Usefulness of Resection for Hepatocellular Carcinoma with Macroscopic Bile Duct Tumor Thrombus

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Abstract. *Background: The prognostic significance of bile duct tumor thrombus (BDTT) in hepatocellular carcinoma (HCC) is unclear and the usefulness of resection for HCC with BDTT is still controversial. The aim of the present study was to evaluate the impact of BDTT on prognosis in HCC and to determine whether resection of HCC with BDTT was useful. Patients and Methods: Out of 820 HCC patients who underwent hepatic resection from 1992 to 2012, 13 HCC patients (1.6%) had macroscopic BDTT. The results of resection for HCC patients with BDTT and the prognostic significance of BDTT were evaluated. Prognoses were also compared according to treatment in patients who had HCC with BDTT. Results: The overall 1-, 3- and 5-year survival rates after resection were 92%, 77% and 48%, respectively, for HCC patients with BDTT, and 88%, 67%, and 52%, respectively, for HCC patients without BDTT; there were no significant differences (p=0.833). In all HCC patients after resection, the unadjusted hazard ratio of the presence of BDTT was 1.08 (95%CI=0.49-2.05; p=0.835) and when adjusted for other significant prognostic factors, the hazard ratio of the presence of BDTT was 0.98 (95%CI=0.42-1.98; p=0.958). The overall 1-, 3- and 5-year survival rates were 14%, 5% and 0%, respectively, for 25 HCC patients with BDTT after other initial treatments. Conclusion: Bile duct tumor thrombus was not a prognostic factor in patients with resected HCC. In HCC with BDTT, surgical treatment is recommended whenever possible because only resected patients achieved long-term survival.*

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Hepatocellular carcinoma (HCC) is responsible for approximately 600,000-700,000 deaths worldwide. It is highly prevalent in the Asia-Pacific region and Africa and is increasing in Western countries (1).

HCC usually spreads through the liver *via* the portal vein, and portal vein invasion is a well-documented prognostic marker (2-5). Meanwhile, bile duct tumor thrombus (BDTT) is relatively rare. The incidence of portal vein invasion is 26.1%, whereas the incidence of BDTT is 3.4%; the incidence of macroscopic BDTT is only 1.4% (6).

Several studies have reported that HCC patients with BDTT had poor survival because of obstructive jaundice, cholestasis, hepatic dysfunction and spread of tumors (7-13). On the other hand, good results of aggressive resection for HCC patients with BDTT have also been reported (14-16).

Survival of all HCC patients has improved due to advances in diagnostic and therapeutic modalities (6). However, the survival of HCC patients with BDTT is unclear.

In the present study, BDTT was assessed as a prognostic factor in patients with resectable HCC.

Patients and Methods

Patients. Between July 1992 and August 2012, 820 HCC patients underwent initial hepatic resection at the National Cancer Center Hospital East. A total of 13 HCC patients (1.6%) with macroscopic BDTT and 783 HCC patients (95.5%) without BDTT were retrospectively reviewed from our database.

Two pathologists evaluated the resected specimens macroscopically and microscopically according to the Japanese TNM Staging System by the Liver Cancer Study Group of Japan (17). Macroscopic BDTT was defined as b2-4 (tumor thrombus in the common hepatic duct or the first to second branches of the bile duct) and microscopic BDTT was defined as b1 (tumor thrombus in the third order or more peripheral branches of the bile duct, but not in second order branches). All BDTTs were confirmed by microscopic examination.

Laboratory data for all patients were obtained at the time of admission. The indocyanine green retention rate at 15 min (ICGR15) was also evaluated preoperatively. Preoperative

Table I. *Clinical features of 13 HCC patients with macroscopic BDTT.*

No	Age (years)	Gender	Hepatitis	Operative procedure	Bile duct resection	Recurrence (days)	Recurence pattern (treatment)	Survival (days)	Outcome
1	50	M	B	Left hepatectomy	No			6716	Died from another cause
2	61	M	C	Right hepatectomy	Yes	127	Double (PEIT)	2205	Died from HCC
3	54	M	non-B,C	Left hepatectomy	Yes	447	Multiple (TACE)	1258	Died from HCC
4	50	M	B	Right hepatectomy, S3LR	No	IR		225	Died from HCC
5	73	F	C	Right hepatectomy	Yes			388	Hospital transfer
6	72	M	non-B,C	Left hepatectomy	No	819	Single (TACE)	1374	Died from HCC
7	65	M	non-B,C	Central Bisegmentectomy	Yes	980	Double (S2/3LR)	3161	Alive
8	56	M	B	Right trisegmentectomy	No			2031	Alive
9	58	M	C	Right hepatectomy	Yes	138	Multiple (BSC)	215	Died from HCC
10	61	M	non-B,C	Right hepatectomy	No			1912	Alive
11	53	M	B	Anterior segmentectomy	No			1430	Alive
12	62	M	C	Posterior segmetectomy	No	118	Multiple (chemotherapy)	286	Died from HCC
13	76	M	C	Left hepatectomy	Yes			305	Alive

