Research Paper

Hepatitis B Virus Infection Predicts Better Survival In Patients With Colorectal Liver-only Metastases Undergoing Liver Resection

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Abstract

Objective: Hepatitis B virus (HBV) infection has been shown to decrease the risk of liver metastasis in patients with non-metastatic colorectal cancer (CRC). However, the prognostic value of HBV infection in long-term survival of patients with colorectal liver-only metastases (CRLM) after liver resection has not yet been evaluated. This study aims to explore the association between HBV infection and survival in CRLM patients.

Methods: A total of 289 CRLM patients undergoing liver resection were recruited at our center from September 1999 to August 2015. Patients were divided into an HBV infection group and a non-HBV infection group. Progression-free survival (PFS) and overall survival (OS) related to HBV infection were analyzed using both Kaplan–Meier and multivariate Cox regression methods.

Results: HBV infection was found in 12.1 %(35/289) of patients. Of these patients, 31.4 %(11/35) had chronic hepatitis B (CHB), 42.9 % (15/35) were inactive hepatitis B surface antigen (HBsAg) carriers (IC) and 25.7 % (9/35) did not undergo HBV DNA detection. HBV infection was associated with more liver metastases (P = 0.025) and larger-sized liver metastases (P = 0.049). The 3-year OS and PFS rates in the HBV infection group were higher than those in the HBV non-infected group (OS: 75.0 % vs 64.8 %, P = 0.031; PFS: 55.9 % vs 39.6 %, P = 0.034). In multivariate Cox analysis, HBV infection was identified as an independent factor for better 3-year OS (hazard ratio (HR), 0.446; 95 %confidence interval (CI), 0.206–0.966; *P* = 0.041) but not an independent factor for 3-year PFS.

Conclusions: HBV-infected CRLM patients survived longer than non-infected patients. In clinical work, therapeutic regimens and follow-up for HBsAg-positive patients may be different from that for HBsAg-negative patients, even though objective prospective studies are still needed.

Key words: Colorectal cancer; Hepatitis B virus; Liver metastases; Liver resection; Prognosis

Introduction

With increasing incidence and mortality, colorectal cancer (CRC) has become the third most common cause of cancer death worldwide[1]. In China, mortality caused by CRC was estimated to reach 191,000 in 2015[2]. In all these deaths, the development of distant metastatic disease was the main cause of death, and the liver was the most common site of CRC metastasis. Approximately 20 – 25 % of CRC patients were initially diagnosed with synchronous liver metastases, and approximately half of the patients

developed metachronous liver metastases after primary tumor resection[3, 4]. Liver metastases resection is the only known option for curing patients with colorectal liver metastases[5, 6]. However, approximately 75 % of patients will experience recurrence within 2 years[7]. Recurrence after colorectal liver metastases resection is common, with approximately 30 % of intrahepatic recurrence patients and more than 50 % extrahepatic recurrence[8, 9].Thus, clinical biomarkers are needed to find suitable patients for corresponding individual interventions.

Hepatitis B virus (HBV) is the most common cause of chronic liver disease in the world, with an estimated 250 – 400 million people chronically infected with HBV [10]. China has a high prevalence of HBV infection, with 97 million HBV carriers and at least 20 million individuals with an active chronic hepatitis B infection[11]. HBV infection was previously shown to play an important role in the progression of hepatocellular carcinoma(HCC) and to present with increased intrahepatic metastasis, thus suggesting the role of HBV infection in survival[12].

Several reports on the relationship between HBV infection and liver metastasis in CRC are available. Utsunomiya et al.[13] reported that CRC patients infected with HBV or hepatitis C virus (HCV)scarcely present with liver metastases. Another study reported that compared with non-infected patients, HBV-infected CRC patients exhibited a reduced liver metastasis rate and increased survival rate[14, 15]. Since HBV-infected CRC patients presented with a low possibility of liver metastases and better prognosis, we hypothesize that HBV infection is associated with better prognosis of CRLM patients undergoing liver metastases resection. In this study, we examined the association between HBV infection and the survival of CRLM patients undergoing liver metastases resection to investigate the predictive value of HBV infection in screening for high-risk patients for individual treatment.

