# Hepatitis Serology Predicts Tumor and Liver-Disease Characteristics But Not Prognosis After Resection of Hepatocellular Carcinoma

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The impact of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection on survival rates after resection of hepatocellular carcinoma (HCC) is controversial. The objective of this study was to determine whether serologic evidence of HBV or HCV infection ("hepatitis serology") can predict underlying liver disease, tumor factors, and survival rates in patients with HCC. Using a multicenter international database, we identified 446 patients with complete HBV and HCV serology. One hundred twenty-six patients were negative for HBV and HCV, 163 patients had HBV infection only, 79 patients had HCV infection only, and 78 patients had coinfection with HBV and HCV. Patients with hepatitis were more likely to have tumors smaller than 5 cm and bilateral HCC involvement. Hepatitis status (negative vs. HBV vs. HCV vs. coinfection with HBV and HCV) did not predict tumor grade or the presence of multiple tumor nodules. Patients with HCV or coinfection with HBV and HCV exhibited a lower incidence of vascular invasion, but worse fibrosis than patients with negative serology or HBV. The median survival rate was 47.9 months. The presence of hepatitis did not significantly affect the survival rate, but hepatic fibrosis and vascular invasion predicted a decreased survival rate. The prognosis after resection of HCC is influenced by tumor factors and liver disease, but not by HBV or HCV infection. The treatment for HCC should be dictated by the extent of underlying liver disease rather than by hepatitis serology.
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Hepatocellular carcinoma (HCC) is the fifth most common malignancy in men and the ninth most common malignancy in women, accounting for 500,000 to 1 million cancer cases annually worldwide.[1] Most cases of HCC occur in areas where viral hepatitis is endemic; hepatitis B virus (HBV) and hepatitis C virus (HCV) are known to be important etiologic factors in HCC.[2,3] Previous studies[4,5] have reported rates of HBV infection ranging from 13%–73% and rates of HCV infection ranging from 11%–88% in patients diagnosed with HCC.

Although the association between viral hepatitis and HCC is well established, the effect of viral infection on tumor characteristics, underlying liver disease, and prognosis after resection of HCC remains controversial. Studies attempting to correlate serologic evidence of HBV or HCV infection ("hepatitis serology") with clinicopathologic features and prognosis in patients with HCC have produced conflicting and inconsistent findings. For example, Haratake and associates[6] determined that patients with HCV exhibited improved survival rates compared with

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patients with HBV, whereas Yamanaka and associates[7] reported that patients with HCV exhibited worse 5-year survival rates compared with patients with HBV (42% vs. 54%). Yamanaka and associates[7] also reported that patients with HCV were more likely to exhibit advanced underlying liver disease and advanced tumor stage, but other authors[8] have not noted this association. On the basis of data indicating that patients with HCV have a worse prognosis after resection, some authors[9] have advocated that HCC patients with serologic evidence of HCV infection and tumors smaller than 5 cm be considered for early liver transplantation rather than hepatic resection. Other investigators,[10] however, have questioned these recommendations, noting that the data supporting treatment based on hepatitis serology are conflicting.

Studies examining hepatitis serology and HCC have come from single-institution experiences exclusively from the East or West. We herein report the results from a multicenter study with regard to surgical resection for HCC among patients with different hepatitis serology status from both the East and the West. The objective of this study was to determine whether differences in hepatitis serology predict underlying liver disease, tumor characteristics, and survival rates after resection in patients with HCC.

## MATERIAL AND METHODS

Using a multicenter international database, we identified 446 patients with complete HBV and HCV serology who underwent hepatic resection for HCC between 1990 and 2000 at five major hepatobiliary centers: The University of Texas M. D. Anderson Cancer Center (Houston, TX), Mayo Clinic (Rochester, MN), Beaujon Hospital (Paris, France), Kyoto University Graduate School of Medicine (Kyoto, Japan), and Queen Mary Hospital (Hong Kong, China). All patients with HCC and no clinical, radiographic, or intraoperative evidence of extrahepatic disease were eligible for resection. Patients were deemed to have surgically resectable disease on the basis of the distribution and extent of tumors and the presence of a functional hepatic reserve adequate to tolerate hepatic resection. In all patients, the intent of the surgical procedure was curative.

For purposes of this study, patient characteristics, underlying liver and tumor characteristics, and survival data were examined. Specifically, the following data were collected for all patients: patient age and sex; tumor histologic subtype, number, location, and size; presence of vascular invasion; degree of underlying hepatic fibrosis; extent of hepatic resection (less than a hemi-hepatectomy, hemi-hepatectomy, or extended hepatic resection [five or more liver segments]);[11] operative details; vital status (living vs. deceased); most recent follow-up date; deceased date; serum alpha-fetoprotein (AFP) level; and hepatitis serology. The serologic presence of HBV surface antigen or HBV core antibody was considered evidence of HBV exposure because both increase the risk of HCC.[12] The serologic presence of HCV antibody was considered evidence of HCV infection. Tumor size was defined as the largest diameter of the tumor specimen. Microscopic vascular invasion was defined as the presence of tumor emboli within the central vein, the portal vein, or the large capsular vessels or the involvement of the segmental or sectoral branches of the portal vein or the hepatic veins.[13,14] Major vascular invasion was defined as gross invasion of the right or left main branches of the portal vein or the hepatic veins.[15] Tumor grade was assessed using the scheme outlined by Edmondson and Steiner[16] and the degree of fibrosis was graded according to the classification of Ishak and associates.[17]

Clinical data were reviewed on site at each of the five study centers by three of the investigators (J.N.V., D.M.N., R.T.P.). The pathologic resection specimens from each patient were similarly reviewed on site by two pathologists (G.Y.L., I.O.N.). Pathologic specimens were prepared at each center using hematoxylin-eosin staining.

