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Hepatobiliary

Early and Late Recurrence of Hepatitis B Virus-Associated Hepatocellular Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • Resection • Hepatitis B • Survival • Recurrence

Abstract

Background. Survival after liver resection of hepatocellular carcinoma (HCC) remains poor because of a high incidence of recurrence. We sought to investigate risk factors, patterns, and long-term prognosis among patients with early and late recurrence after liver resection for hepatitis B virus (HBV)–associated HCC.

Methods. Data of consecutive patients undergoing curative resection for HBV-associated HCC were analyzed. According to the time to recurrence after surgery, recurrence was divided into early (≤2 years) and late recurrence (>2 years). Characteristics, patterns of initial recurrence, and postrecurrence survival (PRS) were compared between patients with early and late recurrence. Risk factors of early and late recurrence and predictors of PRS were identified by univariable and multivariable Cox regression analyses.

Results. Among 894 patients, 322 (36.0%) and 282 (31.5%) developed early and late recurrence, respectively. On multivariable analyses, preoperative HBV-DNA >10^4 copies/mL was associated with both early and late recurrence, whereas postoperative no/irregular antiviral therapy was associated with late recurrence. Compared with patients with late recurrence, patients with early recurrence had a lower proportion of intrahepatic-only recurrence (72.0% vs. 91.1%, $p < .001$), as well as a lower chance of receiving potentially curative treatments for recurrence (33.9% vs. 50.7%, $p < .001$) and a worse median PRS (19.1 vs. 37.5 months, $p < .001$). Multivariable analysis demonstrated that early recurrence was independently associated with worse PRS (hazard ratio, 1.361; 95% confidence interval, 1.094–1.692; $p = .006$).

Conclusion. Although risk factors associated with early recurrence and late recurrence were different, a high preoperative HBV-DNA load was an independent hepatitis-related risk for both early and late recurrence. Early recurrence was associated with worse postrecurrence survival among patients with recurrence. ***The Oncologist*** 2020;25:e1541–e1551

Implications for Practice: Liver resection is the main curative treatment for hepatocellular carcinoma (HCC), but postoperative survival remains poor because of high recurrence rates. This study investigated the risk factors and patterns of early and late recurrence and found that a high preoperative hepatitis B virus (HBV) DNA load was an independent hepatitis-related risk factor for both. Early recurrence was also independently associated with worse postrecurrence survival. These data may provide insights into different biological origin and behavior of early versus late recurrence after resection for HBV-associated HCC, which could be helpful to make individualized treatment decision for recurrent HCC, as well as strategies for surveillance recurrence after resection.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies and a leading cause of cancer-related death globally [1]. Hepatitis B virus (HBV) infection is the main etiology of HCC worldwide, especially in sub-Saharan Africa and East Asia [2]. China alone accounts for more than half of patients with HCC worldwide. Although liver resection is the mainstay of curative therapy for HCC, the high incidence of recurrence remains the major obstacle to improving long-term survival, with almost 70% of patients developing recurrence within 5 years of resection [3, 4]. Thus, investigation of risk factors and patterns of recurrence after curative resection for HCC is important to better define treatment modalities and surveillance, as well as characterize long-term prognosis among patients who develop recurrence.

Relative to the time from surgery to initial recurrence, HCC recurrence is typically divided into early and late recurrence, which has generally been defined using 2 years as the cutoff value [5–10]. Early recurrence most likely originates from occult micrometastasis derived from the initial tumor and is commonly associated with aggressive tumor characteristics, such as multinodularity, large tumor size, macrovascular and microvascular invasion, poor tumor differentiation, and satellite nodules [7, 8, 10–13]. In contrast, late recurrence has a clonal origin that is distinct from the original tumor, suggesting a de novo tumor in the remnant liver with different clonal origins. As such, late recurrence, though sometimes associated with aggressive initial HCC characteristics, is often characterized by several host and viral factors, such as sex, cirrhosis, hepatitis activity, and high viral loads [8–10, 14–17]. Until recently, there have been very few published studies on early and late recurrence of HBV-associated HCC, and most had a limited sample size [8, 16, 17]. For example, in one study of 193 patients with HBV-associated HCC, 134 (69.4%) patients had HCC recurrence after resection [8]. In this study, Wu et al. investigated independent risk factors of early and late recurrence for HBV-associated HCC and concluded that tumor-related factors were associated with early recurrence, whereas viral-related factors were associated with late recurrence [8]. Most past studies did not, however, elucidate details regarding the patterns of recurrence, treatment of recurrence, postrecurrence survival, or the relevant predictors associated with recurrence [8, 16, 17].

Therefore, the objective of the present study was to define risk factors and patterns of early and late recurrence after curative resection of HBV-associated HCC using a large prospectively collected database. In addition, treatment and postrecurrence survival of patients with HCC recurrence were assessed with the aim of providing clinicians with more evidence on appropriate selection of treatment options for recurrent HCC, as well as to inform rational strategies of surveillance after liver resection for HBV-associated HCC.

Materials, Subjects, and Methods

Study Population

Using a prospectively collected database, patients with chronic HBV infection who underwent open curative-intent liver resection for an index HCC at the Eastern Hepatobiliary Surgery Hospital of Shanghai between January 2002 and June 2016 were identified. The diagnosis of HCC was confirmed by postoperative histopathological examination. Curative liver resection was defined as complete removal of all tumor with a microscopically clear margin (R0 resection). Chronic HBV infection was defined as positive serum HBV surface antigen (HBsAg). The exclusion criteria were patients who (a) had recurrent HCC; (b) had concurrent etiologies of liver disease other than HBV infection, such as hepatitis C infection or alcoholic hepatitis; (c) underwent palliative liver resection with microscopically or grossly positive margins (R1 or R2 resection); (d) received preoperative antitumor treatments; (e) had postoperative mortality within 30 days after surgery; (f) were lost to follow-up within 2 years after surgery; and (g) had missing data on essential prognostic variables. The data were censored on December 31, 2018. Written informed consent was obtained from all enrolled patients for their data to be analyzed in clinical researches. This study was approved by the Institutional Review Board and Ethics Committee of the Eastern Hepatobiliary Surgery Hospital of Shanghai, China.

