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ORIGINAL ARTICLE

# Identification of Actual 10-Year Survival After Hepatectomy of HBV-Related Hepatocellular Carcinoma: a Multicenter Study

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## Abstract

**Background** Hepatitis B virus (HBV) infection is the leading cause of hepatocellular carcinoma (HCC) worldwide. The aim of the study was to identify the incidence and predictive factors of actual 10-year survival following liver resection of HBV-related HCC.

**Methods** A Chinese multicenter database of patients undergoing curative hepatectomy of HBV-related HCC was reviewed. Patients who survived ≥ 10 years and patients who died < 10 years after surgery were compared and analyzed. Univariable and multivariable regression analyses were performed to identify predictive factors associated with 10-year survival.

**Results** Among all enrolled 1016 patients, the actuarial 10-year survival rate was 24.1%, while the actual 10-year survival rate was 16.6%. There were 169 patients who survived at least 10 years after surgery and 688 who died within 10 years from surgery. These patients constituted the study population of this study. Multivariable regression analysis revealed that cirrhosis, preoperative HBV viral load > $10^4$ copies/mL, maximum tumor size > 5 cm, multiple tumors, macroscopic and microscopic vascular invasion, postoperative HBV reactivation, and early recurrence (< 2 years after surgery) were independent risk factors associated with actual 10-year survival, while postoperative antiviral therapy, regular recurrence surveillance, and curative treatments for initial recurrence were independent protective factors.

**Conclusions** The actual 10-year survival after curative resection of HBV-related HCC was calculated to be 16.6%. Postoperative antiviral therapy and regular recurrence surveillance were independent protective factors associated with actual 10-year survival after liver resection of HBV-related HCC.

**Keywords** Hepatocellular carcinoma · Hepatectomy · Overall survival · Hepatitis B virus

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**Abbreviations**

| | |
|---|---|
| HCC | Hepatocellular carcinoma |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| BMI | Body mass index |
| ASA | American Society of Anesthesiologists |
| AST | Aspartate transaminase |
| ALT | Alanine aminotransferase |
| AFP | Alpha-fetoprotein |
| CT | Computed tomography |
| MRI | Magnetic resonance imaging |
| TACE | Transcatheter arterial chemoembolization |
| SD | Standard deviation |
| OR | Odds ratios |
| 95% CI | 95% confidence interval |

## Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent and detrimental malignancies worldwide.[1,2] China alone accounts for more than half of HCC cases.[3] The prevalence of hepatitis B virus (HBV) infection is the leading cause of HCC, especially in China, which accounts for more than 80% of all HCC cases in Chinese population.[4,5] For patients with early stage HCC, the most commonly used treatment is liver resection, which has a 5-year survival rate of around 70%.[6–9] In selected patients with locally more advanced HCC, favorable survival benefits can still be obtained from liver resection, provided that the tumor is resectable and the residual liver reserve is adequate.[10–14] As recognized by numerous studies, liver- and tumor-related characteristics such as cirrhosis, tumor size, tumor number, and vascular invasion have been demonstrated as definite risk factors associated with long-term survival after curative resection of HCC.[15,16] The Kaplan-Meier method of actuarial survival analysis is applied in most of these studies. However, given this method tends to overestimate survival outcomes as a result of censorship of data and subgroup analysis, the actual long-term survival rate after resection of HCC is significantly inferior to reported actuarial survival rates. A systematic review which enrolled 14 studies revealed that the actual 10-year survival rate following resection of HCC was 7.2%, whereas the actuarial survival quoted from the same study was 26.8%.[17]

Recently, several investigations have been emphasized on actual long-term (10 years) survival following liver resection of HCC.[18–23] Zheng et al.[18] found that actual 10-year survival was associated with smaller, solitary tumor without vascular invasion, while Koda et al.[23] identified that sustained virologic response and good liver function were protective prognostic factors associated with actual 10-year survival after resection of hepatitis C virus (HCV)-related HCC. However, there was still no investigation focused on the actual 10-year survival after liver resection of HBV-related HCC. Given the predominance of HBV-related HCC all over the world, it is essential to investigate the incidence and predictive factors of the actual 10-year survival following resection of HBV-related HCC.

Based on a Chinese multicenter large cohort, this study aimed to profile the clinical and pathological factors on the association with 10-year actual survival after curative resection of HBV-related HCC, and to identify those predictive factors of actual 10-year survival with a special reference to HBV status, antiviral therapy, and postoperative recurrence surveillance.

