TABLE 2 Survival analysis in all patients ($n = 224$)

Variable	*n*	Survival rate (%)		Univariate	Multivariate	
		3-year	5-year	*P* value	Hazard ratio (95% CI)	*P* value
Age (yr)				0.089		
<66	112	57.4	47.1			
≥66	112	44.1	35.9			
Sex				0.075		
Male	156	55.2	50.9			
Female	68	48.7	37.1			
Preoperative CA19-9 (U/ml)				<0.001*		0.001*
<64	111	68.3	60.2		1	
≥64	113	33.9	24.4		1.90 (1.30–2.79)	
Preoperative CEA (ng/ml)				0.264		
<5	174	53.9	43.8			
≥5	50	39.6	33.4			
Preoperative biliary drainage				<0.001*		
Not performed	90	66.1	56.8			
Performed	134	39.7	30.5			
Bismuth type				0.004*		
I / II / III	134	60.9	51.7			
IV	90	36.0	27.4			
Combined PV and/or HA				<0.001*		0.016*
Not performed	167	57.3	47.6		1	
Performed	57	29.5	21.5		1.64 (1.09–2.45)	
pT[a]				<0.001*		
1 / 2a / 2b	80	71.0	59.4			
3 /4	114	39.6	31.9			
pN[a]				<0.001*		0.001*
0	120	69.5	60.0		1	
1	104	29.3	20.2		1.93 (1.29–2.89)	
pM[a]				<0.001*		0.020*
0	179	58.8	47.9		1	
1	45	19.2	6.0		1.67 (1.08–2.57)	
pStage[a]				<0.001*		
I / II	49	78.2	69.7			
IIIA / IIIB / IVA / IVB	175	42.6	33.4			
Histological grade[a]				<0.001*		0.003*
G1 (well)	53	64.9	62.4		1	
G2 (moderately) / G3 (poorly)	171	46.2	34.6		2.14 (1.30–3.52)	
Microscopic lymphatic invasion				<0.001*		
Absent	127	65.1	57.4			
Present	97	30.5	18.6			
Microscopic venous invasion				<0.001*		
Absent	108	64.0	55.0			
Present	116	36.3	25.5			
Microscopic perineural invasion				<0.001*		0.001*
Absent	83	74.8	64.2		1	
Present	141	35.7	26.9		2.06 (1.33–3.19)	
Microscopic liver invasion,				0.004*		0.035*
Absent	130	57.6	47.7		1	

TABLE 2 continued

Variable		Survival rate (%)		Univariate	Multivariate	
	n	3-year	5-year	*P* value	Hazard ratio (95% CI)	*P* value
Present	94	41.2	33.0		1.59 (1.07–2.37)	
Proximal ductal margin				0.003*		
Negative	192	54.9	44.8			
Positive	32	16.8	16.8			
Distal ductal margin				0.006*		
Negative	203	53.8	43.9			
Positive	21	17.6	17.6			
Radial margin				0.002*		
Negative	190	54.3	45.9			
Positive	34	29.6	15.2			
R				<0.001*		0.020*
0	159	60.1	50.5		1	
1	65	24.8	15.9		1.59 (1.07–2.37)	

* Significantly difference

[a] According to the UICC TNM classification 7th edition

PV portal vein resection, *HA* hepatic artery resection

Fig. 1a). The survival of group C (median: 21.5 months) was significantly worse than that of group A (56.6 months; $P = 0.001$). In addition, the survival of group B (29.4 months) was significantly worse than that of group A (56.6 months; $P = 0.031$), and it was not significantly different from that of group C ($P = 0.215$).

Next, the survival rates of the three groups were compared in the subgroups stratified according to the status of the independent prognostic factors. In the subgroup of CA19-9 < 64, the survival of group B was significantly better than that of group C (HR 0.34; 95 % CI 0.14–0.81; $P = 0.019$). Similarly, in the subgroup of pM0, the survival of group B was significantly better than that of group C (HR 0.40; 95 % CI 0.20–0.81; $P = 0.021$). Figure 2 shows the survival curves of the three groups stratified by (a) CA19-9 < 64 or CA19-9 ≥ 64 and (b) pM0 or pM1. In the subgroups stratified by the other independent prognostic factors (combined vascular resection, pN, histological grade, microscopic perineural invasion, microscopic liver invasion, and the status of the other surgical margins), the survival of group B did not differ significantly from that of group C.

DISCUSSION

The prognostic significance of additional resection of the cancer-positive ductal margin in perihilar cholangiocarcinoma is controversial. Although Ribero et al. (18 patients undergoing additional resection of the PM among 67 patients undergoing intraoperative frozen section diagnosis of the PM) reported a significant survival benefit of additional resection, Endo et al. (15 additional resection among 101 intraoperative frozen section diagnosis) and Shingu et al. (12 additional resection among 138 intraoperative frozen section diagnosis) found that additional resection did not improve survival.[13–15] In the present study (52 additional resection among 217 intraoperative frozen section diagnosis), it was found that, in only limited patients with a lower level of CA19-9 and no distant metastatic disease, the survival of the patients with a negative final PM treated with additional resection was significantly better than that of the patients with a positive final PM. These findings suggest that the efficacy of additional resection of the PM in improving survival is associated with the degree of cancer progression, and the discrepancy in the results of previous reports may be explained by the differences in tumor characteristics of the study populations. For example, in this study, the rate of Bismuth IV disease, one of the most advanced and longitudinal wide spreading perihilar cholangiocarcinoma, was 40 % in all cases, which is similar to that of Shingu et al. (38.9 %).[14] In contrast, the rate was 14.6 % in the study by Ribero et al., thus suggesting that their study population included more patients with less advanced tumors, where additional resection of the PM may have a more favorable impact on survival.[15]

The preoperative CA 19-9 level has been reported to be a useful prognostic marker in patients with common gastrointestinal cancers, such as gastric cancer, colorectal cancer, and pancreatic cancer.[29–31] In contrast, the prognostic value of the preoperative CA19-9 level in patients with biliary tract cancer has been studied in only a few

