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Differences in Long-term Outcome and Prognostic Factors According to Viral Status in Patients with Hepatocellular Carcinoma Treated by Surgery

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Abstract Long-term postoperative survival and prognostic factors were examined retrospectively in patients with hepatocellular carcinoma (HCC) with serum hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCVAb) and in those without virus infection. Subjects were 265 consecutive HCC patients treated surgically at one institution during the period 1990 to 2006. Postoperative survival was analyzed and compared between HBsAg-positive (B-HCC), HCVAb-positive (C-HCC), and hepatitis B- and C-negative (NBNC-HCC) patients. Prognostic factors for overall and recurrence-free survival were also analyzed. Overall and recurrence-free survival rates were significantly higher in the NBNC-HCC group than in the C-HCC group. Significant prognostic factors for overall survival identified by univariate and multivariate analyses were age, serum alkaline phosphatase (ALP) level, tumor multiplicity, portal vein invasion (Vp), hepatic vein invasion (Vv), and operative blood loss in the B-HCC group; serum albumin level, ALP level, tumor size, and Vv in the C-HCC group; and tumor multiplicity in the NBNC-HCC group. Significant factors for recurrence-free survival were age, ALP level, tumor multiplicity, Vp, and operation time in the B-HCC group; ALP level, prothrombin time, tumor size, Vv, and width of the surgical margin in the C-HCC group; and age, tumor size, tumor multiplicity, and Vp in the NBNC-HCC group. Thus, postoperative survival and prognostic factors in cases of HCC differ according to the presence of serologic viral markers.

Keywords Hepatocellular carcinoma · Viral status · Surgery · Prognostic factors

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide. Despite multiple treatment options, including surgical resection, percutaneous ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation, survival rates remain unsatisfactory.[1]

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HCC tends to occur in patients with chronic liver disorder because of hepatitis B (HB) or hepatitis C (HC) infection. Therefore, all patients with HCC are tested for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) before surgery. Does the presence or absence of these markers change the factors influencing postoperative prognosis for HCC patients? Both HB virus (HBV) and HC virus (HCV) cause chronic hepatocellular injury and hepatic regeneration in patients with either virus results in cumulative genetic alterations that may lead to malignant transformation. Differences in carcinogenetic mechanisms between these viruses have been reported. HBV DNA is integrated into the hepatocyte DNA, resulting in genomic instability, and the gene product HBx promotes HCC carcinogenesis.[2] Specific gene products of HCV are also reported to be involved in malignant transformation.[3] Therefore, characteristics of HCC-related viruses may affect HCC characteristics. In addition, there is a substantial population of patients in whom HCC is not related to viral hepatitis.[4] Although there are many reports of differences between HCC associated with HBV

and HCC associated with HCV,[5–8] differences in prognostic factors in relation to the viral status of HCC patients are unclear and have been seldom investigated.[9]

Surgical resection is one of the most effective treatment options for HCC.[1] Prognostic factors are very important in determining whether surgery is indicated. If factors indicate a poor prognosis, other treatments may be chosen or postoperative adjuvant therapy may be applied. To investigate the influence of viral status on prognostic factors in a surgical context, we examined the differences in prognostic factors between three groups of patients treated surgically for HCC who were exclusively HBsAg-positive, HCVAb-positive, or negative for both markers.

Patients and Methods

Two hundred eighty-three patients who underwent hepatic resection for HCC at our institute during the period January 1990 through December 2006 were considered for this study. Of these patients, three patients in whom HCVAb was not tested, nine patients in whom both HBsAg and HCVAb were positive, two patients with autoimmune hepatitis, and four patients who died within 30 postoperative days were excluded from the study. Thus, 265 patients were the subjects of this investigation. HCC was histologically confirmed in all patients. Postoperative follow-up included abdominal ultrasonography (US) or computed tomography (CT) study every 3 months and laboratory testing of serum alpha-fetoprotein (AFP) and/or protein induced by vitamin K absence or antagonist II level every 1 to 3 months at our outpatient clinic. Patients underwent US, CT, and hepatic angiography when recurrence was suspected. Bone scintigraphy or chest CT was performed when clinically indicated. If cancer recurrence was confirmed, various treatments, including repeat hepatectomy, TACE, percutaneous ablation, and radiation therapy were applied as deemed necessary. Treatments and follow-up strategies were not changed on the basis of hepatitis virus status. The median follow-up time was 780 days, and the mean follow-up time was 1,235 days. Recurrence-free survival time was defined as the interval between the day of surgery and diagnosis of recurrence. In the calculation of recurrence-free survival, patients with residual tumor in the remnant liver or other organs at the time of surgery (n=9) and patients in whom the time of recurrence was unknown (n=6) were excluded.