Materials and Methods

Patients

A retrospective analysis was conducted by reviewing the clinicopathological data of 289 CRLM patients who underwent radical liver resection from September 1999 to August 2015 at Sun Yat-sen University Cancer Center (Guangzhou, China). Patients who met the following criteria were enrolled: 1) histologically confirmed colorectal adenocarcinoma, 2) metastases limited to the liver before liver resection, 3) R0 resection for primary lesion and metastases, and 4) no other cancer during follow-up. Patients were excluded if they had extrahepatic metastatic lesions, died in the perioperative period or

underwent palliative liver resection. The primary tumor was completely removed, and liver metastases were radically resected in all eligible patients. Clinicopathological features of CRLM patients; tumor characteristics; and the time of hepatectomy, relapse and last follow-up were all reviewed from the medical records and the follow-up system of Sun Yat-sen University Cancer Center. The present study was undertaken according to the ethical standards of the 1964 Declaration of Helsinki. Institutional Review Board approval was obtained from independent ethics committees at the Sun Yat-sen University Cancer Center with a waiver of informed consent because this research was retrospective and did not involve accessing any patient identification data.

Serologic assay for CRLM patients

Routine peripheral blood biochemical tests and serum tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were acquired about one week before liver metastases resection. CEA levels above 5 ng/ml and CA19-9 levels above 35U/ml were considered to be elevated. Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e-antigen (HBeAg), hepatitis B e-antibody (anti-HBe), and hepatitis B core antibody (anti-HBc) levels were examined in all patients by enzyme-linked immunosorbent assay (ELISA), and HBV DNA was detected by polymerase chain reaction(PCR). Blood samples were collected from all CRLM patients at the first visit, and serum samples were separated for the HBV infection test. A serum HBV DNA result of >1000 copies/ml was considered positive. According to the HBsAg status at their first visit, patients who were HBsAg-positive or HBsAg-negative were divided into an HBV-infected or non-infected group. The infected group was further subdivided into two groups based on HBeAg and serum HBV DNA detection. Chronic hepatitis B (CHB) patients, defined as patients having active HBV replication, were characterized by being HBsAg-positive and positive for either HBeAg or HBV DNA. Inactive HBsAg carriers (IC), indicating HBV infection but without active replication, were identified as HBsAg-positive and negative for both HBeAg and HBV DNA[16, 17].

Follow-up of patients

All patients were followed up after hospital discharge. The patients were followed up every 3 months in the first 2 years after liver resection and then semi-annually until 3 years after liver resection. The follow-up evaluation included a routine blood test, tests for the tumor markers CEA and CA19-9, abdominal ultrasonography, and a chest radiograph. A chest computed tomography scan, abdominal/

pelvic magnetic resonance imaging, and a colonoscopy were performed annually. The follow-up period was terminated in June 2017.

Table 1. Baseline characteristics of 289 colorectal liver metastases patients

Characteristics		n (%)
Sex	Male	185 (64.0)
	Female	104 (36.0)
Age (years)	<=57	150 (51.9)
	>57	139 (48.1)
Primary tumor site[a]	Colon	179 (62.2)
	Rectum	109 (37.8)
Primary tumor size (cm)[b]	<=4	126 (61.2)
	>4	80 (38.8)
T stage (T1-3/T4)[c]	T1-3	170 (64.2)
	T4	95 (35.8)
N stage (N0/N1-2)[d]	N0	110 (42.3)
	N1-2	150 (57.7)
Histological grade (/ poor)[e]	Well/moderate	212 (86.2)
	Poor	34 (13.8)
Albumin (g/dl)	<=35	272 (94.1)
	>35	17 (5.9)
CEA level (ng/ml)[f]	<=5	102 (37.1)
	>5	173 (62.9)
CA199 level (U/ml)[g]	<=35	185 (69.3)
	>35	82 (30.7)
Liver metastases tumor size (cm)[h]	<=2.5	151 (53.0)
	>2.5	134 (47.0)
Liver metastases number	Single	147 (50.9)
	Multiple	142 (49.1)
Liver metastases segments	Oligo	136 (47.1)
	Multiple	153 (52.9)
HBV infection status[i]	Non infection	254 (90.7)
	CHB	11 (3.9)
	IC	15 (5.4)
Liver metastases	Synchronous	190 (65.7)
	Metachronous	99 (34.3)
Hepatic resection timing	Synchronous	131 (45.3)
	Metachronous	158 (54.7)