Statistical analyses were performed to investigate possible associations between hepatitis status and patient characteristics, underlying liver and tumor characteristics, and mortality outcomes. Univariate tests ($\chi^2$) were used to test for differences in these distributions with regard to hepatitis status. Factors that seemed to be significantly associated with hepatitis status were entered into a Cox proportional hazards model to test for significant effects while adjusting for multiple factors simultaneously. Actuarial survival rates were calculated using the Kaplan–Meier method. Differences in survival rates were examined using the log-rank test. A $p$ value of less than 0.05 was considered significant.

## RESULTS

Of the 446 patients with HCC who underwent hepatic resection between 1990 and 2000, 126 patients (28.3%) lacked evidence of HBV or HCV infection and 320 patients (71.7%) exhibited evidence of HBV, HCV, or coinfection with HBV and HCV. In general, patients with positive hepatitis serologies were older ($p = 0.01$), exhibited smaller tumors ($p = 0.0003$), and were more likely to exhibit bilateral

disease ($p = 0.008$). The male-to-female ratio was not significantly different between the two groups ($p = 0.24$).

Patients were divided into four groups for the purposes of analysis. One hundred twenty-six patients (28.3%) were negative for HBV and HCV infection, 163 patients (36.5%) exhibited HBV infection only, 79 patients (17.7%) exhibited HCV infection only, and 78 patients (17.5%) exhibited coinfection with HBV and HCV.

The clinical features of the patients are summarized in Table 1. Although patients negative for HBV and HCV had a median age almost one decade younger than patients with hepatitis, there was no difference in median age among the three subgroups of patients with hepatitis. The male-to-female ratio was higher in patients with HBV infection only than in patients in the other three groups ($p < 0.05$). In contrast, there was no difference in Child's class according to hepatitis status. Patients in China were more likely to have HBV infection only ($p < 0.0001$) and patients in Japan were more likely to exhibit coinfection with HBV and HCV ($p < 0.0001$) (Table 1). Hepatitis status was strongly associated with AFP level at presentation: patients with HBV infection only exhibited a significantly higher median AFP level than patients in the other groups ($p < 0.0001$).

Tumor characteristics and underlying liver disease (degree of fibrosis) are summarized in Table 2. Although the percentage of patients with multiple HCC nodules was similar in the four groups, patients with negative hepatitis serology were less likely to have bilateral disease ($p < 0.05$). The distribution of histologic grade was not significantly different in the four groups ($p = 0.99$). However, median tumor size was significantly larger in patients with negative hepatitis serology and patients with HBV infection only than in patients with HCV infection only and patients with coinfection ($p < 0.0001$).

Hepatitis-negative patients and patients with HBV infection only were also noted to have significantly higher incidences of both major ($p = 0.01$) and microscopic ($p < 0.001$) vascular invasion. Both major and microscopic vascular invasion were more frequent in patients with either negative hepatitis serology or positive serology for HBV only. Whereas the incidence of major vascular invasion in patients who were hepatitis-negative or positive for HBV only was approximately 9%–10%, patients who were either HCV positive or coinfected with HBV and HCV exhibited major vascular invasion approximately half as often ($p = 0.01$). The same overall pattern was noted for microscopic vascular invasion. In contrast, the incidence of coexisting severe fibrosis/cirrhosis (Ishak grade 5–6) was highest in patients with HCV infection only or coinfection with HBV and HCV and lowest in patients with negative hepatitis serology ($p < 0.0001$). This was true even though patients with HCV infection only or coinfection with HBV and HCV tended to exhibit smaller tumors with less associated vascular involvement (Fig. 1).

The extent of hepatic resection is illustrated in Table 3. Approximately half of the patients (n = 221, 49.6%) underwent less than a hemi-hepatectomy; a

**Table 1.** Clinical features*

| Feature | Hepatitis-Negative | HBV Infection Only | HCV Infection Only | Coinfection |
|---|---|---|---|---|
| Number of patients | 126 | 163 | 79 | 78 |
| Median age (years) | 51† | 60 | 60 | 61 |
| Sex ratio (male:female) | 2.5:1 | 5.3:1‡ | 1.6:1 | 2.7:1 |
| Child's class | | | | |
| A | 105 (83.3) | 148 (90.8) | 58 (73.4) | 58 (74.4) |
| B | 21 (16.7) | 15 (9.2) | 21 (26.6) | 20 (25.6) |
| Country of origin | | | | |
| China | 26 (20.6) | 113 (69.3)‡ | 10 (12.7) | 3 (3.8) |
| Japan | 18 (14.3) | 12 (7.4) | 31 (39.2) | 53 (67.9)§ |
| France | 52 (41.3) | 28 (17.2) | 30 (38.0) | 17 (21.8) |
| United States | 30 (23.8) | 10 (6.1) | 8 (10.1) | 5 (6.5) |
| Median AFP level (ng/ml) | 11.5 | 267.0† | 32.0 | 26.0 |

AFP = alpha-fetoprotein; HBV = hepatitis B virus; HCV = hepatitis C virus.
*Values indicate the numbers of patients (percentages) unless otherwise denoted.
†$p < 0.05$ (hepatitis-negative patients vs. other groups).
‡$p < 0.05$ (patients with HBV infection only vs. other groups).
§$p < 0.05$ (patients with coinfection vs. other groups).