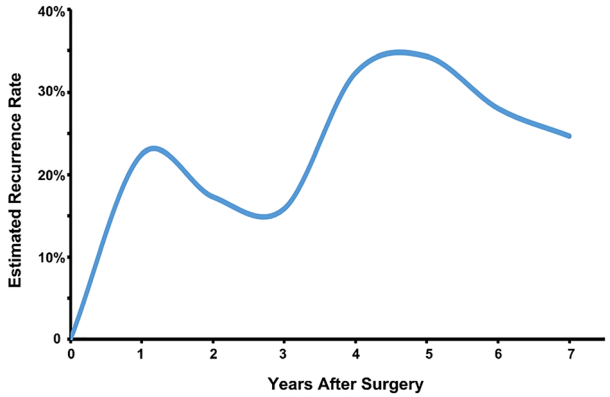

Figure 1. The estimated rate of recurrence (per year) over time after curative liver resection of hepatitis B virus–associated hepatocellular carcinoma.

Clinicopathological and Operative Variables

Potential risk factors contributing to recurrence and survival after HCC resection were classified as factors associated with the host, hepatitis, initial tumor, and the operation. Host-related factors included sex, age, American Society of Anesthesiologists score, obesity (body mass index >30), diabetes mellitus, cirrhosis, portal hypertension, and Child-Pugh grading; hepatitis-related factors included positivity of HBV envelope antigen (HBeAg), preoperative HBV-DNA load, history of preoperative anti-HBV therapy, raised preoperative alanine transaminase and aspartate aminotransferase (AST) levels, and postoperative anti-HBV therapy and HBV reactivation until recurrence or the last follow-up. Initial tumor-related factors included raised preoperative serum alpha-fetoprotein (AFP) level, largest tumor size, tumor number, macrovascular and microvascular invasion, satellite nodules, tumor differentiation, tumor encapsulation, and tumor stage according to the Barcelona Clinic Liver Cancer (BCLC) staging; operation-related factors included intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (minor or major), type of liver resection (anatomical

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Table 1. Comparisons of clinicopathological and operative variables among patients without recurrence, and with early and late recurrence

Variables	Total (*n* = 894)	Without recurrence (*n* = 290)	Early recurrence (*n* = 322)	Late recurrence (*n* = 282)	*p* value[a]	*p* value[b]
Sex, male	805 (90.0)	259 (89.3)	292 (90.7)	254 (90.1)	.852	.890
Age >60 years	156 (17.4)	50 (17.2)	59 (18.3)	47 (16.7)	.861	.668
ASA score >2	100 (11.2)	36 (12.4)	32 (9.9)	32 (11.3)	.621	.598
Obesity	45 (5.0)	6 (2.1)	25 (7.8)	14 (5.0)	.006	.186
Diabetes mellitus	47 (5.3)	11 (3.8)	19 (5.9)	17 (6.0)	.396	.999
Cirrhosis	642 (71.3)	200 (69.0)	241 (74.8)	201 (71.3)	.264	.357
Portal hypertension	273 (30.5)	94 (32.4)	98 (30.4)	81 (28.7)	.631	.656
Child-Pugh grade B	83 (9.3)	25 (8.6)	39 (12.1)	19 (6.7)	.068	.027
HBeAg (+)	194 (21.7)	55 (19.0)	76 (23.6)	63 (22.3)	.362	.771
Preoperative HBV-DNA load >104 copies/mL	486 (54.4)	129 (44.5)	204 (63.4)	153 (54.3)	<.001	.025
Preoperative anti-HBV therapy	189 (21.1)	50 (17.2)	74 (23.0)	65 (23.0)	.216	.999
Preoperative ALT >80 U/L	145 (16.2)	42 (14.5)	59 (18.3)	44 (15.6)	.412	.388
Preoperative AST >80 U/L	110 (12.3)	27 (9.3)	57 (17.7)	26 (9.2)	.001	.003
Preoperative AFP level >400 μg/L	330 (36.9)	97 (33.4)	147 (45.7)	86 (30.5)	<.001	<.001
Tumor size >5.0 cm	379 (42.4)	88 (30.3)	185 (57.5)	106 (37.6)	<.001	<.001
Multiple tumors	188 (21.0)	42 (14.5)	100 (31.1)	46 (16.3)	<.001	<.001
Macrovascular invasion	33 (3.7)	1 (0.3)	20 (6.2)	12 (4.3)	.001	.363
Microvascular invasion	426 (47.7)	116 (40.0)	185 (57.5)	125 (44.3)	<.001	.001
Satellite nodules	195 (21.8)	38 (13.1)	108 (33.5)	49 (17.4)	<.001	<.001
Poor tumor differentiation	714 (79.9)	211 (72.8)	280 (87.0)	223 (79.1)	<.001	.012
Incomplete tumor encapsulation	524 (58.6)	135 (46.6)	246 (76.4)	143 (50.7)	<.001	<.001
BCLC tumor stage of initial tumor						
BCLC stage A	329 (36.8)	138 (47.6)	66 (20.5)	125 (44.3)	<.001	<.001
BCLC stage B	239 (26.7)	66 (22.8)	105 (32.6)	68 (24.1)		
BCLC stage C	326 (36.5)	86 (29.7)	151 (46.9)	89 (31.6)		
Intraoperative blood loss >400 mL	352 (39.4)	99 (34.1)	161 (50.0)	92 (32.6)	<.001	<.001
Intraoperative blood transfusion	171 (19.1)	38 (13.1)	84 (26.1)	49 (17.4)	<.001	.011
Major hepatectomy	192 (21.5)	38 (13.1)	105 (32.6)	49 (17.40	<.001	<.001
Anatomical liver resection	630 (70.5)	198 (68.3)	236 (73.3)	196 (69.5)	.362	.321
Resection margin <1 cm	300 (33.6)	50 (17.2)	159 (49.4)	91 (32.3)	<.001	<.001

[a]Comparison among patients without recurrence, with early recurrence, and with late recurrence.
[b]Comparison between patients with early and late recurrence.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HBeAg, hepatitis B virus envelope antigen.

or nonanatomical), and the width of resection margin. Portal hypertension was diagnosed by the presence of either esophageal varices or splenomegaly with a decreased platelet count ($\leq 100 \times 10^9$/L). Minor hepatectomy was defined as resection of fewer than three Couinaud's segments, whereas major hepatectomy was defined as resection of three or more segments. Nonanatomical liver resection included a limited resection or wedge resection; anatomical resections were defined by the Brisbane 2000 system.