## Patients and Methods

### Patients

A multicenter database of patients who underwent curative-intent liver resection of initial HCC from January 2000 to December 2009 at seven Chinese hospitals was retrospectively reviewed and analyzed. These seven hospitals were the Eastern Hepatobiliary Surgery Hospital, the People's Hospital of Hunan Province, the Mengchao Hepatobiliary Hospital, the Pu'er People's Hospital, the Fourth Hospital of Harbin, the Liuyang People's Hospital, and the Ziyang First People's Hospital. The diagnosis of HCC was confirmed by postoperative pathological examination. The inclusion criteria for the study were as follows: (1) had HBV infection which was defined as a positive serology of hepatitis B surface antigen (HBsAg), (2) without any previous anti-HCC treatment before liver resection, (3) underwent curative liver resection of HCC, which was defined as R0 resection, and (4) had a complete record on those essential prognostic variables. The exclusion criteria were as follows: (1) had concurrent HCV infection which was defined as positive serum HCV antibody; (2) underwent palliative liver resection, i.e., R1 or R2 resection; (3) had recurrent HCC, ruptured HCC, or combined HCC-cholangiocarcinoma; (4) without preoperative HBV-DNA test; and (5) had missing data on essential prognostic variables. This study was censored on June 30, 2018. Informed consent for the data to be used for clinical researches was obtained from all enrolled patients. This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of all the seven enrolled hospitals.

### Clinicopathological and Operative Variables

The patients' demographic characteristics included sex, age, diabetes mellitus history, body mass index (BMI), and American Society of Anesthesiologists (ASA) score. The clinicopathological characteristics included absence/presence of cirrhosis or portal hypertension, Child-Pugh grading,

preoperative serum hepatitis B e Antigen (HBeAg) positivity, preoperative HBV-DNA load, alanine transaminase (ALT), aspartate aminotransferase (AST) and alpha-fetoprotein (AFP) levels within a week before surgery, maximum tumor size, solitary/multiple tumors, satellite nodules, macroscopic or microscopic vascular invasion, and tumor differentiation. Cirrhosis was detected by histopathological examination, and portal hypertension was confirmed as the presence of either esophageal varices, or splenomegaly along with a decline in platelet count ($\leq 100 \times 10^9$/L). The operative variables consisted of intraoperative blood loss, blood transfusion, extent of hepatectomy, and patterns of liver resection. Major hepatectomy involved three or more Couinaud liver segments, while minor hepatectomy was defined as resection of fewer than three segments. Anatomical resections were defined using the Brisbane 2000 Nomenclature of Liver Anatomy and Resections,[24] and nonanatomical resections indicated wedge or limited resection.

### Use of Antiviral Therapy and Follow-up

Once patient's preoperative HBV-DNA test was revealed as ≥ 1000 copies/mL, adjuvant antiviral therapy with lamivudine 100 mg, adefovir dipivoxil 10 mg, or entecavir 0.5 mg orally daily was commenced immediately or after discharge for some voluntary patients under their consent. For patients with renal insufficiency, the daily lamivudine or adefovir dipivoxil dose was adjusted according to creatinine clearance.

Patients were prospectively followed up at each center using a surveillance strategy adopted by all the hospitals for recurrence and HBV serological status. After discharge, patients were followed up using serum AFP level, serum HBV-DNA test, ultrasonography or contrast-enhanced computed tomography (CT) scan, or magnetic resonance imaging (MRI) of the chest and abdomen once every 2 months for 6 months, and then once every 3 months for the next one and a half years. Recurrence surveillance at a 6-monthly interval was carried out on patients who were alive and recurrence-free 2 years after surgery. Regular recurrence surveillance was defined as abdominal imaging and/or AFP surveillance every 6 months, or within 6 months prior to the diagnosis of HCC recurrence, while irregular recurrence surveillance was defined as surveillance with intervals greater than 6 months, or diagnosis of HCC recurrence because of symptoms, or because the patients were investigated for other reasons. Tumor recurrence was suspected with progressive elevation of serum AFP levels and ultrasonographic detection of a new liver lesion. The diagnosis was made when dynamic CT scan or MRI showed contrast enhancement in the arterial phase and wash out in the venous phase, or when hepatic angiography disclosed high tumor vascularity. Once tumor recurrence was suspected, patients were hospitalized to confirm the diagnosis. Appropriate management included re-resection, liver transplantation, local ablation therapy, transcatheter arterial chemoembolization (TACE), molecular targeting therapy, radiotherapy, and supportive therapy. Re-resection, liver transplantation, and local ablation therapy were considered as curative treatments, while the other treatments were considered as non-curative. Actuarial survival was defined as the time interval between the date of surgery and the date of death, which were calculated by the Kaplan-Meier method.

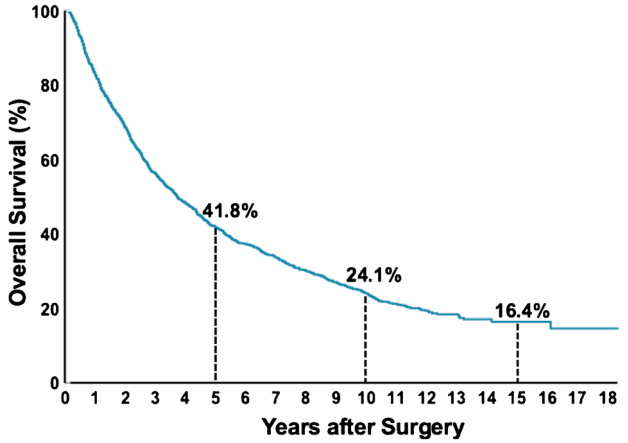
### Statistical Analysis

The patients' clinicopathological and operative variables were summarized using frequency and percentage for categorical covariates and mean ± standard deviation (SD) or median (range) for continuous covariates. Categorical and continuous covariates were compared using the Fisher exact test and the Wilcoxon rank-sum test, respectively.