**Table 2.** Tumor characteristics*

| Characteristics | Hepatitis-Negative (n = 126) | HBV Infection Only (n = 163) | HCV Infection Only (n = 79) | Coinfection (n = 78) |
|---|---|---|---|---|
| Median tumor size (cm) | 7.0 | 7.0 | 3.0† | 3.2† |
| Bilateral disease | 11 (8.7) | 33 (20.2)‡ | 12 (15.2)‡ | 11 (14.1)‡ |
| Multiple (> 1) tumors | 20 (15.8) | 29 (17.8) | 13 (16.9) | 12 (15.2) |
| Microscopic vascular invasion | 69 (54.8) | 85 (52.1) | 32 (40.5)† | 25 (32.1)† |
| Major vascular invasion | 12 (9.5) | 16 (9.8) | 3 (3.8)† | 4 (5.1)† |
| Severe fibrosis/cirrhosis | 45 (35.7) | 82 (50.3) | 49 (62.0)† | 50 (64.1)† |

HBV = hepatitis B virus; HCV = hepatitis C virus.
*Values indicate the numbers of patients (percentages) unless otherwise denoted.
†$p < 0.05$ (patients with HCV infection only or coinfection vs. other groups).
‡$p < 0.05$ (patients with HBV, HCV, or coinfection vs. hepatitis-negative patients).

minority (n = 64, 14.3%) underwent an extended resection.

The 30-day mortality rate was low in all groups (negative hepatitis serology, 1.6%; HBV infection only, 0.6%; HCV infection only, 0%; coinfection, 0%) ($p = 0.45$). At a median follow-up time of 33 months (range 0.2–143 months), the median actuarial survival rate was 47.9 months (95% confidence interval [CI] 39.1–55.6 months) (Fig. 2). There was no significant difference in the median survival rate among the four patient groups (negative hepatitis serology, 48.7 months; HBV infection only, 40.7 months; HCV infection only, 50.5 months; coinfection, 60.6 months) ($p = 0.39$) (Fig. 3). Furthermore, there was no difference in survival rates based on hepatitis status when the subsets of patients with tumors smaller than 5 cm and 5 cm or larger were analyzed separately ($p > 0.05$) (Fig. 4).

Univariate analysis revealed that tumors 5 cm or larger, AFP levels greater than 30 ng/ml, Child's class B disease, the presence of vascular invasion, and the presence of severe fibrosis were all significant predictors of diminished overall survival. Patients with tumors 5 cm or larger exhibited a median survival of 33.7 months compared with 57.0 months for patients with tumors smaller than 5 cm ($p = 0.003$). Whereas patients with AFP levels 30 ng/ml or less exhibited a median survival of 70.9 months, patients with higher AFP levels exhibited a median survival of 31.1 months ($p < 0.0001$). Patients with Child's class B disease similarly fared poorly. Patients with Child's class B disease exhibited a median survival of 18.0 months compared with 50.5 months for patients with Child's class A disease ($p < 0.0001$). Patients with major vascular invasion exhibited a median survival of only 12.5 months vs. 50.5 months for patients without major vascular invasion ($p < 0.0001$). Although not as ominous, microscopic vascular invasion similarly predicted a poor long-term outcome. Whereas patients with no vascular invasion exhibited a median survival of 65.1 months, those with microscopic vascular invasion exhibited a median

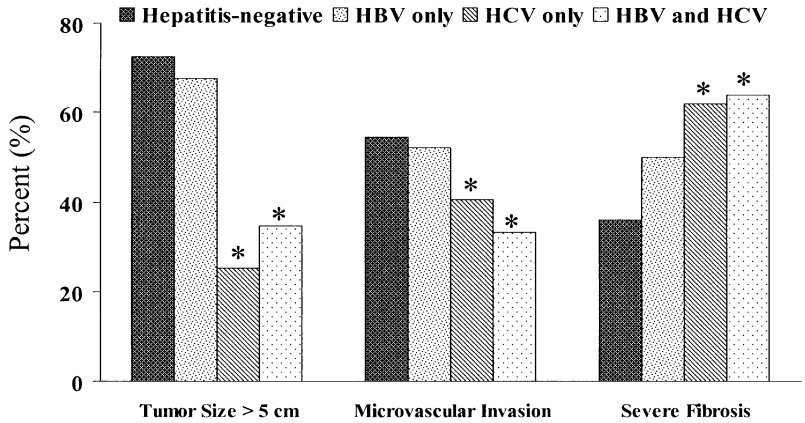


**Fig. 1.** Hepatitis-negative patients and hepatitis B virus (HBV)-positive patients exhibited less fibrosis, but larger tumors with more vascular invasion compared with hepatitis C virus (HCV)-positive patients and patients with coinfection with HBV and HCV (* = HCV-positive or coinfection patients vs. hepatitis-negative or HBV-positive patients; $p < 0.001$).