Abbreviations: CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; HBV, hepatitis B virus; CHB, chronic hepatitis B; IC, inactive carriers.
[a]Data of 288 patients were available
[b]Data of 206 patients were available
[c]Data of 265 patients were available
[d]Data of 260 patients were available
[e]Data of 246 patients were available
[f]Data of 275 patients were available
[g]Data of 267 patients were available
[h]Data of 285 patients were available
[i]Data of 280 patients were available

Statistical analysis

Values are presented as the median (range) or percentage, as appropriate. Differences in baseline clinicopathological characteristics between the two groups were assessed by chi-square test or Fisher's exact test. Progression-free survival (PFS) was defined as the time from the date of liver resection to the date of disease progression, date of death due to any cause or date of the last follow-up. Overall survival (OS) was defined from the date of liver resection until the date of death or last follow-up. OS and PFS curves were evaluated with the Kaplan–Meier method, and the significance differences between the HBsAg-positive and HBsAg-negative groups were compared by using log-rank test. Univariate and multivariate analyses with Cox proportional hazard regression models were performed to determine the hazard ratio (HR) of each prognostic factor. Covariates with P values<0.05 in univariate analysis were subjected to multivariate analysis. All statistical analyses were performed using SPSS 20.0 statistical software (IBM, NY, USA) and GraphPad Prism version 6.01 (GraphPad Software, Inc, La Jolla, CA, USA). A two-tailed P value < 0.05was interpreted as statistically significant.

Results

1. Clinicopathological characteristics of CRLM patients

A total of 289 cases were qualified for the analyses. Liver metastasis occurred in these 289 patients, including 190 cases with synchronous liver metastasis and 99 cases with metachronous liver metastasis. According to the HBsAg infection status, 35 patients (12.1 %) were distributed to the HBV infection group, and 254 patients (87.9 %) were distributed to the non-infected group. Among the 35 HBV-infected CRLM patients, except for 9 HBeAg-negative patients without HBV DNA detection, CHB was identified in 11 patients (3.8 %), and IC was identified in 15patients (5.2 %).

As shown in Table 1, the median age of the 289 patients was 57 years (range, 25 – 82 years), with 185 (64.0 %) males and 104 (36.0 %) females. HBV infection status was significantly associated with fewer liver metastases (P = 0.025) and smaller-sized liver metastases (P = 0.049) (Table 2).

2. Overall survival and progression-free survival difference according to HBV infection status

The median follow-up time after liver resection was 34 months (range 1 – 126) for all 289 patients. Overall, from the start of the study until the date of last follow-up, 115 patients (39.8 %) died of CRC, and 174 patients (60.2 %) had intrahepatic or extrahepatic recurrence. Postoperative recurrence in HBV-infected patients was significantly lower than that in non-infected patients (P = 0.009) (Table 3). The 1-, 3-, and the 5-year OS rates were94.0%, 66.0%, and 52.4%, respectively, and the 1-, 3-, 5-year PFS rates were 62.9 %, 41.5 %, and 36.1 %, respectively. The results showed that OS and PFS of the HBV-infected CRLM patients were significantly better than the rates in the non-infected patients (Fig. 1A and 1B). The 1-, 3-, and 5-year OS rates were 97.0 %, 75.0 %, and 75.0 % in the HBV-infected group and 93.6 %, 64.8 %, and 49.8 % in the non-infected group, respectively (log-rank test, P = 0.031). Similarly, the 1-, 3-, and 5-year PFS rates were 79.0 %, 55.9 %, and 55.9 % in the infected group

and 60.8 %, 39.6 %, and 33.7 % in the non-infected group, respectively (log-rank test, P = 0.034).