Postoperative Follow-Up

After hospital discharge, patients were prospectively followed up with physical examination, serum AFP, ultrasonography or contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen, and chest x-ray once every 2 months for the first 6 months and then every 3 months for the next 1.5 years. For patients who were free of HCC recurrence 2 years after surgery, recurrence surveillance was performed at a 6-month interval thereafter. Regular

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Table 2. Comparisons of long-term outcomes and treatment modality for recurrence among patients with early and late recurrence

Outcomes and treatment modality	Overall recurrence (*n* = 604), *n* (%)	Early recurrence (*n* = 322), *n* (%)	Late recurrence (*n* = 282), *n* (%)	*p* value
Period of follow-up after surgery, median (range), months	53.9 (2.3–192.0)	30.5 (2.0–156.5)	88.9 (28.6–192.0)	<.001
Postoperative anti-HBV therapy until recurrence				
Regular	492 (81.5)	268 (83.2)	224 (79.4)	.249
Irregular	112 (18.5)	54 (16.8)	58 (20.6)	
Postoperative HBV reactivation until recurrence	70 (11.6)	25 (7.8)	45 (16.0)	.002
Postoperative recurrence surveillance				
Regular	403 (66.7)	268 (83.2)	135 (47.9)	<.001
Irregular	201 (33.3)	54 (16.8)	147 (52.1)	
Patterns of initial recurrence				
Intrahepatic only	489 (81.0)	232 (72.0)	257 (91.1)	<.001
Extrahepatic only	28 (4.6)	28 (8.7)	0 (0)	
Intrahepatic and extrahepatic	87 (14.4)	62 (19.3)	25 (8.9)	
Extent of initial recurrence				
Within Milan criteria	276 (45.7)	132 (41.0)	144 (51.1)	.014
Beyond Milan criteria	328 (54.3)	190 (59.0)	138 (48.9)	
Treatment modality for initial recurrence				
Potentially curative treatment	248 (41.1)	109 (33.9)	143 (50.7)	<.001
Noncurative treatment	356 (58.9)	213 (66.1)	139 (49.3)	
Mortality during the follow-up	430 (71.2)	263 (81.7)	167 (59.2)	<.001
Cancer-specific mortality	362 (59.9)	225 (69.9)	137 (48.6)	<.001
Non–cancer-specific mortality	68 (12.5)	38 (11.8)	30 (13.5)	.598
Median OS from surgery (95% CI), months	63.1 (57.4–68.8)	30.6 (27.2–33.9)	106.8 (98.3–115.4)	<.001
1-year OS rate, %	92.9	86.6	100.0	
3-year OS rate, %	68.6	64.5	97.2	
5-year OS rate, %	51.2	43.5	81.0	
Median PRS from recurrence diagnosis (95% CI), months	26.7 (23.2–30.1)	19.1 (15.3–22.8)	37.5 (32.2–42.8)	<.001
1-year PRS rate, %	72.5	67.0	79.1	
3-year PRS rate, %	41.4	33.2	51.8	
5-year PRS rate, %	27.6	20.1	37.4	

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; OS, overall survival; PRS, postrecurrence survival.

surveillance included routine abdominal imaging and/or AFP monitoring every 6 months or less before HCC recurrence was diagnosed; irregular surveillance was defined as long surveillance intervals of more than 6 months or diagnosis of HCC recurrence because of symptoms or other unrelated reasons. Oral antiviral therapy with 100 mg lamivudine, 10 mg adefovir dipivoxil, or 0.5 mg entecavir was administrated daily to patients with chronic HBV infection once the preoperative HBV-DNA content was 1,000 copies/mL or greater.

Tumor recurrence was suspected based on appearance of new intra- or extrahepatic tumor lesion(s) that possessed typical imaging characteristics consistent with HCC on contrast-enhanced CT or MRI, with or without an elevation of serum AFP level. Further examinations including positron emission tomography–CT, full-body bone scan or angiography were carried out when there were clinical suspicions of HCC recurrence or distant metastases after surgery. The diagnosis of HCC recurrence was made based on the results of clinical investigations or was confirmed by histological biopsy of re-resected tumor samples. Tumor recurrence was categorized into early and late recurrence using a cutoff value of 2 years. Patients who developed recurrence were treated with re-resection if feasible, liver transplantation, local ablation, transcatheter arterial chemoembolization, radiotherapy, oral sorafenib, or supportive care, depending on the pattern of recurrence, liver functional reserve, and patient general conditions. Re-resection, liver transplantation, and local ablation therapy were defined as potentially curative treatments,