**Table 3.** Extent of hepatectomy*

| Characteristics | Hepatitis-Nagative (n = 126) | HBV Infection Only (n = 163) | HCV Infection Only (n = 79) | Coinfection (n = 78) |
|---|---|---|---|---|
| Less than a hemi-hepatectomy | 53 (42) | 63 (38) | 66 (84)† | 39 (52)† |
| Hemi-hepatectomy | 48 (38) | 68 (42) | 12 (15) | 30 (40) |
| Extended hepatic resection | 25 (20) | 32 (20) | 1 (1)† | 6 (8)† |

HBV = hepatitis B virus; HCV = hepatitis C virus.
*Values indicate the numbers of patients (percentages) unless otherwise denoted.
†$p < 0.0001$ (patients with HCV infection only or coinfection vs. other groups).

survival of 23.2 months ($p < 0.0001$) (Fig. 5, *A*). Patients with moderate-to-severe fibrosis/cirrhosis (Ishak grade 3–6) had a median survival rate of only 39.4 months compared with 88.5 months for patients with no or minimal fibrosis (Ishak grade 0–2) ($p < 0.0001$) (Fig. 5, *B*). Further analysis indicated a trend toward shorter survival rates for patients with severe fibrosis/cirrhosis (Ishak grade 5–6) (median survival = 36.0 months) than for patients with moderate fibrosis/cirrhosis (Ishak grade 3–4) (median survival = 43.8 months) ($p = 0.09$).

On multivariate survival analysis, both the presence of severe fibrosis and the presence of vascular invasion remained independent predictors of poor overall survival. Patients with moderate-to-severe fibrosis (Ishak grade 3–6) exhibited a higher likelihood of death than those with less severe underlying liver fibrosis (Ishak grade 0–2) (hazard ratio [HR] = 2.16, 95% CI = 1.48–3.15, $p < 0.0001$). Similarly, vascular invasion was associated with an increased risk of death. Patients with major vascular invasion indicated a greater than doubled risk of death (HR = 2.36, 95% CI = 1.50–3.72, $p < 0.0001$). The presence of microscopic vascular invasion conferred a similar, although slightly less, risk of death (HR = 1.88, 95% CI = 1.44–2.46, $p < 0.0001$).

## DISCUSSION

HCC occurs mostly in areas where viral hepatitis is endemic and there is considerable variation in the prevalence of HBV and HCV depending on the patient's country of origin.[18] It is estimated that 25% of patients with HCC in the United States exhibit evidence of HCV infection and HBV and HCV together account for no greater than 40% of HCC cases in the United States.[19,20] In contrast, both HBV and HCV infection are considered to be endemic in many Eastern countries, where the vast majority of HCC patients are positive for HBV or HCV. A survey conducted by the Liver Cancer Study Group of Japan

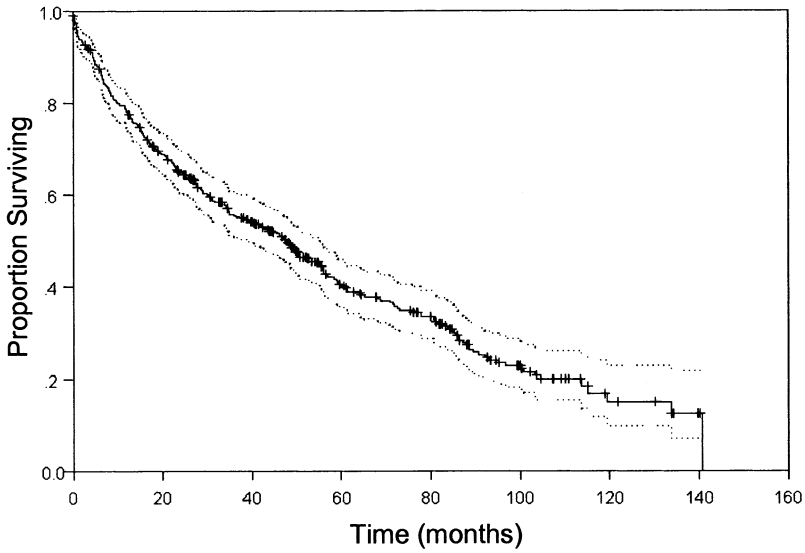


**Fig. 2.** At a median follow-up time of 33 months (range 0.2–143 months), the median actuarial survival rate for all hepatocellular carcinoma (HCC) patients regardless of hepatitis serologic status was 47.9 months (95% confidence interval [CI] 39.1–55.6 months).