The 265 patients were classified into three groups: a B-HCC group in which patients were HBsAg-positive and HCVAb-negative (n=78), a C-HCC group in which patients were HBsAg-negative and HCVAb-positive (n=127), and a NBNC-HCC group in which patients were both HBsAg-negative and HCVAb-negative (n=60). In the NBNC-HCC group, 14 patients (23.3%) abused alcohol (intake of ≥86 g ethanol per day for at least 10 years, as defined by the Liver Cancer Study Group of Japan),[10] and 13 patients (21.7%) were positive for hepatitis B surface antibody (HBsAb). For all three groups, factors possibly influencing overall postoperative survival and recurrence-free survival were listed and classified into one of four categories: patient characteristics, preoperative liver function, tumor characteristics obtained by preoperative imaging (including CT during hepatic arteriography and arterioportography performed in all patients) and blood analysis (serum AFP level), and treatment (Table 1). Overall postoperative survival and recurrence-free survival were also compared between these groups. Univariate analysis was used to identify significant prognostic factors in each group. If more than two factors in each category were shown to be significant, multivariate analysis was used to detect independent prognostic factors. Obtained prognostic factors were evaluated in relation to postoperative survival curves.

Differences in variables between groups were analyzed by unpaired Student's t test (for continuous variables, expressed as the mean±SD) and chi-square test (for categorical variables). Prognostic factors for overall and recurrence-free survival rates in each group were identified by univariate and multivariate analyses with the Cox proportional hazards regression model. To evaluate the obtained prognostic factors, survival curves calculated by the Kaplan–Meier method were compared by log-rank test. Statistical significance was defined as $p<0.05$. All analyses were performed with StatView statistical software (version 5.0; SAS Institute, Cary, NC, USA).

Results

Patient Characteristics and Outcomes

Results of comparisons of various factors examined for prognostic significance in each group are shown in Table 1. Many factors differed between groups. Age was lower in the B-HCC group than in the other two groups. With respect to liver function, the serum total bilirubin (T-Bil) level was higher and the serum albumin (ALB) level was lower in the C-HCC group than in the NBNC-HCC group. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and indocyanine green retention rate at 15 min (ICGR15) were higher in the C-HCC group than in the other two groups. The platelet count (Plt) was higher, and the proportion of patients with liver cirrhosis was lower in the NBNC-HCC group than in the other two groups. With respect to tumor characteristics, tumors were smaller in the C-HCC group, and hepatic vein invasion (Vv) was observed more frequently in the NBNC-HCC

Table 1 Possible Factors Influencing Overall Postoperative and Recurrence-free Survival and Comparison of These Factors Between the Groups