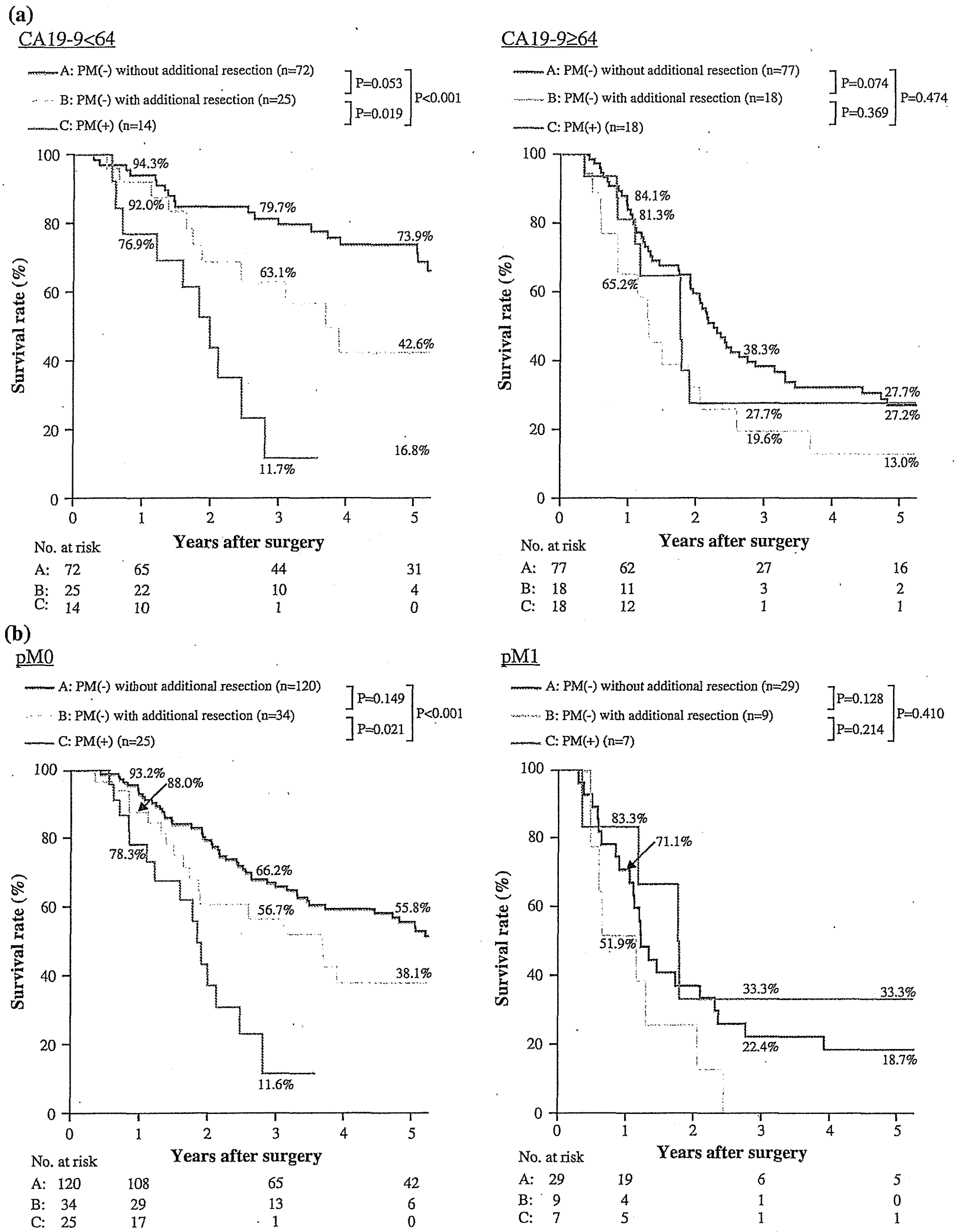

FIG. 2 Overall survival according to the final proximal ductal margin (PM) status with the study population stratified according to CA19-9 < 64 or CA19-9 ≥ 64 (a) and pM0 or pM1 (b). In the subgroups of CA19-9 < 64 and pM0, the survival of group B was significantly better than that of group C ($P = 0.019$ and $P = 0.021$, respectively)

reports, primarily involving intrahepatic cholangiocarcinoma.[32–35] Because perihilar cholangiocarcinoma frequently coexists with obstructive jaundice, which is associated with an increased CA19-9 level, interpreting the meaning of an elevated CA19-9 level is complicated.[20–23] Therefore, evaluating the preoperative serum CA19-9 level following adequate biliary decompression is recommended to predict long-term survival. To the best of our knowledge, few reports have discussed the prognostic significance of the CA19-9 level in perihilar cholangiocarcinoma taking into consideration the presence of concomitant cholestasis or cholangitis.[36,37] The current study demonstrated in a large series of patients that the CA19-9 level is a significant prognostic factor in patients with perihilar cholangiocarcinoma undergoing resection irrespective of preoperative biliary drainage and that the CA19-9 level is useful for selecting patients in whom additional resection of a positive PM will have a more favorable impact on survival. We employed the median value of preoperative CA19-9 in the study population (64 U/ml) as cutoff to evaluate the prognostic significance. When the same analyses were performed using a cutoff of 37 U/ml (the upper limit value of normal range) as well, CA19-9 level was an independent prognostic factor regardless of the presence of preoperative biliary drainage. The significance of the preoperative CA19-9 level for predicting postoperative long-term outcomes will greatly inform surgeons during the decision-making process.

However, individuals with a Lewis^{a-b-} phenotype (i.e., lacking the Lewis antigen glycosyl-transferase) are unable to synthesize CA 19-9.[38] It was reported that approximately 10 % of the Japanese population was Lewis^{a-b-} and that these individuals had completely negative CA19-9 values.[39] Accordingly, it is likely that the result of CA19-9 was false negative in our cases, especially in 19 (8 %) of 224 patients who had CA19-9 value <1.0 unit/ml (namely, undetectable value). When survival analysis was conducted with these 19 patients excluded, CA19-9 was still an independent prognostic factor of overall survival in patients with perihilar cholangiocarcinoma.