IR: Incomplete resection; PEIT: percutaneous ethanol injection therapy; TACE: transcatheter chemoembolization arterial chemotherapy; S2/3LR: segment 2 and 3 limited resection; BSC: best supportive care; B: hepatitis B virus; C: hepatitis C virus.

examination included ultrasonography (US), thin-slice computed tomography (CT) with a bolus injection of contrast medium and magnetic resonance imaging (MRI). The treatment plan was determined at the hospital conference consisting of specialists in medical oncology, surgery, chemotherapy and radiology. After discharge from the hospital, α-fetoprotein (AFP), US and CT with a bolus injection of contrast medium were checked at least every 3-6 months during the follow-up period. When cancer recurred, the treatment plan was determined at the hospital conference in the same way. The survival period starting from the date of initial treatment was recorded. Outcomes were examined in May 2013.

In the 796 HCC patients after resection, the prognostic significance of the presence of BDTT was evaluated by univariate and multivariate analyses with 7 significant prognostic factors that were reported previously: Child-Pugh classification, AFP, anatomical resection, curative resection, numbers, tumor size and portal vein invasion.

Additionally, 25 HCC patients (1.6%) with macroscopic BDTT who underwent other initial treatments in the same period were also examined. They were diagnosed by imaging studies and AFP and/or biopsy specimens.

This study was approved by the Institutional Review Board of the National Cancer Center.

Statistical analysis. Data are presented as medians (ranges) or numbers. Statistical differences between groups were assessed by the Student's *t*-test for continuous variables and by the Pearson's chi-square test for categorical variables. Survival rates were estimated using the Kaplan-Meier method and compared by the log-rank test. A Cox proportional hazards model was used to perform univariate and multivariate analyses. *p*-Values <0.05 were considered significant. All statistical analyses were conducted using JMP® 9 (SAS Institute Inc., Cary, NC, USA).

Results

The clinical features of the 13 HCC patients with macroscopic BDTT after resection are shown in Table I. All patients underwent systemic resection. There was no hospital mortality. Six patients (46%) underwent bile duct resection and bilioenteric anastomosis (Figure 1). Intrahepatic recurrence was seen in 6 patients. The pattern of recurrence and second treatments were as follows: one patient with single tumor underwent transcatheter arterial chemoembolization (TACE); 2 patients with double tumors underwent percutaneous ethanol injection therapy (PEIT) and limited resection of segments 2 and 3, respectively; and 3 patients with multiple tumors underwent TACE, best supportive care (BSC) and systemic chemotherapy (sorafenib), respectively. There seemed to be no relationship between bile duct resection and the patterns of recurrence.

The overall 1-, 3- and 5-year survival rates after resection were 92%, 77% and 48%, respectively. The median survival time (MST) was 47 months (range=9.5-223.9 months). Five patients have survived for more than 5 years.

The clinicopathological features of HCC patients with and without BDTT are shown in Table II. There were no significant differences between the two groups regarding age, sex, hepatitis, liver cirrhosis, Child-Pugh classification, curative resection, numbers or tumor size. However, ICGR15 (8% *vs*. 14%, $p=0.01$) and AFP (20.4 ng/ml *vs*. 24.6 ng/ml, $p=0.003$) were significantly lower in HCC patients with BDTT than in those without BDTT. The incidence of portal vein invasion or hepatic vein invasion was significantly