				p value		
	B-HCC	C-HCC	NBNC-HCC	(B/NBNC)[a]	(C/NBNC)[b]	(B/C)[c]
Patient characteristics						
Age (years, mean±SD)	54.7±11.6	67.2±6.7	67.9±10.3	*<0.0001*	0.6164	*<0.0001*
Sex (male/female)	58/20	94/33	43/17	0.7234	0.7348	0.9565
Liver function						
T-Bil (mean±SD, mg/dl)	0.82±0.35	0.82±0.29	0.73±0.26	0.0913	*0.0496*	0.9120
ALB (mean±SD, g/dl)	3.75±0.42	3.66±0.42	3.87±0.54	0.1619	*0.0048*	0.1304
ALP (mean±SD, IU/l)	288±165	306±178	307±148	0.4851	0.9869	0.4580
AST (mean±SD, IU/l)	47.6±46.4	59.4±28.6	42.7±29.8	0.4814	*0.0003*	*0.0253*
ALT (mean±SD, IU/l)	43.1±28.8	56.5±34.2	39.8±35.5	0.5595	*0.0026*	*0.0048*
Plt (mean±SD, /μl)	14.1±6.1	14.1±7.5	18.0±7.9	*0.0015*	*0.0014*	0.9955
PT (mean±SD, %)	85.6±15.9	87.5±15.0	88.6±16.3	0.2771	0.6323	0.4134
ICGR15 (mean±SD, %)	15.5±9.9	20.8±11.4	16.6±7.6	0.4752	*0.0129*	*0.0009*
Liver cirrhosis (+/−)	42/36	70/57	17/43	*0.0027*	*0.0006*	0.8590
Tumor characteristics						
Maximum diameter (mean±SD, cm)	6.2±4.5	4.9±3.6	6.2±3.4	0.9398	*0.0296*	*0.0271*
Tumor number (St/Mt)	57/21	85/42	48/12	0.3446	0.0656	0.3543
Portal vein invasion (Vp, +/−)	15/63	13/114	11/49	0.8937	0.1223	0.0687
Hepatic vein invasion (Vv, +/−)	3/75	5/122	8/52	*0.0414*	*0.0184*	0.9740
AFP (mean±SD, $\times 10^3$ ng/ml)	58.7±255.2	2.8±7.3	3.4±8.8	0.1048	0.4567	*0.0138*
Treatment						
Preoperative TACE (+/−)	18/60	42/85	17/43	0.4817	0.5152	0.1268
Resection (nonanatomic/anatomic)	19/59	43/84	9/51	0.1753	*0.0072*	0.1505
Operative blood loss (mean±SD, ml)	1594±1702	1216±1245	1326±1252	0.3079	0.5748	0.0690
Operation time (mean±SD, min)	387±163	331±161	375±163	0.6648	0.0898	*0.0182*
SM ≥5 mm (+/−)	41/37	75/52	32/28	0.9285	0.4604	0.3626

p values <0.05 are italicized.

T-Bil: total bilirubin, *ALB*: albumin, *ALP*: alkaline phosphatase, *AST*: aspartate aminotransferase, *ALT*: alanine aminotransferase, *Plt*: platelet count, *PT*: prothrombin time, *ICGR15*: indocyanine green retention rate at 15 min, *St*: single tumor, *Mt*: multiple tumors, *AFP*: alpha-fetoprotein, *TACE*: transcatheter arterial chemoembolization, *SM*: surgical margin

[a] B-HCC group vs NBNC-HCC group.

[b] C-HCC group vs NBNC-HCC group.

[c] B-HCC group vs C-HCC group.

group than in the other two groups. The serum AFP level was higher in the B-HCC group than in the C-HCC group. With respect to treatment, anatomic resection was performed more often in the NBNC-HCC group than in the C-HCC group. Operation time was shorter in the C-HCC group than in the B-HCC group.

Both overall survival and recurrence-free survival rates, as calculated by the Kaplan–Meier method, were higher in the NBNC-HCC group than in the C-HCC group (Fig. 1). Although there was a tendency toward higher overall and recurrence-free survival rates in the NBNC-HCC group compared to those in the B-HCC group, these differences