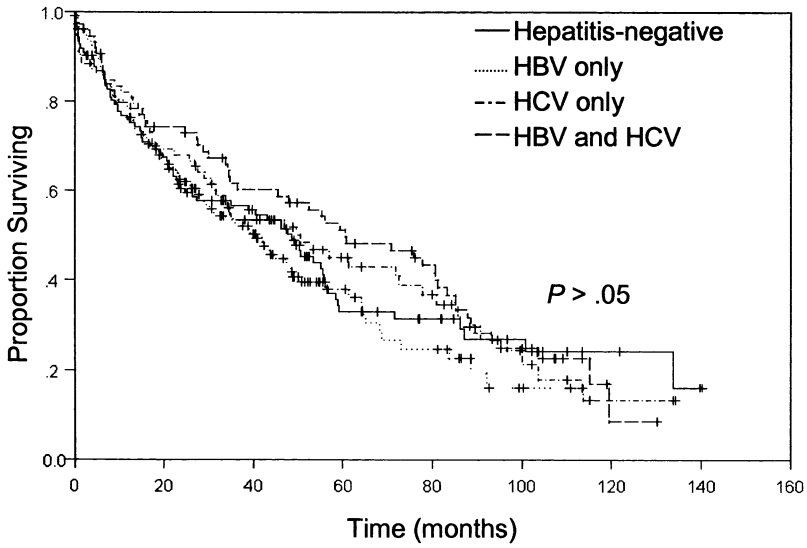


**Fig. 3.** Median survival rates did not differ by hepatitis serology. Hepatitis-negative patients exhibited a median survival rate (48.7 months) similar to that of hepatitis B virus (HBV)-positive patients (40.7 months), hepatitis B virus (HCV)-positive patients (50.5 months), and coinfected patients (60.6 months) ($p = 0.39$).

revealed that 72% of Japanese patients with HCC were positive for HCV and 26% were positive for HBV.[21] In the current study, we identified a similar incidence of HCV in Japanese patients (73.7%), however, the incidence of HBV was higher (57.0%). One possible explanation for the increased rate of HBV noted in the current study is that the serologic presence of HBV surface antigen or HBV core antibody was considered evidence of HBV exposure. The presence of HBV core antibody has previously been associated with an increase in the risk of HCC even after the seroconversion of HBV surface antigen (HBsAg).[12] In fact, HBV DNA can still be present after the seroconversion of HBsAg in patients[22,23] and HBV sequences are often found in HCC tissues in patients without HBsAg.[24,25] These data suggest that HBV genes play a role in the development of HCC in patients who are HBV core antibody positive, but HBsAg negative.[25,26] In support of this, the presence of HBV core antibody alone was previously shown to be an excess risk factor for HCC.[27,28]

Despite the endemic nature of hepatitis, there seems to be geographic variations even in Eastern countries. For example, in contrast to the situation in Japan, in Taiwan the HBV infection rate among patients with HCC is 80%–85%, whereas the HCV infection rate is low.[29,30] Similar to findings in previous epidemiologic reports, in the current study, more patients from the West (France and United States) than from the East (Hong Kong and Japan) exhibited negative hepatitis serology (65.1% vs. 34.9%). Furthermore, we identified regional differences in hepatitis infection rates among Eastern patients: Hong Kong patients were most likely to exhibit HBV infection only, whereas Japanese patients were most likely to exhibit coinfection with HBV and HCV. Geographical variations in the seroprevalence of hepatitis can make comparative studies of HBV and HCV infection and HCC difficult. However, international cooperative studies, such as the current one, may be more informative as they allow for meaningful comparison of results across hepatobiliary centers.

Several studies have investigated differences in the mechanisms of carcinogenesis between HBV-related and HCV-related HCC.[31] HCC carcinogenesis in patients with HBV infection is believed to be initiated by integration of HBV proviral DNA into the host DNA.[32] The integration of HBV double-stranded DNA into the host genome has been shown to enhance expression of the C-myc and N-myc oncogenes and to inactivate the tumor suppressor gene p53.[33,34] Such alterations can adversely affect cell cycle control, signal pathways, and apoptosis, thereby leading to an increased risk of carcinogenesis.[35] In contrast, HCC carcinogenesis in patients with HCV infection is unrelated to insertional mutagenesis, as HCV is an RNA virus that is not integrated. Rather, HCV most likely leads to carcinogenesis by inducing fibrosis and subsequent cirrhosis, thereby creating a "field of cancerization."[36,37] Whereas HBV-related chronic liver diseases tend to subside with seroconversion in approximately 90% of patients, HCV-related chronic liver diseases are characterized by persistent inflammatory activity with little decrease in their carcinogenic potential.[31,38] This fact supports

