) | 91 (48.7%) | |
| ALB (g/L)† | 39.2 (36.0-42.0) | 37.2 (34.4-40.6) | 39.5 (36.1-42.4) | 0.007* |
| TBil (mg/dL)† | 2.7 (1.0-9.1) | 7.2 (3.1-13.0) | 2.2 (0.9-8.6) | 0.011* |
| ALT (U/L)† | 77.0 (43.0-134.5) | 82.0 (53.7-123.8) | 77.0 (41.0-214.0) | 0.588 |
| GGT (IU/L)† | 341.0 (194.5-616.0) | 365.5 (192.5-505.1) | 331.0 (195.0-619.0) | 0.811 |
| PT (s)† | 12.2 (11.3-13.0) | 12.8 (12.2-13.5) | 12.0 (11.3-12.9) | 0.005* |

HCC: hepatocellular carcinoma; BDTT: bile duct tumor thrombus; EBDR: extrahepatic bile duct resection; HBsAg: hepatitis B surface antigen; AFP: α-fetoprotein; ALB: albumin; TBil: total bilirubin; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; PT: prothrombin time. †Mann-Whitney *U* test; others: chi-square test. *P values with statistical significance.


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**Table S2** Operative and pathologic data of patients with HCC and BDTT before PSM

| Variables | All (217) | EBDR group (30) | Thrombectomy group (187) | P |
|---|---|---|---|---|
| Extent of hepatectomy | | | | 0.465 |
| Major | 139 (64.1%) | 21 (70.0%) | 118 (63.1%) | |
| Minor | 78 (35.9%) | 9 (30.0%) | 69 (36.9%) | |
| Type of hepatectomy | | | | 0.947 |
| Anatomic | 129 (59.4%) | 18 (60.0%) | 111 (59.4%) | |
| Non-anatomic | 88 (40.6%) | 12 (40.0%) | 76 (40.6%) | |
| Intraoperative blood loss (mL)† | 400.0 (200.0-725.0) | 400.0 (275.0-850.0) | 350.0 (200.0-600.0) | 0.197 |
| Pathologic liver cirrhosis | | | | 0.529 |
| Presence | 120 (55.3%) | 15 (50.0%) | 105 (56.1%) | |
| Absence | 97 (44.7%) | 15 (50.0%) | 82 (43.9%) | |
| Tumor diameter (cm)† | 5.2 (3.8-7.6) | 4.8 (2.5-6.0) | 6.0 (4.0-8.0) | 0.002* |
| Number of tumor | | | | 0.203 |
| Solitary | 145 (66.8%) | 17 (56.7%) | 128 (68.4%) | |
| Multiple | 72 (33.2%) | 13 (43.3%) | 59 (31.6%) | |
| Microscopic margin involvement | | | | 0.180 |
| Positive | 30 (13.8%) | 7 (23.3%) | 23 (12.3%) | |
| Negative | 187 (86.2%) | 23 (76.7%) | 164 (87.7%) | |
| Tumor capsule | | | | 0.032* |
| Absence | 156 (71.9%) | 27 (90.0%) | 129 (69.0%) | |
| Incomplete | 34 (15.7%) | 2 (6.7%) | 32 (17.1%) | |
| Complete | 27 (12.4%) | 1 (3.3%) | 26 (13.9%) | |
| Tumor differentiation | | | | 0.033* |
| Well/moderate | 78 (35.9%) | 16 (53.3%) | 62 (33.2%) | |
| Poor/undifferentiated | 139 (64.1%) | 14 (46.7%) | 125 (66.8%) | |
| Tumor TNM stage | | | | 0.067 |
| I/II | 134 (61.8%) | 14 (46.7%) | 120 (64.2%) | |
| III/IV | 83 (38.2%) | 16 (53.3%) | 67 (35.8%) | |
| Grade of BDTT | | | | 0.022* |
| B3 | 50 (23.0%) | 2 (6.7%) | 48 (25.7%) | |
| B4 | 167 (77.0%) | 28 (93.3%) | 139 (74.3%) | |
| Concurrent PVTT | | | | 0.311 |
| Presence | 43 (19.8%) | 8 (26.7%) | 35 (18.7%) | |
| Absence | 174 (80.2%) | 22 (73.3%) | 152 (81.3%) | |

HCC: hepatocellular carcinoma; BDTT: bile duct tumor thrombus; EBDR: extrahepatic bile duct resection; TNM: tumor-node-metastasis; PVTT: portal vein tumor thrombus. †Mann-Whitney *U* test; others: chi-square test. *P values with statistical significance.


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**Table S3** Recurrence patterns in 161 patients who experienced recurrence before PSM

| Variables | EBDR group (n=19) | Thrombectomy group (n=142) | Total (n=161) |
|---|---|---|---|
| Time to recurrence | | | |
| <1 year | 11 (57.9%) | 104 (73.2%) | 115 (71.4%) |
| ≥1 year | 8 (42.1%) | 38 (26.8%) | 46 (28.6%) |
| Location of recurrence | | | |
| Intrahepatic recurrence | 14 (73.6%) | 82 (57.7%) | 96 (59.7%) |
| Extrahepatic metastasis | 1 (5.3%) | 10 (7.1%) | 11 (6.8%) |
| Bile duct recurrence only | 1 (5.3%) | 13 (9.2%) | 14 (8.7%) |
| Intrahepatic and extrahepatic recurrence | 1 (5.3%) | 9 (6.3%) | 10 (6.2%) |
| Intrahepatic and bile duct recurrence | 2 (10.5%) | 25 (17.6%) | 27 (16.8%) |
| Extrahepatic and bile duct recurrence | 0 (0%) | 1 (0.7%) | 1 (0.6%) |
| Synchronous intrahepatic, extrahepatic and bile duct recurrence | 0 (0%) | 2 (1.4%) | 2 (1.2%) |

EBDR: extrahepatic bile duct resection.


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