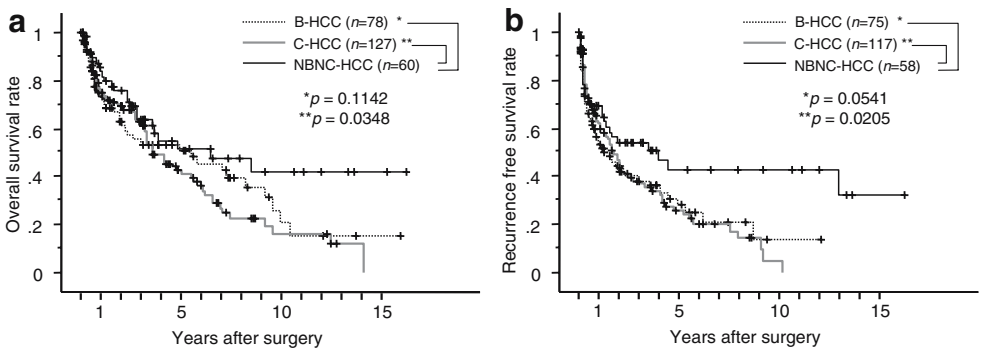

Figure 1 Overall postoperative survival rates (**a**) and recurrence-free survival rates (**b**) in the B-HCC group, C-HCC group, and NBNC-HCC group. Both survival rates were significantly higher in the NBNC-HCC group than in the C-HCC group. The same tendency was observed for the NBNC-HCC group compared to the B-HCC group, but this tendency was not statistically significant.

were not statistically significant. No difference in survival rate was found between the B-HCC and C-HCC groups.

Prognostic Factors for Overall Survival in Each Group

B-HCC group Univariate analysis by the Cox proportional hazards model showed that age in the patient characteristics category; alkaline phosphatase (ALP) level in the liver function category; and tumor size, number of tumors, portal vein invasion (Vp), Vv, and AFP level in the tumor characteristics category were significant prognostic factors (Table 2). Operative blood loss in the treatment category was also a significant factor. Stepwise multivariate Cox proportional hazards analysis of the tumor characteristics category showed that tumor number, Vp, and Vv were independent prognostic factors (Table 2).

C-HCC group Serum ALB, ALP, and AST levels and ICGR15 in the liver function category and tumor size, Vv, and AFP level in the tumor characteristics category were shown to be significant prognostic factors by univariate analysis (Table 2). Multivariate analysis showed that of the

Table 2 Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival in Each Group

	p value					
	B-HCC		C-HCC		NBNC-HCC	
	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate
Patient characteristics						
Age	*0.0030* (0.958, 0.932–0.986)		0.8172		0.1381	
Sex	0.8526		0.9154		0.4201	
Liver function						
T-Bil	0.3231		0.4314		0.2426	
ALB	0.1688		*0.0007* (0.507, 0.265–0.970)	*0.0400*	0.2369	
ALP	*<0.0001* (1.003, 1.002–1.004)		*<0.0001* (1.002, 1.001–1.004)	*0.0002*	*0.0242* (1.003, 1.000–1.005)	
AST	0.9903		*0.0135*	0.3900	0.1705	
ALT	0.6180		0.2545		0.5174	
Plt	0.7628		0.2835		0.7990	
PT	0.9425		0.8816		0.0922	
ICGR15	0.2878		*0.0287*	0.5919	0.2901	
Liver cirrhosis	0.8971		0.7001		0.0584	
Tumor characteristics						
Maximum diameter	*0.0042*	0.4411	*<0.0001* (1.171, 1.096–1.251)	*<0.0001*	0.0516	
Tumor number (St/Mt)	*0.0030* (2.291, 1.160–4.523)	*0.0169*	0.1450		*0.0034* (3.586, 1.527–8.426)	
Portal vein invasion (Vp)	*0.0001* (0.339, 0.139–0.826)	*0.0174*	0.4271		0.0639	
Hepatic vein invasion (Vv)	*0.0061* (0.286, 0.084–0.974)	*0.0453*	*0.0156* (0.125, 0.028–0.567)	*0.0070*	0.5881	
AFP	*0.0064*	0.9125	*0.0182*	0.3876	0.6261	
Treatment						
Preoperative TACE	0.7942		0.6219		0.1609	
Resection (nonanatomic/anatomic)	0.0751		0.6626		–[a]	
Operative blood loss	*0.0048* (1.000, 1.000–1.000)		0.1059		0.8290	
Operation time	0.1504		0.8392		0.5598	
SM ≥5 mm	0.0711		0.0906		0.5061	

Risk ratios and 95% confidence intervals are shown under the significant independent prognostic factors in each category identified in each group by univariate or multivariate analysis. *p* values <0.05 are italicized. Abbreviations are the same as those in Table 1.
CI: confidence interval
[a] Could not be evaluated because no event was observed in patients who underwent nonanatomic resection.

liver function factors, ALB and ALP levels were independent prognostic factors, and of the tumor characteristics, tumor size and Vv were independent prognostic factors (Table 2).