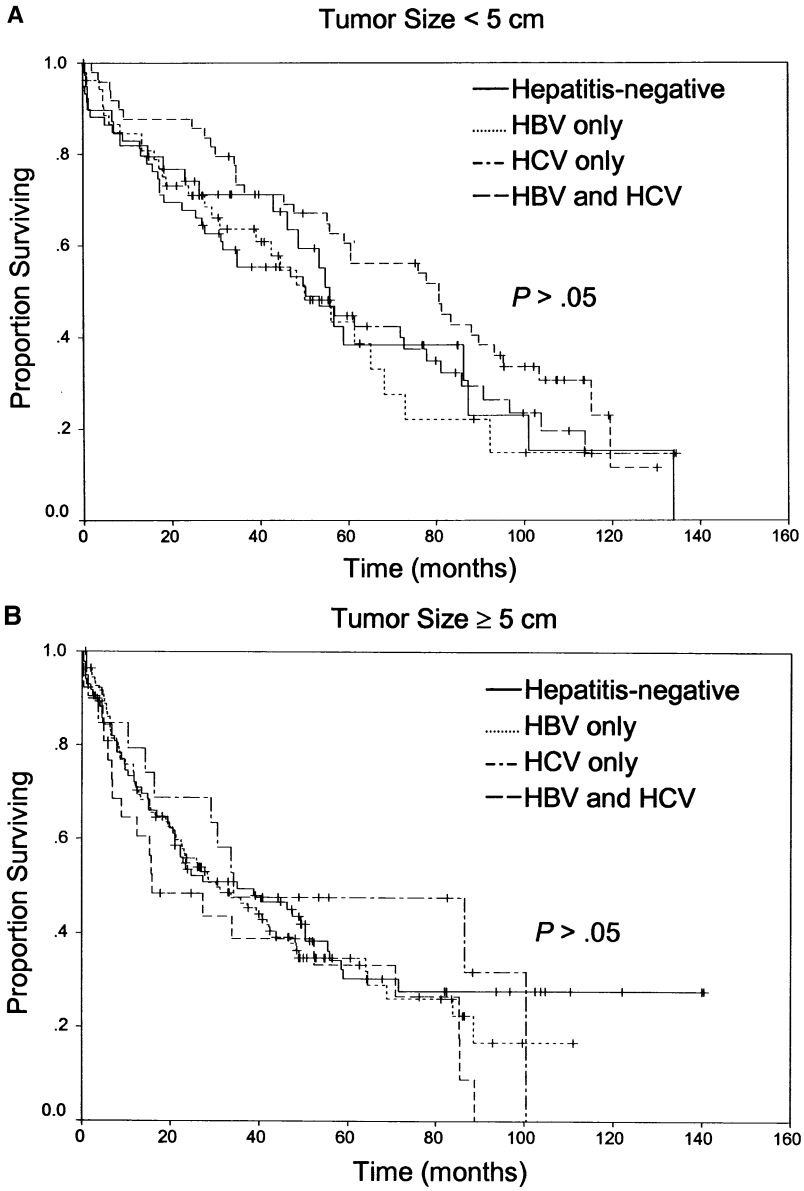


**Fig. 4.** In both patients with tumors smaller than 5 cm (**A**) and patients with tumors 5 cm or larger (**B**), survival rates did not differ by hepatitis status ($p > 0.05$). HBV = hepatitis B virus; HCV = hepatitis C virus.

the theory that HCV probably leads to HCC through chronic inflammatory stimulation.[31] Coinfection with HBV and HCV has been reported to cause much more severe liver disease in terms of histologic findings and clinical decompensation.[39,40] In fact, dual HBV and HCV positivity is an independent and significant risk factor for the development of HCC.[41] Taken together, these distinct viral mechanisms of carcinogenesis may explain the clinically relevant differences in the clinicopathologic features of patients with HCC with different hepatitis profiles observed in the current study.[9]

In this series, patient and tumor characteristics varied dramatically according to hepatitis serologic status. For example, the median age of patients with positive hepatitis serology was significantly higher than that of patients in the hepatitis-negative group. This is consistent with previous reports[30,42,43] and may be caused by the delayed carcinogenesis observed in patients with long-term inflammation of the liver induced by viral hepatitis. Although there was no significant difference between the groups with and without evidence of viral hepatitis in the overall number of tumors resected, patients with HBV,