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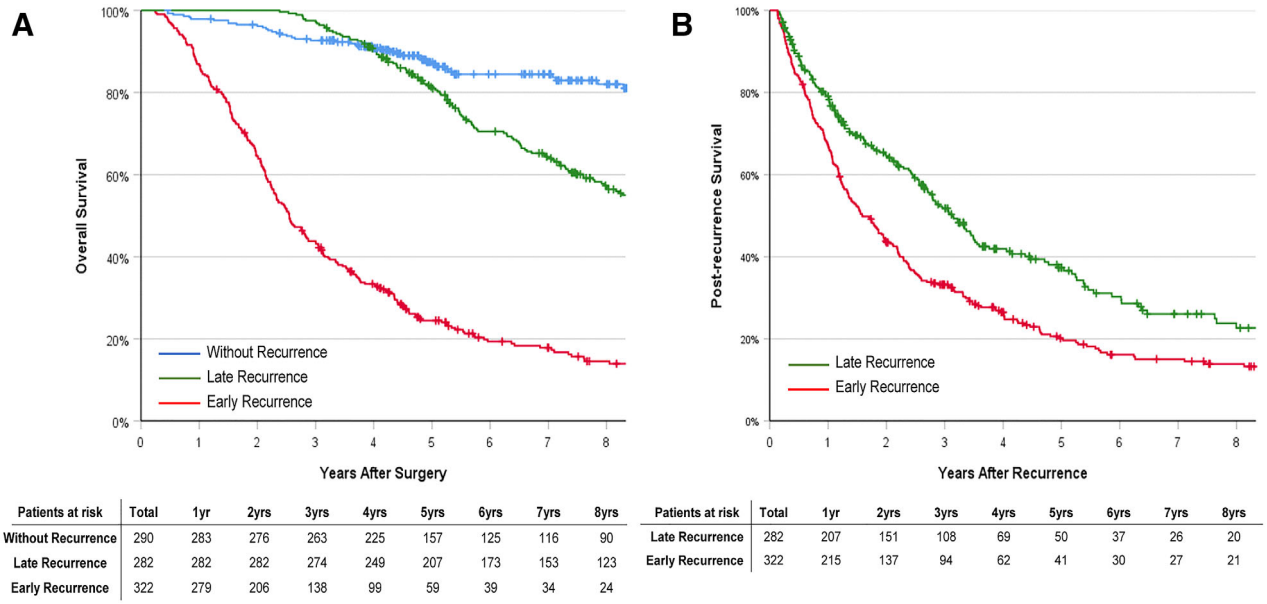

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
Without Recurrence	290	283	276	263	225	157	125	116	90
Late Recurrence	282	282	282	274	249	207	173	153	123
Early Recurrence	322	279	206	138	99	59	39	34	24

Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs
Late Recurrence	282	207	151	108	69	50	37	26	20
Early Recurrence	322	215	137	94	62	41	30	27	21

Figure 2. Kaplan-Meier analysis of overall survival and postrecurrence survival. **(A):** Kaplan-Meier analysis of overall survival in patients without recurrence, patients with early recurrence, and patients with late recurrence after curative liver resection of hepatitis B virus–associated hepatocellular carcinoma: $p < .001$ (without recurrence vs. early recurrence), $p < .001$ (without recurrence vs. late recurrence), and $p < .001$ (early recurrence vs. late recurrence) (log-rank test). **(B):** Kaplan-Meier analysis of postrecurrence survival in patients with early and late recurrence after curative liver resection of hepatitis B virus–associated hepatocellular carcinoma: $p < .001$ (log-rank test).

whereas other treatments were considered as noncurative treatments. To investigate the predictors of postrecurrence survival (PRS) among patients who developed recurrence, data on diagnosis of recurrence, interval to recurrence (early or late recurrence), positivity of HBeAg, HBV-DNA load, cirrhosis, Child-Pugh grading, AFP level, patterns of recurrence (sole intrahepatic, sole extrahepatic, or intrahepatic and extrahepatic), extent of recurrence (within or beyond Milan criteria), treatment modality for recurrence (potentially curative vs. noncurative), and postrecurrence anti-HBV therapy and HBV reactivation were assessed. Overall survival (OS) was calculated from the date of initial liver resection to either the date of death or the date of the last follow-up, whereas PRS was calculated from the date of the diagnosis of initial recurrence to the date of death or the date of the last follow-up.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (range). Categorical variables were reported as number (*n*) or proportion (%). Student's *t* test was used for comparisons of continuous variables when applicable; otherwise, the Mann-Whitney *U* test was applied. Categorical variables were compared with the χ^2 test with the Yates correction or the Fisher's exact test, as appropriate. The Kaplan-Meier method was used to compare the OS and PRS rates. Univariable and multivariable Cox proportional hazard regression analyses were performed to identify risk factors contributing to early and late recurrence, as well as to evaluate predictors associated with PRS among patients who developed recurrence. The statistical analyses were performed using the SPSS software version 25.0 (SPSS, Chicago, IL). A two-tailed *p* value <.05 was considered statistically significant.

Results

HCC Recurrence During Follow-Up

Overall 2,046 patients who underwent curative-intent liver resection for HCC were screened for inclusion (supplemental online Fig. 1). The final analytic cohort included 894 patients with HBV-associated HCC. With a median follow-up period of 53.9 months, 604 (67.6%) of 894 patients developed recurrence. Among the 604 patients with recurrence, 322 (53.3%) and 282 (46.7%) had early and late recurrence, respectively. Among the remaining 290 patients who did not develop recurrence before their death or the last follow-up, 68 experienced a non–cancer-specific death (14 within 2 years of resection and 54 after 2 years of resection), and 222 were alive and recurrence-free at the last follow-up.

The estimated overall recurrence curve after HCC resection is depicted in Figure 1. Of note, there was an initial peak of recurrence that occurred at 1–2 years after surgery (approximately 23% per year). The incidence of recurrence gradually decreased until 2–3 years postoperative. Interestingly, the rate then increased again with a second peak at 4–5 years after surgery (approximately 35% per year).