NBNC-HCC group Serum ALP level in the liver function category and number of tumors in the tumor characteristics category were shown to be significant prognostic factors by univariate analysis (Table 2).

Overall postoperative survival rates (1-, 3-, 5-, 7-, and 10-year) calculated by the Kaplan–Meier method and according to the independent prognostic factors for the B-HCC, C-HCC, and NBNC-HCC groups are shown in Table 3. Significant differences in overall postoperative survival rates were observed in relation to these factors with the exception of ALP in the NBNC-HCC group. For this factor, the biggest difference in overall survival rates was obtained when the patients were classified into those with ≥350 IU/l serum ALP and those with <350 IU/l serum ALP, but this difference did not reach significance by log-rank test.

Prognostic Factors for Recurrence-free Survival in Each Group

B-HCC group Univariate analysis by the Cox proportional hazards model showed that age in the patient characteristics category; serum ALP level in the liver function category; tumor size, number of tumors, Vp, Vv, and AFP level in the tumor characteristics category; and operation time in the treatment category were significant prognostic factors (Table 4). Stepwise multivariate analysis by the Cox proportional hazards model of the tumor characteristics category showed the number of tumors and Vp to be independent prognostic factors (Table 4).

C-HCC group Serum ALP level and prothrombin time (PT) in the liver function category; tumor size and Vv in the tumor characteristics category; and distance of the surgical margin (SM ≥5 mm or not) in the treatment category were shown to be significant prognostic factors by univariate analysis (Table 4). Multivariate analysis of the liver function category and the tumor characteristics category

Table 3 Postoperative Overall Survival Rates According to the Prognostic Factors for Each Group

Prognostic factors	Survival rate					
	1-year	3-year	5-year	7-year	10-year	*p* value (log-rank test)
B-HCC						
Age ≥55 years (*n*=38)	92	69	69	62	39	
Age <55 years (*n*=40)	56	40	36	30	10	*0.0024*
ALP ≥350 IU/l (*n*=17)	41	16	0			
ALP <350 IU/l (*n*=61)	83	64	64	57	32	*<0.0001*
Tumor number, single (*n*=57)	83	71	68	57	29	
Tumor number, multiple (*n*=21)	57	17	17	17	17	*0.0021*
Portal vein invasion (Vp) + (*n*=15)	40	24	24	8	–	
Portal vein invasion (Vp) − (*n*=63)	82	64	62	57	32	*<0.0001*
Hepatic vein invasion (Vv) + (*n*=3)	32	0				
Hepatic vein invasion (Vv) − (*n*=75)	75	58	56	47	27	*0.0020*
Operative blood loss ≥1,000 ml (*n*=45)	64	41	41	34	23	
Operative blood loss <1,000 ml (*n*=33)	87	74	71	61	32	0.0307
C-HCC						
ALB ≥3.7 g/dl (*n*=61)	85	69	54	44	31	
ALB <3.7 g/dl (*n*=66)	66	56	29	8	0	*0.0003*
ALP ≥350 IU/l (*n*=33)	62	42	21	10	0	
ALP <350 IU/l (*n*=94)	81	68	48	33	20	*0.0028*
Maximum diameter ≥6 cm (*n*=34)	54	40	21	21	0	
Maximum diameter <6 cm (*n*=93)	83	71	49	27	16	*0.0009*
Hepatic vein invasion (Vv) + (*n*=5)	0					
Hepatic vein invasion (Vv) − (*n*=122)	78	64	43	27	16	*0.0055*
NBNC-HCC						
ALP ≥350 IU/l (*n*=17)	76	40	40	30	30	
ALP <350 IU/l (*n*=43)	89	74	54	54	46	0.0973
Tumor number, single (*n*=48)	91	72	61	56	48	
Tumor number, multiple (*n*=12)	61	30	15	15	15	*0.0017*

p values <0.05 are italicized. Abbreviations are the same as those in Table 1.