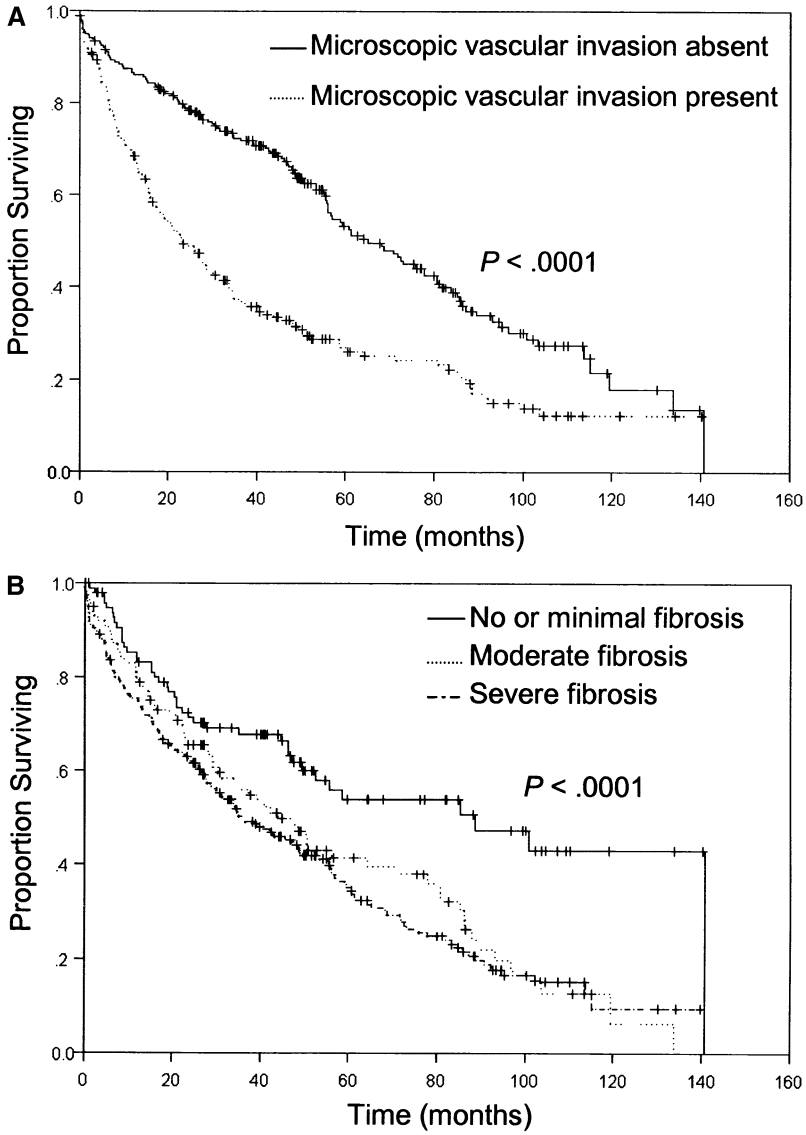


**Fig. 5.** The presence of severe fibrosis or vascular invasion adversely affected overall survival rates. (**A**) Patients with microscopic vascular invasion exhibited a significantly shorter median survival rate (23.2 months) than patients with no vascular invasion (65.1 months) ($p < 0.0001$). (**B**) Similarly, patients with moderate-to-severe fibrosis exhibited a significantly worse survival rate than patients with no or minimal fibrosis ($p < 0.0001$).

HCV, or coinfection with HBV and HCV were more likely to exhibit multicentric or bilateral disease. Other studies[35,43] have also indicated higher rates of multicentricity in patients with HBV or HCV infection.

Hepatitis-negative and HBV-positive patients exhibited significantly larger tumors than patients with HCV or coinfection with HBV and HCV. Both Takenaka and associates[43] and Yamanaka and associates[7] have previously reported that HBV-positive Japanese patients exhibit larger tumors, whereas Chen and associates[44] reported smaller tumors in Taiwanese patients infected with HCV. HBV-positive patients were also noted to exhibit significantly higher preoperative AFP levels. Although the higher AFP levels in HBV-positive patients may in part be explained by the larger median tumor size in this cohort, tumor burden cannot completely account for the differences. AFP levels were significantly higher in HBV-positive patients (267.0 ng/ml) than in hepatitis-negative patients (11.5 ng/ml) despite the fact that the two groups exhibited the same median tumor size. Others[7,45] have also reported elevated AFP levels in HBV-positive patients and have postulated

that the AFP value may reflect both tumor burden and the degree of acute inflammatory activity of the hepatitis infection.

Some have suggested that HCV-positive patients with small (< 5 cm) resectable tumors be given special consideration for early transplantation because of allegedly worse overall survival after resection.[9] In the current study, when patients were analyzed separately, there was no difference in survival rates based on hepatitis status in patients with tumors smaller than 5 cm ($p = 0.26$) or in patients with tumors 5 cm or larger ($p = 0.50$) (Fig. 4). Given these findings, we advocate that the mere presence of positive HBV or HCV infection should not be used to exclude patients from consideration for resection. Rather, individual tumor characteristics and underlying liver function should determine whether resection or transplantation is most appropriate.

Histopathologically detected vascular invasion and histopathologically detected adjacent severe fibrosis/cirrhosis of the nontumorous liver are known prognostic factors after resection of HCC.[13] In the current series, patients with negative hepatitis serology and patients with HBV infection only were significantly more likely to exhibit both microscopic and major vascular invasion. Tsai and associates[46] noted an association between increasing tumor size and increasing rates of both microscopic and macroscopic vascular invasion. Our finding that hepatitis-negative and HBV-positive patients—the two groups with the largest median tumor size—also exhibited the highest incidence of vascular invasion is consistent with earlier investigations correlating tumor size with vascular invasion.

Several studies[47,48] have documented an association between cirrhosis and recurrence of HCC that is presumably caused by continued carcinogenesis in the affected liver remnant. In the current series, patients with HCV infection only and patients with coinfection with HBV and HCV were significantly more likely to exhibit severe fibrosis/cirrhosis of the adjacent nontumorous liver. Given the distinct viral mechanisms of carcinogenesis, it is not surprising that a significantly higher proportion of patients with HCV than of patients with HBV exhibited cirrhosis in the surrounding parenchyma. Although two Japanese studies[43,49] examining the same topic indicated no significant difference in the incidence of cirrhosis between HCC patients infected with HCV and HBV, other studies[9,35] have demonstrated a significantly increased risk of severe fibrosis/cirrhosis with HCV infection. Scheuer and associates[38] and Takenaka and associates[43] noted that hepatitis activity was more serious and that liver function was generally more depressed in patients with HCV infection than in patients with HBV infection. Earlier studies[39,40] have also revealed that patients with coinfection with HBV and HCV tend to exhibit more severe and progressive liver disease. Our study confirms these earlier findings that implicate HCV and coinfection with HBV and HCV as significant risk factors for severe fibrosis/cirrhosis.

Given that severe fibrosis/cirrhosis is a strong predictor of poor overall survival, shorter survival rates after resection might have been predicted for patients with HCV infection or coinfection with HBV and HCV. However, in the current study, the survival rate curves for all four groups of patients, regardless of hepatitis status, were similar (Fig. 3). Others have reported inconsistent long-term results after resection of HCC in patients with different hepatitis serologic status. Yamanaka and associates[7] reported that patients with HBV-associated HCC had higher 5-year survival rates than patients with HCV-associated HCC (54% vs. 42%). In contrast, Haratake and associates[6] determined that patients with HCV-associated HCC had higher 1-, 2-, and 3-year survival rates compared with patients with HBV-associated HCC. However, the majority of series[43,49,50] have not shown a difference in overall survival rates between HBV-positive and HCV-positive patients. The current trial provides a multicenter international validation of these findings.