In this study, the rate of patients with pM1 disease was 20 %, including those with metastasis to lymph nodes beyond the regional lymph nodes, microscopic liver metastasis, and localized peritoneal dissemination around the percutaneous transhepatic biliary drainage route. Although none of these metastatic diseases were suspected preoperatively, approximately 30 % of cases of pM1 disease were diagnosed intraoperatively based on excisional biopsy specimens. The survival rate of the patients with pM1 disease was 19.2 % at 3 years and 16.5 % at 5 years, with a median survival of 14.6 months. Although the prognosis was dismal, it was better than the previously reported survival of unresected patients.[5,10,40,41] Hence, we do not consider distant node metastasis and/or localized peritoneal dissemination detected during surgery to be absolute contraindications to surgery. However, the present study suggests that additional resection of the positive PM in patients with pM1 disease does not improve survival. Therefore, performing an excisional biopsy of suspicious lesions during surgery is recommended in order to detect pM1 disease, which may be used as reference to decide to what extent the surgeon should be persistent in trying to achieve a negative PM with additional resection.

In conclusion, the clinical significance of additional resection of the PM is associated with the degree of cancer progression. Additional resection should not always be attempted when finding a positive PM and may be warranted only in limited patients with a lower level of CA19-9 and no distant metastatic disease.

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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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Key Words: Bile duct tumor thrombus, hepatocellular carcinoma, prognostic significance, resection.

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

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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

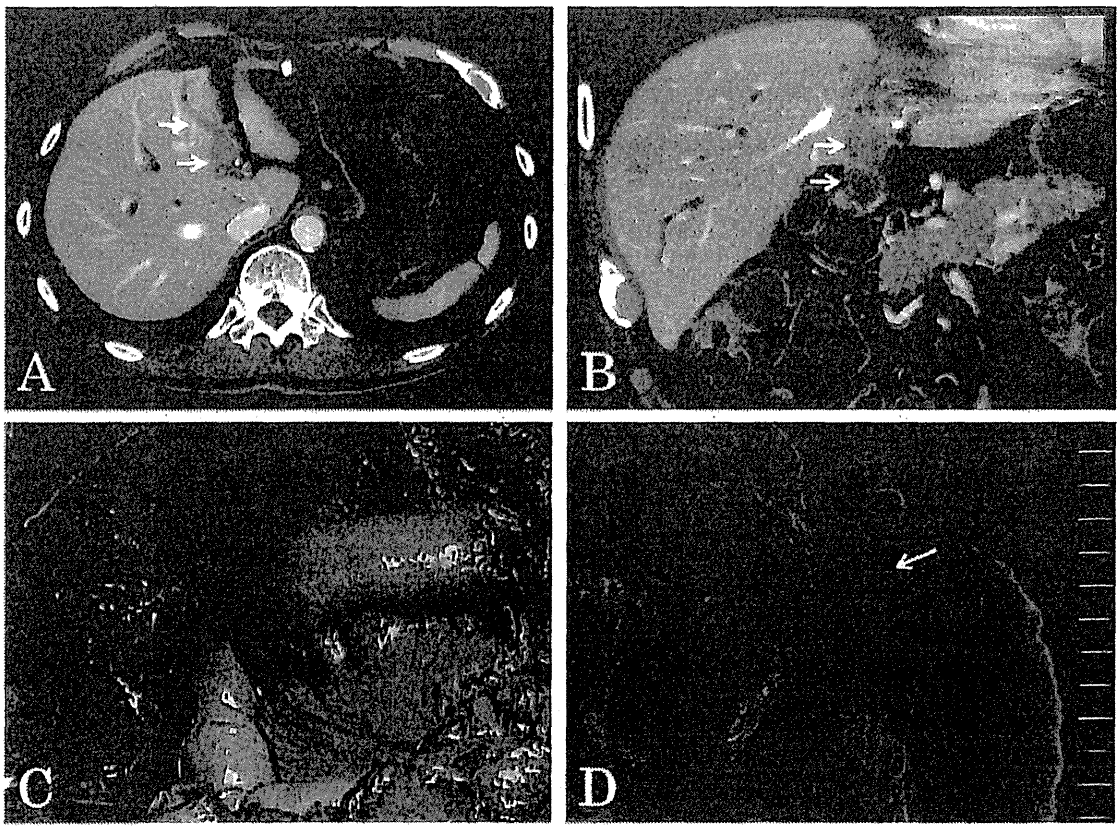

Figure 1. *Left hepatectomy with bile duct resection for HCC patient with BDTT. A and B: CT scans revealed BDTT (arrows). C: Intraoperative photograph after left hepatectomy and biloenteric anastomosis. D: The resected specimen. BDTT extended to left hepatic duct (arrow). HCC, hepatocellular carcinoma;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

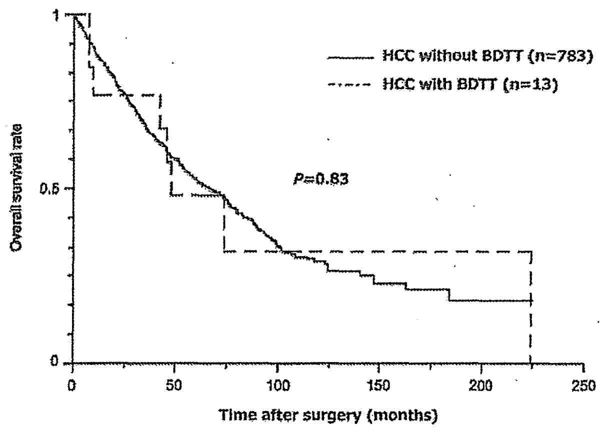

Figure 2. *Cumulative survival curves of HCC patients after resection with or without BDTT. There are no significant differences between the two groups (p=0.83).*

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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ORIGINAL ARTICLE