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for Recurrence-free Survival in Each Group

	p value					
	B-HCC		C-HCC		NBNC-HCC	
	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate	Univariate (Risk ratio, 95%CI)	Multivariate
Patient characteristics						
Age	*0.0171* (0.972, 0.949–0.996)		0.8975		*0.0298* (1.061, 1.008–1.116)	
Sex	0.7671		0.5601		0.7725	
Liver function						
T-Bil	0.0758		0.8747		0.3941	
ALB	0.3971		0.1195		0.2134	
ALP	*<0.0001* (1.003, 1.002–1.004)		*<0.0001* (1.002, 1.001–1.003)	*<0.0001*	0.1905	
AST	0.9265		0.0529		0.4544	
ALT	0.2501		0.5497		0.4459	
Plt	0.9100		0.2631		0.3467	
PT	0.3326		*0.0291* (0.980, 0.961–1.000)	*0.0481*	0.1085	
ICGR15	0.4278		0.2441		0.2268	
Liver cirrhosis	0.6795		0.2537		0.5203	
Tumor characteristics						
Maximum diameter	*0.0052*	0.2875	*0.0023* (1.099, 1.019–1.184)	*0.0016*	*0.0127* (1.136, 1.023–1.262)	*0.0195*
Tumor number (St/Mt)	*<0.0001* (3.413, 1.722–6.762)	*0.0016*	0.2064		*0.0196* (3.538, 1.492–8.391)	*0.0130*
Portal vein invasion (Vp)	*0.0002* (0.396, 0.177–0.885)	*0.0070*	0.1959		*0.0118* (0.318, 0.131–0.776)	*0.0327*
Hepatic vein invasion (Vv)	*0.0014*	0.0536	*<0.0001* (0.069, 0.021–0.227)	*<0.0001*	0.1204	
AFP	*0.0003*	0.2376	0.1560		0.9504	
Treatment						
Preoperative TACE	0.6040		0.2589		0.1267	
Resection (nonanatomic/anatomic)	0.0683		0.8254		0.1270	
Operative blood loss	0.0711		0.0861		*0.0227* (1.000, 1.000–1.001)	
Operation time	*0.0088* (1.002, 1.000–1.003)		0.5726		0.7846	
SM ≥5 mm	0.1791		*0.0211* (1.657, 1.058–2.596)		0.0995	

Risk ratios and 95% confidence intervals are shown under the significant independent prognostic factors in each category identified in each group by univariate or multivariate analysis. *p* values <0.05 are italicized. Abbreviations are the same as those in Table 1.
CI: confidence interval

showed ALP level, PT, tumor size, and Vv to be independent prognostic factors (Table 4).

NBNC-HCC group In the patient characteristics category, age was shown to be a significant prognostic factor by univariate analysis. No significant factor was found in the liver function category. In the tumor characteristics category, tumor size, number of tumors, and Vp were shown to be significant prognostic factors by univariate analysis. All of these factors were significant by multivariate analysis (Table 4). Operative blood loss in the treatment category was shown to be a significant prognostic factor by univariate analysis (Table 4).

Recurrence-free survival rates (1-, 3-, 5-, 7-, and 10-year) calculated by the Kaplan–Meier method and according to the independent prognostic factors for the B-HCC, C-

Table 5 Postoperative Recurrence-free Survival Rate According to the Prognostic Factors in Each Group