The actuarial survival was calculated based on the Kaplan-Meier method, while the actual survival was indicated by the number of patients alive at 10 years divided by the number of patients enrolled. The analytic cohort was categorized into patients who survived ≥ 10 years after surgery (the 10-year survival group) vs. patients who died < 10 years from the date of surgery (the 10-year nonsurvival group). Univariable and multivariable logistic regression analyses were performed to identify the associations between potentially important clinical factors and the actual 10-year survival after resection of HBV-related HCC. The coefficients from the logistic regression models were subsequently reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical analyses were performed using the SPSS software version 25.0 (SPSS, Chicago, IL, USA). *P* values were two-sided and < 0.05 were considered statistically significant.

## Results

During the time period, there were 1016 patients with chronic HBV infection undergoing curative resection who met the inclusion criteria. Given that the primary endpoint of our study was the actual 10-year survival, 159 patients who were still alive at the last follow-up but with a follow-up of less than 10 years after surgery were excluded. The remaining 857 patients constituted the study population. There were 169 patients who survived ≥ 10 years (19.7%, the 10-year survival group) and 688 who died < 10 years after surgery (80.3%, the 10-year nonsurvival group). In the entire cohort of those patients undergoing liver resection of HBV-related HCC, the actuarial 10-year survival rate was 24.1% (Fig. 1), while the actual 10-year survival rate was 16.6%.




| | Median OS (months) | 1-year OS (%) | 5-year OS (%) | 10-year OS (%) |
|---|---|---|---|---|
| Total patients (n=1016) | 44.8 (39.9-49.7) | 83.2 | 41.8 | 24.1 |

**Fig. 1** Cumulative incidence of overall survival (OS) curves in the entire cohort

## Comparisons Between the 10-Year Survival and Nonsurvival Groups

Comparisons of the patients' clinicopathological variables between the 10-year survival and nonsurvival groups were illustrated in Table 1. There were no differences in age, sex, diabetes mellitus, ASA score, preoperative BMI, and the percentage of anatomical resection between them. However, there were significant or marginal differences between the 10-year survival and nonsurvival groups in many clinicopathological and operative variables, including the presence of cirrhosis ($P = 0.001$), portal hypertension ($P = 0.074$) and Child-Pugh grade B ($P = 0.054$), preoperative AST level ($P < 0.001$), ALT level ($P = 0.001$), AFP level ($P < 0.001$) and HBV viral load ($P = 0.003$), the positiveness of HBeAg ($P = 0.037$), maximum tumor size > 5 cm ($P < 0.001$), multiple tumor ($P < 0.001$), macroscopic vascular invasion ($P < 0.001$), microscopic vascular invasion ($P < 0.001$), poor tumor differentiation ($P < 0.001$), intraoperative blood loss ($P < 0.001$), intraoperative blood transfusion ($P < 0.001$), and extent of hepatectomy (major vs. minor) ($P < 0.001$).

Comparisons of outcomes and postoperative variables during follow-up between the 10-year survival and nonsurvival groups were also shown in Table 2. Compared with the patients in the 10-year nonsurvival group, the patients in the 10-year survival group had significantly higher percentages of postoperative antiviral treatment (48.5% vs. 35.9%, $P = 0.003$) and regular recurrence surveillance (57.4% vs. 35.3%, $P < 0.001$), but significantly lower percentages of postoperative HBV reactivation (8.9% vs. 24.6%, $P < 0.001$). The cumulative 1-, 3-, and 5-year rates of undetectable HBV-DNA viral load in patients with 10-year survival were 87.6%, 89.3%, and 91.1%, which were significantly higher than those in patients without 10-year survival (66.1%, 69.5%, and 77.5%, all $P < 0.001$). Patients in the 10-year survival group had significantly lower cumulative overall recurrence (58.0% vs. 88.2%, $P < 0.001$) and early recurrence (< 2 years) rates (28.4% vs. 58.3%, $P < 0.001$). With respect to the treatments for initial recurrence, the