Anatomic Versus Nonanatomic Hepatectomy for a Solitary Hepatocellular Carcinoma

A Case-Controlled Study with Propensity Score Matching

Yukiyasu Okamura · Takaaki Ito · Teiichi Sugiura · Keita Mori · Katsuhiko Uesaka

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Abstract
Background It remains controversial whether anatomical resection (AR) improves the prognosis for hepatocellular carcinoma (HCC) or not. To our knowledge, there have been a few well-matched studies about this issue. The aim of the present study was to compare the recurrence-free survival of AR versus nonanatomical resection (NAR) for a solitary HCC using propensity score matching.
Methods The present study included 236 patients who had a solitary HCC without macroscopic vessel thrombosis. Those patients were divided into AR (n=139) and NAR (n=97) groups. A propensity score matching was performed to minimize the effect of potential confounders.
Results Sixty-four patients from each group were matched. Preoperative confounding factors were balanced between the two groups. The median recurrence-free survival times in the AR and NAR groups were 33.8 and 30.8 months, respectively (P=0.520). There were no significant differences in the intrahepatic recurrence pattern (P=0.097). Operative procedure was not a significant risk factor for recurrence in both uni- and multivariate analyses.
Conclusions This case-matching study using a propensity score shows that there is no superiority of AR to NAR relevant to the recurrence-free survival in patients with a single HCC.

Keywords Hepatocellular carcinoma · Anatomic resection · Propensity score matching · Recurrence-free survival · Recurrence pattern

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in Japan and occurs frequently in patients with virally infected cirrhotic livers.[1] Liver resection for HCC is a widely accepted standard treatment owing to its proven impact on the prognosis[2] and its low morbidity and mortality rates. However, a high incidence of postoperative recurrence remains a serious problem.[3,4]

One of the major forms of HCC recurrence is intrahepatic metastasis via vascular invasion because HCC has a high propensity to invade the portal and hepatic veins.[5] Anatomical resection (AR) has therefore been recommended to resect a hepatic segment with tumor-bearing portal tributaries, which may result in prophylactic removal of potential intrahepatic metastases.[6] On the other hand, multicentric carcinogenesis, which is uncontrollable by AR of the liver, is also considered to affect the cancer-free survival rate.[7,8]

Some papers have shown survival benefits for AR of the liver for HCC,[9–16] whereas others have not been able to demonstrate any significant survival benefits.[16–18] Thus, the superiority of AR compared to nonanatomical resection (NAR) remains controversial. The reason why a common consensus on this issue has not been obtained is that the patient background, therapeutic strategy, and definition of AR were different among the previous studies. Although propensity score matching has been increasingly used in observational studies in medical research to reduce the impact of

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non-randomized control using observational data,[19–21] there have been few well-matched studies on this issue,[22,23] to the best of our knowledge.

The aims of the present study were to compare the recurrence-free survival rates of AR with NAR for HCC using propensity score matching and to elucidate the true impact of AR on the recurrence pattern after curative surgery.

Patients and Methods

A total of 358 patients with HCC underwent liver resection as the initial treatment with curative intent at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, between September 2002 and May 2013. We retrospectively reviewed a prospectively accumulated database on these patients, including data up to November 2013.

Among the 358 patients, 122 were excluded from this analysis for the following reasons: multiple tumors (86 patients), macroscopic cancer spread into major vessels (29 patients),[9] intrahepatic metastasis (6 patients), and spontaneous tumor rupture (1 patient). The remaining 236 patients with a solitary HCC were included in this study and divided into two groups: the AR (n=139) and NAR (n=97) groups.

All patients underwent preoperative viral serological testing, tumor markers such as alpha-fetoprotein (AFP) and des-r-carboxy prothrombin (DCP), laboratory assessment of liver function, and computed tomography. The hepatic reserve was assessed using the Child-Pugh classification[24] and liver damage criteria,[25] including the indocyanine green retention rate at 15 min (ICG R15). Blood tests were routinely performed on postoperative days 1, 3, and 6 or 7. All patients presented with a confirmed diagnosis of HCC based on the surgical pathology. The tumor stage was assessed using the seventh edition of the Union Internationale Contra le Cancer classification (UICC).[26]

The type (AR or NAR) and extent of liver resection in each patient was decided by a weekly surgical conference. AR was defined as resection of the neoplasm together with the portal vein branches related to the tumor and the corresponding hepatic territory. NAR was defined as resection of the liver, regardless of the anatomical distribution of the portal vein branches. The extent of liver resection was largely chosen according to Makuuchi's criteria.[8] In cases with lobectomy or sectionectomy, liver resection was mostly performed along the demarcation line after occlusion of the corresponding portal vein and hepatic artery. In anatomical monosegmentectomy, liver resection was mostly performed after injection of a dye into the portal vein under intraoperative ultrasound guidance,

Table 1 Patient demographics and preoperative laboratory analysis of the entire study population

Variables	Anatomical n=139	Nonanatomical n=97	P value
Patient's background			
Age (years)	69 (41–83)	68 (39–83)	0.491
Gender (M/F)	111/28	80/17	0.737
HBsAg (positive/negative)	25/114	19/78	0.865
Anti-HCV-Ab (positive/negative)	45/94	57/40	<0.001
Child-Pugh classification (A/B)	136/3	96/1	0.646
Liver damage (A/B)	120/19	72/25	0.027
Background liver (noncirrhosis/cirrhosis)[a]	114/21	59/37	<0.001
Preoperative data			
Total bilirubin (mg/dL)	0.6 (0.2–1.1)	0.6 (0.2–2.3)	0.113
Albumin (g/dL)	4.2 (2.3–5.1)	4.1 (2.9–5.0)	0.290
PT (%)	90 (66–130)	87 (55–118)	0.016
ICG R_{15} (%)	16 (5–32)	18 (5–37)	<0.001
AST (U/L)	32 (18–135)	37 (16–143)	0.167
ALT (U/L)	33 (7–185) 10.0	39 (11–281)	0.090
AFP (ng/mL)[b]	(1.6–214,812)	12.5 (1.4–43,943)	0.717
DCP (mAL/mL)[b]	373 (11–198,000)	37 (0–87,000)	<0.001

M male, *F* female, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus, *Ab* antibody, *PT* prothrombin time, *ICG* R_{15} indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a] Background liver was not known in five patients

[b] Median (range)