Prognostic factors	Survival rate					
	1-year	3-year	5-year	7-year	10-year	*p* value (log-rank test)
B-HCC						
Age ≥55 years (*n*=37)	68	48	36	29	29	
Age <55 years (*n*=38)	44	28	24	12	0	*0.0236*
ALP ≥350 IU/l (*n*=17)	32	8	–			
ALP <350 IU/l (*n*=58)	61	48	37	24	17	*<0.0001*
Tumor number, single (*n*=56)	66	50	41	27	19	
Tumor number, multiple (*n*=19)	17	0				<0.0001
Portal vein invasion (Vp) + (*n*=15)	22	11	11	–	–	
Portal vein invasion (Vp) − (*n*=60)	76	61	47	47	47	<0.0001
Operation time ≥6 h (*n*=38)	39	22	22	22	–	
Operation time <6 h (*n*=37)	68	53	41	26	12	*0.0179*
C-HCC						
ALP ≥350 IU/l (*n*=29)	39	11	–	–	–	
ALP <350 IU/l (*n*=67)	66	38	27	22	–	*0.0062*
PT ≥80% (*n*=77)	66	47	33	26	7	
PT <80% (*n*=32)	45	21	13	–	–	*0.0099*
Maximum diameter ≥6 cm (*n*=32)	41	21	–	–	–	
Maximum diameter <6 cm (*n*=85)	69	43	29	23	5	*0.0165*
Hepatic vein invasion (Vv) + (*n*=5)	0					
Hepatic vein invasion (Vv) − (*n*=112)	64	39	27	21	4	*<0.0001*
SM ≥5 mm (*n*=68)	71	44	27	27	6	
SM <5 mm (*n*=49)	48	27	23	9	–	*0.0195*
NBNC-HCC						
Age ≥65 years (*n*=44)	62	46	32	32	32	
Age <65 years (*n*=14)	92	81	81	81	81	*0.0200*
Maximum diameter ≥6 cm (*n*=28)	45	24	24	24	24	
Maximum diameter <6 cm (*n*=30)	92	84	62	62	62	*<0.0001*
Tumor number, single (*n*=47)	73	61	47	47	47	
Tumor number, multiple (*n*=11)	50	25	25	25	25	*0.0146*
Portal vein invasion (Vp) + (*n*=10)	36	17	17	17	17	
Portal vein invasion (Vp) − (*n*=48)	76	61	47	47	47	*0.0080*
Operative blood loss ≥1,000 ml (*n*=33)	58	38	38	38	38	
Operative blood loss <1,000 ml (*n*=25)	83	71	50	50	50	0.0837

p values <0.05 are italicized. Abbreviations are the same as those in Table 1.

HCC, and NBNC-HCC groups are shown in Table 5. Significant differences in postoperative recurrence-free survival rates were observed in relation to these factors with the exception of operative blood loss in the NBNC-HCC group. For this factor, the biggest difference in recurrence-free survival rate was obtained when the patients were classified into those with ≥1,000 ml blood loss and those with <1,000 ml blood loss, but this difference did not reach significance by log-rank test.

Discussion

It should be mentioned that the NBNC-HCC group and the C-HCC group may have included patients with HBV in the present study. Recent studies have shown that HBV DNA can be detected in the hepatic parenchyma of many HBsAg-negative HCC patients.[11,12] However, the determination of HBV DNA in liver tissue was not carried out in the present study and is not routinely checked during the clinical course of HCC. We believe that the investigation of prognostic factors based on generally accepted serologic virus markers, HBsAg and HCVAb, is reasonable. In addition, 21.7% of patients in the NBNC-HCC group were positive for HBsAb. In such patients, the contribution of HBV to the occurrence of HCC is unknown and the influence of HBV on the function or carcinogenesis of the remnant liver during the postoperative course is not as strong as that in HBsAg-positive patients. Therefore, HBsAb-positive patients were included in the NBNC-HCC

group. Because HB core antibody was not measured in many patients, we did not review it in the present study.

Multiple differences were observed between the three study groups. The finding that the patients in the B-HCC group were younger than those in the other groups is consistent with previously reported findings in Japan,[6,8,13] but not with findings from a study based on a multicenter international database including patients from Japan, China, France, and the United States.[5] In the liver function category, many parameters reflected that the incidence and severity of chronic hepatitis or cirrhosis were greatest in C-HCC patients, followed by B-HCC patients. Among the three groups, liver function was the best in the NBNC-HCC group. The smaller tumors and lower AFP level in the C-HCC group may be because of periodic screening for HCC in these patients. The reason for the high incidence of Vv in the NBNC-HCC group is unknown. Analysis of treatment factors suggests that in the NBNC-HCC group, the increased frequency of anatomic resection may have been related to good liver function compared to that in the C-HCC group. In the C-HCC group, short operation time may have been related to the smaller tumor size compared to that in the B-HCC group.