Table 2. Relationships between HBV infection and patient characteristics

Clinicaopathological features		HBV infection (n=35)	HBV non-infection (n=254)	*P* value
Age (years)	<=57	20	130	0.508
	>57	15	124	
Sex	Male	22	163	0.879
	Female	13	91	
T stage[a]	T1-3	25	145	0.079
	T4	7	88	
N stage[b]	N0	15	95	0.577
	N1-2	17	133	
Primary tumor location[c]	Left-sided colon	13	99	0.221
	Right-sided colon	12	55	
	Rectum	10	99	
Primary tumor size (cm)[d]	<=4	13	113	0.085
	>4	15	65	
Histological grade[e]	Well/Moderate	27	185	0.518
	Poor	3	31	
Albumin (g/dL)	<=35	34	238	0.668
	>35	1	16	
Total bilirubin (mg/dL)	<=20.5	34	244	1.000
	>20.5	1	10	
LDH (IU/L)	<=245	32	222	0.683
	>245	3	32	
GGT (IU/L)[c]	<=50	27	188	0.718
	>50	8	65	
Liver matastases segments	Oligo	19	117	0.361
	Multiple	16	137	
Liver matastases numbers	Single	24	123	0.025
	Multiple	11	131	
Liver metastasis timing	Synchronous	27	163	0.130
	Metachronous	8	91	
Liver metastases largest size (cm)[f]	<=2.5	24	127	0.049
	>2.5	11	123	
Surgical margin (cm)[g]	<=0.5	9	84	0.778
	>0.5	9	73	
CEA level (ng/ml)[h]	<=5	16	86	0.149
	>5	17	156	
CA199 level (U/ml)[i]	<=35	21	164	0.843
	>35	10	72	
Neoadjuvant chemotherapy	Yes	14	126	0.286
	No	21	128	
Adjuvant chemotherapy	Yes	7	81	0.152
	No	28	173	

Abbreviations: HBV, hepatitis B virus; LDH, lactate dehydrogenase; GGT, gamma-glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.
[a]Data of 265 patients were available
[b]Data of 260 patients were available
[c]Data of 288 patients were available
[d]Data of 206 patients were available
[e]Data of 246 patients were available
[f]Data of 285 patients were available
[g]Data of 175 patients were available
[h]Data of 275 patients were available
[i]Data of 267 patients were available

3. Prognostic factors for overall survival and progression-free survival

For patients with CRLM undergoing liver resection, univariate analysis revealed that older patients (HR,1.515; 95 % confidence interval(CI),1.048 – 2.192; P = 0.027), HBV non-infection (HR,2.258; 95 % CI,1.050 – 4.853; P = 0.037),lower albumin (ALB) level (g/dL) (HR,0.479; 95 % CI,0.250 – 0.918; P = 0.027), higher lactate dehydrogenase (LDH)level (IU/L) (HR,1.772; 95 % CI,1.092 – 2.876;P = 0.02), higher gamma-glutamyl transpeptidase (GGT) level (IU/L) (HR, 1.759; 95 % CI, 1.188 – 2.604; P = 0.005), multiple liver metastatic segments (HR, 1.815; 95 % CI, 1.241 – 2.655; P = 0.002), more liver metastases(HR, 1.827; 95 % CI,1.256 – 2.657; P = 0.002), and patients undergoing neoadjuvant chemotherapy (HR, 1.817; 95 % CI, 1.252 – 2.638; P = 0.002) were associated with worse OS (Table 4). For PFS, lymph node metastasis (HR, 1.800; 95 % CI, 1.295 – 2.503; P < 0.001), smaller-sized primary tumor (≤ 4 cm) (HR, 1.534; 95 % CI,1.062 – 2.216; P = 0.023), HBV non-infection (HR,1.779; 95 % CI,1.030 – 3.072; P = 0.039), higher GGT level (HR, 1.561; 95 % CI, 1.128 – 2.162; P = 0.007), multiple liver metastatic segments (HR, 1.847; 95 % CI, 1.360 – 2.507; P < 0.001), more liver metastases (HR, 1.94; 95 % CI, 1.432 – 2.628; P < 0.001),larger-sized metastases tumor (>2.5 cm) (HR, 1.355; 95 % CI, 1.002 – 1.831; P = 0.048), closer liver resection surgery margin(≤ 0.5 cm) (HR,1.755; 95 % CI,1.195 – 2.578; P = 0.004), higher CEA level (HR, 1.403; 95 % CI, 1.014 – 1.942; P = 0.041), and patients undergoing neoadjuvant chemotherapy (HR, 2.282; 95 % CI, 1.681 – 3.099; P < 0.001) were associated with worse PFS (Table 4).