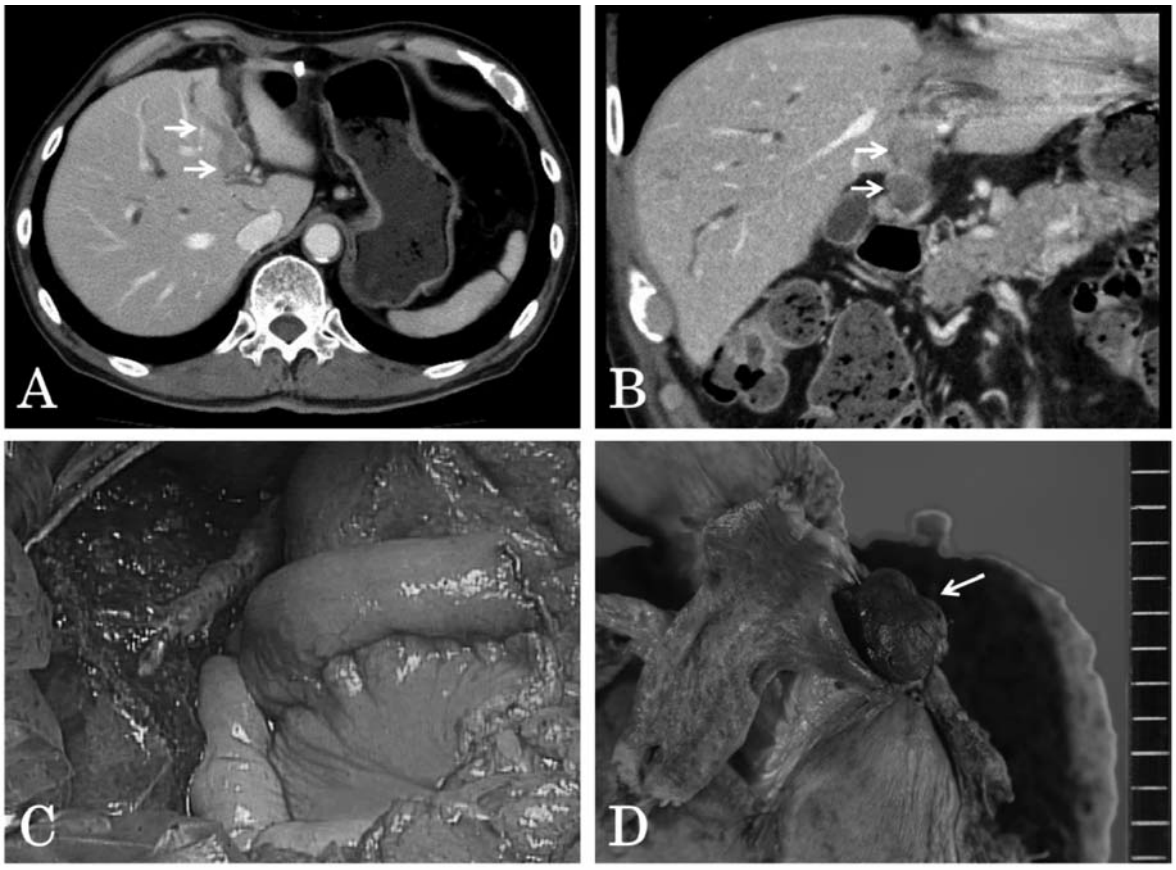

Figure 1. *Left hepatectomy with bile duct resection for HCC patient with BDTT. A and B: CT scans revealed BDTT (arrows). C: Intraoperative photograph after left hepatectomy and biloenteric anastomosis. D: The resected specimen. BDTT extended to left hepatic duct (arrow). HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; CT, computed tomography.*

Table II. *Clinicopathological features of HCC patients with and without BDTT.*

	HCC with BDTT (n=13)	HCC without BDTT (n=783)	*p*-Value
Age (years)	61 (50-76)	65 (27-85)	0.246
Gender (Male/Female)	12/1	651/132	0.380
Hepatitis (HBV/HCV/nonB,C)	4/5/4	152/416/215	0.494
Liver cirrhosis (Yes/No)	3/10	332/464	0.170
ICGR15 (%)	8 (2.8-19.9)	14 (1.0-90.0)	0.010
Child-Pugh classification (A/B/C)	12/1/0	690/93/0	0.643
AFP (ng/mL)	20.4 (1.2-8731)	24.6 (0.6-974200)	0.003
Anatomical resection (Yes/No)	13/0	321/462	<0.001
Curative resection (Yes/No)	12/1	670/113	0.492
Numbers (Solitary/Multiple)	11/2	488/295	0.099
Tumor size (mm)	44 (17-150)	40 (7-250)	0.937
Vp (0/1/2/3/4)	1/9/1/1/1	678/52/26/23/4	<0.001
Vv (0/1/2/3)	11/2/0/0	752/15/10/6	0.010
pStage (I/II/III/IVa/IVb)	0/1/10/2/0	74/353/229/117/10	0.005

Values are expressed as numbers or medians (ranges). AFP: α-Fetoprotein; ICGR15: indocyanine green retention rate at 15 min. The staging and the abbreviations in the tables conform to The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 3rd English edition, proposed by the Liver Cancer Study Group of Japan (17). Vp: Microscopic portal vein invasion, Vv: hepatic vein invasion.

higher in HCC patients with BDTT than in those without BDTT. Of the HCC patients without BDTT, the overall 1-, 3- and 5-year survival rates after resection were 88%, 67% and 52%, respectively; there were no significant differences between the two groups (p=0.83) (Figure 2).