The question of the relation of postoperative survival rates to viral status has been quite controversial. Some reports note a higher overall or recurrence-free survival rate in HB-negative and HC-negative patients than in HB-positive patients.[4,6,14] However, previous studies showed no difference in survival with respect to viral status.[5,8] In the present study, improved overall postoperative survival and recurrence-free survival were observed in the NBNC-HCC group compared to that in the C-HCC group. This is attributed to a low incidence of multicentric carcinogenesis, which is caused by chronic viral attack. This theory is supported by the large difference in survival curves between the NBNC-HCC group and the C-HCC group that began to be observed at 2 years (recurrence-free survival) or 3 years (overall survival) after surgery. Comparison of the survival curves between the NBNC-HCC group and the B-HCC group showed the same tendency, but it was not statistically significant. A feature of the postoperative survival curve in the NBNC-HCC group is that the overall survival rate did not decrease beyond the ninth postoperative year, and the recurrence-free survival rate showed only a small decrease beyond the fifth postoperative year. Patients who survived longer than this are expected to be completely cured.

Many reports pertaining to differences in tumor characteristics and post therapeutic survival rates according to hepatitis virus status have been published, but the findings are controversial. One of the important issues is how to determine treatment strategy according to viral status, and prognostic factors are an important part of this question. In our examination of prognostic factors, we found many differences between the B-HCC, C-HCC, and NBNC-HCC groups. In the B-HCC group, patients younger than 55 years of age showed significantly lower survival rates than those 55 years of age or older. This indicates that careful follow-up and early diagnosis of HCC is important in patients less than 55 years of age with chronic HBV infection. The importance of ALP as a prognostic factor was emphasized in a previous study of liver cirrhosis.[15] ALP may also belong to the tumor characteristics category because it can reflect bile duct compression by a large or rapidly growing tumor. Patients with a high ALP level (≥350 IU/l), multiple tumors, or vascular-invading tumors have a very poor prognosis and may have to undergo challenging postoperative adjuvant therapy. Operative blood loss and operation time may affect the postoperative overall and recurrence-free survival rates, respectively, in this group.

In the C-HCC group, protein production by the liver, as represented by serum ALB level or PT, affects postoperative overall or recurrence-free survival rate. These factors representative of liver function were observed exclusively in the C-HCC group, and no liver function factor other than ALP level affected prognosis in the other two groups. ALP level was a strong prognostic factor, similar to that in the B-HCC group. The fact that large tumor size (≥6 cm) was related to poor prognosis indicates that the tumor should be detected and removed before it has grown beyond 6 cm. Patients with HCC with Vv have an extremely poor prognosis (0%, 1-year survival), and these patients may not be candidates for hepatic resection. There is a possibility that the distance of the surgical margin (≥5 mm or not) affects the postoperative recurrence-free survival rate in this group.

In the NBNC-HCC group, tumor recurrence was more frequent in elderly patients (≥65 years of age) and in patients with multiple, large tumors (≥6 cm), or Vp, and careful postoperative follow-up is required. The only significant prognostic factor for overall postoperative survival revealed by both the Cox proportional hazards model and the Kaplan–Meier method and log-rank test was tumor multiplicity. In this group, liver function, tumor characteristics of tumor size and vascular invasion, and treatment factors were not prognostic for overall survival, indicating that if the tumor is solitary, aggressive surgery can result in a good prognosis in patients with a large tumor and vascular invasion.

Conclusion

In the light of our findings, we conclude that prognostic factors obtained before surgery differ according to viral status in surgically treated HCC patients. This should be considered in the determination of the surgical treatment strategy for such patients.

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