Table 3. Postoperative recurrence in patients with colorectal liver-only metastases after radical liver resection between HBV infection and non-infection group

Parameters	HBV infection (n, %)	HBV non-infection (n, %)	*P* value
Median follow-up time (month, range)	33.0 (1.0-126.0)	35.0 (1.0-121.0)	0.344
Postoperative recurrence (n=289)			
Yes	14 (40.0)	160(63.0)	0.009
No	21(60.0)	94(37.0)	
Recurrence period (n=173)			
Early recurrence (≤ 6 months)	3(21.4)	45(28.3)	0.811
Latter recurrence (> 6 months)	11(78.6)	114(71.7)	
Recurrence pattern (n=142)			
Intrahepatic metastases	4(30.8)	76(58.9)	0.051
Extrahepatic metastases	9(69.2)	53(41.1)	

Abbreviations: HBV, hepatitis B virus

A multivariate Cox proportional hazard model was used to further analyze the prognostic factors that were significantly associated with OS or PFS in univariate analysis including HBV infection status. As shown in Table 4, the multivariate analysis demonstrated that HBV non-infection (HR,2.242; 95 % CI,1.035 – 4.853; P = 0.041) as well as older age (HR,1.702; 95 % CI, 1.171–2.474; P = 0.005), higher blood GGT level (HR, 1.597; 95 % CI, 1.073 – 2.377; P = 0.021), multiple liver metastatic segments (HR, 1.538; 95 % CI, 1.034 – 2.286; P = 0.033) and neoadjuvant chemotherapy (HR, 1.632; 95 % CI, 1.103 – 2.416; P =

0.014) were all independent predictors of worse OS for patients with CRLM undergoing liver resection. Furthermore, lymph node metastasis (HR,2.023; 95 % CI,1.229 – 3.329; P = 0.006), blood GGT level (HR, 1.806; 95 % CI, 1.099 – 2.967; P = 0.02), and number of liver metastases (HR, 1.748; 95 % CI, 1.043 – 2.929; P = 0.034), but not HBV infection, were independent predictors of PFS.
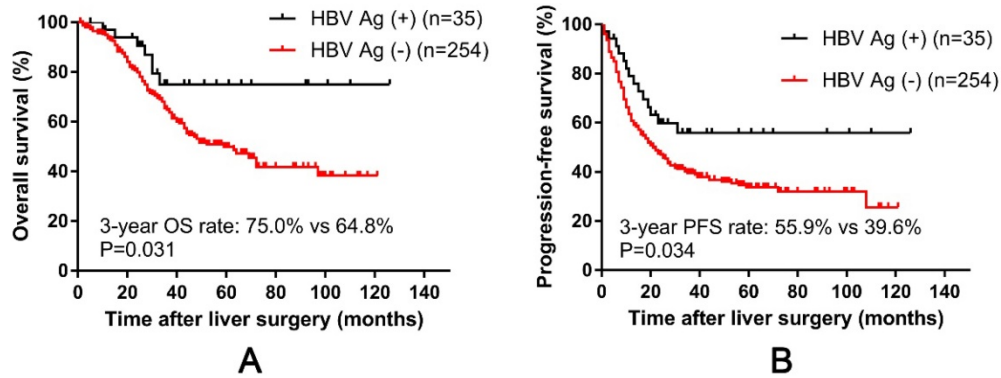
Figure 1. Correlation of hepatitis B surface antigen (HBsAg) status with progression-free survival and overall survival in 289 colorectal liver metastases (CRLM) patients. Kaplan–Meier survival curve showing better progression-free survival (A) and overall survival (B) in HBsAg-positive CRLM patients.