Table 2 Operative results and tumor factors of the entire study population

Variables	Anatomical n=139 (%)	Nonanatomical n=97 (%)	P value
Operative results			
Operation time (min)[a]	286 (102–636)	217 (71–619)	<0.001
Intraoperative blood loss (mL)[a]	715 (5–5,136)	360 (12–3,006)	<0.001
Perioperative blood transfusion	8 (5.8)	4 (4.1)	0.766
Postoperative hospitalization (days)[a]	11 (6–46)	11 (5–57)	0.056
Mortality	0 (0)	0 (0)	
Morbidity			
Clavien grade 1 or more	41 (29.5)	23 (23.7)	0.373
Clavien grade 3 or more	18 (12.9)	6 (6.2)	0.125
Tumor factors			
Size (mm)[a]	48 (7–175)	25 (9–160)	<0.001
Microscopic portal invasion	13 (9.4)	8 (8.2)	0.820
Microscopic venous invasion	6 (4.3)	4 (4.1)	1.000
Microsatellite lesions	20 (14.4)	5 (5.2)	0.030
Tumor differentiation			
Well/moderately, poorly	22/117	23/74	0.134
Surgical margin (mm)[a]	5 (0–42)	6 (0–25)	0.498
UICC stage			
I/II	121/18	86/11	0.841

Values in parentheses are percentages unless indicated otherwise

UICC The Union Internationale Contra le Cancer classification

[a] Median (range)

confining the resection to the tumor-bearing area.[27] Liver dissection was mainly done using an ultrasonic device. For liver dissection, we basically used the Pringle maneuver, with clamping for 15 min followed by a 5-min de-clamping, or the selective hemi-hepatic clamping method if indicated.[28] In the present study, postoperative mortality was defined as all in-hospital deaths that occurred after surgery. Complications were classified into six grades according to the modified Clavien classification.[29]

Following surgery, patients were subjected to physical examinations and blood tests for AFP and DCP every 3 months. Serial computed tomography or liver ultrasonography was performed in each patient every 3 to 6 months. Any recurrence of disease was treated as vigorously as possible.

Statistical Analysis

To minimize the influence of potential confounders on the selection bias, propensity scores were generated by using binary logistic regression. The independent variables entered into the propensity model included preoperative information such as gender; age; hepatitis virus status; serum levels of AFP, DCP, albumin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT); prothrombin time (PT); liver damage score;[25] and tumor size. One-to-one matching between the groups was accomplished by using the nearest-neighbor matching method.

To determine the predictors of the recurrence-free survival rate after liver resection, 19 clinicopathological parameters were analyzed. The predictors of recurrence-free survival were analyzed using the Cox proportional hazards regression model. The cutoff points for the laboratory data were defined as the upper limit of normal at our institution, and the cutoff values for the ICG R15, length of the operation, and blood loss were defined as median values. The significant variables in the univariable analysis and the surgical procedure were included in the multivariate analysis in order to identify the independent predictors of recurrence.

Continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test, where appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, where appropriate. The overall and disease-free survival rates were analyzed by the Kaplan-Meier method, with comparison by the log rank test. All statistical analyses were performed using the SPSS 21.0 software program (SPSS Inc., Chicago, IL, USA). Values of $P \leq 0.05$ in the two-tailed test were considered to be significant.

Results

Preoperative Characteristics of the Entire Study Population

Table 1 shows the preoperative characteristics of both groups. The AR group significantly included fewer patients with HCV-Ab-positive HCC and cirrhosis than the NAR group. Prothrombin time and ICG R15 value in the AR group were significantly better than those in the NAR group. Serum concentration of DCP in the AR group was significantly higher than that in the NAR group.

The Surgical Outcomes and Tumor Characteristics of the Entire Study Population

Table 2 shows the surgical outcomes and tumor characteristics of both groups. Length of the operation in the AR group was significantly longer than that in the NAR group, and blood loss in the AR group was significantly higher than that in the NAR group. Incidence of red cell transfusion and length of the hospital stay were not significantly different between the two groups. No deaths occurred during the perioperative period in either group.

The tumor characteristics are also summarized in Table 2. The size of the tumors in the AR group was significantly larger than that in the NAR group. Microsatellite lesions were found significantly more in patients in the AR group than those of the NAR group.

Postoperative Survival of the Entire Study Population

The cumulative 1-, 3-, and 5-year recurrence-free survival rates were 78.0, 46.9, and 35.2 % in the AR group and 77.2, 48.3, and 34.3 % in the NAR group, respectively (Fig. 1a). The cumulative 1-, 3-, and 5-year overall survival rates were 97.0, 85.3, and 72.2 % in the AR group and 95.5, 82.3, and 71.8 % in the NAR group, respectively (Fig. 1b). No significant differences were detected in the recurrence-free or overall survival rates between the two groups.

The Pattern of Recurrence and Treatment for Intrahepatic Recurrence in the Entire Study Population

The pattern of recurrence and primary treatment for remnant liver recurrence of the entire study population are shown in Table 3. The rate of extrahepatic recurrence in the AR group was significantly higher than that in the NAR group (P= 0.016). There were no significant differences in the intrahepatic recurrence pattern classified by Poon et al.[30] and the initial treatment used for intrahepatic recurrence between the two groups.

Comparison of the Preoperative Characteristics After One-to-One Propensity Score Matching

The one-to-one propensity score matching selected 64 patients in each group. The preoperative confounding factors became balanced between the two groups (Table 4).

Comparison of the Surgical Results and Tumor Characteristics After One-to-One Propensity Score Matching

Table 5 shows the surgical results of both groups after one-to-one propensity score matching. Even after matching, the length of the operation in the AR group was significantly longer than that in the NAR group (P=0.049), and the blood loss in the AR group was significantly higher than that in the NAR group (P=0.008). The tumor factors become balanced between the two groups.

