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Survival after surgery for hepatocellular carcinoma in relation to presence or absence of viral infection

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Abstract

BACKGROUND: The aim of this study was to compare postoperative survival between hepatocellular carcinoma (HCC) patients with and without viral infection.

METHODS: From among 398 HCC patients in our collected database, 377 who underwent surgery were enrolled. The patients were divided into 2 groups: group 1, those who had no hepatitis B virus or hepatitis C virus infection, and group 2, those who had hepatitis B virus or hepatitis C virus infection. Univariate analysis was performed to compare clinical factors, including viral infection, with overall survival. Kaplan-Meier analysis and the log-rank test were used to evaluate the overall and disease-free survival curves for the 2 groups.

RESULTS: Univariate analysis showed that viral infection showed no such association. Moreover, Kaplan-Meier analysis and the log-rank test revealed no significant intergroup differences in either overall or disease-free survival.

CONCLUSIONS: The presence or absence of viral infection shows no significant association with the postoperative survival of patients undergoing surgery for HCC.

Infection with viruses such as hepatitis B virus (HBV)[1] and/or hepatitis C virus (HCV)[2] is a major risk factor for not only chronic hepatitis (CH) and liver cirrhosis (LC) but also hepatocellular carcinoma (HCC).[3,4] Because most patients undergoing surgery for HCC have CH or LC caused by a viral infection, the indications for hepatic resection are rigidly dependent on the accurate estimation of liver function and residual liver volume.[5,6]

However, numerous epidemiologic and molecular-biologic studies have shown that there are some differences in characteristics between patients in whom HCC originates from HBV infection (B-HCC) and those in whom HCV infection (C-HCC) is responsible.[7] First, B-HCC is induced through integration,[8] transactivation,[9] and mutation of tumor suppressor genes followed by additional carcinogenesis during the sequential transformation of CH to LC.[10] Because B-HCC is induced through the direct oncogenic effect of HBV, fibrosis of the liver at the carcinogenesis stage may not be very severe. On the other hand, because HCV is an RNA virus that does not integrate with the DNA of hepatocytes, its effect on HCC oncogenesis is still unclear.

Second, most cases of B-HCC are attributable to vertical transmission during delivery, whereas most cases of C-HCC are attributable to transfusion of blood products during adulthood. Therefore, the mean age for the occurrence of HCC is lower for patients with B-HCC than for

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patients with C-HCC. In addition, there is evidence that both HBV and HCV might affect HCC recurrence or death through disease progression or liver deterioration.[11–13]

On the other hand, evidence from recent studies indicates that the major cause of cryptogenic HCC without viral infection is nonalcoholic fatty liver disease (NAFLD)[14] caused by hepatic manifestation of metabolic syndrome,[15] and the increased risk of HCC among individuals with features of metabolic syndrome worsens the resulting cancer outcome.[16–18] Therefore, in the present study, we attempted to compare postoperative survival between HCC patients with and without viral infection.

Methods

We retrospectively reviewed a database of 398 patients who had undergone surgery for HCC performed by the same trained surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, Tochigi, Japan, between April 2000 and December 2008. Among these patients, we excluded those who had undergone surgery for ruptured HCC (n = 3) and those who had synchronous malignant tumors (n = 18, esophagus 2, stomach 9, colorectum 6, other 1). Consequently, we selected 377 patients (male:female = 299:78) for an accurate estimation of the influence of viral infections on postoperative survival, among whom 76 had undergone surgery for recurrent HCC.

On the day of admission, all patients underwent routine laboratory tests including those for tumor markers such as α-fetoprotein (AFP) (upper physiologic value: 6 ng/mL)[19] and protein induced by vitamin K absence or antagonists II (PIVKA II) (upper physiologic value: 37 U/mL).[20–22] Pathological features such as background liver (ie, normal liver [NL], chronic hepatitis [CH], and liver cirrhosis [LC]) and tumor histology (ie, well differentiated, moderately differentiated, poorly differentiated, and undetermined) were evaluated by the same pathologists. The stage was based on tumor dimension, lobar distribution, and the presence or absence of vascular invasion as outlined in The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th Edition, February 2008, Liver Cancer Study Group of Japan).[23] Other stages conducted were as follows:

1. Child-Pugh classification is based on prothrombin time, albumin level, and the presence and degree of ascites and encephalopathy.[24]
2. The Model for End-Stage Liver Disease (MELD) score, which is based on 3 items (ie, serum levels of creatinine and bilirubin and prothrombin time international normalized ratio), was calculated by accessing home page described elsewhere (http://www.mayoclinic.org/meld/mayomodel6.html).
3. The Cancer of the Liver Italian Program (CLIP) score is based on 4 items with a score ranging from 0 to 6. These 4 items include Child-Pugh stage (A = 0, B = 1, C = 2), tumor morphology (uninodular, <50%, 0; multinodular, <50%, 1; massive or >50%, 2), AFP level (<400 ng/mL, 0; ≥400 ng/mL, 1), and the presence of portal vein thrombosis (no, 0; yes, 1).[25,26]

Because the indications for HCC surgery were based on the Makuuchi criteria, no patients were evaluated as Child-Pugh C in this study.[27]

Diagnosis of NAFLD and NASH

NAFLD. The diagnosis of NAFLD[28] was based on the following criteria: (1) the detection of hepatic steatosis (or steatohepatitis) by liver biopsy or imaging; (2) an intake of less than 20 to 30 g ethanol per day; and (3) the appropriate exclusion of other liver diseases.

NASH. The diagnosis of NASH[29] was established on biopsy by the presence of steatosis affecting more than 10% of hepatocytes in conjunction with necroinflammatory activity, ballooning hepatocytes, and/or fibrosis. An elevated amino transaminase level (ie, a minimum of 1.5 times the upper limit of normal on 2 occasions at least 3 months apart) was also required. Patients with secondary causes of NASH were excluded. Viral, autoimmune, biliary, drug-induced, and metabolic liver diseases were excluded by routine serologic testing, abdominal imaging, and liver biopsy in every patient.

Patients were divided into 2 groups: group 1, those who had no HBV or HCV infection, and group 2, those who had HBV or HCV infection. HBV infection was defined as positivity for HBV antigens such as Hepatitis B surface antigen (HBs Ag) and Hepatitis B e antigen (HBe Ag) or positivity for HBV antibodies such as Hepatitis B core antibody (HBc Ab), Hepatitis B e antibody (HBe Ab), and Hepatitis B surface antibody (HBs Ab). HCV infection was defined as positivity for HCV antibody. Kaplan-Meier analysis and the log-rank test were used to evaluate the overall and disease-free survival curves for these 2 groups.

Univariate analyses were performed to examine the relationship between overall survival and clinical factors such as sex (female/male), age (years), maximum tumor diameter (≤2/>2 cm), number of HCCs (1/≥2), prothrombin time (%), aspartate aminotransferase (AST) (IU/L), alanine aminotransferase (ALT) (IU/L), total bilirubin (mg/dL), AFP (ng/mL), PIVKA II (U/mL), histology (well, moderately, undetermined/poorly differentiated), background liver (NL, CH/LC), indocyanine green retention ratio at 15 minutes (ICG R 15) (%), Child-Pugh classification (A/B), CLIP score (0, 1/≥2), stage (I, II/III, IV), and viral infection (group 1/group 2).

Statistical analysis

Data are presented as mean ± standard deviation. Differences between groups were analyzed using the chi-square test and the Mann-Whitney *U* test. Odds ratios with