Clinicopathological and Operative Variables

Comparisons of clinicopathological and operative variables among patients with early and late recurrence, as well as patients without recurrence, are demonstrated in Table 1. Of note, there were differences among the three groups related to host-, hepatitis-, and operation-specific factors, as well as almost all tumor-related factors. Compared with patients who had late recurrence, patients with early recurrence more often had Child-Pugh grade B, a

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Table 3. Univariate and multivariate Cox regression analyses predicting early recurrence in 894 patients who underwent liver resection of hepatitis B virus–associated hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV *p* value	MV HR (95% CI)	MV *p* value[a]
Age	>60 vs. ≤60 years	1.055 (0.796–1.400)	.708		
Sex	Male vs. female	1.100 (0.755–1.602)	.619		
ASA score	>2 vs. ≤2	0.806 (0.560–1.162)	.248		
Obesity	Yes vs. no	1.824 (1.213–2.744)	.004	NS	NS
Diabetes mellitus	Yes vs. no	1.194 (0.751–1.899)	.453		
Cirrhosis	Yes vs. no	1.207 (0.938–1.552)	.143		
Portal hypertension	Yes vs. no	0.983 (0.775–1.246)	.885		
Child-Pugh grade	B vs. A	1.397 (0.999–1.952)	.051	NS	NS
Preoperative ALT	>80 vs. ≤80 U/L	1.197 (0.903–1.588)	.212		
Preoperative AST	>80 vs. ≤80 U/L	1.804 (1.355–2.402)	<.001	NS	NS
Preoperative HBV-DNA load	$>10^4$ vs. $\leq 10^4$ copies/mL	1.549 (1.235–1.944)	<.001	1.557 (1.239–1.956)	<.001
HBeAg (+)	Yes vs. no	1.171 (0.905–1.515)	.229		
Preoperative anti-HBV therapy	No vs. yes	1.278 (0.714–1.987)	.578		
Preoperative AFP level	>400 vs. ≤400 μg/L	1.664 (1.336–2.073)	<.001	1.419 (1.133–1.777)	.002
Tumor size	>5.0 cm vs. ≤5.0 cm	2.188 (1.754–2.730)	<.001	1.512 (1.196–1.910)	.001
Multiple tumors	Yes vs. no	2.012 (1.589–2.549)	<.001	1.323 (1.024–1.709)	.032
Macrovascular invasion	Yes vs. no	2.253 (1.433–3.543)	<.001	1.904 (1.522–2.381)	<.001
Microvascular invasion	Yes vs. no	1.645 (1.319–2.051)	<.001	1.394 (1.113–1.745)	.004
Satellite nodules	Yes vs. no	2.283 (1.810–2.878)	<.001	1.736 (1.368–2.204)	<.001
Poor tumor differentiation	Yes vs. no	1.897 (1.372–2.624)	<.001	NS	NS
Incomplete tumor encapsulation	Yes vs. no	2.716 (2.099–3.513)	<.001	2.057 (1.579–2.679)	<.001
Resection margin	<1 cm vs. ≥1 cm	2.383 (1.915–2.966)	<.001	1.942 (1.553–2.430)	<.001
Intraoperative blood loss	>400 vs. ≤400 mL	1.730 (1.391–2.153)	<.001	NS	NS
Intraoperative blood transfusion	Yes vs. no	1.695 (1.322–2.174)	<.001	NS	NS
Extent of hepatectomy	Major vs. minor	2.214 (1.753–2.796)	<.001	NS	NS
Type of resection	Anatomical vs. nonanatomical	0.870 (0.680–1.114)	.269		
Postoperative anti-HBV therapy until recurrence or last follow-up	No/irregular vs. regular	0.593 (0.221–1.592)	.299		
Postoperative HBV reactivation until recurrence or last follow-up	Yes vs. no	0.918 (0.707–1.191)	.520		

[a]Those variables found significant at $p < .1$ in univariable analyses were entered into multivariable Cox regression analyses.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; CI, confidence interval; HBeAg, hepatitis B virus envelope antigen; HBV, hepatitis B virus; HR, hazard ratio; MV, multivariate; NS, not significant; UV, univariate.

higher preoperative HBV-DNA load, AST level and AFP level, larger tumor size, multiple tumors, microvascular invasion, satellite nodules, poor tumor differentiation, incomplete tumor encapsulation, more intraoperative blood loss, more blood transfusions, a higher proportion of major hepatectomy, and a smaller width of resection margin. Related to the initial tumor staging of HCC, the proportion of intermediate or advanced HCC (BCLC stage B or C) among patients with early recurrence was higher than among patients who had late recurrence ($p < .001$).

Long-Term Outcomes and Treatment Modality for Recurrence

Comparison of long-term outcomes, treatment modality for recurrence, and other relevant prognostic variables during follow-up among patients with early versus late recurrence are noted in Table 2. With regard to hepatitis-related factors, although there was no difference in the proportion of patients who received postoperative regular anti-HBV therapy until recurrence between the two groups (83.2% vs. 79.4%, $p = .249$), the incidence of postoperative HBV reactivation among patients with early recurrence was lower than among patients who had late recurrence (7.8% vs. 16.0%, $p < .001$). Among 282 patients with late recurrence, there were 257 (91.1%) patients who developed intrahepatic-only recurrence, which was higher than the incidence among patients with early recurrence (72.0%, 232/322, $p < .001$). Moreover, the incidence of initial recurrence within Milan criteria among patients with late recurrence was also higher than that noted in patients with early recurrence (51.1% vs. 41.1%,