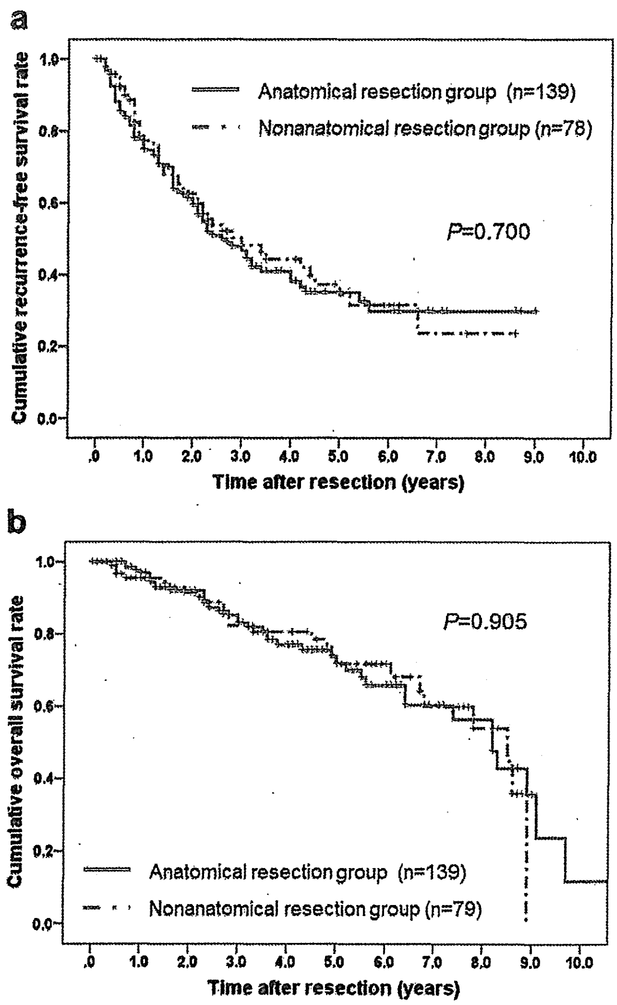

Fig. 1 **a** Recurrence-free survival of the anatomical resection group and nonanatomical resection group in the entire study population. **b** Cumulative overall survival of the anatomic resection group and nonanatomic resection group in the entire study population

Table 3 Site of recurrence, pattern of intrahepatic recurrence, and treatment for intrahepatic recurrence before and after the adjustment by propensity score matching

	Pre-propensity score matching (*n*=236)			Post-propensity score matching (*n*=128)		
	Anatomical (*n*=139)	Nonanatomical (*n*=97)	*P*	Anatomical (*n*=64)	Nonanatomical (*n*=64)	*P*
Site of recurrence						
Extrahepatic recurrence	15	2	0.016	6	2	0.254
Intrahepatic recurrence	60	45		24	28	
Pattern of intrahepatic recurrence						
Marginal recurrence	5	3	0.062	2	1	0.097
Recurrence at an adjacent segment	8	11		3	6	
Recurrence at a distant segment	21	6		10	3	
Multisegmental recurrence	26	25		9	18	
Treatment for intrahepatic recurrence						
Repeat liver resection	11	6	0.407	5	2	0.267
TACE	29	22		14	10	
RFA	16	11		6	11	
Radiation	9	1		1	4	
Other treatment	9	5		3	3	
Unknown	1	2		1	0	

TACE transcatheter arterial chemoembolization, *RFA* radiofrequency ablation

Postoperative Survival After One-to-One Propensity Score Matching

The cumulative 1-, 3-, and 5-year recurrence-free survival rates were 80.8, 65.5, and 50.0 % in the AR group and 69.7, 46.5, and 31.9 % in the NAR group, respectively (Fig. 2a). The cumulative 1-, 3-, and 5-year overall survival rates were 98.3, 91.2, and 71.0 % in the AR group and 96.4, 90.1, and 79.7 % in the NAR group, respectively (Fig. 2b). No significant difference was detected in

Table 4 Patient demographics and preoperative laboratory analyses with one-to-one nearest-neighbor matching method

Variables	Anatomical *n*=64	Nonanatomical *n*=64	*P* value
Patient's background			
Age (years)	71 (44–83)	67 (39–83)	0.194
Gender (M/F)	55/9	51/10	1.000
HBsAg (positive/negative)	14/50	14/50	1.000
Anti-HCV-Ab (positive/negative)	29/35	34/30	0.480
Child-Pugh classification (A/B)	63/1	64/0	1.000
Liver damage (A/B)	50/14	50/14	1.000
Background liver (noncirrhosis/cirrhosis)	52/12	42/22	0.071
Preoperative data			
Total bilirubin (mg/dL)	0.6 (0.3–1.0)	0.6 (0.2–1.9)	0.721
Albumin (g/dL)	4.3 (3.5–5.1)	4.2 (3.2–5.0)	0.537
PT (%)	91 (67–117)	87 (55–118)	0.099
ICG R_{15} (%)	16 (5–32)	17 (7–37)	0.071
AST (U/L)	31 (18–75)	36 (17–143)	0.170
ALT (U/L)	31 (10–150)	37 (11–281)	0.214
AFP (ng/mL)[a]	8.7 (1.6–82,587)	11.8 (2.1–24,982)	0.598
DCP (mAL/mL)[a]	117 (14–56,500)	63 (10–87,000)	0.092

M male, *F* female, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus, *Ab* antibody, *PT* prothrombin time, *ICG R_{15}* indocyanine green retention rate at 15 min, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

[a] Median (range)

Table 5 Operative results and tumor factor analyses with one-to-one nearest-neighbor matching method

Variables	Anatomical n=64 (%)	Nonanatomical n=64 (%)	P value
Operative results			
Operation time (min)[a]	271 (133–575)	229 (83–619)	0.049
Intraoperative blood loss (mL)[a]	551 (76–3,225)	465 (12–2,569)	0.008
Perioperative blood transfusion	0 (0)	0 (0)	
Postoperative hospitalization (days)[a]	11 (7–35)	11 (5–57)	0.569
Mortality	0 (0)	0 (0)	
Morbidity			
Clavien grade 1 or more	14 (21.9)	12 (18.8)	0.826
Clavien grade 3 or more	8 (12.5)	5 (7.8)	0.560
Tumor factors			
Size (mm)[a]	30 (7–160)	25 (10–160)	0.062
Microscopic portal invasion	3 (4.7)	7 (10.9)	0.820
Microscopic venous invasion	2 (3.1)	4 (6.3)	0.680
Microsatellite lesions	5 (7.8)	5 (7.8)	1.000
Tumor differentiation			
Well/moderately, poorly	12/52	10/54	0.815
Surgical margin (mm)[a]	7 (0–42)	7 (0–25)	0.590
UICC stage			
I/II	58/6	54/10	0.424

Values in parentheses are percentages unless indicated otherwise

UICC The Union Internationale Contra le Cancer classification

[a] Median (range)

the recurrence-free and overall survivals between the two groups.