**Table 1** Comparisons of clinicopathological and operative variables between the 10-year survival and nonsurvival groups

| *N* (%) | Total (*N* = 857) | 10-year survival group (*N* = 169) | 10-year nonsurvival group (*N* = 688) | Univariable *P* value |
|---|---|---|---|---|
| Age > 60 years | 145 (16.9) | 27 (16.0) | 118 (17.2) | 0.715 |
| Male | 766 (89.4) | 151 (89.3) | 615 (89.4) | 0.988 |
| Diabetes mellitus | 48 (5.6) | 6 (3.6) | 42 (6.1) | 0.196 |
| ASA score > 2 | 93 (10.9) | 19 (11.2) | 74 (10.8) | 0.855 |
| Preoperative BMI > 24.0 kg/m$^2$ | 300 (35.0) | 54 (32.0) | 246 (35.8) | 0.353 |
| Cirrhosis | 645 (75.3) | 111 (65.7) | 534 (77.6) | 0.001 |
| Portal hypertension | 304 (35.5) | 50 (29.6) | 254 (36.9) | 0.074 |
| Preoperative Child-Pugh grade B | 103 (12.0) | 13 (7.7) | 90 (13.1) | 0.054 |
| Preoperative AST level > 40 U/L | 423 (49.4) | 60 (35.5) | 363 (52.8) | < 0.001 |
| Preoperative ALT level > 40 U/L | 441 (51.5) | 67 (39.6) | 374 (54.4) | 0.001 |
| Preoperative AFP level > 400 μg/L | 357 (41.7) | 49 (29.0) | 308 (44.8) | < 0.001 |
| Preoperative HBV viral load > 10$^4$ copies/-mL | 376 (43.9) | 57 (33.7) | 319 (46.4) | 0.003 |
| HBeAg (+) | 188 (21.9) | 27 (16.0) | 161 (23.4) | 0.037 |
| Maximum tumor size > 5 cm | 463 (54.0) | 51 (30.2) | 412 (59.9) | < 0.001 |
| Multiple tumor | 259 (30.2) | 20 (11.8) | 239 (34.7) | < 0.001 |
| Macroscopic vascular invasion | 147 (17.2) | 3 (1.8) | 144 (20.9) | < 0.001 |
| Microscopic vascular invasion | 518 (60.4) | 74 (43.8) | 444 (64.5) | < 0.001 |
| Poor tumor differentiation | 725 (84.6) | 128 (75.7) | 597 (86.8) | < 0.001 |
| Intraoperative blood loss > 400 ml | 421 (49.1) | 56 (33.1) | 365 (53.1) | < 0.001 |
| Intraoperative blood transfusion | 236 (27.5) | 24 (14.2) | 212 (30.8) | < 0.001 |
| Major hepatectomy | 270 (31.5) | 25 (14.8) | 245 (35.6) | < 0.001 |
| Nonanatomical resection | 596 (69.5) | 115 (68.0) | 481 (69.9) | 0.637 |

*AFP*, alpha-fetoprotein; *ASA*, American Society of Anesthesiologists; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *HBeAg*, hepatitis B e antigen; *HBV*, hepatitis B virus

**Table 2** Comparisons of outcomes and postoperative variables during follow-up between the 10-year survival and nonsurvival groups

| *N* (%) | Total (*N* = 857) | 10-year survival group (*N* = 169) | 10-year nonsurvival group (*N* = 688) | Univariable *P* value |
|---|---|---|---|---|
| Postoperative antiviral therapy | 329 (38.4) | 82 (48.5) | 247 (35.9) | 0.003 |
| Regular recurrence surveillance | 340 (39.7) | 97 (57.4) | 243 (35.3) | < 0.001 |
| Postoperative HBV reactivation | 184 (21.5) | 15 (8.9) | 169 (24.6) | < 0.001 |
| Cumulative rates of undetectable HBV-DNA viral load (%) | | | | |
| 1-year | 603 (70.4) | 148 (87.6) | 455 (66.1) | < 0.001 |
| 3-year | 629 (73.4) | 151 (89.3) | 478 (69.5) | < 0.001 |
| 5-year | 687 (80.2) | 154 (91.1) | 533 (77.5) | < 0.001 |
| Cumulative recurrence rates | 705 (82.3) | 98 (58.0) | 607 (88.2) | < 0.001 |
| < 2 years (early recurrence) | 449 (52.4) | 48 (28.4) | 401 (58.3) | < 0.001 |
| ≥ 2 years (late recurrence) | 256 (29.9) | 50 (29.6) | 206 (29.9) | 0.928 |
| Location of initial recurrence | | | | |
| Intrahepatic only | 490 (57.2) | 89 (52.7) | 401 (58.3) | 0.186 |
| Intrahepatic and extrahepatic | 149 (17.4) | 6 (3.6) | 143 (20.8) | < 0.001 |
| Extrahepatic | 66 (7.7) | 3 (1.8) | 63 (9.2) | 0.001 |
| Treatments for initial recurrence | | | | |
| Curative treatments | 225 (26.3) | 64 (37.9) | 161 (23.4) | < 0.001 |
| Liver transplantation* | 34 (4.0) | 12 (7.1) | 22 (3.2) | |
| Re-resection | 156 (18.2) | 42 (24.9) | 114 (16.6) | |
| Local ablation | 35 (4.1) | 10 (5.9) | 25 (3.6) | |
| Non-curative treatments | 480 (56.0) | 34 (20.1) | 446 (64.8) | < 0.001 |
| TACE | 286 (33.4) | 21 (12.4) | 265 (38.5) | |
| Radiotherapy | 73 (8.5) | 5 (3.0) | 68 (9.9) | |
| Molecular targeting therapy | 82 (9.6) | 5 (3.0) | 77 (11.2) | |
| Supportive therapy | 39 (4.6) | 3 (1.8) | 36 (5.2) | |