The results of Cox univariate and multivariate analyses of the presence of BDTT and other significant prognostic factors in all HCC patients after resection are shown in Table III. The unadjusted hazard ratio of the presence of BDTT was 1.08 (95%CI=0.49-2.05; p=0.835) and when adjusted for other significant prognostic factors, the hazard ratio of the presence of BDTT was 0.98 (95%CI=0.42-1.98; p=0.958).

The clinical features of HCC patients with BDTT who underwent resection or other initial treatments in the same period are shown in Table IV. ICGR15 and Child-Pugh classification were significantly worse in the other treatment group than in the resection group. The incidences of liver cirrhosis, multiple tumors and portal vein invasion were significantly higher in the other treatment group than in the resection group. The MST for each treatment for all 38 HCC patients with BDTT is listed in Table V. Overall, 14 patients underwent TACE and their MST was 6.7 months (range=3.4-10.8 months). One patient required exploratory laparotomy and underwent TACE later. One patient who could not undergo resection because of his hepatic function underwent proton irradiation and is alive without recurrence more than 3 years later. The overall 1-, 3- and 5-year survival rates were 14%, 5% and 0%, respectively, for HCC patients with BDTT who underwent other treatments; these rates were significantly lower than those for HCC patients with BDTT after resection (p<0.001).

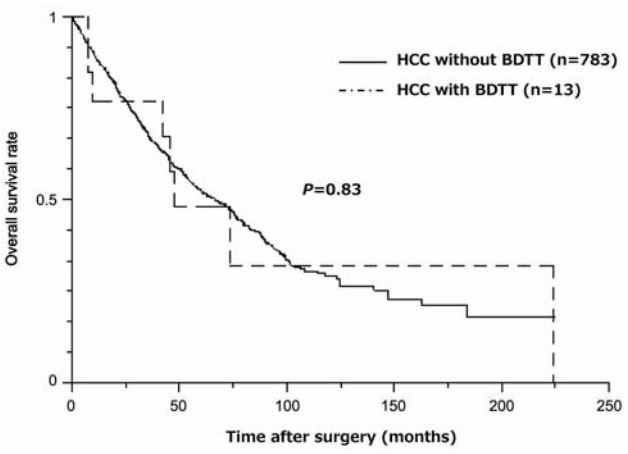

Figure 2. *Cumulative survival curves of HCC patients after resection with or without BDTT. There are no significant differences between the two groups (p=0.83).*

Discussion

The efficacy of resection for HCC with BDTT is still controversial (10-13, 15, 16). However, most previous studies reported that the prognosis of BDTT was similar to or worse than that of no BDTT without considering the effects of differences in other prognostic factors, for example, good liver function of HCC patients with BDTT who could undergo resection and a high incidence of portal vein invasion. There was a possibility that the high frequency of patients with good liver function brought about the favorable results of resection for HCC with BDTT almost equal to those for HCC without BDTT. Actually, in the present study, ICGR15 was significantly lower in HCC patients with BDTT than in those without BDTT. Hepatectomies for HCC with BDTT tend to be large resections extending over several sections. Thus, patients with excellent liver function were selected for resection of HCC with BDTT. On the other hand, HCC patients with BDTT and impaired liver function tended to receive treatments other than resection.

Multivariate analyses were performed to assess the prognostic significance of BDTT in resected patients. The prognostic factors of HCC patients after resection have been well-discussed in previous reports (2, 18, 19). The Cancer of the Liver Italian Program (CLIP) score and the Japan Integrated Staging (JIS) score also use these factors: Child-Pugh classification, portal vein invasion, AFP, numbers and tumor size (5, 17, 20, 21). Anatomical resection and curative resection were also significant factors (22-24). In the present study, these seven factors were used in the assessment. The multivariate-adjusted hazard ratio of the presence of BDTT was 0.98 (95%CI=0.42-1.98; p=0.958). Thus, the present analysis suggested that the presence of BDTT did not affect the prognosis after resection, even on multivariate analyses.

The etiology of BDTT remains unclear. Portal vein tumor thrombus (PVTT) was observed in HCC with BDTT more frequently than in HCC without BDTT. According to the results, BDTT and PVTT might have similar tumor biology. Moreover, there might be different pathogeneses between macroscopic BDTT and microscopic BDTT. Esaki *et al*. (22) reported that the prognosis after resection was significantly longer in the macroscopic-BDTT group than in the microscopic-BDTT group. In the present study, however, the focus was on macroscopic BDTT rather than microscopic BDTT, because macroscopic BDTT could be diagnosed before treatment and the diagnosis could affect the subsequent treatment.