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Table 4. Univariate and multivariate Cox regression analyses predicting late recurrence in 558 patients who were free of early recurrence at 2 years after liver resection of hepatitis B virus–associated hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV *p* value	MV HR (95% CI)	MV *p* value[a]
Age	>60 vs. ≤60 years	1.036 (0.757–1.417)	.826		
Sex	Male vs. female	1.309 (1.056–1.998)	.040	1.750 (1.017–3.011)	.043
ASA score	>2 vs. ≤2	0.967 (0.669–1.398)	.860		
Obesity	Yes vs. no	1.227 (0.969–1.554)	.090	NS	NS
Diabetes mellitus	Yes vs. no	1.447 (0.886–2.363)	.140		
Cirrhosis	Yes vs. no	2.537 (1.252–5.142)	.010	1.302 (1.022–1.658)	.032
Portal hypertension	Yes vs. no	0.914 (0.706–1.184)	.497		
Child-Pugh grade	B vs. A	1.103 (0.852–1.428)	.456		
Preoperative ALT	>80 vs. ≤80 U/L	0.953 (0.691–1.315)	.769		
Preoperative AST	>80 vs. ≤80 U/L	0.946 (0.632–1.417)	.789		
Preoperative HBV-DNA load	$>10^4$ vs. $\leq 10^4$ copies/mL	1.345 (1.064–1.701)	.013	1.463 (1.095–1.955)	.010
HBeAg (+)	Yes vs. no	1.143 (0.863–1.514)	.350		
Preoperative anti-HBV therapy	No vs. yes	1.262 (0.941–1.691)	.120		
Preoperative AFP level	>400 vs. ≤400 μg/L	0.937 (0.727–1.208)	.616		
Tumor size	>5.0 cm vs. ≤5.0 cm	1.288 (1.012–1.640)	.039	1.295 (1.017–1.650)	.036
Multiple tumors	Yes vs. no	1.365 (0.995–1.874)	.054	NS	NS
Macrovascular invasion	Yes vs. no	4.504 (2.516–8.065)	<.001	5.480 (3.012–9.973)	<.001
Microvascular invasion	Yes vs. no	2.113 (1.643–2.718)	<.001	1.554 (1.135–2.129)	.006
Satellite nodules	Yes vs. no	1.499 (1.101–2.042)	.010	1.347 (1.007–1.800)	.044
Poor tumor differentiation	Yes vs. no	1.341 (1.006–1.787)	.045	NS	NS
Incomplete tumor encapsulation	Yes vs. no	1.113 (0.881–1.407)	.368		
Resection margin	<1 cm vs. ≥1 cm	1.191 (0.940–1.508)	.147		
Intraoperative blood loss	>400 vs. ≤400 mL	1.002 (0.781–1.286)	.987		
Intraoperative blood transfusion	Yes vs. no	1.257 (0.924–1.712)	.146		
Extent of hepatectomy	Major vs. minor	1.292 (0.949–1.759)	.104		
Type of resection	Anatomical vs. nonanatomical	0.957 (0.743–1.234)	.735		
Postoperative anti-HBV therapy until recurrence or last follow-up	No/irregular vs. regular	1.872 (1.092–3.207)	.023	1.704 (1.036–2.802)	.036
Postoperative HBV reactivation until recurrence or last follow-up	Yes vs. no	1.296 (0.909–1.847)	.152		

[a]Those variables found significant at $p < .1$ in univariable analyses were entered into multivariable Cox regression analyses.
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; CI, confidence interval; HBeAg, hepatitis B virus envelope antigen; HBV, hepatitis B virus; HR, hazard ratio; MV, multivariate; NS, not significant; UV, univariate.

$p = .014$). Similar results were noted among patients undergoing potentially curative treatment for initial recurrence (patients with late recurrence: 50.7% vs. patients with early recurrence: 33.9%, $p < .001$). In addition, the proportion of patients with overall mortality and cancer-specific mortality among patients with early recurrence was higher than among patients with late recurrence (81.7% and 69.9% vs. 59.2% and 48.6%, both $p < .001$).

OS for patients without recurrence, as well as for patients with early and late recurrence, are demonstrated in Figure 2A. As expected, among the three groups, OS was highest in patients without recurrence, followed by patients with late recurrence; the worst OS was noted among patients with early recurrence (all $p < .001$). As noted in Table 2, the 1-, 3- and 5-year OS for patients with early recurrence was 86.6%, 64.5%, and 43.5%, which was lower than among patients with late recurrence (100%, 97.2%, and 81.0%, $p < .001$).

Comparison of PRS among patients with early and late recurrence are noted in Table 2 and Figure 2B. The median PRS of patients with early recurrence was worse than patients with late recurrence (19.1 vs. 37.5 months, $p < .001$). Meanwhile, 1-, 3-, and 5-year PRS among patients with early recurrence was 67.0%, 33.2%, and 20.1%, which was lower than the corresponding PRS in patients with late recurrence (79.1%, 51.8%, and 37.4%, $p < .001$).

Risk Factors of Early and Late Recurrence

Table 3 and Table 4 summarize the results of univariable and multivariable Cox regression analyses predicting early and late recurrence after curative liver resection for HBV-

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Table 5. Univariate and multivariate Cox regression analyses predicting postrecurrence survival in 604 patients who developed recurrence after curative liver resection for hepatitis B virus–associated hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV *p* value	MV HR (95% CI)	MV *p* value[a]
BCLC tumor staging of the initial tumor	BCLC stage B/C vs. A	1.238 (0.994–1.542)	.057	NS	NS
Interval to recurrence	Early recurrence vs. late recurrence	1.580 (1.301–1.919)	<.001	1.361 (1.094–1.692)	.006
Postoperative recurrence surveillance	Irregular vs. regular	1.371 (1.133–1.659)	.001	1.293 (1.059–1.578)	.012
Age at diagnosis of recurrence	>60 vs. ≤60 years	1.024 (0.806–1.299)	.847		
Sex	Male vs. female	0.986 (0.714–1.360)	.930		
HBeAg (+) at diagnosis of recurrence	Yes vs. no	0.891 (0.562–1.413)	.623		
HBV-DNA load at diagnosis of recurrence	$>10^4$ vs. $\leq 10^4$ copies/mL	1.032 (0.850–1.252)	.751		
Cirrhosis at diagnosis of recurrence	Yes vs. no	1.193 (0.956–1.488)	.118		
Portal hypertension at diagnosis of recurrence	Yes vs. no	1.310 (1.069–1.605)	.009	1.248 (1.028–1.516)	.025
Child-Pugh grade at diagnosis of recurrence	B/C vs. A	1.356 (0.924–1.578)	.229		
AFP level at diagnosis of recurrence	>400 vs. ≤400 μg/L	1.357 (1.102–1.671)	.004	1.325 (1.086–1.615)	.006
Patterns of recurrence	Only intrahepatic vs. extrahepatic ± intrahepatic	1.442 (1.192–1.744)	<.001	NS	NS
Extent of recurrence	Beyond vs. within Milan criteria	1.814 (1.252–2.628)	.001	1.359 (1.115–1.654)	.002
Treatment modalities for recurrence	Noncurative vs. potentially curative	1.769 (1.565–1.998)	<.001	1.517 (1.253–1.835)	<.001
Postrecurrence anti-HBV therapy	Irregular vs. regular	0.748 (0.600–0.933)	.010	NS	NS
Postrecurrence HBV reactivation	Yes vs. no	1.409 (0.947–2.097)	.090	NS	NS