*HBV*, hepatitis B virus; *TACE*, transcatheter arterial chemoembolization

*Patients ($n = 18$) suffered from liver failure were excluded, involving 9 patients (5.3%) in the 10-year survival group and 9 patients (1.3%) in the 10-year nonsurvival group

patients in the 10-year survival group underwent more curative treatments for recurrence (37.9% vs. 23.4%, $P < 0.001$), while the patients in the 10-year nonsurvival group underwent more non-curative treatments for recurrence (64.8% vs. 20.1%, $P < 0.001$).

### Multivariable Analyses for Independent Factors Associated with 10-Year Survival

Multivariable logistic regression analyses were performed to determine those independent factors associated with actual 10-year survival after liver resection of HBV-related HCC. Those variables with $P < 0.1$ on univariable analyses were entered into multivariable analyses. As shown in Table 3, cirrhosis, preoperative HBV viral load > $10^4$ copies/mL, maximum tumor size > 5 cm, multiple tumors, macroscopic and microscopic vascular invasion, postoperative HBV reactivation, and postoperative early recurrence were independent risk factors associated with actual 10-year survival, while postoperative antiviral therapy, regular recurrence surveillance, and curative-intent treatments for initial recurrence were independent protective factors associated with the actual 10-year survival.

## Discussion

Although liver resection is the mainstay curative treatment for patients with HCC, the long-term prognosis is still unfavorable. It was reported that the actuarial 10-year survival rate following liver resection of HCC ranged from 20 to 40%, and the actual 10-year survival was much lower than the actuarial 10-year survival rate indeed.[25] To the best of our knowledge, the present study is the first study focused on the actual 10-year survival after resection of HBV-related HCC, the predominant type of HCC worldwide nowadays. In our study, among all enrolled 1016 patients, the actuarial 10-year survival rate was 24.1%, while the actual 10-year survival rate was 16.6%. Multivariable regression analysis revealed that cirrhosis, preoperative HBV viral load > $10^4$ copies/mL, maximum tumor size > 5 cm, multiple tumors, macroscopic and microscopic vascular invasion, postoperative HBV reactivation, and

**Table 3** Multivariable logistic regression analyses of predictive factors associated with 10-year survival

| Variables with $P < 0.1$ in univariable analyses | Multivariable OR (95% CI) | Multivariable $P$ value |
|---|---|---|
| Risk factors | | |
| Cirrhosis | 1.630 (1.039–2.807) | 0.018 |
| Portal hypertension | NS | 0.185 |
| Preoperative Child-Pugh grade B | NS | 0.265 |
| Preoperative AST level > 40 U/L | NS | 0.652 |
| Preoperative ALT level > 40 U/L | NS | 0.268 |
| Preoperative AFP level > 400 μg/L | NS | 0.133 |
| Preoperative HBV viral load > $10^4$ copies/mL | 1.842 (1.010–2.960) | 0.042 |
| HBeAg (+) | NS | 0.425 |
| Maximum tumor size > 5 cm | 1.837 (1.152–2.977) | 0.001 |
| Multiple tumor | 1.549 (1.106–2.638) | 0.005 |
| Satellites nodules | NS | 0.131 |
| Macroscopic vascular invasion | 4.810 (2.733–18.191) | < 0.001 |
| Microscopic vascular invasion | 2.522 (1.015–3.172) | 0.031 |
| Poor tumor differentiation | NS | 0.478 |
| Intraoperative blood loss > 400 ml | NS | 0.366 |
| Intraoperative blood transfusion | NS | 0.169 |
| Major hepatectomy | NS | 0.553 |
| Resection margin (< 1 cm) | NS | 0.188 |
| Postoperative HBV reactivation | 1.397 (1.005–1.944) | 0.045 |
| Postoperative early recurrence (< 2 years) | 2.075 (1.251–4.439) | 0.001 |
| Protective factors | | |
| Postoperative antiviral therapy | 0.458 (0.287–0.997) | 0.046 |
| Regular recurrence surveillance | 0.551 (0.322–0.917) | 0.018 |
| Curative treatments for initial recurrence | 0.566 (0.375–0.950) | 0.025 |

*AFP*, alpha-fetoprotein; *BMI*, body mass index; *CI*, confidence interval; *HBV*, hepatitis B virus; *OR*, odds ratio

postoperative early recurrence were independent risk factors associated with actual 10-year survival, while postoperative antiviral therapy, regular recurrence surveillance, and curative treatments for initial recurrence were independent protective factors. Our study was based on a Chinese multicenter cohort with a very large sample size, which would provide robust evidence on the issue of actual 10-year survival after resection of HBV-related HCC.