Table 4. Prognostic factors for OS and PFS in univariate and multivariate analysis

Clinicaopathological features		OS univariate analysis		Multivariate analysis		PFS univariate analysis		Multivariate analysis	
		Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age (years)	≤ 57	1.515(1.048-2.192)	0.027	1.702(1.171-2.474)	0.005	1.199 (0.891-1.615)	0.231		
	> 57								
Gender	Male	1.305(0.882-1.932)	0.183			1.365 (0.991-1.880)	0.057		
	Female								
T stage	T1-3	1.154(0.772-1.725)	0.484			1.607 (0.773-1.472)	0.695		
	T4								
N stage	N0	1.448(0.966-2.171)	0.073			1.8 (1.295-2.503)	<0.001	2.023 (1.229-3.329)	0.006
	N1-2								
Primary tumor location	Left-sided colon	1.235(0.966-1.580)	0.092			1.164 (0.957-1.416)	0.127		
	Right-sided colon								
	Rectum								
Primary tumor size (cm)	> 4	1.537(0.960-2.460)	0.074			1.534 (1.062-2.216)	0.023		
	≤ 4								
Histological grade	Well/Moderate	1.164(0.856-1.582)	0.334			1.097 (0.851-1.414)	0.477		
	Poor								
HBV infection	Yes	2.258(1.050-4.853)	0.037	2.242(1.035-4.853)	0.041	1.779 (1.030-3.072)	0.039		
	No								
Albumin (g/dL)	≤ 35	0.479(0.250-0.918)	0.027			0.590 (0.335-1.040)	0.068		
	> 35								
Total bilirubin (mg/dL)	≤ 20.5	1.062(0.431-2.616)	0.897			1.179 (0.577-2.408)	0.652		
	> 20.5								
LDH (IU/L)	≤ 245	1.772(1.092-2.876)	0.02			1.454 (0.957-2.209)	0.079		
	> 245								
GGT (IU/L)	≤ 50	1.759(1.188-2.604)	0.005	1.597(1.076-2.377)	0.021	1.561 (1.128-2.162)	0.007	1.806 (1.099-2.967)	0.020
	> 50								
Liver matastases segments	Oligo	1.815(1.241-2.655)	0.002	1.538(1.034-2.286)	0.033	1.847(1.360-2.507)	<0.001		
	Multiple								
Liver matastases numbers	Single	1.827 (1.256-2.657)	0.002			1.940 (1.432-2.628)	<0.001	1.748(1.043-2.929)	0.034
	Multiple								
Liver metastasis timing	Synchronous	0.920 (0.628-1.348)	0.668			0.964 (0.704-1.319)	0.818		
	Metachronous								
Liver metastases largest size (cm)	≤ 2.5	1.329 (0.915-1.932)	0.136			1.355 (1.002-1.831)	0.048		
	> 2.5								
Surgical margin of liver resection (cm)	> 0.5	1.583 (0.985-2.543)	0.058			1.755(1.195-2.578)	0.004		
	≤ 0.5								
CEA level (ng/ml)	≤ 5	1.137 (0.769-1.681)	0.519			1.403(1.014-1.942)	0.041		
	> 5								
CA199 level (U/ml)	≤ 35	1.285 (0.864-1.912)	0.216			1.125(0.809-1.566)	0.483		
	> 35								
Neoadjuvant chemotherapy	No	1.817 (1.252-2.638)	0.002	1.632(1.103-2.416)	0.014	2.282(1.681-3.099)	<0.001		
	Yes								
Adjuvant chemotherapy	No	0.964 (0.650-1.430)	0.854			0.943(0.681-1.305)	0.723		
	Yes								