[a]Those variables found significant at $p < .1$ in univariable analyses were entered into multivariable Cox regression analyses.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBeAg, hepatitis B virus envelope antigen; HBV, hepatitis B virus; HR, hazard ratio; MV, multivariate; NS, not significant; UV, univariate.

associated HCC, respectively. On multivariable Cox regression analyses, independent risk factors associated with early recurrence included preoperative HBV-DNA load $>10^4$ copies/mL, preoperative AFP level >400 μg/L, tumor size >5 cm, multiple tumors, macrovascular and microvascular invasion, satellite nodules, incomplete tumor encapsulation, and resection margin <1 cm. Independent risk factors associated with late recurrence included male sex, cirrhosis, preoperative HBV-DNA load $>10^4$ copies/mL, tumor size >5 cm, macrovascular and microvascular invasion, satellite nodules, and irregular postoperative anti-HBV therapy.

Predictors of PRS in Patients with Recurrence

Univariable and multivariable Cox regression analyses were also performed to identify predictors associated with PRS in 604 patients who developed recurrence after curative liver resection for HBV-associated HCC. As noted in Table 5, independent risk factors predicting worse PRS included early recurrence (≤2 years after surgery; hazard ratio [HR], 1.361; 95% confidence interval [CI], 1.094–1.692; $p = .006$), postoperative irregular recurrence surveillance (HR, 1.293; 95% CI, 1.059–1.578; $p = .012$), presence of portal hypertension at diagnosis of recurrence (HR, 1.248; 95% CI, 1.028–1.516; $p = .025$), AFP level >400 μg/L at diagnosis of recurrence (HR, 1.325; 95% CI, 1.086–1.615; $p = .006$), recurrent HCC beyond Milan criteria (HR, 1.359; 95% CI, 1.115–1.654; $p = .002$), and noncurative treatments for recurrence (HR, 1.517; 95% CI, 1.253–1.835; $p < .001$).

Discussion

In this large study from a prospectively collected database, the risk factors, patterns, and long-term survival outcomes of patients with both early and late recurrence after curative resection for HBV-associated HCC were evaluated. Using multivariable Cox regression analyses, host-, hepatitis-, tumor-, and operation-related risk factors were found to be associated with either early or late recurrence. Several risk factors contributing to early recurrence were related to initial tumor characteristics (e.g., preoperative AFP level >400 μg/L, tumor

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size >5 cm, multiple tumors, macrovascular and microvascular invasion, satellite nodules, and incomplete tumor encapsulation), whereas fewer were related to the operation (resection margin <1 cm) or hepatitis (preoperative HBV-DNA load $>10^4$ copies/mL). In addition, multiple factors were associated with late recurrence including initial tumor characteristics (e.g., tumor size >5 cm, macrovascular and microvascular invasion, and satellite nodules), host-related factors (male sex and cirrhosis), and hepatitis-related factors (preoperative HBV-DNA load $>10^4$ copies/mL and postoperative no/irregular anti-HBV therapy). In addition, patterns and extent of initial recurrence were different among patients with early and late recurrence, as patients with early recurrence had a lower proportion of intrahepatic-only recurrence (72.0% vs. 91.1%, $p < .001$) and recurrence within Milan criteria (41.0 vs. 51.1%, $p = .014$), as well as a lower chance of receiving potentially curative treatments for recurrence (33.9% vs .50.7%, $p < .001$) and a worse median PRS (19.1 vs. 37.5 months, $p < .001$). Moreover, early recurrence, post operative irregular recurrence surveillance, presence of portal hypertension at diagnosis of recurrence, AFP level >400 μg/L at diagnosis of recurrence, recurrent HCC beyond Milan criteria, and noncurative treatments for recurrence were independently associated with worse PRS among patients with recurrence after curative resection for HBV-associated HCC. In turn, data from the current study may provide insights into different biological origin and behavior of early versus late recurrence after resection for HBV-associated HCC, which could be helpful to inform decision making about treatment options for recurrent HCC, as well as rational strategies for recurrence surveillance after HCC resection.

After the early peak of recurrence (at around 1 year postoperatively), the recurrence rate decreased over the next 2 years, followed by a second peak 4–5 years postoperatively (Fig. 1). This finding was most likely to be related to recurrence caused by occult micrometastasis of the initial HCC being mainly responsible for the early peak. In contrast, the majority of the second recurrence peak was likely to be attributable to new tumor(s) developing de novo with different clonal origins. These results were consistent with the data reported by Imamura et al. [10]. In our study, we also identified independent risk factors associated with early recurrence after HCC resection to be mainly related to the initial tumor characteristics and operative variables. In contrast, cirrhosis and male sex were independent risk factors of late recurrence, which supported the hypotheses that late recurrence is more likely to be due to multicentric tumors or de novo cancer formation from the underlying liver background of hepatitis and cirrhosis, as well as the potentially tumorigenic effects of sex hormones [6, 7, 14, 18–20]. Differences in risk factors for late recurrence highlight the need for close and stringent recurrence surveillance among male patients with cirrhosis in the late postoperative period of follow-up [15]. In addition, postoperative regular anti-HBV therapy was independently associated with reduced late recurrence, which could be explained by suppression of viral replication and inflammation within the liver microenvironment [8, 17, 21, 22]. In aggregate, the data emphasized the importance of regular postoperative antiviral therapy in preventing late HCC recurrence after curative resection for HBV-associated HCC.