In our study, those known clinicopathological variables, such as cirrhosis, maximum tumor size > 5 cm, multiple tumors, and macroscopic and microscopic vascular invasion, were identified as risk factors associated with actual 10-year survival after HCC resection, which was similar to some previous studies.[18,25] In particular, in this HBV-specific cohort, preoperative HBV viral load > $10^4$ copies/mL was an independent risk factor, while postoperative antiviral therapy was an independent protective factor associated with actual 10-year survival. As indicated by several studies, an active HBV-DNA replication in HCC may initiate hepatocarcinogenesis via both direct and indirect carcinogenic mechanisms after curative resection. And patients with sustained viremia may have impaired tumor immune surveillance and are more likely to induce multicentric carcinogenesis in the liver remnant, which may accelerate tumor development and spread.[26,27] Continuous antiviral therapy in patients with HBV-related HCC could inhibit hepatitis activity and reduce chronic inflammation in the liver remnant, thus decrease the chance of developing a recurrent HCC. Also, improvement in liver function could enhance the tolerance of patients to receive further treatment for recurrence.[26,27] These factors contributed to a preferable 10-year survival in patients receiving postoperative antiviral therapy.

The comparisons of postoperative variables during follow-up between the two groups further echoed the significance of postoperative HBV status on long-term survival. Patients in the 10-year survival group experienced a significantly lower percentage of HBV reactivation and higher cumulative 1-, 3-, and 5-year rates of undetectable HBV-DNA, and HBV reactivation was an independent risk factor of 10-year survival. HBV reactivation may modulate the status of liver dysfunction, tumor biology, and postoperative course in HBV-related HCC. Previous studies[28] have found that HBV reactivation negatively influenced postoperative hepatic functions and thereafter induced poorer survival rates in patients with HBV-related HCC. In accordance with these findings, our studies showed that preferable

postoperative HBV status (absence of HBV reactivation) could also predict actual 10-year survival in patients undergoing curative resection of HBV-related HCC.

In the present study, 97 patients (57.4%) received postoperative regular surveillance for recurrence in the 10-year survival group, while only 243 (35.3%) patients did so in the 10-year nonsurvival group. Meanwhile, curative-intent treatment for recurrence was significantly higher in patients who survived for longer than 10 years ($n = 64$, 37.9%) compared to patients who survived for less than 10 years ($n = 161$, 23.4%). In addition, on multivariable analyses, regular recurrence surveillance was identified as an independent factor associated with favorable actual 10-year survival. The possible explanations were early detection of changes in HBV status and liver function, and early diagnosis of tumor recurrence, allowed early treatment of HBV reactivation and recurrent tumors.[29–31] In clinical practice, many patients do not take postoperative surveillance seriously, and consequently lose the chance to curative-intent treatments when symptoms develop. Our study also showed that curative-intent treatments for initial recurrence were also an independent factor of favorable actual 10-year survival in patients after curative liver resection for HCC.

It is generally acknowledged that HCC recurrence can be divided into early (< 2 years) and late recurrences (> 2 years) according to the time-to-recurrence after surgery. Early recurrence within 2 years after surgery is most likely to be due to occult metastases from the initial tumor. Late recurrence after 2 years of surgery is often of a different clonal origin from the original tumor, suggesting a de novo second primary HCC.[32–37] In our study, the incidence of early recurrence (< 2 years after surgery) was identified as an independent risk factor of 10-year survival. Previous studies have shown that many tumor-specific characteristics of the initial HCC were independently associated with early recurrence, including large tumor size, multiple tumors, macro- and microscopic vascular invasion, and poor tumor differentiation.[32–37] These risk factors were also showed to be associated with a decreased 10-year survival rate in this study. Additionally, in the present study, among 169 patients who survived for more than 10 years after surgery, 50 (29.6%) patients developed late recurrence after 2 years of surgery, and curative-intent treatments were possible in 23 (46.0%) of these 50 patients. Among 688 patients who died within 10 years after surgery, 206 (29.9%) patients developed late recurrence, curative-intent treatments were possible in only 53 (25.7%) patients. Thus, for patients who are alive and recurrence-free at 2 years after surgery, regular recurrence surveillance is recommended.

There are limitations in our study. First, this is a retrospective study with its inherent biases. Second, there still were 159 patients censored in the present study, although they accounted for a small proportion (15.6%) of all enrolled patients, compared to those previously reported studies on the actual 10-year survival rates.[17–19,38–42] Admittedly, this part of patients may bring about potential effects on the real 10-year survival rates in patients undergoing curative resection of HBV-related HCC. For a multicenter retrospective study with a follow-up period of more than 10 years, it was really difficult to have no any censored data. Our study requires a prospective study with more rigorous and accurate follow-up in the future.