Comparison of the Pattern of Recurrence and Treatment for Intrahepatic Recurrence After One-to-One Propensity Score Matching

The pattern of recurrence and the primary treatment for remnant liver recurrence after matching are shown in Table 3. There was no significant difference in the site of recurrence, intrahepatic recurrence pattern, and primary treatment used for intrahepatic recurrence between the two groups.

Risk Factors for Recurrence After One-to-One Propensity Score Matching

The results using the Cox regression hazards model for the predictors of recurrence-free survival are shown in Table 6. In the univariate analysis, liver damage B, positivity for hepatitis C virus antibodies (HCV-Ab), AFP≥20 ng/mL, ICG R15> 16 %, and microsatellite lesions were significant predictors of a poorer recurrence-free survival. The multivariate analysis revealed that an AFP≥20 ng/mL (hazard ratio [HR] 2.73, 95 % confidence interval [CI] 1.58–4.71, P<0.001), microsatellite lesions (HR 2.32, 95 % CI 1.02–5.29, P=0.044), and positivity for HCV-Ab (HR 1.84, 95 % CI 1.07–3.19, P= 0.029) remained as significant independent predictors of a poorer recurrence-free survival. The surgical procedure (AR or NAR) was not a significant risk factor for a poorer recurrence-free survival in both the uni- and multivariate analyses.

Discussion

The survival advantage of AR for HCC has long been a controversial issue. To identify a specific solution for this problem, we performed a retrospective comparative study using propensity score matching. The surgical procedure must be decided preoperatively, so we used the independent variables entered into the propensity model that included preoperative information, such as the factors mentioned in the "Statistical Analysis." The present study revealed that there was no superiority of AR compared to NAR in terms of either the recurrence-free or overall survival in patients with a single HCC.

Propensity score matching offers investigators the ability to balance two groups across all putative risk factors and allows for the easy inspection of the achieved balance across the

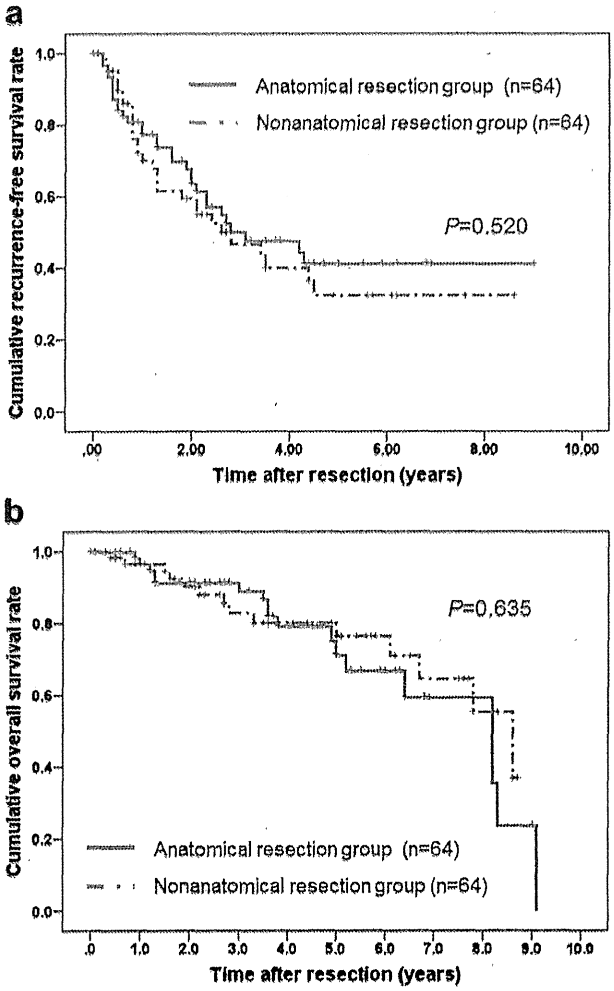

Fig. 2 a Recurrence-free survival of the anatomical resection group and nonanatomical resection group after propensity score matching. **b** Cumulative overall survival of the anatomic resection group and nonanatomic resection group after propensity score matching

measured covariates.[19-21] Consequently, there were no significant differences in the patients' background, preoperative data, or pathological results between the two groups after matching. However, even after matching, the length of the operation in the AR group was significantly longer than that in the NAR group, and the amount of blood loss in the AR group was significantly higher than that in the NAR group. These are understandable given the differences in the liver resection areas between the two groups.

While our manuscript was being prepared, two papers were published that showed comparisons between anatomic and nonanatomic liver resection for HCC using propensity score matching.[22,23] The study by Cucchetti et al., which was the largest series among the three papers (including our present paper), suggested that AR for early HCC could reduce the early recurrence rate after surgery, and this was true for patients who had poorly differentiated HCC or microvascular invasion.[22] On the other hand, Ishii et al. showed that AR conveyed a survival advantage, but not an advantage with regard to the recurrence rate, compared to NAR in specific subpopulations of HCC patients with single tumors ≤5 cm in diameter and with good liver function.[23] Therefore, the results of the two previous studies were inconsistent.

Intrahepatic recurrence is the most frequent mode of HCC recurrence. If the true benefit of AR can be confirmed, the patients with multiple tumor or vascular invasion were excluded from the study design because it is impossible to distinguish intrahepatic metastasis and multicentric tumors in multiple tumor cases can be considered to be contraindicated, and AR is therefore inevitable in terms of macroscopic vascular invasion. Therefore, our study analyzed only the patients with a solitary tumor in light of the metastatic pathway in HCC. On the contrary, the previous two studies included the patients with multiple tumors and/or vascular invasion.