Abbreviations: OS, overall survival; PFS, progression-free survival; HBV, hepatitis B virus; LDH, lactate dehydrogenase; GGT, gamma-glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Discussion

In this study, 289 colorectal liver metastases patients all underwent a radical liver resection. There were fewer and smaller-sized liver metastases in the HBV-infected group than in the non-infected group, indicating that HBV infection and clinicopathological features of CRLM patients were significantly correlated. In this study, the OS and PFS rates of CRLM patients in the HBV-infected group were higher than those in the non-infected group (P=0.031 and P = 0.034, respectively), and there was a significant difference in survival rate between these two groups, suggesting that HBV infection may have a strong correlation with survival of CRLM patients undergoing liver resection. We also found that HBV-infected CRLM patients had less postoperative recurrence than non-infected patients (P = 0.009). In addition, the recurrence pattern between these two groups differed. HBV-infected patients were more likely to have extrahepatic metastases than HBV non-infected patients, who had intrahepatic metastases; however, this result was not statistically significant (P = 0.051). In multivariate Cox analysis, HBV infection was identified as an independent factor for better OS but not an independent factor for PFS. We also analyzed the difference in the survival rate between patients in the CHB and IC groups, but there was no significant difference. (Figure S1.)

Reports are available on the relationship between HBV infection and liver metastasis in CRC patients. In a previous cohort study[15], HBV infection was demonstrated to decrease the risk of liver metastasis in patients with CRC and elevate the surgical resection rate of liver metastatic lesions. Utsunomiya et al. reported that CRC seldom metastasized to the liver in patients infected with HBV or HCV; however, most of the patients in the study were HCV-infected[13].Song et al. suggested that chronic HBV infection with viral replication could reduce liver metastasis and prolong the survival of CRC patients[14]. In our study, we also demonstrated that HBV-negative CRLM patients are more likely to develop recurrence after liver resection than HBV-positive patients and that the former are more likely to develop intrahepatic recurrence than the latter. The reasons why HBV-positive patients scarcely metastasize to the liver or are not prone to intrahepatic recurrence are not completely understood, but some investigations have been conducted. Approximately 5241 consecutive autopsies in the Trieste area and 6511 consecutive autopsies in the Tokyo-Chiba area were analyzed to study the frequency of liver metastases in cirrhosis[18]. The results showing that metastases in cirrhotic liver are rare were similar in both areas, which implied that in HBV-infected patients, the scarce metastasis of CRC to the liver maybe due to the hostile "soil" in the liver caused by viral replication.

However, whether the liver-associated immunity in HBV-infected patients hindered liver metastasis of CRC and prolonged survival needs further exploration. Viral clearance and disease pathogenesis are largely mediated by the adaptive immune response in HBV infection [19]. Previous studies reported that the liver has a considerable number of innate immune cells, especially lymphocytes including natural killer cells[20]. Several cells with phagocytic and antigen-presenting properties, including Kupffer cells and dendritic cells, play an important role in the local innate immunity of the liver[21].HBV receptors are expressed in a variety of extrahepatic cells, and HBV can alter the biological characteristics of these cells through their receptors[22].In addition, it has been reported that HBV replication can activate specific lytic pathways of cell damage by cytotoxic lymphocytes (CTLs)and Kupffer cells[23]. It is widely believed that the HBV specific CD8+ T cell response plays a fundamental role in viral clearance. Investigation of experimentally induced hepatic metastasis of colon cancer indicated that changes in liver-related immunity may play an important role in the impediment of liver metastasis[24].