The current study may provide insight into why long-term survival rates among the four groups of patients is similar. We believe that the similar long-term survival rates may be related to differences in the characteristics of the tumors and the adjacent liver (Fig. 1). Whereas hepatitis-negative and HBV-positive patients exhibited larger tumors and a higher incidence of vascular invasion, HCV-positive patients and patients with HBV and HCV coinfection had a higher incidence of severe fibrosis/cirrhosis. On multivariate analysis, the relative risk of death for these two factors was similar (for vascular invasion, HR = 2.36; for severe fibrosis/cirrhosis, HR = 2.16). Therefore, although the profile of poor prognostic factors differed according to hepatitis status, the cumulative risk of death after resection seemed to be the same when all risk factors were considered.

## CONCLUSION

Data from a large international cohort of patients with HCC revealed that hepatitis-negative and HBV-positive patients had larger tumors with a higher frequency of both microscopic and major vascular invasion, whereas HCV-positive patients and patients with HBV and HCV coinfection were more

likely to have severe fibrosis/cirrhosis. Differences in tumor characteristics and underlying liver disease may relate to different mechanisms of viral infection and viral oncogenesis. The long-term surgical outcomes in hepatitis-negative, HBV-positive, HCV-positive, and coinfected patients were almost identical. Our data suggest that this finding may be related to the distinct, but off-setting, adverse prognostic factors particular to each hepatitis subgroup. Because hepatitis status does not, per se, dictate overall prognosis, we advocate against the use of serologic evidence of HBV or HCV infection as a surgical selection criteria. Rather, tumor and underlying liver characteristics such as the presence of vascular invasion or severe fibrosis/cirrhosis should take priority in formulating the treatment plan for patients with HCC.

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## *Discussion*

***Dr. M. Choti*** (Baltimore, MD): Thank you, Dr. Pawlik, for an excellent talk and an opportunity to review the manuscript in advance. I would like to congratulate this group of investigators on another excellent study using this international cooperative retrospective database. It appears that what you found is that the nonhepatitis and the hepatitis B patient exhibit poor oncologic prognostic factors such as vascular invasion and size and the hepatitis C patient experiences earlier stage cancers, but a higher degree of cirrhosis or severe fibrosis.

First of all, as implied from the title, the real question is does the hepatitis itself contribute to a poorer prognosis? Did you compare the patients with hepatitis

versus nonhepatitis with the same degree of cirrhosis? How do patients with severe fibrosis or cirrhosis from alcoholic or idiopathic cirrhosis compare with those patients with hepatitis C?

The second question relates to the pattern of recurrence. We often grapple regarding patients with cirrhosis, in particular those with hepatitis C, as to whether a recurrence is related to a new multifocal cancer or a true intrahepatic recurrence. Did you analyze the recurrence pattern regarding the patients with hepatitis C? Did they die of liver failure and did recurrence within the liver occur more frequently compared with patients with nonhepatitis or with hepatitis B in which one might expect the recurrence to more likely be extrahepatic?

Again, thank you for an excellent presentation.

***Dr. T. M. Pawlik:*** With regard to the first question, I agree with you. I think hepatitis serologic status may be acting as a surrogate. As you know, the two most important prognostic factors for long-term survival after resection for hepatocellular carcinoma are vascular invasion, whether it is major or microscopic, and fibrosis. So, when looking at patients who are hepatitis negative but who also have severe fibrosis, that is, Ishak grade V or VI, compared with patients who are hepatitis positive and also have severe fibrosis, they have a similar long-term outcome. In the current study, we are recognizing that patients who have hepatitis C, or B and C, are much more likely to develop severe fibrosis. However, if you have severe fibrosis, regardless of how you acquired it, it is a poor prognostic factor and these patients have a similar long-term outcome.

With regard to your second question, I think that patients with hepatitis C or coinfection with B and C suffer from a field cancerization effect. Both hepatitis C and coinfected patients are more likely to exhibit bilobar disease. Additionally, in the literature, these two cohorts of patients have been determined to be much more likely to recur intrahepatically. So, although we did not look specifically at the pattern of recurrence in our study, I think that you are correct in stating that patients who have hepatitis C or coinfection are much more likely to develop intrahepatic recurrence and therefore need to be followed closely with regard to this.

***Dr. K. Kelly*** (Scottsdale, AZ): Is it possible that severe hepatic fibrosis identified in patients with hepatitis C could prevent or impair vascular invasion by hepatic tumors indicated in patients who also exhibit hepatitis B?

***Dr. Pawlik:*** I think vascular invasion is related more to the tumor size. It is well established in both the published literature, as well as work that we are in the process of publishing, that as tumors become larger, there is an incremental increase in the amount of vascular invasion. So, in patients with hepatitis B who exhibit larger tumors, vascular invasion is more likely. If you are implying that the actual fibrosis may act as insulation for the liver thereby preventing vascular invasion, I would say that this may be possible, but is purely speculative. Our data has more likely indicated that large tumor size associated with hepatitis B is probably more of a direct effect and is also why we are seeing greater vascular invasion in this cohort of patients. It is not surprising that we do not observe as much vascular invasion in the group of patients with hepatitis C or coinfection because their tumors had a median size of only 3 cm, whereas hepatitis B patients had a median tumor size over twice that (7 cm). Thus, I really think the main reason for the vast difference regarding the incidence of vascular invasion relates more to tumor size.