## Conclusion

In the present study, the actual 10-year survival rate of patients undergoing curative resection for HBV-related HCC was 16.6%. Cirrhosis, preoperative HBV viral load > $10^4$ copies/mL, tumor size > 5 cm, multiple tumors, macroscopic and microscopic vascular invasion, postoperative HBV reactivation, and early recurrence (< 2 years after surgery) were independent risk factors associated with actual 10-year survival, while postoperative antiviral therapy, regular recurrence surveillance, and curative treatments for initial recurrence were independent protective factors associated with actual 10-year survival. In pursuit of long-term postoperative survival for patients with HBV-related HCC, antiviral therapy and regular postoperative surveillance for recurrence and HBV status are highly warranted.

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## Compliance with Ethical Standards

Informed consent for the data to be used for clinical researches was obtained from all enrolled patients. This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of all the seven enrolled hospitals.

**Conflict of Interest** The authors declare that they have no conflicts of interest.

## References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin, 2014, 64:9–29.
2. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic

analysis for the Global Burden of Disease Study 2013. Lancet, 2015, 385:117–171.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin, 2016, 66:115–132.
4. Nguyen VT, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. J Viral Hepat, 2009, 16:453–463.
5. Yang T, Lu JH, Zhai J, Lin C, Yang GS, Zhao RH, Shen F, Wu MC. High viral load is associated with poor overall and recurrence-free survival of hepatitis B virus-related hepatocellular carcinoma after curative resection: a prospective cohort study. Eur J Surg Oncol, 2012, 38:683–691.
6. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology, 1999, 30:1434–1440.
7. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, Kosuge T, Okada S, Takayasu K, Yamasaki S. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology, 1998, 28:1241–1246.
8. Cunningham SC, Tsai S, Marques HP, Mira P, Cameron A, Barroso E, Philosophe B, Pawlik TM. Management of early hepatocellular carcinoma in patients with well-compensated cirrhosis. Ann Surg Oncol, 2009, 16:1820–1831.
9. Nathan H, Bridges JF, Schulick RD, Cameron AM, Hirose K, Edil BH, Wolfgang CL, Segev DL, Choti MA, Pawlik TM. Understanding surgical decision making in early hepatocellular carcinoma. J Clin Oncol, 2011, 29:619–625.
10. Dhir M, Melin AA, Douaiher J, Lin C, Zhen WK, Hussain SM, Geschwind JF, Doyle MB, Abou-Alfa GK, Are C. A review and update of treatment options and controversies in the management of hepatocellular carcinoma. Ann Surg, 2016, 263:1112–1125.
11. Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS, Li LQ. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg, 2014, 260:329–340.
12. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology, 2014, 146:1691–1700.e3.
13. Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, Volk M, Giannini EG, Ciccarese F, Piscaglia F, Rapaccini GL, Di MM, Caturelli E, Zoli M, Borzio F, Cabibbo G, Felder M, Gasbarrini A, Sacco R, Foschi FG, Missale G, Morisco F, Svegliati BG, Virdone R, Cillo U. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol, 2015, 62:617–624.
14. Yang T, Lu JH, Lau WY, Zhang TY, Zhang H, Shen YN, Alshebeeb K, Wu MC, Schwartz M, Shen F. Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma: a Propensity Score Matching Analysis. J Hepatol, 2016, 64:583–593.
15. Hyun MH, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, Yim HJ, Yeon JE, Byun KS. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: a meta-analysis of high-quality studies. Hepatology, 2018. DOI: https://doi.org/10.1002/hep.29883.
16. Trevisani F, Bucci L, Garuti F. Is it time to extend criteria for hepatic resection in the treatment of hepatocellular carcinoma. Hepatology, 2016, 64:2257–2258.
17. Gluer AM, Cocco N, Laurence JM, Johnston ES, Hollands MJ, Pleass HC, Richardson AJ, Lam VW. Systematic review of actual 10-year survival following resection for hepatocellular carcinoma. HPB (Oxford), 2012, 14:285–290.
18. Zheng J, Kuk D, Gönen M, Balachandran VP, Kingham TP, Allen PJ, D'Angelica MI, Jarnagin WR, DeMatteo RP. Actual 10-Year Survivors After Resection of Hepatocellular Carcinoma. Ann Surg Oncol, 2017, 24:1358–1366.
19. Shimada K, Sano T, Sakamoto Y, Kosuge T. A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. Cancer, 2005, 104:1939–1947.
20. Wu KT, Wang CC, Lu LG, Zhang WD, Zhang FJ, Shi F, Li CX. Hepatocellular carcinoma: clinical study of long-term survival and choice of treatment modalities. World J Gastroenterol, 2013, 19:3649–3657.
21. Zhou XD, Tang ZY, Ma ZC, Fan J, Wu ZQ, Qin LX, Zhou J, Yu Y, Sun HC, Qiu SJ. Twenty-year survivors after resection for hepatocellular carcinoma-analysis of 53 cases. J Cancer Res Clin Oncol, 2009, 135:1067–1072.
22. Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL, Wu ZQ, Fan J, Qin LX, Zheng BH. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer, 2001, 91:1479–1486.
23. Zhu Y, Wen L, Shao S, Tan Y, Meng T, Yang X, Liu Y, Liu X, Yuan H, Hu F. Inhibition of tumor-promoting stroma to enforce subsequently targeting AT1R on tumor cells by pathological inspired micelles. Biomaterials, 2018, 161:33–46.
24. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg, 2013, 257:377–382.
25. Franssen B, Jibara G, Tabrizian P, Schwartz ME, Roayaie S. Actual 10-year survival following hepatectomy for hepatocellular carcinoma. HPB (Oxford), 2014, 16:830–835.
26. Huang G, Li PP, Lau WY, Pan ZY, Zhao LH, Wang ZG, Wang MC, Zhou WP. Antiviral therapy reduces hepatocellular carcinoma recurrence in patients with low HBV-DNA levels: a randomized controlled trial. Ann Surg, 2018. DOI: https://doi.org/10.1097/SLA.0000000000002727.
27. Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP, Wu MC. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. Ann Surg, 2015, 261:56–66.
28. Huang G, Lai EC, Lau WY, Zhou WP, Shen F, Pan ZY, Fu SY, Wu MC. Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. Ann Surg, 2013, 257:490–505.
29. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, Shiozaki A, Kuriu Y, Kubota T, Nakanishi M, Ichikawa D, Fujiwara H, Okamoto K, Sakakura C, Ochiai T, Otsuji E. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. World J Gastroenterol, 2015, 21:1207–1215.
30. Mittal S, Kanwal F, Ying J, Chung R, Sada YH, Temple S, Davila JA, El-Serag HB. Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: a United States cohort. J Hepatol, 2016, 65:1148–1154.
31. Khalaf N, Ying J, Mittal S, Temple S, Kanwal F, Davila J, El-Serag HB. Natural history of untreated hepatocellular carcinoma in a US cohort and the role of cancer surveillance. Clin Gastroenterol Hepatol, 2017, 15:273–281.e1.
32. Zheng J, Chou JF, Gönen M, Vachharajani N, Chapman WC, Majella DMB, Turcotte S, Vandenbroucke-Menu F, Lapointe R, Buettner S, Groot KB, JNM I, Chan CY, BKP G, Teo JY, Kam JH, Jeyaraj PR, Cheow PC, AYF C, PKH C, LLPJ O, Balachandran VP, Kingham TP, Allen PJ, D'Angelica MI, DeMatteo RP, Jarnagin WR, Lee SY. Prediction of hepatocellular carcinoma recurrence beyond Milan criteria after resection:

validation of a clinical risk score in an international cohort. Ann Surg, 2017, 266:693–701.
33. Poon RT. Differentiating early and late recurrences after resection of HCC in cirrhotic patients: implications on surveillance, prevention, and treatment strategies. Ann Surg Oncol, 2009, 16:792–794.
34. Du ZG, Wei YG, Chen KF, Li B. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients. Hepatobiliary Pancreat Dis Int, 2014, 13:153–161.
35. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer, 2000, 89:500–507.
36. Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, Giulini SM. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. Ann Surg, 2006, 243:229–235
37. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol, 2003, 38:200–207.
38. Bagante F, Spolverato G, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Soubrane O, Martel G, Groot KB, Guglielmi A, Itaru E, Pawlik TM. Defining long-term survivors following resection of intrahepatic cholangiocarcinoma. J Gastrointest Surg, 2017, 21:1888–1897
39. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, Kemeny N, Brennan MF, Blumgart LH, D'Angelica M. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol, 2007, 25:4575–4580.
40. Tran TB, Postlewait LM, Maithel SK, Prescott JD, Wang TS, Glenn J, Phay JE, Keplinger K, Fields RC, Jin LX, Weber SM, Salem A, Sicklick JK, Gad S, Yopp AC, Mansour JC, Duh QY, Seiser N, Solorzano CC, Kiernan CM, Votanopoulos KI, Levine EA, Hatzaras I, Shenoy R, Pawlik TM, Norton JA, Poultsides GA. Actual 10-year survivors following resection of adrenocortical carcinoma. J Surg Oncol, 2016, 114:971–976.
41. Creasy JM, Sadot E, Koerkamp BG, Chou JF, Gonen M, Kemeny NE, Balachandran VP, Kingham TP, DeMatteo RP, Allen PJ, Blumgart LH, Jarnagin WR, D'Angelica MI. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure. Surgery, 2018, 163:1238–1244.
42. Chua TC, Saxena A, Chu F, Zhao J, Morris DL. Predictors of cure after hepatic resection of colorectal liver metastases: an analysis of actual 5- and 10-year survivors. J Surg Oncol, 2011, 103:796–800.