In HBV transgenic mice, the CTL response to HBV by inducing several inflammatory factors. Indeed, they purge HBV replication in the liver by secreting type 1 inflammatory cytokines to limite virus spread to uninfected cells [25]. Furthermore, HBV replication is inhibited by stimulus which could induce IFNγ or IFN α/β in the liver, including CD4+ T cells, NK and NKT cells, as well as toll-like receptor activation [26,27]. In studies of HBV-infected chimpanzees, intrahepatic gene expression profiling in these animals revealed that the early phase of HBV clearance was associated with CD3, CD8 and IFNγ mRNA and other T cell-derived and interferon gamma (IFNγ)-stimulated genes [28,29]. Furthermore, HBV replication can promote the production of tumor necrosis factor a (TNF-a) by residual immune cells as well as hepatocytes in the liver[30,31], which can exhibit an antitumor effect on tumor cells. A previous study showed that the liver microenvironment in patients with HBV-positive liver metastases can greatly alter their gene expression profiles, and two significant clusters in the profile showed significant changes associated with gene products involved in immune function. In fact, over 30% of the genes in these clusters are related to immunity[23]. Another study on the interaction of tumor and stroma showed that

liver-prone metastatic tumors were inherent in tumor cells and affected by the local environment of metastatic sites[32]. In conclusion, the soil (liver microenvironment) and activation of liver-associated immunity due to HBV infection may partially explain the reduction in the incidence of liver metastasis in CRC patients and the prolonged survival rate of CRLM patients undergoing liver resection. In our study, we found that the survival rates in the CHB and IC groups are similar. Thus, it is reasonable to postulate that HBV infection with or without HBeAg infection or viral replication may affect survival of colorectal liver metastases in patients undergoing liver resection.

There are a number of limitations to our study. First, our study included a retrospective study with a relatively small sample size of patients from a single-institution experience. Second, the follow-up period was not long enough, which may have resulted in bias during analysis. Third, molecular detections are lacking. This retrospective result did not consider the status of KRAS, NRAS, or BRAF expression, which may have an influence on disease progression. Accordingly, further investigations of KRAS, NRAS, and BRAF expression in tumor tissues are needed to elucidate the precise contribution to the development of CRLM together with HBV. Finally, a previous study found that maintaining a relatively low level of HBV DNA plays a strong protective role in the overall and long-term recurrence-free survival of patients with HBV-related HCC[33]. In our study, we did not analyze the effect of HBV DNA copy number on survival of CRLM patients undergoing liver resection because of the small sample population of HBV-positive patients and the lack of HBV DNA detection for several cases. Future studies should increase the sample size and include the effect of HBV viral load on survival of those patients. Therefore, objective prospective studies with more comprehensive clinical data and a longer follow-up period are needed to confirm our results.

In conclusion, we first found that HBV infection correlates with a good prognosis in infected patients; however, the mechanisms still need to be further explored and clarified. In clinical work, when HBsAg-positive patients may have two viable options for therapeutic regimens, patients can choose the less aggressive option. In addition, these patients can consider undertaking a less strict follow-up. However, larger and more objective prospective studies are needed to guide clinical decision making.

Abbreviations

HBV: Hepatitis B virus; CRC: colorectal cancer; CRLM: colorectal liver metastases; PFS: progression-free survival; OS: overall survival; CHB: chronic hepatitis B; HBsAg: hepatitis B surface antigen; IC: inactive carriers; HR: hazard ratio; CI: confidence interval; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; CEA: carcinoembryonic antigen; CA199: carbohydrate antigen 19-9; anti-HBs: hepatitis B surface antibody; HBeAg: hepatitis B e-antigen; anti-HBe: hepatitis B e-antibody; anti-HBc: hepatitis B core antibody; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; ALB: albumin; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transpeptidase; CTLs: cytotoxic lymphocytes; TNF-a: tumor necrosis factor a.

Supplementary Material

Supplementary figure.
http://www.jcancer.org/v09p1560s1.pdf

Ethics Committee Approval and Patient Consent

All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Institutional Review Board approval was also obtained from the independent ethics committee at Sun Yat-sen University Cancer Center. Informed consent was waived for this non-interventional, observational, and retrospective study, in which the patient data used were kept strictly confidential.

Competing Interests

The authors have declared that no competing interest exists.

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