If AR theoretically prevents intrahepatic recurrence, it is bound to improve the recurrence-free survival rate and reduce the proportion of marginal recurrence and recurrence at an adjacent segment, as previously proposed by Poon et al.[30] Thus, the end points of the present study were defined as the recurrence-free survival rate and the recurrence pattern after propensity score matching.

It is important to consider the etiology of the liver diseases when analyzing the outcomes of HCC. The etiology of the virus infection status was different between our study and the previous two studies. The patients who were positive for hepatitis B surface antigen (HBsAg) accounted for over half of the study patients in the previous two studies, while in our study, the patients with HBsAg comprised less than one fifth of the study patients.

For the reasons indicated above, while the present study is the third paper about this issue using propensity score matching, it is still considered to be of value.

Although there was no significant difference in the recurrence-free survival rate between the AR and NAR groups after propensity score matching, it is interesting to note that the recurrence-free survival rate of the AR group 2 years after surgery exceeded that of the NAR group after matching. This result suggests that AR has a certain prophylactic potential for intrahepatic metastases. Conversely, the recurrence-free survival rate gradually decreased, even after matching, because multicentric carcinogenesis cannot be controlled by AR.

With regard to the hepatitis virus infection status, the HCC recurrence rate decreases beginning 3 years after liver resection in patients with HBV or no hepatitis virus infection, whereas it increases gradually in patients with HCV infection in whom multicentric carcinogenesis is notably more common.[31,32] After propensity score matching, the positive status for HCV-Ab remained an independent risk factor for HCC recurrence in the present study. Therefore, our study

Table 6 Prognostic factors for recurrence-free survival in patients with HCC by univariate and multivariate analyses after matching

Variables	Univariable		Multivariable	
	Hazard ratio (95 % confidence interval)	P	Hazard ratio (95 % confidence interval)	P
Age (≥70 years)	1.16 (0.69–1.93)	0.577		
Gender (male)	0.80 (0.40–1.57)	0.512		
Child-Pugh class (B)	1.76 (0.24–12.8)	0.575		
Liver damage (B)	1.87 (1.09–3.23)	0.024	1.26 (0.68–2.32)	0.462
Cirrhosis (present)	1.70 (1.00–2.88)	0.051		
Etiology of liver disease (viral)	1.87 (0.99–3.51)	0.053		
HBsAg (positive)	0.68 (0.34–1.35)	0.271		
Anti-HCV (positive)	2.08 (1.23–3.53)	0.007	1.84 (1.07–3.19)	0.029
Albumin (<40 g/L)	1.27 (0.72–2.22)	0.410		
AFP (≥20 ng/mL)	2.64 (1.59–4.40)	<0.001	2.73 (1.58–4.71)	<0.001
DCP (≥40 mAL/mL)	1.52 (0.87–2.64)	0.138		
ICG R_{15} (>16 %)	1.70 (1.01–2.86)	0.046	1.37 (0.78–2.40)	0.280
Tumor size (≥5 cm)	1.63 (0.74–3.58)	0.227		
Microscopic vessel invasion (present)	1.54 (0.78–3.05)	0.211		
Microsatellite lesions (present)	2.63 (1.24–5.58)	0.012	2.32 (1.02–5.29)	0.044
UICC tumor stage (II)	1.47 (0.74–2.90)	0.268		
Operative procedure (anatomical)	0.84 (0.51–1.40)	0.502	0.80 (0.46–1.38)	0.418
Operation time (>250 min)	0.91 (0.54–1.51)	0.700		
Blood loss (>500 mL)	0.91 (0.55–1.52)	0.729		
Surgical margin (<5 mm)	0.81 (0.49–1.36)	0.430		

HBsAg hepatitis B surface antigen, *HCV* hepatitis C virus, *Ab* antibody, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *ICG R_{15}* indocyanine green retention rate at 15 min, *UICC* the Union Internationale Contra le Cancer classification

suggests that AR should be performed for HCC in patients with HBV or no hepatitis infection whenever possible, whereas patients with HCV infection should generally be treated with NAR. On the other hand, the rate of a sustained virological response (SVR) for HCV is very low, with a rate ≤10 %. There is no denying that the low SVR rate for HCV resulted in the finding that a positive status for HCV-Ab remained an independent risk factor for HCC recurrence in the present study.

With regard to the recurrence pattern, to the best of our knowledge, only three papers comparing AR and NAR have described the recurrence patterns after liver resection.[15,17,18] One paper reported that marginal recurrence in the AR group was significantly less common than that in the NAR group, and the prognosis of the AR group was also better than that of the NAR group.[15] Conversely, the other paper found that AR did not offer any significant benefit in terms of the recurrence pattern, which is in line with the results of the present study.[17,18].

We found that AR did not benefit the general population of HCC patients who underwent liver resection. However, we cannot rule out the possibility that some HCC patients did obtain a benefit from AR. For instance, AR could improve the recurrence-free survival rate in a limited number of patients with small tumors (2–5 cm in diameter), as described in previous papers.[33] Similarly, as previously reported, NAR may be superior in other subgroups of patients, especially in those with liver damage B, for whom AR could decrease the recurrence-free survival period.[16]

The present study was associated with some limitations even though it was a balanced, comparative study that employed propensity score matching. First, the total number of patients was relatively small in both groups (64 patients each). Additionally, it was a retrospective, nonrandomized, observational study; therefore, there was a possibility of selection bias despite the use of propensity score matching. Among the baseline covariates compared, some variables were different between the two groups, although these differences were not significant. To elucidate the true benefit of AR, further prospective studies are required to fully evaluate the relative merits of these two procedures. To the best of our knowledge, two randomized control trial studies about this issue are currently in progress (registered on ClinicalTrial.gov, identifier NCT01236989, and the World Health Organization, identifier JPRN-C00000008). We look forward to the publication of these trial results.

Conclusion

This is the first case-matching study using propensity scoring to show that there is no superiority of AR with regard to the recurrence-free survival rate or recurrence pattern compared with NAR in cases with a single HCC.

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