If the tumor is resectable, HCC with BDTT should be treated by resection, because BDTT is not a poor prognostic factor in this category of patients.

With regard to unresectable HCC with BDTT, prognosis after non-surgical treatments was not good in the 25 patients

Table III. *Results of Cox univariate and multivariate analyses of BDTT and other prognostic factors after resection.*

	Univariate analysis	Multivariate analysis		
Variables	*p*-Value	*p*-Value	Hazard ratio†	95%CI
BDTT (Yes *vs*. No)	0.835	0.958	0.98	0.42-1.98
Child-Pugh classification (A *vs*. B)	0.0003	0.175	0.81	0.61-1.10
AFP(ng/ml)*	<0.001	0.216	4.06	0.38-22.36
Anatomical resection (Yes *vs*. No)	0.008	0.023	0.75	0.58-0.96
Curative resection (Yes *vs*. No)	<0.001	<0.001	0.56	0.42-0.75
Numbers (Solitary *vs*. Multiple)	<0.001	0.002	0.70	0.56-0.88
Tumor size (mm)*	<0.001	<0.001	6.71	3.50-12.60
Portal vein invasion (Vp0-4)*	<0.001	<0.001	3.12	1.80-5.13

*These are treated as continuous variables. †For an increase from the minimum value to the maximum value for continuous variables or A *vs*. B for categorical variables.

Table IV. *Clinical features of HCC patients with BDTT who underwent resection or other treatments*

	Resection (n=13)	Other treatment (n=25)	*p*-Value
Age (years)	61 (50-76)	65 (43-79)	0.259
Sex (Male/Female)	12/1	9/16	0.060
Hepatits (HBV/HCV/nonB,C)	4/5/4	5/15/5	0.449
Liver cirrhosis (Yes/No)	3/10	7/18	0.003
ICGR15 (%)	8 (2.8-19.9)	33.5 (13.6-69.1)	0.0002
Child-Pugh classification (A/B/C)	12/1/0	11/9/5	0.014
AFP (ng/ml)	20.4 (1.2-8731)	710 (2.8-1402800)	0.138
Numbers (Solitary/Multiple)	11/2	7/18	0.0009
Tumor size (mm)*	46 (20-150)	70 (15-170)	0.506
Vp (≥2/<2)*	3/10	15/10	0.031
Vv (≥2/<2)*	0/13	5/20	0.084

*By imaging studies.

in the present series. According to the 18th nationwide follow-up survey of primary liver cancer in Japan (6), 2-year survival after TACE was 59% and that after ablation therapy was 81%. MSTs of patients with HCC with BDTT treated by TACE or external radiation therapy were less than one year. Obstructive jaundice, cholangitis and hepatic dysfunction following obstructive jaundice are obstacles for treatment and may cause a poor prognosis in patients with BDTT.

Determining whether bile duct resection and bilioenteric anastomosis are needed constitutes an issue in hepatic resection for HCC with macroscopic BDTT. In the present study, there seemed to be no relationship between bile duct resection and prognosis or the pattern of recurrence. On the other hand, Noda *et al*. (12) reported that bile duct resection might be avoided because non-operative treatments such as PEIT, ablation and TACE were known to result in serious complications such as liver abscess after bile duct resection and bilioenteric anastomosis (25, 26). Since postoperative recurrence after resection often occurs in the liver, bile duct resection and bilioenteric anastomosis should be avoided when possible in order to avoid limiting later treatment options.

Table V. *The median survival time with each treatment for HCC patients with BDTT.*

Treatment	n	MST (months)	(95% CI or outcome)
Resection	13	47.7	(9.5-223.9)
Exploratory laparotomy	1	9.9	(Died)
TACE	14	6.7	(3.4-10.8)
Radiation	3	11.6	(10.4-30.0)
BSC	6	1.6	(0.7-3.8)
Proton irradiation	1	36.9	(Alive without recurrence)

MST: Median survival time.

The limitation of the present study was the small number of BDTT patients. Further studies are required because of the expected increase in the number of resections and improved results thanks to recent progress in pre- and postoperative management.

In conclusion, BDTT is not a poor prognostic factor in patients with resectable HCC. On the other hand, BDTT is an obstacle for treatments other than resection. Hepatic resection should be performed whenever possible in HCC with BDTT.

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