In contrast to some previous studies [5–7], tumor size >5 cm, multiple tumors, macro- and microvascular invasion, and satellite nodules were independent risk factors of late recurrence, suggesting that late recurrence was also correlated with the initial tumor. The use of 2 years as the cutoff value to differentiate metastasis from the initial tumor from de novo tumors remains controversial. Actual examination of clonal differences within the tumors is difficult from a practical point of view in the clinical setting, and there is a lack of reliable and clinically applicable markers. Further novel histopathological and genetic tests of both the initial and recurrent tumors are needed to better define whether recurrent tumors originate from the initial tumor or represent a clonally different lesion [23, 24].

Notedly, a high preoperative HBV-DNA load was identified as an important risk factor associated with both early and late recurrence. The relationship between a high HBV-DNA load and late recurrence has clinical "face validity" [8, 16, 17, 22], as sustained viremia and succedent active viral replication may contribute to HCC development by generating a carcinogenic microenvironment in the liver, known as the "field effect" [16]. Specifically, integration of subgenomic HBV-DNA fragments into the host hepatic cells may activate cellular genes directly to allow selective growth advantages. The production of HBV X-protein could then act as a trans-activator on various cellular genes for HCC development [25, 26]. Continuing HBV replication could, in turn, induce chronic hepatitis inflammation and fibrosis and alter the production of alpha-2 macroglobulin and transform the growth factor-beta1, thereby leading to carcinogenesis [27]. The upregulation of adhesion molecules on the cells lining the sinusoids may also enhance tumor development and spread [28]. However, the effect of a high preoperative HBV-DNA load on early recurrence had not been well defined previously. One study suggested a high preoperative HBV-DNA load to be an independent risk factor of microvascular invasion of HCC, and preoperative antiviral therapy administered more than 90 days before surgery was associated with a reduced incidence of microvascular invasion and early tumor recurrence at 6 months, 1 year, and 2 years after surgery [29]. Other studies have also revealed that the HBV-initiated tumorigenic process may play a role in development of vascular invasion of HCC [30, 31]. These data support an association of a high preoperative HBV-DNA load and early recurrence of HCC. Because HBV-mediated inflammatory response, genome integration, and mutations play central roles in HCC development, patients with a high HBV-DNA load should be followed up closely. These patients should be given lifelong antiviral therapy to suppress HBV replication in an attempt to prevent HCC recurrence. A recent randomized controlled trial demonstrated that antiviral therapy for patients with a low preoperative HBV-DNA load not only prevented HBV reactivation but also reduced tumor recurrence and improved postoperative survival [32]. These data suggested that even for patients with a low

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preoperative HBV-DNA load, early and regular antiviral treatment after HCC resection should be given.

Understanding the patterns, extents, and long-term prognosis of early and late recurrence after HCC resection can assist in designing surveillance strategies. The liver is recognized as the predominant organ involved in initial recurrence after HCC resection [6, 12]. In our study, compared with patients who had late recurrence, patients with early recurrence had a lower proportion of intrahepatic-only recurrence (72.0% vs. 91.1%, $p < .001$) and recurrence within the Milan criteria (41.0 vs. 51.1%, $p = .014$). Moreover, among patients with late recurrence, there was no patient who had sole extrahepatic metastasis without intrahepatic recurrence. These data indicated that screening for late recurrence after 2 years of surgery should focus on intrahepatic recurrence, whereas screening for extrahepatic metastasis using skeletal emission computerized tomography and chest CT may be unnecessary for patients who have no intrahepatic recurrence. According to our data, the time to recurrence and the patterns of recurrence should be taken into account to establish an individualized and a more cost-effective surveillance strategy for patients with HCC after surgery.

In this study, the long-term survival of patients with early recurrence was worse than that of patients with late recurrence (median PRS, 19.1 vs. 37.5 months, $p < .001$). For patients with early recurrence, the higher occurrence of extrahepatic recurrence indicated a worse prognosis with no chance to undergo any curative treatment. On the other hand, patients with late recurrence had a better chance to undergo potentially curative-intent therapy for recurrent HCC (50.7% vs. 33.9%, $p < .001$). Meanwhile, as most recurrent lesions that developed within a short time after the initial resection were more likely to be related to intrahepatic occult micrometastasis, even if the recurrent lesions could be resected with curative intent, the tumor re-relapse is expected to be high because of the possibility of other undetectable micrometastases. Thus, a good selection of suitable treatment modalities for the initial recurrence and appropriate selection of patients who will benefit from treatment are of paramount clinical importance. Our study also identified irregular postoperative recurrence surveillance to be an independent risk factor of PRS for patients with recurrence, suggesting that a stringent recurrence surveillance program on follow-up is helpful to detect and treat recurrent lesions early to improve the long-term prognosis. In clinical practice, many patients do not take surveillance seriously, and they lose the chance to undergo curative treatment when symptoms develop.

The present study had several limitations. First, inherent biases are inevitable because of the retrospective nature of the study. Second, because of medical insurance payment restrictions, some hepatitis-related indicators were also not routinely tested, such as HBV genotypes [33], quantitative detection of HBsAg [17], intrahepatic covalently closed circular DNA [34], and precore and basal core promoter mutations in the HBV genome [35]. These indicators have previously been reported to show some association with recurrence after resection of HBV-associated HCC. Third, this study was conducted on HBV-related HCC. The results of this study may not be applied to other etiologies of HCC. Lastly, further novel histopathological examinations and genetic tests on both the initial and recurrent tumors are worth carrying out to find out whether recurrent tumors originate from micrometastasis of the initial tumors or de novo second primary HCCs.

Conclusion

Early and late recurrence after resection of HBV-associated HCC were related to different risk factors. A high preoperative HBV-DNA load was an independent hepatitis-related risk factor of both early and late recurrence of HBV-associated HCC, whereas regular postoperative antiviral therapy was associated with a decreased late recurrence rate. In addition, early recurrence, irregular recurrence surveillance, presence of portal hypertension, recurrent HCC beyond the Milan criteria, noncurative treatments for recurrence, a high HBV-DNA load, and AFP level at diagnosis of recurrence were independently associated with worse PRS in patients who developed recurrence after curative resection of HBV-associated HCC.

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Disclosures

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